Richard J. Sundberg

Advanced Organic Chemistry

Reactions and Synthesis

Second Edition

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SECOND EDITION

Part B: Reactions and Synthesis

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Preface to the Second Edition

The gratifying response to the first edition has encouraged us to undertake the revision of Part B to reflect the rapid development in synthetic methodology which has occurred since the first edition was prepared. The organizational format is similar to the first edition with two major exceptions. A new chapter (Chapter 3) "Functional Group Interconversion by Nucleophilic Substitution," has been added. This chapter summarizes synthetically valuable nucleophilic substitutions at both sp^3 and sp^2 carbon. Thus such common functional group transformations as conversion of alcohols to halides, preparation of nitriles and acylation of amines, among others, are covered in the new chapter. The classical methods for such reactions are well-covered in introductory texts but the development of milder and more selective methods and the basic importance of such transformations in synthesis seemed to necessitate the inclusion of this material. Chapter 11, which dealt with synthesis of polymers, polypeptides, and polynucleotides, has been dropped. The adequate description of these highly developed but somewhat specialized techniques now seems beyond the scope of a chapter of reasonable size.

As in the first edition, the references presented are considered to be examples and do not reflect any effort to recognize author's priority of discovery. Where possible, examples which illustrate improved methodologies for well-established reactions have been used but in many cases other equally satisfactory techniques are available. Although the authors of the referenced papers are an international group, the predominance of the references are to the *Journal of the American Chemical Society* and to the *Journal of Organic Chemistry*, with *Tetrahedron Letters* also being well-represented.

About half of the problems are new. As in the first edition, they have been drawn from published literature. Very few of the questions are of the drill variety, and students, particularly undergraduates, will find them challenging. We have

found them to be an excellent basis for discussion in class as well as being exercises which can provide the student with the opportunity to apply the factual material presented in the chapter and to develop routes for synthesis of specific molecules. Many of the synthesis problems have been presented in the retrosynthetic mode which has received wide acceptance in the research literature. A formal discussion of retrosynthetic analysis of complex molecules is presented in the final chapter.

We thank numerous colleagues for their encouraging responses to the first edition and their help in pointing out errors and suggesting modifications. We hope this revised edition will serve as a bridge for students to pass from an introductory course in organic chemistry to the independent study of the research and review literature in organic synthesis.

Charlottesville, Virginia
December, 1981

Francis A. Carey
Richard J. Sundberg

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Alkylation of Nucleophilic Carbon. Enolates and Enamines

Since practically all syntheses of any complexity involve carbon–carbon bond-forming steps as an essential feature, the availability of methods which allow two molecular fragments to be connected by the reaction of a nucleophilic carbon with an electrophilic one can be crucial to the success of a synthetic plan. The emphasis in this chapter is on *enolate ions* and *enamines*, two of the most useful kinds of carbon nucleophiles, their preparation, and their reactions with *alkylating agents*. Certain related nucleophilic carbon species will also be discussed.

1.1. Generation of Carbon Nucleophiles by Deprotonation

The most general means of generating carbon nucleophiles involves removal of a proton from a carbon by a Bronsted base. The anions produced are *carbanions*. Both the rate of deprotonation and the stability of the resulting carbanion are enhanced by the presence of substituent groups that can stabilize negative charge. A carbonyl group bonded directly to the carbanionic carbon can delocalize negative charge by resonance and is an especially important function in carbanion chemistry. The anions formed by deprotonation of the carbon *alpha* to a carbonyl group bear most of their negative charge on oxygen and are commonly referred to as *enolates*. Several typical examples of proton abstraction equilibria are listed in Scheme 1.1. Electron delocalization in the resulting carbanions is represented by the resonance structures presented in Scheme 1.2.

Scheme 1.1. Generation of Carbon Nucleophiles by Deprotonation

1 $RCH_2\overset{O}{\overset{\|}{C}}OR' + \bar{N}R_2'' \rightleftharpoons R\bar{C}H\overset{O}{\overset{\|}{C}}OR' + HNR_2''$

2 $RCH_2\overset{O}{\overset{\|}{C}}R' + NH_2^- \rightleftharpoons R\bar{C}H\overset{O}{\overset{\|}{C}}R' + NH_3$

3 $CH_3CH_2O\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 + CH_3CH_2O^- \rightleftharpoons CH_3CH_2O\overset{O}{\overset{\|}{C}}\bar{C}H\overset{O}{\overset{\|}{C}}OCH_2CH_3 + CH_3CH_2OH$

4 $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 + CH_3CH_2O^- \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}\bar{C}H\overset{O}{\overset{\|}{C}}OCH_2CH_3 + CH_3CH_2OH$

5 $N{\equiv}CCH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 + CH_3CH_2O^- \rightleftharpoons N{\equiv}C\bar{C}H\overset{O}{\overset{\|}{C}}OCH_2CH_3 + CH_3CH_2OH$

6 $RCH_2NO_2 + HO^- \rightleftharpoons R\bar{C}HNO_2 + H_2O$

The efficient generation of a significant equilibrium concentration of a carbanion requires careful choice of a proper Bronsted base. The acidity of the carbon acid must be greater than that of the conjugate acid corresponding to the base used or the equilibrium will be unfavorable. Acidity is usually expressed as pK_a,

Scheme 1.2. Resonance in Some Carbanions

1 Enolate of ketone

$$R\bar{C}H-\overset{O}{\overset{\|}{C}}R' \leftrightarrow RCH=\overset{O^-}{\overset{|}{C}}R'$$

2 Malonic ester anion

$$CH_3CH_2O\overset{O}{\overset{\|}{C}}-CH=\overset{O^-}{\overset{|}{C}}OCH_2CH_3 \leftrightarrow CH_2CH_2O\overset{O}{\overset{\|}{C}}-\bar{C}H-\overset{O}{\overset{\|}{C}}OCH_2CH_3 \leftrightarrow CH_3CH_2O\overset{O^-}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}OCH_2CH_3$$

3 Acetoacetic ester anion

$$CH_3\overset{O}{\overset{\|}{C}}-CH=\overset{O^-}{\overset{|}{C}}OCH_2CH_3 \leftrightarrow CH_3\overset{O}{\overset{\|}{C}}-\bar{C}H-\overset{O}{\overset{\|}{C}}OCH_2CH_3 \leftrightarrow CH_3\overset{O^-}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}OCH_2CH_3$$

4 Cyanoacetic ester anion

$$N{\equiv}C-CH=\overset{O^-}{\overset{|}{C}}OCH_2CH_3 \leftrightarrow N{\equiv}C-\bar{C}H-\overset{O}{\overset{\|}{C}}OCH_2CH_3 \leftrightarrow \bar{N}=C=CH-\overset{O}{\overset{\|}{C}}OCH_2CH_3$$

5 Nitronate anion

$$R\bar{C}H-\overset{O}{\overset{\|}{\overset{+}{N}}}\diagdown O^- \leftrightarrow RCH=\overset{O^-}{\overset{|}{\overset{+}{N}}}\diagdown O^-$$

which is equal to $-\log K_a$ and applies by definition to dilute aqueous solution. Since many important carbon acids are quite weak acids ($pK_a > 15$), accurate measures of their equilibria in aqueous solutions are impossible and acidities are determined in a variety of organic solvents and secondarily referenced to water in an approximate way. The data produced are not true pK_a's and their approximate nature is indicated by referring to them as simply pK values rather than as pK_a's. Table 1.1

Table 1.1. Approximate p*K* Values for Some Carbon Acids and Some Common Bases

Carbon acid	pK[a]	(pK_{DMSO})	Common bases[a,b]	pK[c]	(pK_{DMSO})
$O_2NCH_2NO_2$	3.6		$CH_3CO_2^-$	4.2	(11.6)
$CH_3COCH_2NO_2$	5.1				
$PhCH_2NO_2$		(12.2)[d]			
$CH_3CH_2NO_2$	8.6	(16.7)[e]			
$CH_3COCH_2COCH_3$	9				
$PhCOCH_2COCH_3$	9.6		PhO^-	9.9	(16.4)
CH_3NO_2	10.2	(17.2)[e]			
$CH_3COCH_2CO_2CH_2CH_3$	10.7		$(CH_3CH_2)_3N$	10.7	
$CH_3COCH(CH_3)COCH_3$	11		$(CH_3CH_2)_2NH$	11	
$NCCH_2CN$	11.2	(11.1)[e]			
$CH_2(SO_2CH_2CH_3)_2$	12.2	(14.4)[f]			
$CH_2(CO_2CH_2CH_3)_2$	12.7				
Cyclopentadiene	15				
$PhSCH_2COCH_3$		(18.7)[g]			
$PhCH_2COCH_3$		(19.8)[e]	CH_3O^-	15.5[i]	(29.0)[j]
$CH_3CH_2CH(CO_2CH_2CH_3)_2$	15		HO^-	15.7[i]	(31.4)[j]
$PhSCH_2CN$		(20.8)[g]			
$PhCH_2CN$		(21.9)[d]			
$(PhCH_2)_2SO_2$		(23.9)[e]	$CH_3CH_2O^-$	15.9	(29.8)[j]
			$(CH_3)_3CO^-$	19	(32.2)[j]
$PhCOCH_3$	15.8[k]	(24.7)[e]			
CH_3COCH_3	20	(26.5)[e]			
$CH_3CH_2COCH_2CH_3$		(27.1)[e]			
Fluorene	20.5	(22.6)[e]			
$PhSO_2CH_3$		(29.0)[e]			
$PhCH_2SOCH_3$		(29.0)			
CH_3CN	25	(31.3)[e]			
Ph_3CH	33	(30.6)[e]	NH_2^-	35	(40.7)[k]
			$CH_3SOCH_2^-$	35	(35.1)[e]
			$(CH_3CH_2)_2N^-$	36	
$PhCH_3$		(42)[h]			
CH_4		(55)[h]			

a. D. J. Cram, *Fundamentals of Carbanion Chemistry*, Academic Press, New York (1965), pp. 8–20, 41.
b. H. O. House, *Modern Synthetic Reactions*, second edition, W. A. Benjamin, Menlo Park, CA, 1972, p. 494.
c. p*K* of the conjugate acid.
d. F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. J. McCollum, M. Van Der Puy, N. R. Vanier, and W. S. Matthews, *J. Org. Chem.* **42**, 321 (1977).
e. W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.* **97**, 7006 (1975).
f. F. G. Bordwell, J. E. Bartmess, and J. A. Hantala, *J. Org. Chem.* **43**, 3095 (1978).
g. F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. E. Drucker, J. Gerhold, G. J. McCollum, M. Van Der Puy, N. R. Vanier, and W. S. Matthews, *J. Org. Chem.*, **42**, 326 (1977).
h. Estimated: D. Algrim, J. E. Bares, J. C. Branca, and F. G. Bordwell, *J. Org. Chem.* **43**, 5024 (1978).
i. True pK_a in water: P. Ballinger and F. A. Long, *J. Am. Chem. Soc.* **82**, 795 (1960).
j. W. N. Olmsted, Z. Margolin, and F. G. Bordwell, *J. Org. Chem.* **45**, 3295 (1980).
k. In water: M. Novak and G. M. Loudon, *J. Org. Chem.* **45**, 2494 (1977).

presents a listing of the pK data for some typical carbon acids. The table includes a listing of the customary bases used for deprotonation. A favorable equilibrium between a carbon acid and its carbanion will be established if the base which is used appears below the acid in the table. The strongest acids appear at the top of the table, the strongest bases at the bottom. Also included in the table are pK values determined in dimethyl sulfoxide (pK_{DMSO}). The range of acidities which can be directly measured in dimethyl sulfoxide is much greater than can be measured in aqueous media, thereby allowing direct comparisons between species to be made more confidently. The pK values are normally greater in dimethyl sulfoxide than in water because water stabilizes anions by hydrogen bonding more effectively than does dimethyl sulfoxide. While it would be desirable to have all acidity data on a common scale, especially the pK_a scale, it is likely that pK_{DMSO} will become the more readily accessible data and be more useful in carbanion chemistry.[1]

From the pK values reported in Table 1.1 an approximate ordering of some substituents with respect to their ability to stabilize carbanions can be established. The order suggested is $NO_2 > COR > CN \approx CO_2R > SO_2R > SOR > Ph \approx SR \gg H > R$.

By comparing the approximate pK values of the conjugate acids of the bases with those of the carbon acid of interest, it is possible to estimate the position of the acid–base equilibrium for a given reactant–base combination. If we consider the case of a simple alkyl ketone, in a protic solvent, for example, it can be seen that hydroxide ion and primary alkoxide ions will convert only a fraction of such a ketone to its anion:

$$\underset{\displaystyle\underset{\displaystyle O}{\|}}{RCCH_3} + RCH_2O^- \rightleftharpoons \underset{\displaystyle\underset{\displaystyle O^-}{|}}{RC{=}CH_2} + RCH_2OH$$

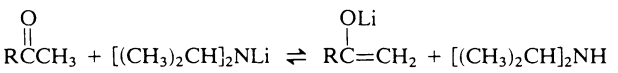
The slightly more basic tertiary alkoxides are comparable to the enolates in basicity, and a more favorable equilibrium will be established with such bases:

$$\underset{\displaystyle\underset{\displaystyle O}{\|}}{RCCH_3} + R_3CO^- \rightleftharpoons \underset{\displaystyle\underset{\displaystyle O^-}{|}}{RC{=}CH_2} + R_3COH$$

Stronger bases, such as amide anion, methylsulfinylcarbanion (the conjugate base of dimethyl sulfoxide),[2] and triphenylmethyl anion, are capable of effecting rapid and essentially complete conversion of a ketone to its enolate. Lithium diisopropylamide, generated by addition of *n*-butyllithium to diisopropylamine, is widely used for this purpose.[3] It is a very strong base, yet is sufficiently bulky so as to be relatively nonnucleophilic—a feature that is important in reducing a number of side reactions. The lithium and sodium salts of hexamethyldisilazane $[(CH_3)_3Si]_2NH$ are easily prepared and handled compounds with properties similar

1. W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.* **97**, 7006 (1975).
2. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **87**, 1345 (1965).
3. H. O. House, W. V. Phillips, T. S. B. Sayer, and C.-C. Yau, *J. Org. Chem.* **43**, 700 (1978).

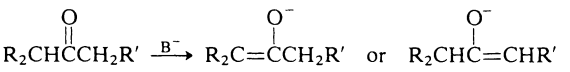
to lithium diisopropylamide.[4]



For any of the other carbon acids in Table 1.1, similar consideration allows us to estimate the position of the equilibrium with a given base. It is important to bear in mind the position of such equilibria as other aspects of reactions of carbanions are considered.

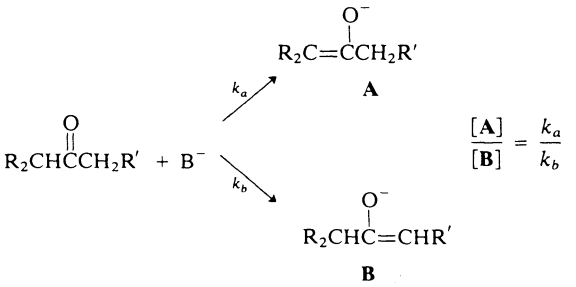
1.2. Regioselectivity and Stereoselectivity in Enolate Formation

An unsymmetrical dialkyl ketone can form two *regioisomeric* enolates on deprotonation:



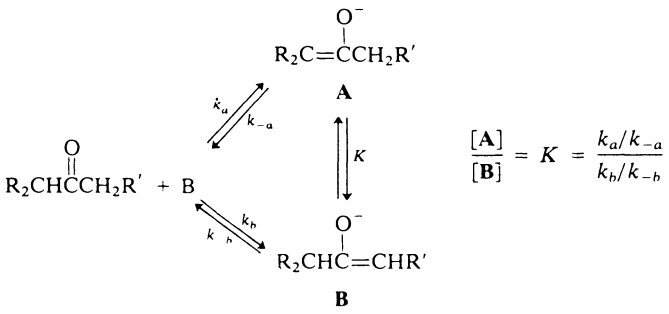
In order to exploit fully the synthetic potential of enolate ions, some control over the regioselectivity of their formation is required. While, in most cases, it is not possible to direct deprotonation so as to form one enolate to the exclusion of the other, experimental conditions can be chosen which will provide a reasonable excess of the desired regioisomer. So that we may understand the reasons why a particular set of experimental conditions leads to the preferential formation of one enolate while a different set leads to the other, we need to examine enolate generation in more detail.

The composition of an enolate mixture may be governed by kinetic or thermodynamic factors. In the former case, the product composition is governed by the relative *rates* of two competing proton-abstraction reactions. The enolate ratio is governed by *kinetic control.*



On the other hand, if enolates **A** and **B** can be interconverted rapidly, equilibrium will be established and the product composition will reflect the relative thermodynamic stability of the enolates. The enolate ratio is governed by *thermodynamic control.*

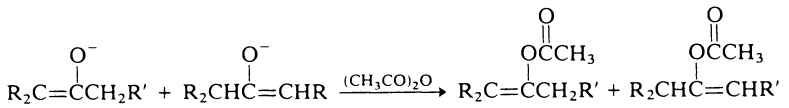
4. E. H. Amonoco-Neizer, R. A. Shaw, D. O. Skovlin, and B. C. Smith, *J. Chem. Soc.*, 2997 (1965); C. R. Kruger and E. G. Rochow, *J. Organometal Chem.* **1**, 476 (1964).



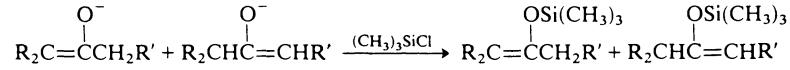
$$\frac{[\mathbf{A}]}{[\mathbf{B}]} = K = \frac{k_a/k_{-a}}{k_b/k_{-b}}$$

By adjusting the conditions under which an enolate mixture is formed from a ketone, it is possible to establish either kinetic or thermodynamic control. *Ideal conditions for kinetic control of enolate formation are those in which deprotonation is rapid, quantitative, and irreversible.*[5] This ideal is approached experimentally by using a very strong base such as lithium diisopropylamide or triphenylmethyllithium in an aprotic solvent in the absence of excess ketone. Lithium as the counterion is better than sodium or potassium for regioselective generation of the kinetic enolate. Protic solvents promote enolate equilibration by allowing protonation–deprotonation pathways to operate on the isomeric enolates. Excess ketone seems to catalyze equilibration in much the same way by acting as a proton source.

The composition of enolate mixtures can be determined by allowing the enolates to react with acetic anhydride. Rapid formation of enol acetates occurs, and subsequent determination of the ratio of enol acetates reveals the ratio of enolates present in the solution.[6]



Alternatively, chlorotrimethylsilane can be used to react with the enolate mixture to give the corresponding enol trimethylsilyl ethers.[7] The enol acetate or enol trimethylsilyl ether mixture can be analyzed by gas chromatography or by nuclear magnetic resonance (nmr). Table 1.2 shows the data obtained for several ketones. Some of the data were measured by the techniques just mentioned. In a number of cases the data are more qualitative and indicate the enolate which gave rise to isolated products on subsequent reaction with electrophiles.

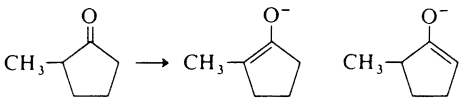


5. For a review, see J. d'Angelo, *Tetrahedron* **32**, 2979 (1976).
6. H. O. House and B. M. Trost, *J. Org. Chem.* **30**, 1341 (1965).
7. H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.* **36**, 2361 (1971).

Table 1.2. Compositions of Enolate Mixtures

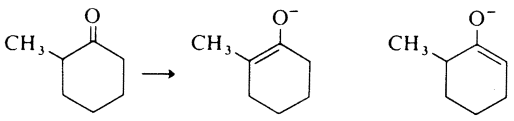
A. Regioselectivity

1[a]



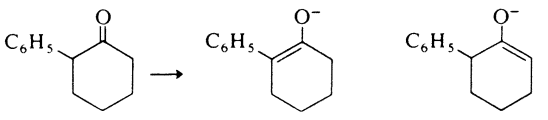
Kinetic control (Ph_3CLi/ dimethoxyethane)	28	72
Thermodynamic control (Ph_3CLi/ equilibration in the presence of excess ketone)	94	6

2[b,c]



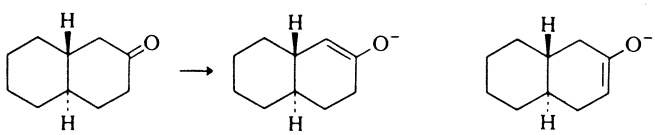
Kinetic control (LDA/ dimethoxyethane)	1	99
Thermodynamic control (Et_3N/DMF)	78	22

3[d]



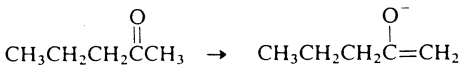
Kinetic control (LDA/tetrahydrofuran, −70°C)[d]	Only enolate	Only enolate
Thermodynamic control (KH, tetrahydrofuran)[e]		

4[a]



Kinetic control (Ph_3CLi/ dimethoxyethane)	13	87
Thermodynamic control (equilibration in the presence of excess ketone)	53	47

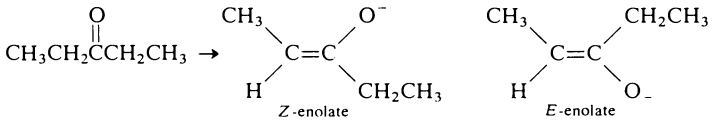
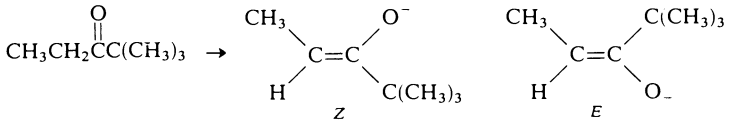
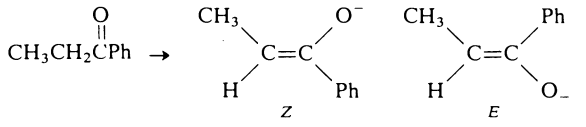
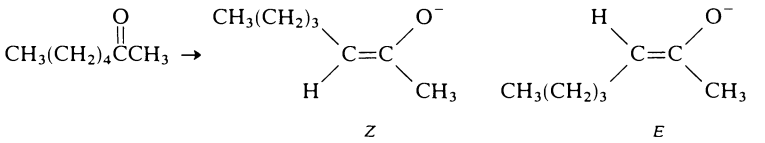
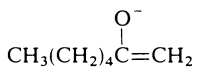
5[f]



Kinetic control (LDA/tetrahydrofuran, −78°C)	Only enolate detected

Table 1.2—*continued*

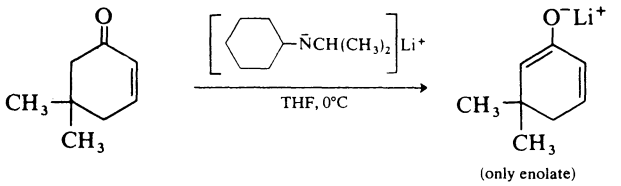
B. Stereoselectivity

6[g]			
		Z-enolate	*E*-enolate
Kinetic control (lithium 2,2,6,6-tetramethylpiperidide/ tetrahydrofuran)		13	87
Thermodynamic control (equilibration in the presence of excess ketone)		84	16
7[h]			
		Z	*E*
Kinetic control (LDA/ tetrahydrofuran)		>98	<2
8[h]			
		Z	*E*
Kinetic control (LDA/Tetrahydrofuran)		>98	<2
			
		Z	*E*
Kinetic control (Ph_3CK/dimethoxyethane)		37	9
Thermodynamic control (Ph_3CK/ equilibration in presence of excess ketone)		46	12
			
Kinetic control		54	
Thermodynamic control		42	

a. H. O. House and B. M. Trost, *J. Org. Chem.* **30**, 1341 (1965).
b. H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.* **36**, 2361 (1971).
c. H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.* **34**, 2324 (1969).
d. E. Vedejs, *J. Am. Chem. Soc.* **96**, 5944 (1974); H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.* **97**, 5434 (1975).
e. E. Vedejs, D. A. Engier, and J. E. Telschow, *J. Org. Chem.* **43**, 188 (1978).
f. G. Stork, G. A. Kraus, and G. A. Garcia, *J. Org. Chem.* **39**, 3459 (1974).
g. 'Z. A. Fataftah, I. E. Kopka, and M. W. Rathke, *J. Am. Chem. Soc.* **102**, 3959 (1980).
h. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.* **45**, 1066 (1980).

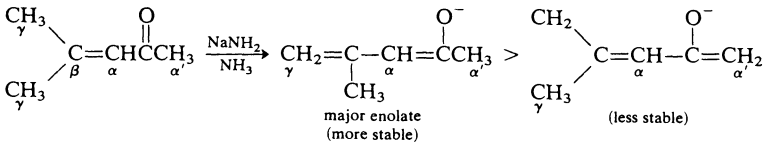
A fairly consistent relationship is found in these and related data. Conditions of kinetic control usually favor the less-substituted enolate. The principal reason for this result is that removal of the less hindered hydrogen is more rapid, for steric reasons, than removal of more hindered protons, and this more rapid reaction leads to the less substituted enolate. Similar results are obtained using either lithium diisopropylamide or triphenylmethyllithium. On the other hand, at equilibrium it is the more substituted enolate that is usually the dominant species. The stability of carbon–carbon double bonds increases with increasing substitution, and it is this substituent effect that leads to the greater stability of the more substituted enolate. Highly substituted enolates, especially if the substituents are bulky, are not solvated effectively, however, and may be present in only minor amounts at equilibrium.

Kinetic deprotonation of α,β-unsaturated ketones usually occurs preferentially adjacent to the carbonyl group. The electron-withdrawing inductive effect of the carbonyl group is probably responsible for the faster rate of deprotonation at this position.



Ref. 8

Under conditions of thermodynamic control, it is the enolate corresponding to deprotonation of the γ-carbon atom which is present in greater amounts.



Ref. 9

These isomeric enolates differ in stability because the first is fully conjugated, whereas cross-conjugaton is present in the second. The cross-conjugated isomer restricts the delocalization of the negative charge to the oxygen and α' carbon, whereas in the conjugated system the oxygen, α carbon, and γ carbon all bear part of the negative charge.

The terms *kinetic control* and *thermodynamic control* are applicable to other reactions besides enolate formation; this concept was covered in general terms in Part A, Section 4.9. In discussions of other reactions in this chapter, it may be stated that a given reagent or set of conditions favors the "thermodynamic product." This statement means that the mechanism operating is such that the various possible products are equilibrated after initial formation. When this is true, the dominant product can be predicted by considering the relative stabilities of the various possible products. On the other hand, if a given reaction is under "kinetic control," prediction

8. R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, *Tetrahedron Lett.*, 965 (1973).
9. G. Büchi and H. Wüest, *J. Am. Chem. Soc.* **96**, 7573 (1974).

or interpretation of the relative amounts of products must be made by analyzing the competing rates of formation of the products.

The *stereoselectivity* of enolate formation, either under conditions of kinetic or thermodynamic control, is less well understood. Clearly, as entries 7 and 8 of Table 1.2 show, the stereoselectivity can be very high under conditions of kinetic control. Apparently, *Z*-enolates of ketones are both more stable and formed faster than *E*-enolates.[10]

1.3. Other Means of Generating Enolates

The development of conditions under which lithium enolates do not equilibrate with other possible isomeric enolates has permitted the use of reactions that are more regioselective than proton abstraction to generate specific enolates. Three such methods are shown in Scheme 1.3. The synthetic use of solutions containing specific enolate species is described in the following section.

Cleavage of enol trimethylsilyl ethers or enol acetates by methyllithium (entries 1 and 3, Scheme 1.3) as a route to specific enolate formation is limited by the availability of these materials. Preparation of the enol trimethylsilyl ethers and enol acetates from the corresponding ketones usually affords a mixture of the two possible derivatives, which must be then separated. It is sometimes possible to find conditions that favor the formation of one isomer; for example, reaction of 2-methylcyclohexanone with lithium diisopropylamide and trimethylchlorosilane affords the less highly substituted enol ether preferentially by 99 : 1 over the more highly substituted one (kinetically controlled conditions).[11]

Enol trimethylsilyl ethers may be cleaved by benzyltrimethylammonium fluoride (entry 2, Scheme 1.3). The driving force for this cleavage is the formation of the very strong Si–F bond, which has a bond energy of 142 kcal/mol.

Lithium–ammonia reduction of α,β-unsaturated ketones (entry 4, Scheme 1.3)[12] provides a more generally useful method for generating specific enolates since the desired starting material is often readily available by the use of various condensation reactions (Chapter 2).[11]

1.4. Alkylation of Enolates

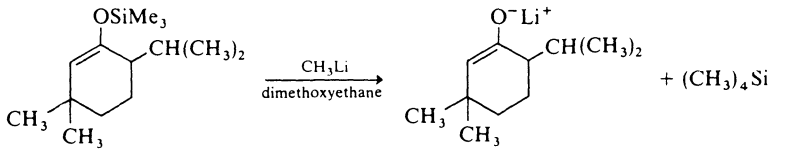
The alkylation of relatively acidic substances such as β-diketones, β-ketoesters, and esters of malonic acid can be carried out in alcoholic solvents using metal

10. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.* **45**, 1066 (1980).
11. (a) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.* **34**, 2324 (1969); (b) for a review of the chemistry of O-silyl enol ethers, see J. K. Rasmussen, *Synthesis*, 91 (1977).
12. For a review, see D. Caine, *Org. React.* **23**, 1 (1976).

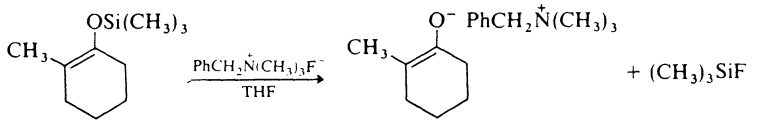
Scheme 1.3. Generation of Specific Enolates

A. Cleavage of enol trimethylsilyl ethers

1[a]

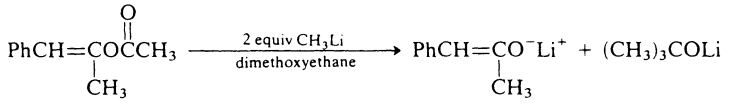


2[b]



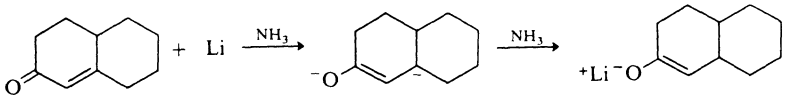
B. Cleavage of enol acetates

3[c]



C. Lithium–ammonia reduction of α,β-unsaturated ketones

4[d]



a. G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.* **90**, 4464 (1968); see also, H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.* **34**, 2324 (1969).
b. I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.* **97**, 3258 (1975).
c. G. Stork and S. R. Dowd, *Org. Synth.* **55**, 46 (1976); see also H. O. House and B. M. Trost, *J. Org. Chem.* **30**, 2502 (1965).
d. G. Stork, P. Rosen, N. Goldman, R. V. Coombs and J. Tsuji, *J. Am. Chem. Soc.* **87**, 275 (1965).

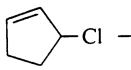
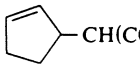
alkoxides as bases. The presence of two electron-withdrawing substituents favors formation of a single enolate by removal of a proton from the carbon situated between them. Alkylation then occurs by an S_N2 process.

Some examples of the more important alkylation reactions with relatively acidic carbon acids are included in the reactions shown in Scheme 1.4. These reactions are all mechanistically similar in that a carbanion, formed by deprotonation using a suitable base, attacks an electrophilic substrate in an S_N2 manner. The alkylating agent must be a reactive one toward nucleophilic displacement. Primary halides and sulfonates, especially allylic and benzylic ones, are the best alkylating agents. Secondary substrates usually give poor to moderate yields because of competing elimination. Tertiary halides give only elimination products.

Methylene groups can be dialkylated if sufficient amounts of base and alkylating agent are used. Dialkylation can be an undesirable side reaction if the monoalkyl derivative is the desired product. Use of dihalides as the alkylating reagents leads to ring formation, as illustrated by the diethyl cyclobutanedicarboxylate synthesis (entry 7) shown in Scheme 1.4. This example, as well as entry 8, illustrates the synthesis of cyclic compounds by *intramolecular* alkylation reactions. Five-membered rings are formed with particular ease in these reactions. The relative

Scheme 1.4. Alkylations of Relatively Acidic Carbon Acids

1[a] $CH_3COCH_2CO_2C_2H_5 + CH_3(CH_2)_3Br \xrightarrow{NaOEt} CH_3COCHCO_2C_2H_5$ (69–72%)
$(CH_2)_3CH_3$

2[b] $CH_2(CO_2C_2H_5)_2 +$  $\xrightarrow{NaOEt}$  (61%)

3[c] $CH_3COCH_2COCH_3 + CH_3I \xrightarrow{K_2CO_3} CH_3COCHCOCH_3$ (75–77%)
CH_3

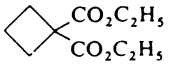
4[d] $CH_3COCH_2CO_2C_2H_5 + ClCH_2CO_2C_2H_5 \xrightarrow{NaOEt} CH_3COCHCO_2C_2H_5$
$CH_2CO_2C_2H_5$

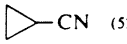
5[e] $Ph_2CHCN + KNH_2 \rightarrow Ph_2\bar{C}CN$

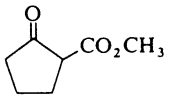
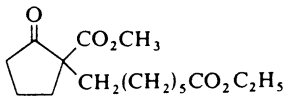
$Ph_2\bar{C}CN + PhCH_2Cl \rightarrow Ph_2CCN$ (98–99%)
CH_2Ph

6[f] $PhCH_2CO_2C_2H_5 + NaNH_2 \rightarrow PhC\bar{H}CO_2C_2H_5$

$PhC\bar{H}CO_2C_2H_5 + PhCH_2CH_2Br \rightarrow PhCHCO_2C_2H_5$ (77–81%)
CH_2CH_2Ph

7[g] $CH_2(CO_2C_2H_5)_2 + BrCH_2CH_2CH_2Cl \xrightarrow{NaOEt}$  (53–55%)

8[h] $ClCH_2CH_2CH_2CN + NaNH_2 \rightarrow$  (52–53%)

9[i]  $+ BrCH_2(CH_2)_5CO_2C_2H_5 \xrightarrow[DMF]{NaH}$ 
(85% on 1-mol scale)

a. C. S. Marvel and F. D. Hager, *Org. Synth.* I, 248 (1941).
b. R. B. Moffett, *Org. Synth.* **IV**, 291 (1963).
c. A. W. Johnson, E. Markham, and R. Price, *Org. Synth.* **42**, 75 (1962).
d. H. Adkins, N. Isbell, and B. Wojcik, *Org. Synth.* **II**, 262 (1943).
e. C. R. Hauser and W. R. Dunnavant, *Org. Synth.* **IV**, 962 (1963).
f. E. M. Kaiser, W. G. Kenyon, and C. R. Hauser, *Org. Snyth.* **47**, 72 (1967).
g. R. P. Mariella and R. Raube, *Org. Synth.* **IV**, 288 (1963).
h. M. J. Schlatter, *Org. Synth.* **III**, 223 (1955).
i. K. F. Bernardy, J. F. Poletto, J. Nocera, P. Miranda, R. E. Schaub, and M. J. Weiss, *J. Org. Chem.* **45**, 4702 (1980).

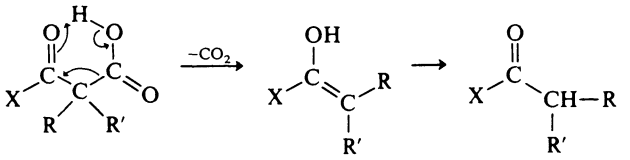
rates of the reaction are 650,000 : 1 : 6500 : 5 for formation of three-, four-, five-, and six-membered rings, respectively.[13]

$$Cl(CH_2)_nCH(CO_2CH_2CH_3)_2 \xrightarrow[t\text{-BuOH}]{KO\text{-}t\text{-}Bu} (CH_2)_nC(CO_2CH_2CH_3)_2$$

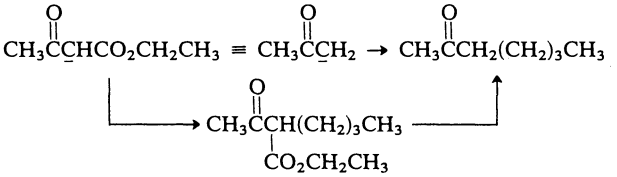
The preparation of 2-substituted β-ketoesters (entries 1, 4, and 9) and 2-

13. A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc. B*, 67 (1968). For a summary of factors which affect intramolecular alkylation of enolates, see J. Janjatovic and Z. Majerski, *J. Org. Chem.* **45**, 4892 (1980).

substituted derivatives of malonic ester (entries 2 and 7) by the methods illustrated in Scheme 1.4 play an important role in the synthesis of ketones and carboxylic acids. Both β-ketoacids and substituted derivatives of malonic acid undergo a ready decarboxylation reaction:



Examples of this approach to the synthesis of ketones and carboxylic acids are presented in Scheme 1.5. In the preparation of 2-heptanone (entry 1), ethyl acetoacetate functions as a synthetic equivalent to acetone.

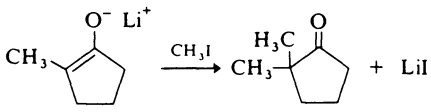


The reason for using ethyl acetoacetate as the source of a carbon nucleophile rather than using acetone itself is based on several considerations.

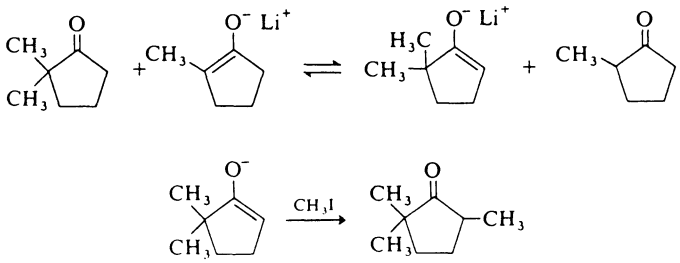
(a) The pK_a of ethyl acetoacetate is 10.7 while that of acetone is 20. Thus, much weaker bases will suffice to give a much higher equilibrium concentration of carbanion. In addition, the alkyl halide used as the alkylating agent will be less likely to undergo elimination in a less basic medium.

(b) Acetone can undergo self-condensation by reaction of its enolate with acetone itself. Because ethyl acetoacetate can be converted quantitatively to its enolate, it will not self-condense.

(c) It is often difficult to convert a ketone cleanly to a monoalkylation product. Once the monoalkylation product is formed, it too can be converted to an enolate which can react with the alkylating agent. Thus, methylation of the thermodynamic enolate of 2-methylcyclopentanone gives a mixture of 2,2-dimethyl (63%) and 2,2,5-trimethylcyclopentanone (16%).[14] These processes can occur very rapidly in

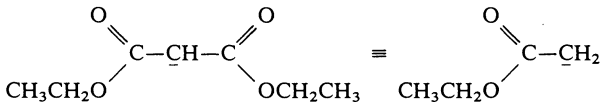


14. H. O. House and B. M. Trost, *J. Org. Chem.* **30**, 2502 (1965).



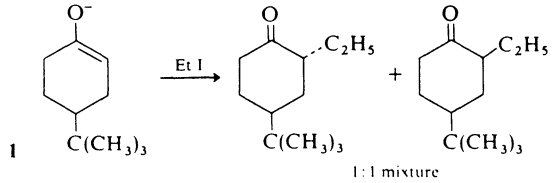
protic solvents or when a weakly coordinating cation is used. It is for this reason that base-catalyzed alkylations of ketones in protic solvents seldom give good yields of monoalkylation products. The use of specific lithium enolates in aprotic solvents minimizes these difficulties.[15]

Similar to the use of ethyl acetoacetate as a synthetic equivalent to acetone, malonic ester is a popular choice as a synthetic equivalent to ethyl acetate in the synthesis of carboxylic acids (Scheme 1.5, entries 2 and 3).



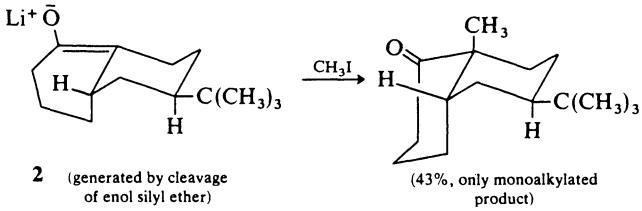
Some examples of regioselective alkylations of simple ketones are presented in Scheme 1.6. These examples illustrate the most useful modes of enolate generation, including deprotonation (entries 3 and 4), enone reduction (entries 1, 2, and 5), and cleavage of silyl enol ethers (entries 6 and 7).

The stereochemistry of enolate alkylations has been studied by determining the stereochemistry of products from alkylation of cyclic ketones. The stereochemistry of alkylation of the enolates **1** and **2** has been determined. While



Ref. 16

1 (generated by cleavage of the enol acetate with methyllithium) shows no preference for the two possible approaches by alkylating agent, **2** undergoes alkylation



Ref. 17

15. H. O. House, *Rec. Chem. Progr.* **28**, 98 (1967).
16. H. O. House, B. A. Terfertiller, and H. D. Olmstead, *J. Org. Chem.* **33**, 935 (1968).
17. H. O. House, W. V. Phillips, and D. VanDerveer, *J. Org. Chem.* **44**, 2400 (1979).

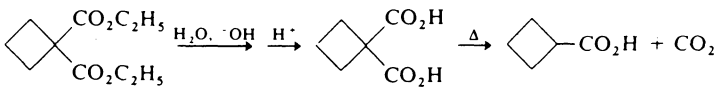
Scheme 1.5. Synthesis of Ketones and Carboxylic Acid Derivatives via Alkylation Techniques

1[a] $CH_3COCHCO_2C_2H_5$ ($CH_2)_3CH_3$ (see Scheme 1.4) $\xrightarrow{H_2O,\ ^-OH}$ $CH_3COCHCO_2^-$ ($CH_2)_3CH_3$ $\xrightarrow[\Delta]{H^+}$ $CH_3CO(CH_2)_4CH_3$ (52–61 %)

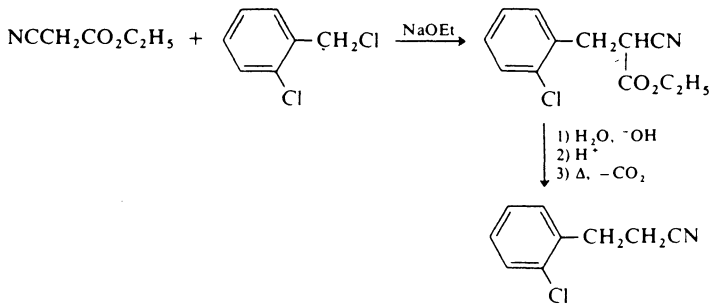
2[b] $CH_2(CO_2C_2H_5)_2 + C_7H_{15}Br \xrightarrow{NaOBu} C_7H_{15}CH(CO_2C_2H_5)_2$

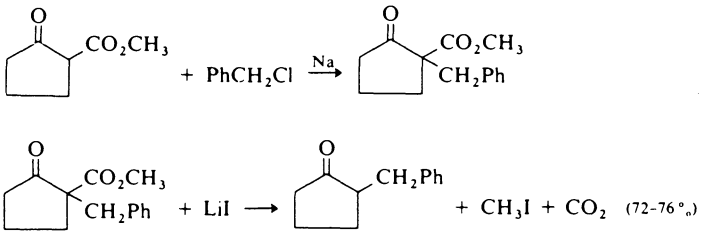
$C_7H_{15}CH(CO_2C_2H_5)_2 \xrightarrow{H_2O,\ ^-OH} \xrightarrow{H^+} C_7H_{15}CH(CO_2H)_2$

$C_7H_{15}CH(CO_2H)_2 \xrightarrow{\Delta} C_8H_{16}CO_2H + CO_2$ (66–75 %)

3[c] 

(see Scheme 1.4)

4[d] 

5[e] 

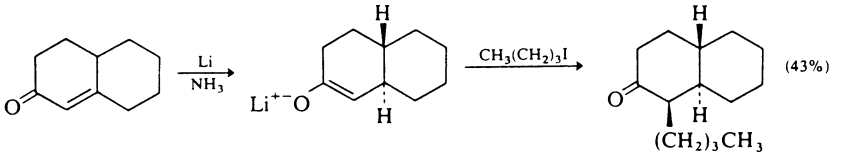
(72–76 %)

a. J. R. Johnson and F. D. Hager, *Org. Synth.* **I**, 351 (1941).
b. E. E. Reid and J. R. Ruhoff, *Org. Synth.* **II**, 474 (1943).
c. G. B. Heisig and F. H. Stodola, *Org. Synth.* **III**, 213 (1955).
d. J. A. Skorcz and F. E. Kaminski, *Org. Synth.* **48**, 53 (1968).
e. F. Elsinger, *Org. Synth.* **V**, 76 (1973).

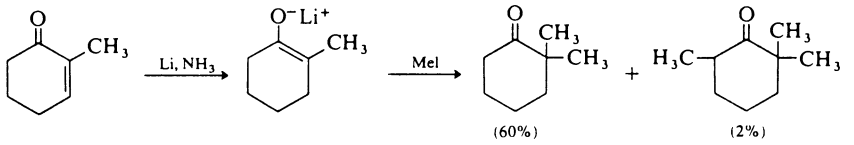
faster from its less hindered side. In general, the transition state for alkylation of an enolate ion appears early along the reaction coordinate and resembles the enolate ion more than it does the products. High stereoselectivity is to be expected only if one face of the enolate ion is appreciably more hindered than the other.

Scheme 1.6. Regioselective Enolate Alkylation

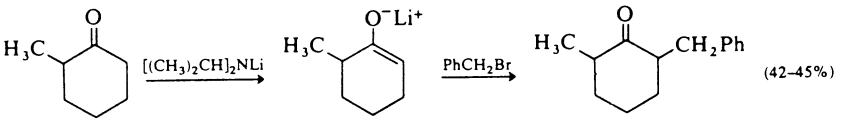
1[a]



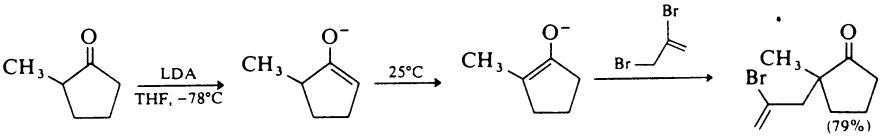
2[b]



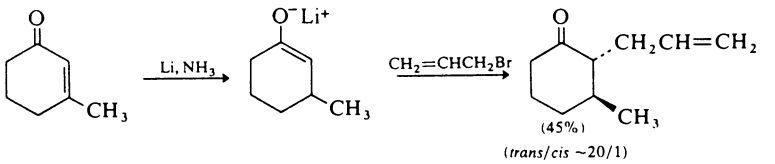
3[c]



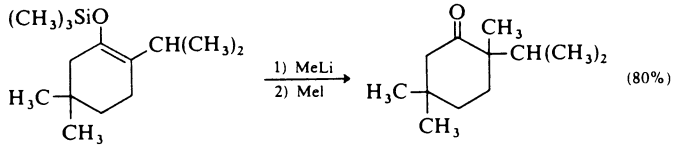
4[d]



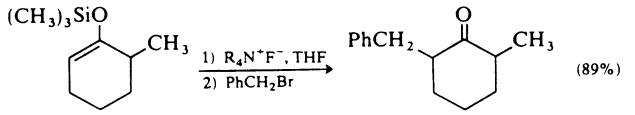
5[e]



6[f]



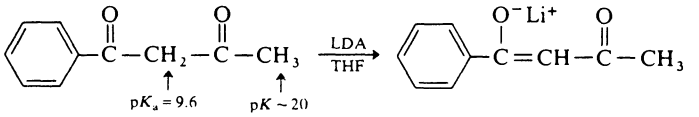
7[g]



a. G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsugji, *J. Am. Chem. Soc.* **87**, 275 (1965).
b. H. A. Smith, B. J. L. Huff, W. J. Powers, III, and D. Caine, *J. Org. Chem.* **32**, 2851 (1967).
c. M. Gall and H. O. House, *Org. Synth.* **52**, 39 (1972).
d. S. C. Welch and S. Chayabunjonglerd, *J. Am. Chem. Soc.* **101**, 6768 (1979).
e. D. Caine, S. T. Chao, and H. A. Smith, *Org. Synth.* **56**, 52 (1977).
f. G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.* **90**, 4464 (1968).
g. I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.* **97**, 3257 (1975).

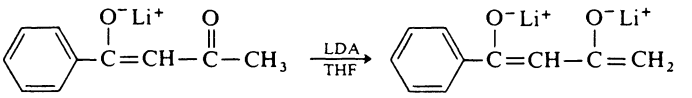
1.5. Generation and Alkylation of Dianions[18]

In the presence of a very strong base, such as an alkyllithium, potassium or sodium amide, or lithium diisopropylamide, 1,3-dicarbonyl compounds may be converted to their *dianions* by sequential deprotonation. For example, reaction of benzoylacetone with lithium diisopropylamide leads first to the enolate generated

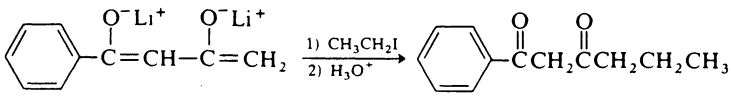


Ref. 19

by deprotonation of the methylene group between the two carbonyl groups. A second equivalent of base can deprotonate the methyl group to give a dienolate.



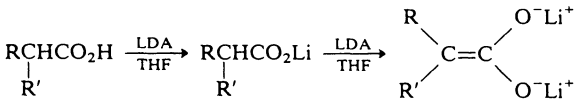
Alkylation reactions of dianions occur at the *more basic* enolate function.[19] The beauty of this technique is that it allows alkylation of 1,3-dicarbonyl compounds



Ref. 19

to be carried out cleanly at the less activated position. Since, as discussed earlier, alkylation of the monoanion occurs at the carbon between the two carbonyl groups, the site of monoalkylation can be controlled by proper choice of the amount and nature of the base. This approach has significantly expanded the synthetic utility of enolate alkylations. A few examples of the formation and alkylation of dianions are collected in Scheme 1.7.

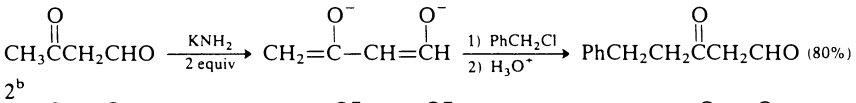
A procedure for the direct metalation of a variety of carboxylic acids, using two equivalents of lithium diisopropylamide in tetrahydrofuran, has been described.[20] These dianions can be alkylated on the α-carbon atom (entry 6, Scheme 1.7).



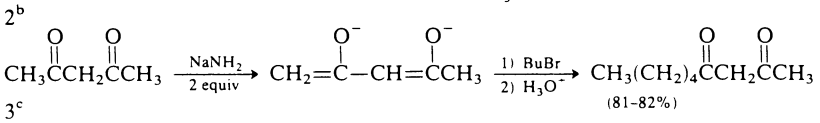
18. For reviews, see (a) T. M. Harris and C. M. Harris, *Org. React.* **17**, 155 (1969); (b) E. M. Kaiser, J. D. Petty, and P. L. A. Knutson, *Synthesis*, 509 (1977).
19. G. Stork, G. A. Kraus, and G. A. Garcia, *J. Org. Chem.* **39**, 3459 (1974).
20. P. L. Creger, *J. Org. Chem.* **37**, 1907 (1972).

Scheme 1.7. Generation and Alkylation of Dianions

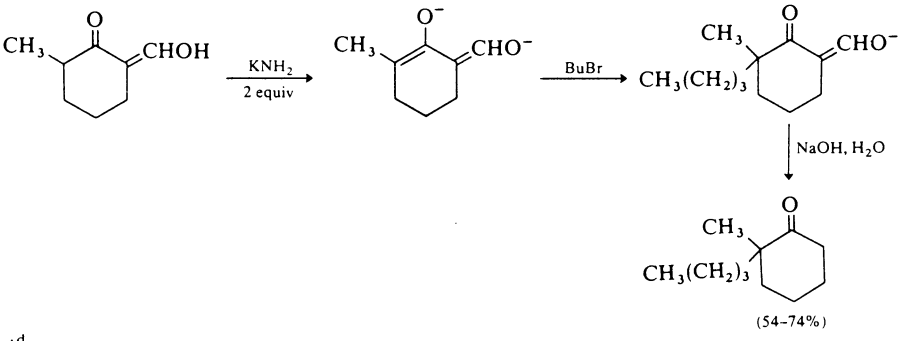
1[a]



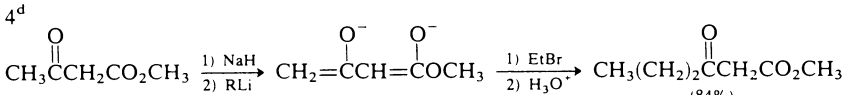
2[b]



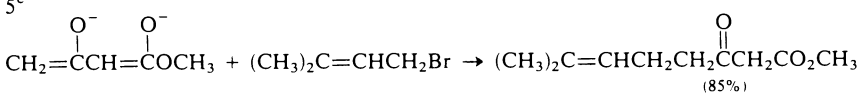
3[c]



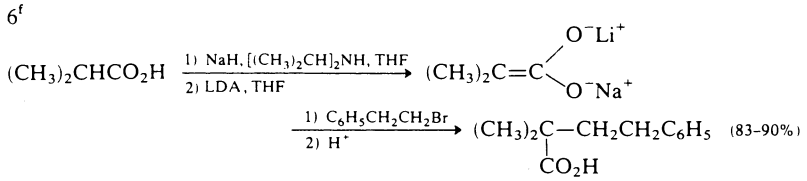
4[d]



5[e]



6[f]



a. T. M. Harris, S. Boatman, and C. R. Hauser, *J. Am. Chem. Soc.* **85**, 3273 (1963); S. Boatman, T. M. Harris, and C. R. Hauser, *J. Am. Chem. Soc.* **87**, (1965); K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.* **28**, 1946 (1963).
b. K. G. Hampton, T. M. Harris, and C. R. Hauser, *Org. Synth.* **47**, 92 (1967).
c. S. Boatman, T. M. Harris, and C. R. Hauser, *Org. Synth.* **48**, 40 (1968).
d. S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.* **96**, 1082 (1974).
e. F. W. Sum and L. Weiler, *J. Am. Chem. Soc.* **101**, 4401 (1979).
f. P. L. Creger, *Org. Synth.* **50**, 58 (1970).

1.6. Medium Effects in the Alkylation of Enolates

The rate of alkylation of enolate ions is strongly dependent on the solvent in which the reaction is carried out.[21] The relative rates of reaction of the sodium enolate of diethyl *n*-butylmalonate with *n*-butyl bromide are shown in Table 1.3.

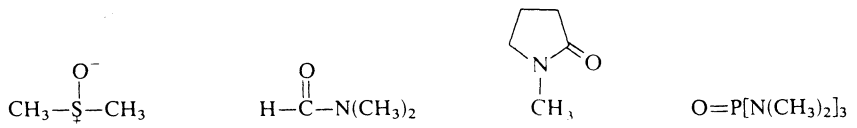
21. For reviews, see (a) A. J. Parker, *Chem. Rev.* **69**, 1 (1969); (b) L. M. Jackman and B. C. Lange, *Tetrahedron* **33**, 2737 (1977).

Table 1.3. Relative Alkylation Rates of Sodium Diethyl *n*-Butylmalonate in Various Solvents[a]

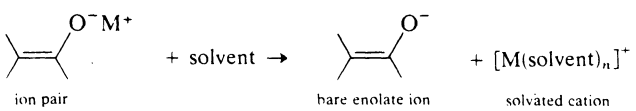
Solvent	Dielectric constant, ϵ	Relative rate
Benzene	2·3	1
Tetrahydrofuran	7·3	14
Dimethoxyethane	6·8	80
Dimethylformamide	37	970
Dimethyl sulfoxide	47	1420

a. From H. E. Zaugg, *J. Am. Chem. Soc.* **83**, 837 (1961).

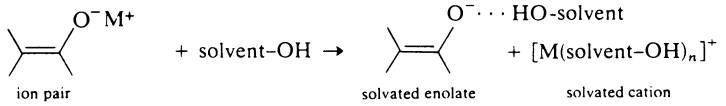
Dimethyl sulfoxide and *N,N*-dimethylformamide, as Table 1.3 shows, are particularly effective in enhancing the reactivity of enolate ions. Both of these compounds belong to a class of solvents called *polar aprotic*. Some other members of this class, also often used as solvents in reactions between anions and alkyl halides, include *N*-methylpyrrolidone and hexamethylphosphoric triamide. Polar aprotic solvents, as their name implies, are materials which have high dielectric constants but which lack hydroxyl groups or similar hydrogen-bonding functionalities.



The reactivity of an alkali metal (Li^+, Na^+, K^+) enolate is very sensitive to its state of aggregation, which is, in turn, influenced by the reaction medium. The highest level of reactivity, often difficult to achieve, is given by the "bare" unsolvated enolate anion. Given an enolate ion–metal cation pair, we expect that a medium in which the full measure of enolate reactivity could be expressed would be one in which the cation was strongly solvated and the enolate ion not solvated at all. Polar aprotic solvents of the kind just shown are good cation solvators and poor anion solvators. Each one (DMSO, DMF, HMPA, and *N*-methylpyrrolidone) has a negatively polarized oxygen available for coordination to the alkali metal cation. Coordination to the enolate ion is much less effective because the positively polarized atom of these polar aprotic substances is not nearly as exposed as the oxygen; it occupies a relatively shielded position. Thus, these solvents provide a medium in which enolate ion–alkali metal cation pairs are dissociated to give a less encumbered, more reactive enolate ion.

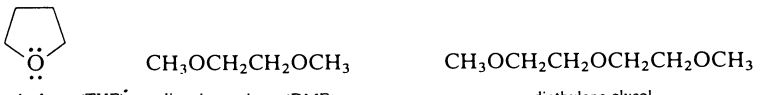


Polar protic solvents also possess a pronounced ability to separate ion pairs, but are less useful as solvents in enolate alkylation reactions because they can coordinate to both the alkali metal cation and to the enolate ion. Coordination to the enolate occurs through hydrogen bonding. The solvated enolate will be relatively less reactive because solvation lowers its energy. The hydrogen-bonded enolate must, in effect, shed some of its solvent molecules in order to react with an alkyl halide. Polar protic solvents include water, ammonia, and alcohols. Consequently, if a particular enolate can be generated with potassium *tert*-butoxide as the base, the enolate could be alkylated at a faster rate if dimethyl sulfoxide, rather than *tert*-butyl alcohol, were chosen as the solvent.



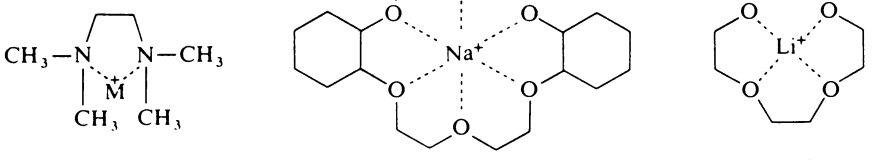
ion pair — solvated enolate — solvated cation

Tetrahydrofuran, dimethoxyethane (see Table 1.3), and diethylene glycol dimethyl ether are weakly polar solvents which are good cation solvators. Coordination to metal cations involves the oxygen lone pairs and the opportunity for chelated structures makes dimethoxyethane and diglyme more effective than tetrahydrofuran. All of these solvents, because of their low dielectric constants, are less effective at separating ion pairs and higher aggregates than are polar aprotic solvents. This is advantageous when a kinetically controlled regioselective alkylation is desired and tetrahydrofuran and dimethoxyethane are the solvents of choice in such reactions. These solvents also have advantages over the polar aprotic solvents in terms of product isolation and purification.



tetrahydrofuran (THF) — dimethoxyethane (DME) — diethylene glycol dimethyl ether (diglyme)

Sometimes enolate reactivity can be enhanced by adding a reagent to the medium which can bind alkali metal cations strongly by chelation. One popular choice for this purpose is tetramethylethylenediamine (TMEDA), which



metal chelate of tetramethylethylenediamine — dicyclohexyl-18-crown-6-Na^+ complex — 12-crown-4-Li^+ complex

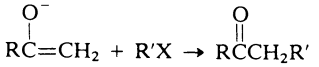
chelates metal ions through lone pairs on both nitrogens. The interior of dicyclohexyl-18-crown-6 is of such size as to allow sodium or potassium ions to fit comfortably in the cavity. This macrocyclic polyether is a good chelating agent with high selectivity for these cations. The smaller macrocyclic polyether 12-crown-4 binds Li^+ preferentially. Strong binding of the cation lowers the state of aggregation

of alkali metal enolates and increases their reactivity. The addition of hexamethylphosphoric triamide (HMPA) to nonpolar media such as ether and tetrahydrofuran is often used as a means to increase the reactivity of enolates and other carbanionic reagents.

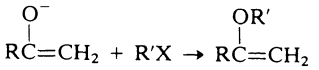
1.7. Oxygen versus Carbon as the Site of Alkylation

Enolate anions are *ambident nucleophiles*. Alkylation of an enolate anion may occur at either of two sites, carbon or oxygen.

C-alkylation

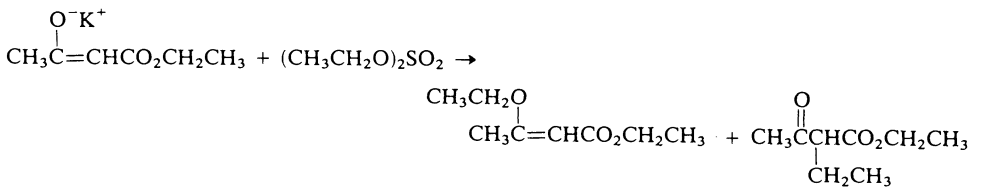


O-alkylation



Since most of the negative charge of an enolate ion is on the oxygen atom, it might be supposed that O-alkylation would dominate. A number of factors other than charge density can intervene to affect the C/O-alkylation ratio, however, and it is normally possible to direct the alkylation of enolates toward carbon in synthetically useful amounts.

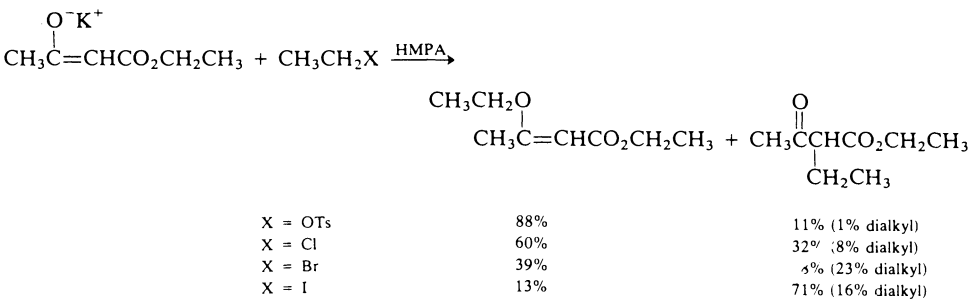
O-Alkylation will be most pronounced when the enolate ion is most free. When the potassium salt of ethyl acetoacetate is treated with ethyl sulfate in the polar aprotic solvent hexamethylphosphoric triamide, the major product (83%) is O-alkylated. In tetrahydrofuran, where ion pairing occurs, all of the product is C-alkylated. In *t*-butanol, where the acetoacetate anion is hydrogen bonded to the solvent, again only C-alkylation is observed.[22]



in hexamethylphosphoric triamide	83%	15% (2% dialkyl)
in *t*-butanol	0%	94% (6% dialkyl)
in tetrahydrofuran	0%	94% (6% dialkyl)

Higher C/O ratios are observed with alkyl halides than with alkyl *p*-toluenesulfonates. The highest C/O-alkylation ratios are given by alkyl iodides. For ethylation of potassio ethylacetoacetate in hexamethylphosphoric triamide, the product compositions shown below were obtained[23]:

22. A. L. Kurts, A. Masias, N. K. Genkina, I. P. Beletskaya, and O. A. Reutov, *Dokl. Akad. Nauk. SSSR* (*Eng.*) **187**, 595 (1969).
23. A. L. Kurts, N. K. Genkina, A. Masias, I. P. Beletskaya, and O. A. Reutov, *Tetrahedron* **27**, 4777 (1971).



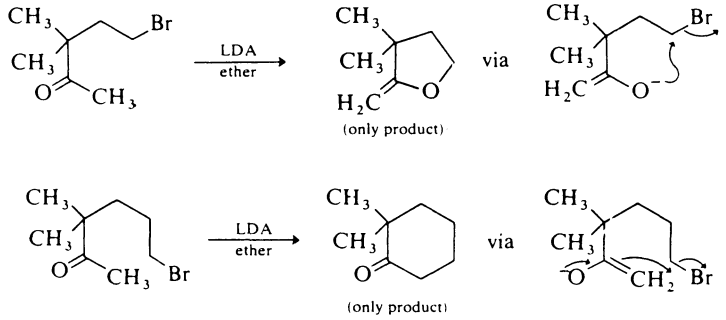
X = OTs	88%	11% (1% dialkyl)
X = Cl	60%	32% (8% dialkyl)
X = Br	39%	38% (23% dialkyl)
X = I	13%	71% (16% dialkyl)

Leaving group effects on the ratio of C- to O-alkylation are customarily correlated with reference to the "hard–soft acid–base" (HSAB) rationale.[24] Of the two nucleophilic sites in an enolate ion, oxygen is harder than carbon. Nucleophilic substitution reactions of the S_N2 type proceed best when the nucleophile and leaving group are either both hard or both soft.[25] Consequently, ethyl iodide, with the very soft leaving group iodide, reacts preferentially with the softer carbon site rather than the harder oxygen. Oxygen-containing leaving groups (*p*-toluenesulfonate and sulfate) are hard, and alkylating agents derived from them react faster with the harder nucleophilic site (oxygen) of the enolate.

More basic enolates exhibit generally similar behavior. The sodium enolate of isobutyrophenone reacts with ethyl bromide in dimethoxyethane to give five times as much C-alkylation as O-alkylation.[26]

In brief, we can maximize the amount of *O-alkylation* through the use of an alkyl *p*-toluenesulfonate in a polar aprotic solvent. We can maximize the amount of *C-alkylation* by using an alkyl iodide in a nonpolar or hydrogen-bonding solvent.

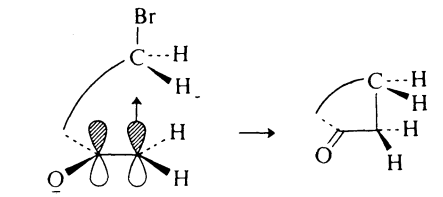
Cyclization of enolate anions by intramolecular nucleophilic substitution is subject to an element of stereoelectronic control which determines whether C- or O-alkylation occurs. This can be illustrated by the following two reactions[27]:



In order for C-alkylation to occur, the *p* orbital of the α-carbon atom must be aligned with the C–Br bond in the usual geometry associated with the S_N2

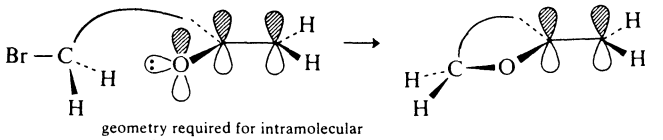
24. T.-L. Ho, *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, New York (1977).
25. R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.* **89**, 1827 (1967).
26. H. D. Zook, T. J. Russo, E. F. Ferrand, and D. S. Stotz, *J. Org. Chem.* **33**, 2222 (1968).
27. J. E. Baldwin and L. I. Kruse, *J. Chem. Soc. Chem. Commun.*, 233 (1977).

transition state.[3,27] When the ring to be closed is six membered, this geometry is



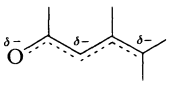
geometry required for intramolecular
C-alkylation of enolate

accessible and cyclization to the cyclohexanone occurs. When the ring to be closed is five membered, however, colinearity cannot be achieved as easily. Cyclization at oxygen then occurs faster than does cyclopentanone formation. The transition state for O-alkylation involves electrons in a lone-pair orbital on oxygen and is less strained than the transition state for C-alkylation in this system.

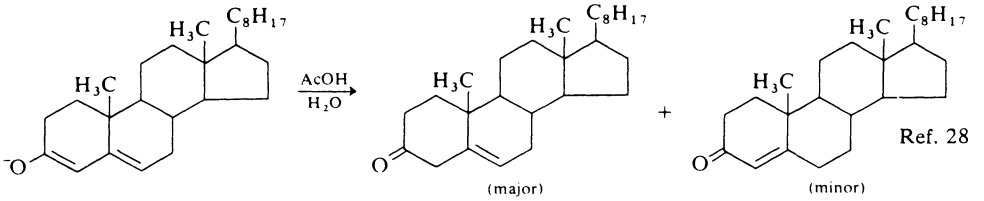


geometry required for intramolecular
O-alkylation of enolate

In enolates formed from α,β-unsaturated ketones by proton abstraction from the γ-carbon, there are three potential sites for attack by electrophiles: the oxygen, the α-carbon, and the γ-carbon. The kinetically preferred site for both protonation and alkylation is the α-carbon. Protonation of the enolate provides a method for



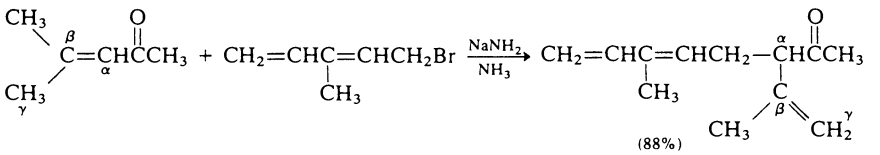
converting α,β-unsaturated ketones and esters to the less stable β,γ-unsaturated isomers:



$$CH_3CH{=}CHCO_2C_2H_5 \xrightarrow{LiNR_2} \xrightarrow{H_2O} CH_2{=}CHCH_2CO_2C_2H_5\ (87\%) + CH_3CH{=}CHCO_2C_2H_5\ (13\%)\quad \text{Ref. 29}$$

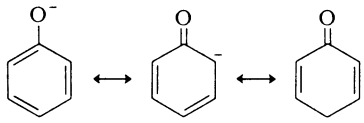
28. J. H. Ringold and S. K. Malhotra, *Tetrahedron Lett.*, 669 (1962); S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.* **85**, 1538 (1963).
29. M. W. Rathke and D. Sullivan, *Tetrahedron Lett.*, 4249 (1972).

Alkylation also takes place selectively at the α-carbon:

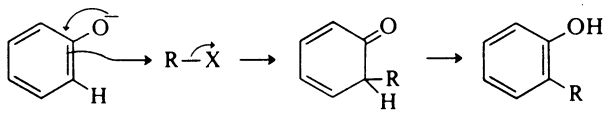


Ref. 9

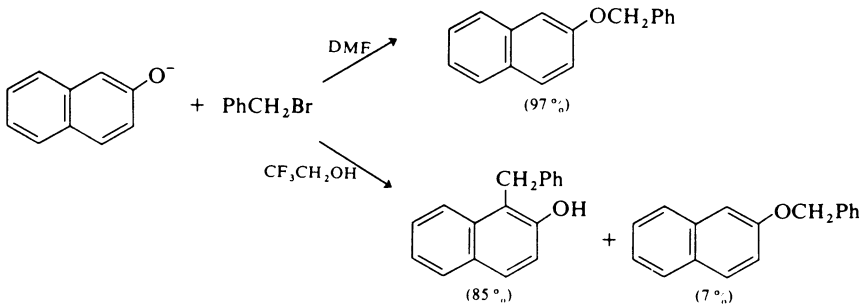
Phenoxide ions offer opportunities for C- or O-alkylation which are closely balanced:



In this case, C-alkylation is burdened energetically by the fact that aromaticity is destroyed as C-alkylation proceeds:



The effect of solvent on the site of alkylation has been clearly demonstrated. In solvents such as dimethyl sulfoxide, dimethylformamide, ethers, and alcohols, O-alkylation dominates. In water, phenol, and trifluoroethanol, however, extensive amounts of C-alkylation occur.[30] These latter solvents form particularly strong hydrogen bonds with the oxygen atom of the phenolate anion. This strong solvation decreases the reactivity at oxygen and favors carbon alkylation.



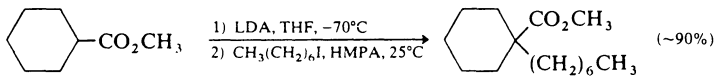
1.8. Alkylations of Aldehydes, Esters, and Nitriles

Among the groups of compounds having functionalities that can stabilize negative charge on carbon, ketones have been the most widely studied. Alkylation

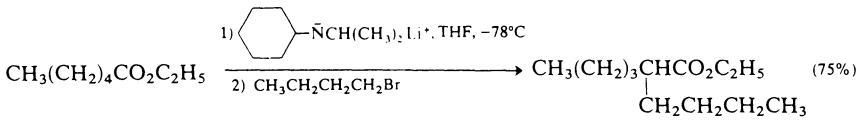
30. N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *J. Am. Chem. Soc.* **85**, 1141 (1963); N. Kornblum, R. Seltzer, and P. Haberfield, *J. Am. Chem. Soc.* **85**, 1148 (1963).

Scheme 1.8. Alkylation of Esters and Lactones

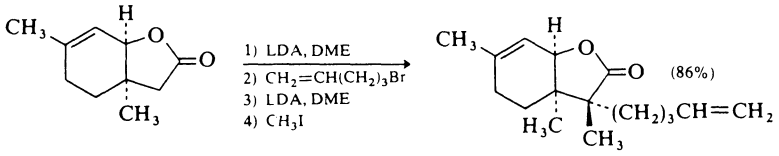
1[a]



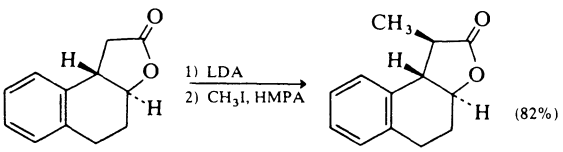
2[b]



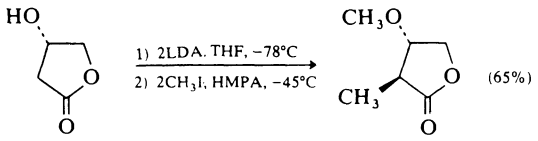
3[c]



4[d]

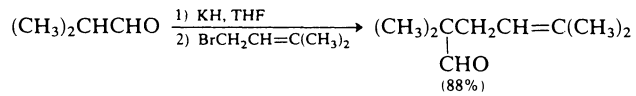


5[e]



a. T. R. Williams and L. M. Sirvio, *J. Org. Chem.* **45**, 5082 (1980).
b. M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.* **93**, 2320 (1971).
c. S. C. Welch, A. S. C. Prakasa Rao, C. G. Gibbs, and R. Y. Wong, *J. Org. Chem.* **45**, 4077 (1980).
d. W. H. Pirkle and P. E. Adams, *J. Org. Chem.* **45**, 4111 (1980).
e. H.-M. Shieh and G. D. Prestwich, *J. Org. Chem.* **46**, 4319 (1981).

of aldehyde enolates is rare because of the pronounced tendency of aldehydes to undergo aldol condensation (Chapter 2). Rapid and quantitative conversion of the aldehyde to the enolate is required in order to minimize aldol condensation, suggesting the use of very strong bases. Only a few examples of this approach have been reported. Success has been achieved using potassium amide in liquid ammonia[31] and potassium hydride in tetrahydrofuran.[32] Alkylation via enamines or imine magnesium salts provides an indirect procedure for alkylation of aldehydes. These reactions will be discussed in Section 1.9.



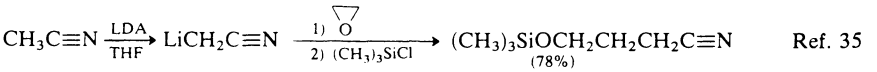
Ref. 32

31. S. A. G. De Graaf, P. E. R. Oosterhof, and A. van der Gen, *Tetrahedron Lett.*, 1653 (1974).
32. P. Groenewegen, H. Kallenberg, and A. van der Gen, *Tetrahedron Lett.*, 491 (1978).

Base-catalyzed alkylations of simple esters require strongly basic catalysts. Relatively weak bases such as alkoxides promote condensation reactions (Chapter 2). The techniques for successful formation of ester enolates which have been developed typically involve amide bases, most commonly lithium diisopropylamide, at low temperature.[33] The resulting enolates can be successfully alkylated with alkyl bromides or iodides. Some examples of the alkylation of enolates of esters and lactones are presented in Scheme 1.8.

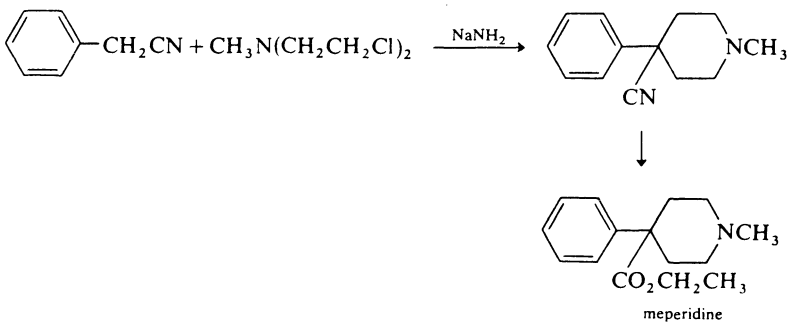
Less hindered bases can be used to form the enolate, provided tertiary butyl esters are employed to retard reactions at the carbonyl group. For example, lithium amide in liquid ammonia has been successfully used for the alkylation of *t*-butyl acetate.[34]

Acetonitrile (pK_{DMSO} 31.3) can be deprotonated provided relatively strong, nonnucleophilic bases such as lithium diisopropylamide are used.[20] The lithio



Ref. 35

derivative can be alkylated on carbon. Phenylacetonitrile (pK_{DMSO} 21.9) is considerably more acidic than acetonitrile and is more easily deprotonated. Dialkylation of phenylacetonitrile has been used as a key step in the synthesis of meperidine, an analgesic substance[36]:

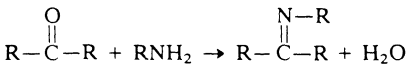


1.9. The Nitrogen Analogs of Enols and Enolates—Enamines and Metalloenamines

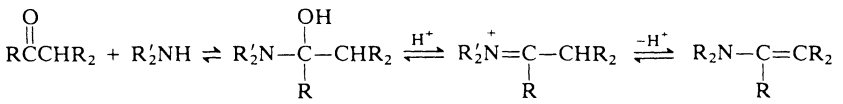
The nitrogen analogs of ketones and aldehydes are known as *imines* or *azomethines*. These compounds can be prepared by condensation of amines with

33. (a) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.* **93**, 2318 (1971); (b) R. J. Cregge, J. L. Herrmann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 2425 (1973); (c) J. L. Herrmann and R. H. Schlessinger, *Chem. Commun.*, 711 (1973).
34. W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.* **25**, 1693 (1960); H. Sisido, K. Sei, and M. Nozaki, *J. Org. Chem.* **27**, 2681 (1962).
35. S. Murata and I. Matsuda, *Synthesis*, 221 (1978).
36. O. Eisleb, *Ber.* **74**, 1433 (1941); cited in H. Kagi and K. Miescher, *Helv. Chim. Acta* **32**, 2489 (1949).

ketones and aldehydes.[37] When secondary amines are heated with ketones and

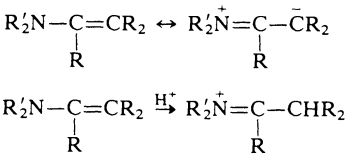


aldehydes in the presence of an acidic catalyst, a related condensation reaction occurs and can be driven to completion by removal of water. This is often accomplished by azeotropic distillation. The condensation product is a substituted vinylamine or *enamine*.

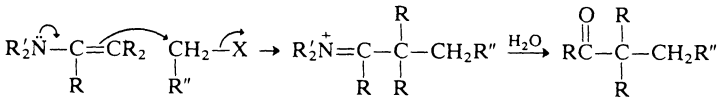


There are other methods for preparing enamines from ketones that utilize strong dehydrating reagents to drive the reaction to completion. For example, mixing carbonyl compounds and secondary amines followed by addition of titanium tetrachloride rapidly gives enamines. This method is applicable to hindered as well as to ordinary amines.[38] Another procedure involves converting the secondary amine to its trimethylsilyl derivative. Because of the higher affinity of silicon for oxygen than nitrogen, enamine formation is favored and takes place under mild conditions.[39]

The β-carbon atom of an enamine is a nucleophilic site because of conjugation with the nitrogen atom. Indeed, acidification of enamines results in protonation at the carbon atom, giving an iminium ion. The nucleophilicity of the β-carbon atom

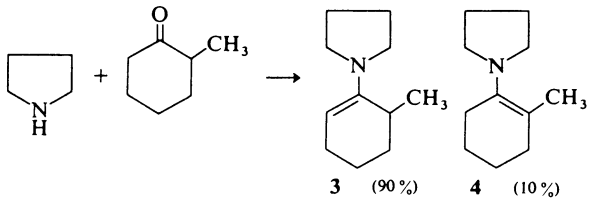


of enamines can be utilized in certain synthetically useful alkylation reactions:

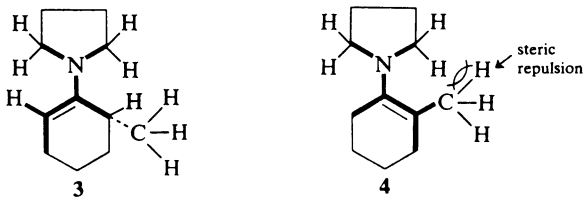


The enamines derived from cyclohexanones have been of particular interest. The enamine mixture formed from pyrrolidine and 2-methylcyclohexanone is predominantly **3**.[40] The tendency of pyrrolidine to provide the less substituted cyclohexanone enamine is quite general. A steric effect is responsible for this preference

37. P. Y. Sollenberger and R. B. Martin, in *Chemistry of the Amino Group*, S. Patai (ed.), Interscience, New York (1968), Chap. 7.
38. W. A. White and H. Weingarten, *J. Org. Chem.* **32**, 213 (1967).
39. R. Comi, R. W. Franck, M. Reitano, and S. M. Weinreb, *Tetrahedron Lett.*, 3107 (1973).
40. W. D. Gurowitz and M. A. Joseph, *J. Org. Chem.* **32**, 3289 (1967).



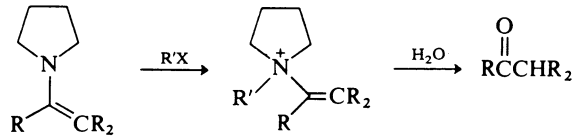
for the less substituted enamine. Interaction of the nitrogen lone pair with the π system of the double bond requires coplanarity of the darkened bonds in the structures shown:



A serious nonbonded repulsion destabilizes the more substituted isomer **4**.

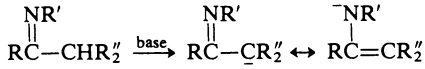
Because of the predominance of the less substituted enamine, alkylations occur primarily at the less substituted α-carbon. Synthetic advantage can be taken of this selectivity. Hydrolysis of the alkylated enamine produces the alkylated ketone. Some typical reactions are shown in Scheme 1.9.

Enamines, like enolate anions, are ambient nucleophiles. Alkylation at nitrogen is sometimes a competing reaction. The product of *N*-alkylation, after hydrolysis, leads to recovery of starting ketone.



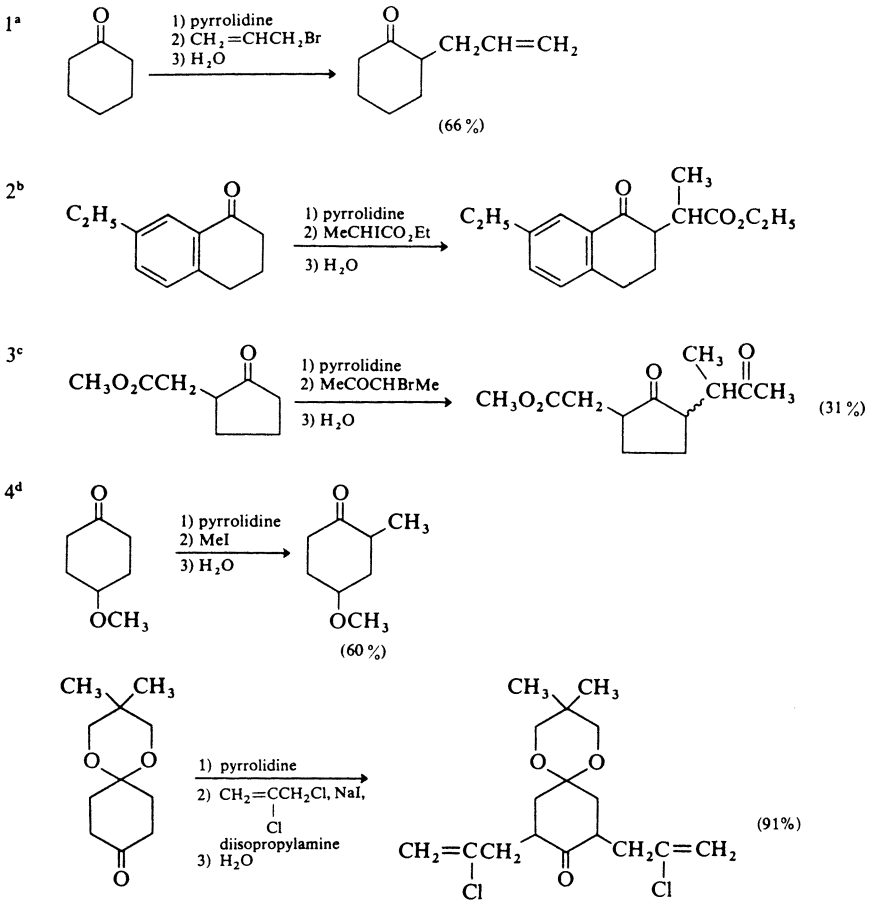
Alkylation of enamines requires relatively reactive alkylating agents, such as methyl iodide, benzyl halides, α-haloketones, α-haloesters, and α-haloethers. Enamines react efficiently with electrophilic olefins by conjugate addition, an aspect of their chemistry which will be described in Section 1.10.

The nitrogen analogs of enolate ions, referred to as *metalloenamines*, can be prepared by deprotonation of imines:

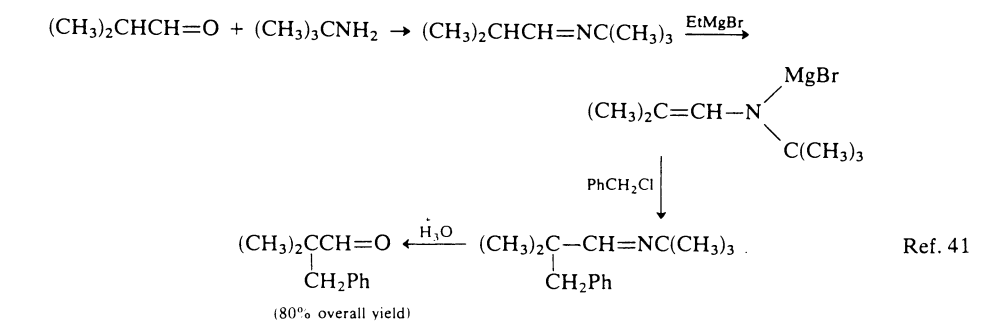


Just as enamines are more nucleophilic than enols, metalloenamines are more nucleophilic than enolate anions and react efficiently with alkyl halides. One useful application of metalloenamine chemistry is that it permits α-alkylation of aldehydes.

Scheme 1.9. Enamine Alkylations

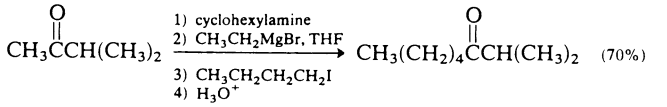


a. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.* **85**, 207 (1963).
b. D. M. Locke and S. W. Pelletier, *J. Am. Chem. Soc.* **80**, 2588 (1958).
c. K. Sisido, S. Kurozumi, and K. Utimoto, *J. Org. Chem.* **34**, 2661 (1969).
d. G. Stork and S. D. Darling, *J. Am. Chem. Soc.* **86**, 1761 (1964).
e. J. A. Marshall and D. A. Flynn, *J. Org. Chem.* **44**, 1391 (1979).

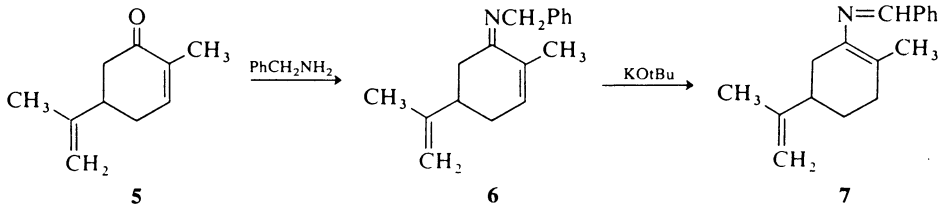


Ref. 41

With imines of unsymmetrical ketones, alkylation occurs at the less substituted α-carbon.[41]

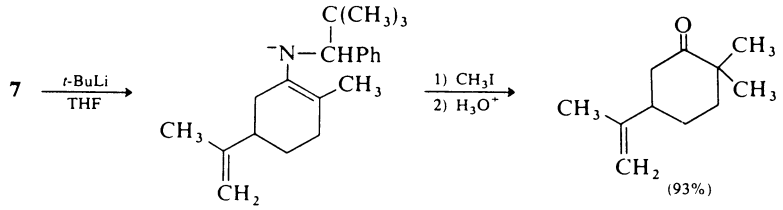


N-benzylimines undergo double-bond migration on treatment with catalytic quantities of base.



5 **6** **7**

Compound **7** can be converted to a metalloenamine by *addition* (not deprotonation) of *tert*-butyllithium. Alkylation and hydrolysis gives the alkylated ketone. The product of this sequence is the same one which would be expected[42]

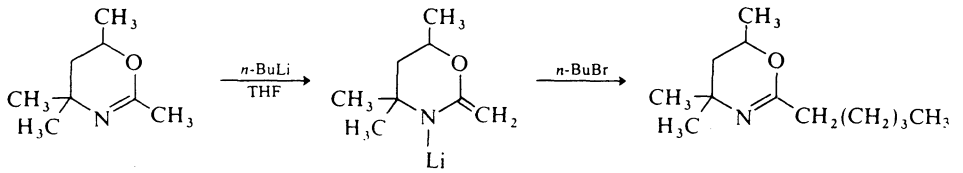


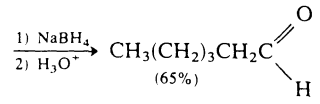
Ref. 42

from the lithium–ammonia reduction–alkylation of cyclohexenone **5**, but it is claimed that the procedure involving the metalloenamine is more efficient.

Metalloenamines derived from dihydro-1,3-oxazines are key intermediates in an alkylation reaction leading to aldehydes.

41. G. Stork and S. R. Dowd, *J. Am. Chem. Soc.* **85**, 2178 (1963).
42. P. A. Wender and M. A. Eissenstat, *J. Am. Chem. Soc.* **100**, 292 (1978).



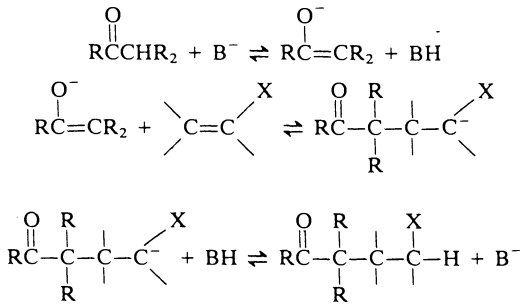


Ref. 43

1.10. Alkylation of Carbon by Conjugate Addition

The previous sections have dealt primarily with reactions in which the new carbon–carbon bond is formed in an S_N2 reaction between the nucleophilic carbon species and the alkylating reagent. There is another general and important method for alkylation of carbon that should be discussed at this point. This reaction involves the addition of a nucleophilic carbon species to an electrophilic multiple bond. The reaction is applicable to a wide variety of enolates and enamines. The electrophilic reaction partners are typically α,β-unsaturated ketones, esters, or nitriles, but other electron-withdrawing substituents also activate the carbon–carbon double bond to nucleophilic attack. The reaction is called either the *Michael reaction* or *conjugate addition*.[44] The process can also occur with other nucleophiles, such as alkoxide ions or amines, but these reactions are outside the scope of the present discussion.

In contrast to the reaction of enolate anions with alkyl halides, which require an equivalent of base, alkylation by conjugate addition is catalytic in base.



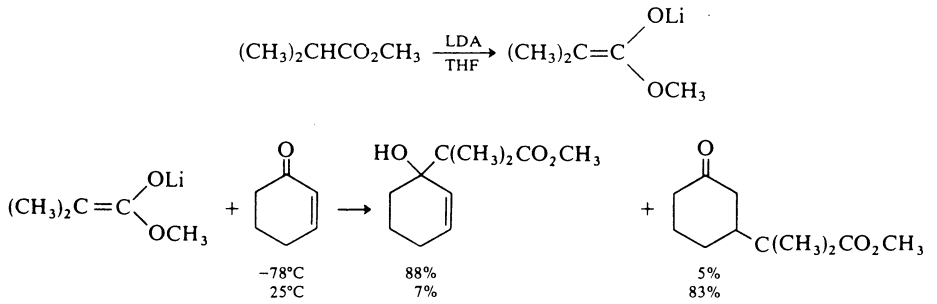
All the steps are reversible. A favorable equilibrium is assured if the starting material is a stronger acid than the product and the reaction is carried out in a medium (usually an alcohol) which is capable of protonating the anionic adduct. The kinetic or thermodynamic enolate can be used depending on the reaction conditions. By far the most common, however, are those reactions involving the thermodynamic enolate in weakly basic media such as sodium ethoxide in ethanol.

43. A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.* **38**, 36 (1973).

44. E. D. Bergmann, D. Ginsberg, and R. Pappo, *Org. React.* **10**, 179 (1959).

The reaction is most familiar with such nucleophiles as the enolates of malonate esters or β-keto esters, which are stabilized by two electron-attracting substituents. Good yields of alkylation products of simple ketones and nitroalkanes, however, have been obtained.

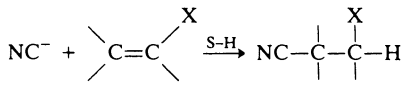
Evidence has been obtained that addition of ester enolates to the *carbonyl* group of α,β-unsaturated ketones can be faster than conjugate addition.[45] Conjugate addition leads to the more stable product and, since these reactions are normally carried out under conditions of equilibrium control, is the course which is usually observed.



Enamines are also reactive as nucleophiles in the Michael reaction. A wide variety of olefins having one or more electron-attracting groups in conjugation with the double bond have been employed as the acceptor molecule. Acetylenes can also function as the electrophilic species.

Some typical examples of Michael reactions are recorded in Scheme 1.10. The reaction is of very broad scope, and a large number of examples have been tabulated.[43]

Cyanide ion acts as a carbon nucleophile toward electrophilic alkenes, leading to overall addition of hydrogen cyanide:

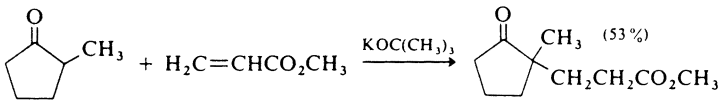


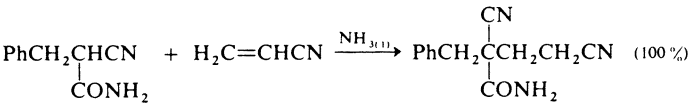
The standard conditions for such reactions involve alcoholic solutions of potassium or sodium cyanide. Triethylaluminum–hydrogen cyanide and diethylaluminum cyanide have been introduced for the same purpose.[46] These reagents have been successful in instances where the more standard procedures involving cyanide ion fail. These reagents also provide a degree of control over the stereochemistry of the reaction. The former reagent gives kinetically controlled product, while the latter leads to the thermodynamically more stable nitrile. Some examples of these additions are given in Scheme 1.11.[47]

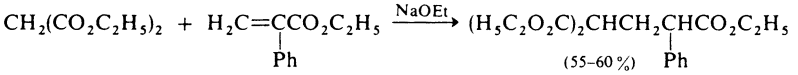
45. A. G. Schultz and Y. K. Lee, *J. Org. Chem.* **41**, 4045 (1976).
46. W. Nagata, M. Yoshioka, and S. Hirai, *J. Am. Chem. Soc.* **94**, 4635 (1972); W. Nagata, M. Yoshioka, and M. Murakami, *J. Am. Chem. Soc.* **94**, 4654 (1972).
47. For a review, see W. Nagata and M. Yoshioka, *Org. React.* **25**, 255 (1977).

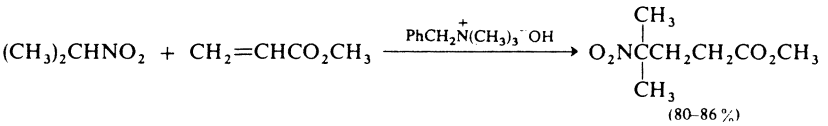
Another very important method for adding a carbon chain at the β-carbon atom of an α,β-unsaturated carbonyl system involves organometallic reagents. This reaction will be discussed in Chapter 6.

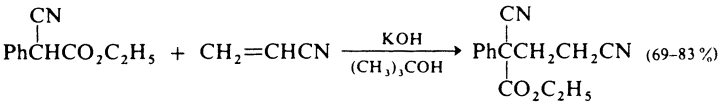
Scheme 1.10. Alkylation of Carbon by Conjugate Addition

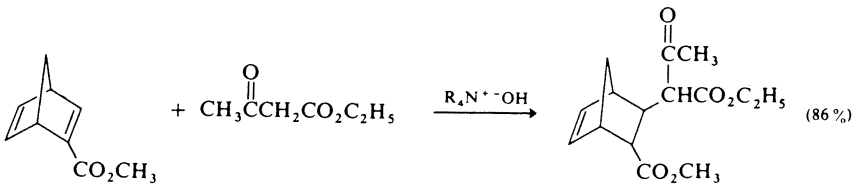
1[a] 

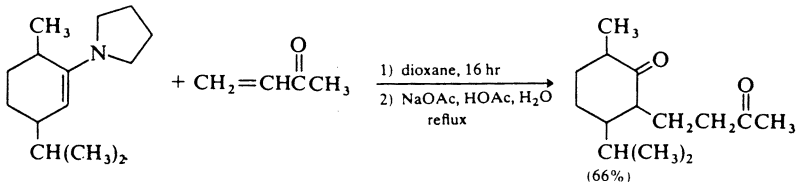
2[b] 

3[c] 

4[d] 

5[e] 

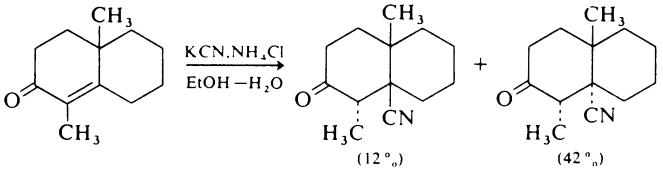
6[f] 

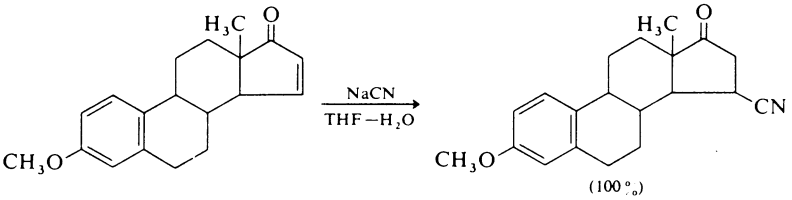
7[g] 

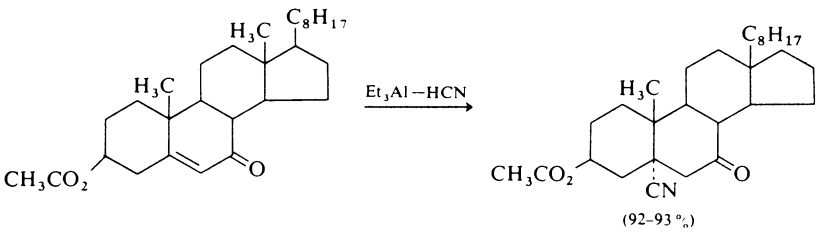
a. H. O. House, W. L. Roelofs, and B. M. Trost, *J. Org. Chem.* **31**, 646 (1966).
b. S. Wakamatsu, *J. Org. Chem.* **27**, 1285 (1962).
c. E. M. Kaiser, C. L. Mao, C. F. Hauser, and C. R. Hauser, *J. Org. Chem.* **35**, 410 (1970).
d. R. B. Moffett, *Org. Synth.* **IV**, 652 (1963).
e. E. C. Horning and A. F. Finelli, *Org. Synth.* **IV**, 776 (1963).
f. K. Alder, H. Wirtz, and H. Koppelberg, *Justus Liebigs Ann. Chem.* **601**, 138 (1956).
g. K. D. Croft, E. L. Ghisalberti, P. R. Jeffries, and A. D. Stuart, *Aust. J. Chem.* **32**, 2079 (1979).

Scheme 1.11. Addition of Cyanide Ion to Electrophilic Alkenes

1[a] $PhCH{=}CPh(CN) \xrightarrow[CH_3OH,\ H_2O]{KCN} PhCH(NC)-CHPh(CN)$ (95-98 %)

2[b] 

3[c] 

4[d] 

5[e] $(CH_3)_2C{=}CHC(=O)CH_3 \xrightarrow{(C_2H_5)_2AlCN} (CH_3)_2C(CN)CH_2C(=O)CH_3$ (55%)

a. J. A. McRae and R. A. B. Bannard, *Org. Synth.* **IV**, 393 (1963).
b. O. R. Rodig and N. J. Johnston, *J. Org. Chem.* **34**, 1942 (1969).
c. E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.* **29**, 64 (1964).
d. W. Nagata and M. Yoshioka, *Org. Synth.* **52**, 100 (1972).
e. R. V. Stevens, C. G. Christensen, W. L. Edmonson, M. Kaplan, E. B. Reid, and M. P. Wentland, *J. Am. Chem. Soc.*, **93**, 6629 (1971).

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J. R. Jones, *The Ionization of Carbon Acids*, Academic Press, New York (1973).
L. M. Jackman and B. C. Lange, *Tetrahedron* **33**, 2737–2769 (1977).
D. J. Cram, *Fundamentals of Carbanion Chemistry*, Academic Press, New York (1965).
H. O. House, *Modern Synthetic Reactions*, second edition, W. A. Benjamin, Menlo Park, California (1972), Chap. 9.
A. G. Cook, *Enamines: Synthesis, Structure and Reactions*, Marcel Dekker, New York (1969).

Problems

(*References for these problems will be found on page* 619.)

1. Arrange in order of decreasing acidity:

(a) $CH_3CH_2NO_2$, $(CH_3)_2CHC(=O)Ph$, CH_3CH_2CN, $CH_2(CN)_2$

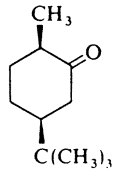
(b) $[(CH_3)_2CH]_2NH$, $(CH_3)_2CHOH$, $(CH_3)_2CH_2$, $(CH_3)_2CHPh$

(c) $CH_3C(=O)CH_2CO_2CH_3$, $CH_3C(=O)CH_2C(=O)CH_3$, $CH_3OC(=O)CH_2Ph$, $CH_3C(=O)OCH_2Ph$

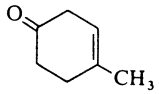
(d) $PhC(=O)CH_2Ph$, $(CH_3)_3CC(=O)CH_3$, $(CH_3)_3CC(=O)CH(CH_3)_2$, $PhC(=O)CH_2CH_2CH_3$

2. Write the structure of all possible enolates for each ketone. Indicate which you would expect to be favored in a kinetically controlled deprotonation. Which would you expect to be the most stable enolate in each case?

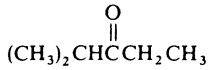
(a)



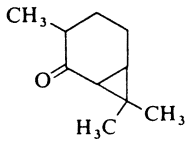
(b)



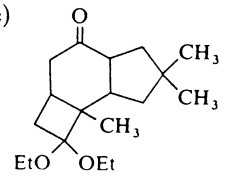
(c)



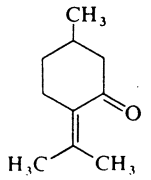
(d)



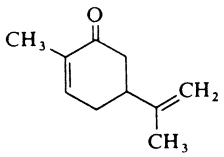
(e)



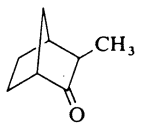
(f)



(g)

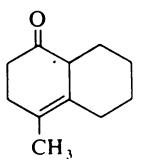
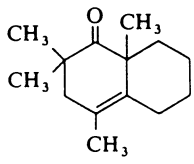


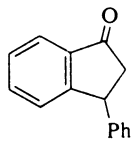
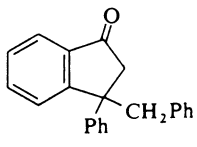
(h)

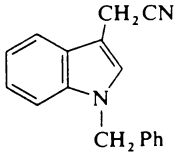
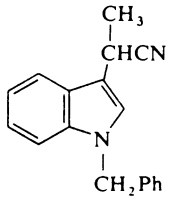


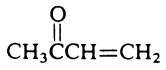
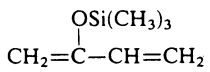
3. Suggest reagents and reaction conditions suitable for effecting each of the following conversions:

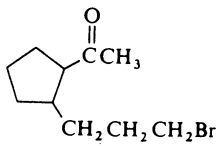
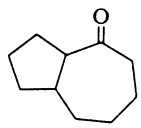
(a) 2-methylcyclohexanone to 2-benzyl-6-methylcyclohexanone.

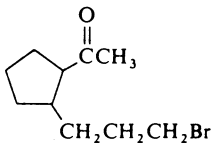
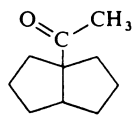
(b)  to 

(c)  to 

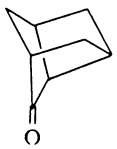
(d)  to 

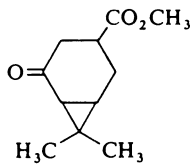
(e)  to 

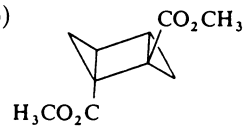
(f)  to 

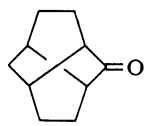
(g)  to 

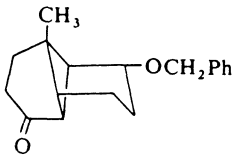
4. Intramolecular alkylation of enolates has been used to advantage in synthesis of bi- and tricyclic compounds. Indicate how such a procedure could be used to synthesize each of the following molecules by drawing the structure of a suitable precursor:

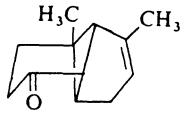
(a) 

(c) 

(b) 

(d) 

(e) 

(f) 

5. Predict the major product of each of the following reactions:

(a) $PhCH(CO_2Et)CH_2CO_2Et$ $\xrightarrow[(2)\ CH_3I]{(1)\ 1\ equiv\ LiNH_2/NH_3}$

(b) $PhCH(CO_2Et)CH_2CO_2H$ $\xrightarrow[(2)\ CH_3I]{(1)\ 2\ equiv\ LiNH_2/NH_3}$

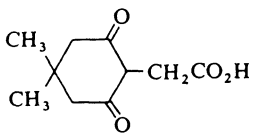
(c) $PhCH(CO_2H)CH_2CO_2Et$ $\xrightarrow[(2)\ CH_3I]{(1)\ 2\ equiv\ LiNH_2/NH_3}$

6. Treatment of 2,3,3-triphenylpropionitrile with one equivalent of potassium amide in liquid ammonia followed by addition of benzyl chloride affords 2-benzyl-2,3,3-triphenylpropionitrile in 97% yield. Use of two equivalents of potassium amide gives an 80% yield of 2,3,3,4-tetraphenylbutyronitrile under the same reaction conditions. Explain.

7. Suggest readily available starting materials and reaction conditions suitable for obtaining each of the following compounds by a procedure involving alkylation of nucleophilic carbon:

(a) $PhCH_2CH_2CH(Ph)CN$

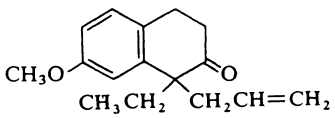
(b) $(CH_3)_2C{=}CHCH_2CH_2C(=O)CH_2CO_2CH_3$

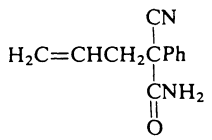
(c) 

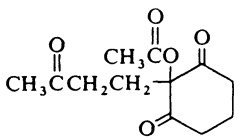
(d) $CH_2{=}CHCH{=}CHCH_2CH_2CO_2H$

(e) 2,3-diphenylpropanoic acid

(f) 2,6-diallylcyclohexanone

(g) 

(h) 

(i) 

(j) $CH_2{=}CHCH(CO_2CH_2CH_3)CH_2C{\equiv}CH$

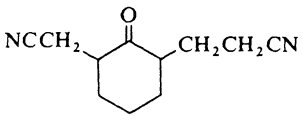
8. Suggest starting materials and reaction conditions suitable for obtaining each of the following compounds by a procedure involving a Michael reaction:

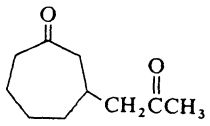
(a) 4,4-dimethyl-5-nitropentan-2-one

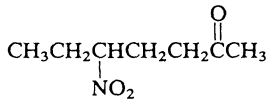
(b) diethyl 2,3-diphenylglutarate

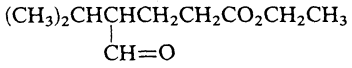
(c) ethyl 2-benzoyl-4-(2-pyridyl)butyrate

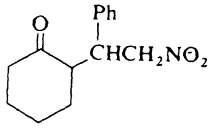
(d) 2-phenyl-3-oxocyclohexaneacetic acid

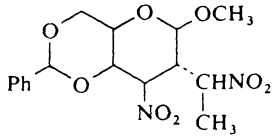
(e) 

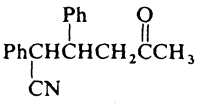
(f) 

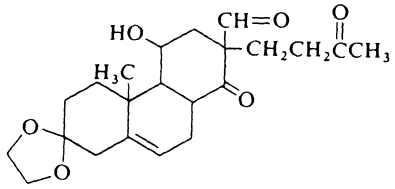
(g) 

(h) 

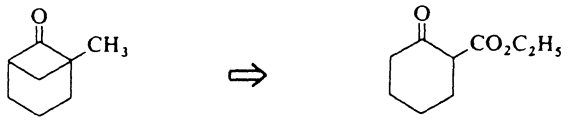
(i) 

(k) 

(j) 

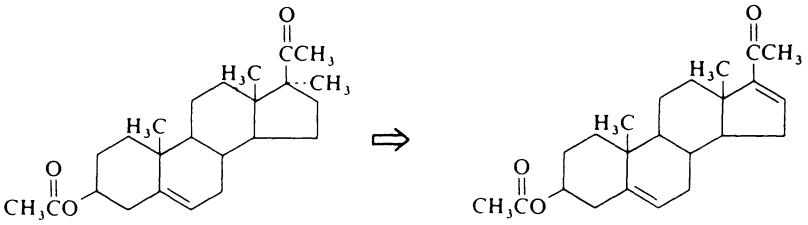
(l) 

9. In planning a synthesis, the most effective approach is to reason backwards from the target molecule to some readily available starting material. We call this *retrosynthetic analysis* and specify a retrosynthesis by an arrow of the type shown below. In each of the following problems, the target molecule is shown on the left and the starting material on the right. Determine how you could prepare the target molecule from the indicated starting material using any necessary organic or inorganic reagents. In some cases more than one step is necessary.

(a) 

(b) 

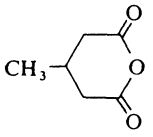
(c)



(d) $(CH_3O)_2PCH_2C(CH_2)_4CH_3$ ⇨ $(CH_3O)_2PCH_2CCH_3$

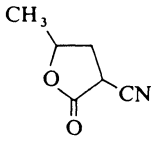
(e) $PhCH_2CH_2CHCO_2C_2H_5$ (Ph) ⇨ $PhCH_2CO_2C_2H_5$

(f)



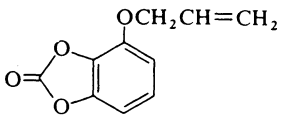
⇨ $CH_3CH{=}CHCO_2CH_3$

(g)

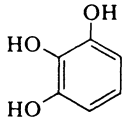


⇨ $NCCH_2CO_2C_2H_5$

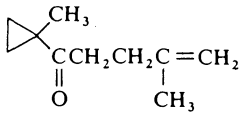
(h)



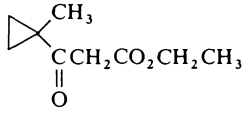
⇨



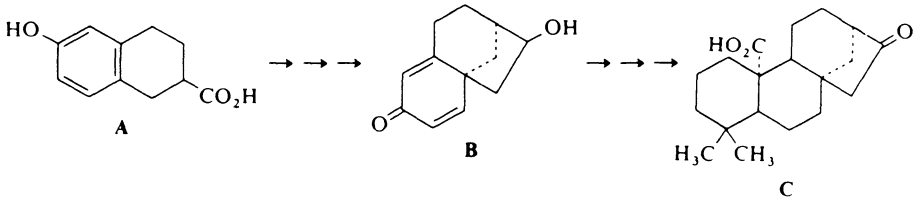
(i)



⇨

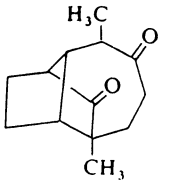


10. In a synthesis of diterpenes via compound **C**, a key intermediate **B** was obtained from carboxylic acid **A**. Suggest a series of reactions for obtaining **B** from **A**:



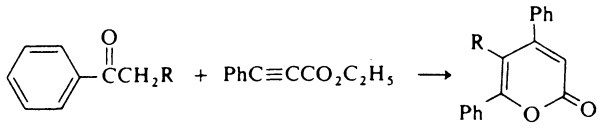
A **B** **C**

11. In a synthesis of the terpene longifolene, the tricyclic intermediate **D** was obtained from a bicyclic intermediate by an intramolecular Michael addition. Deduce the possible structure(s) of the bicyclic precursor.



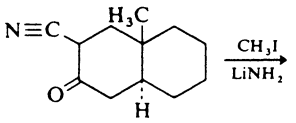
D

12. Substituted acetophenones react with ethyl phenylpropiolate under the conditions of the Michael reaction to give pyrones. Formulate a mechanism.



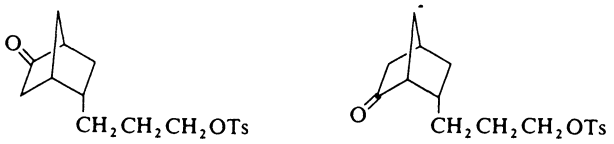
13. The reaction of simple ketones such as 2-butanone or phenylacetone with α,β-unsaturated ketones gives cyclohexenones when the reaction is effected by heating in methanol with potassium methoxide. Explain how the cyclohexenones are formed. What structures are possible for the cyclohexenones? Can you suggest means for distinguishing between possible isomeric cyclohexenones?

14. Predict the structure and stereochemistry of the product of alkylation of **E** with methyl iodide.

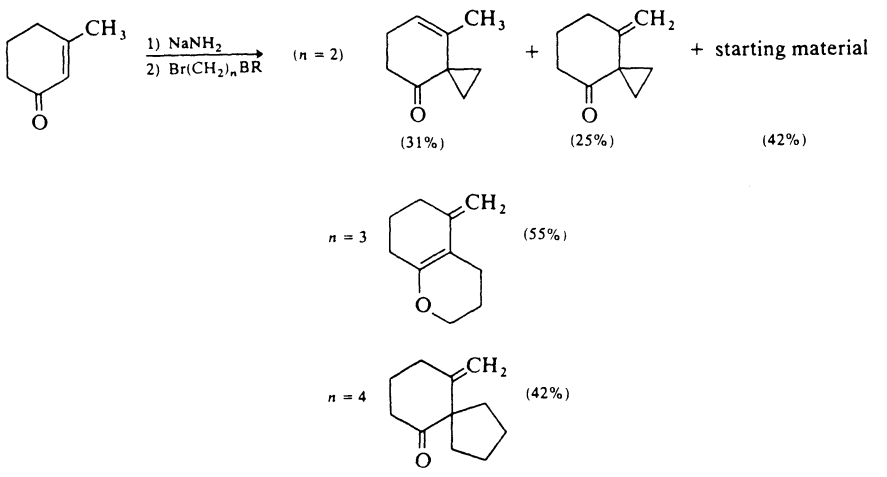


E

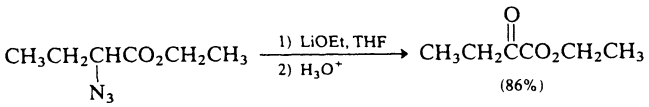
15. One of the compounds shown below undergoes intramolecular cyclization to give a tricyclic ketone on being treated with $[(CH_3)_3Si]_2NNa$. The other does not. Suggest a structure for the product. Explain the difference in reactivity.



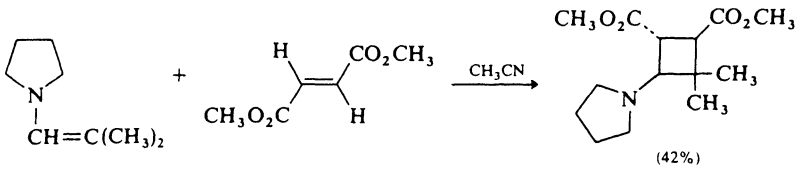
16. The alkylation of 3-methyl-2-cyclohexenone with several dibromides led to the products shown below. Discuss the course of each reaction and suggest an explanation for the dependence of the product structure on the identity of the dihalide.



17. Treatment of ethyl 2-azidobutanoate with catalytic quantities of lithium ethoxide in tetrahydrofuran leads to the evolution of nitrogen. On quenching the resulting solution with 3*N* hydrochloric acid, ethyl 2-oxobutanoate is isolated in 86% yield. Suggest a reasonable mechanism for this process.



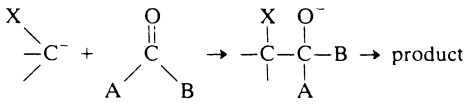
18. Suggest a reasonable mechanism for the reaction



2

Reactions of Carbon Nucleophiles with Carbonyl Groups

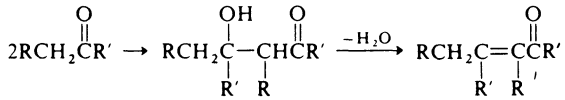
The reactions described in this chapter include some of the most useful and frequently employed synthetic methods for carbon–carbon bond formation: *aldol and Claisen condensation reactions, the Wittig and related olefination reactions, and the Robinson annulation.* All of these processes involve, at some point, the addition of a carbon nucleophile to a carbonyl group. The type of product which is isolated depends on the nature of the substituent (X) on the carbon nucleophile, the substituents (A and B) on the carbonyl group, and the ways in which A, B, and X affect the reaction pathways available to the intermediate formed in the addition step.



2.1. Aldol Condensation

In Chapter 1 we mentioned that efficient alkylation of aldehydes and ketones requires essentially quantitative formation of their enolates. When a low concentration of an enolate ion is generated, it may react more competitively with the parent aldehyde or ketone present in the reaction mixture than it does with an alkyl halide. The aldol condensation reaction is this acid- or base-catalyzed self-condensation of

a ketone or aldehyde.[1-3] Under certain conditions, the reaction product may undergo further transformations, especially dehydration. The reaction may also occur between two different carbonyl compounds, in which case the term *mixed aldol condensation* is applied.

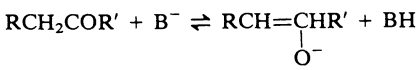


R′ = H, or alkyl or aryl

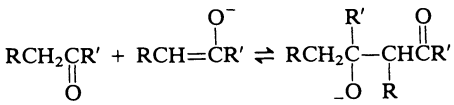
The mechanism of the base-catalyzed reaction involves, in the carbon–carbon bond-forming step, the nucleophilic addition of an enolate ion to a carbonyl group.

Base-Catalyzed Mechanism

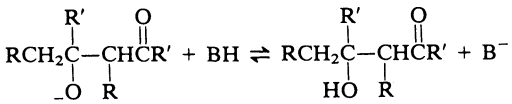
1. Addition phase
   a. Enolate formation:



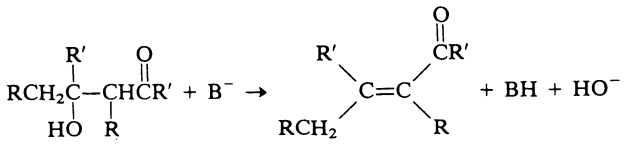
   b. Nucleophilic addition:



   c. Proton transfer:



2. Dehydration phase



Entries 1 and 2 in Scheme 2.1 illustrate the preparation of aldol condensation products by the base-catalyzed reaction. In entry 1 the product is a β-hydroxy aldehyde, while in entry 2 dehydration has provided an α,β-unsaturated aldehyde.

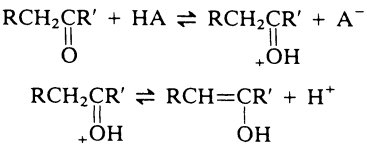
Under conditions of acid catalysis it is the enol which acts as the nucleophile and the protonated carbonyl is the electrophile.

1. A. T. Nielsen and W. J. Houlihan, *Org. React.* **16**, 1 (1968).
2. R. L. Reeves, in *Chemistry of the Carbonyl Group*, S. Patai (ed.), Interscience, New York (1966), pp. 580–593.
3. H. O. House, *Modern Synthetic Reactions*, second edition, W. A. Benjamin, Menlo Park, California (1972), pp. 629–682.

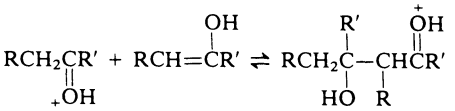
Acid-Catalyzed Mechanism

1. Addition phase

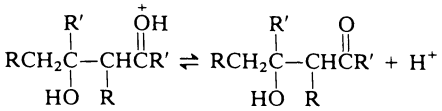
a. Enolization:



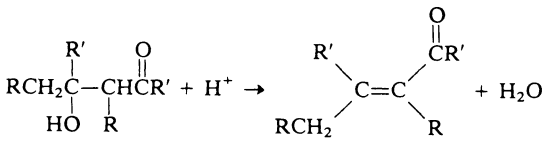
b. Nucleophilic addition:



c. Proton transfer:



2. Dehydration phase



Entry 4 in Scheme 2.1 depicts an acid-catalyzed aldol condensation with dehydration. In entry 5, the Lewis acid catalyst aluminum tri-*tert*-butoxide is used in place of a proton donor.

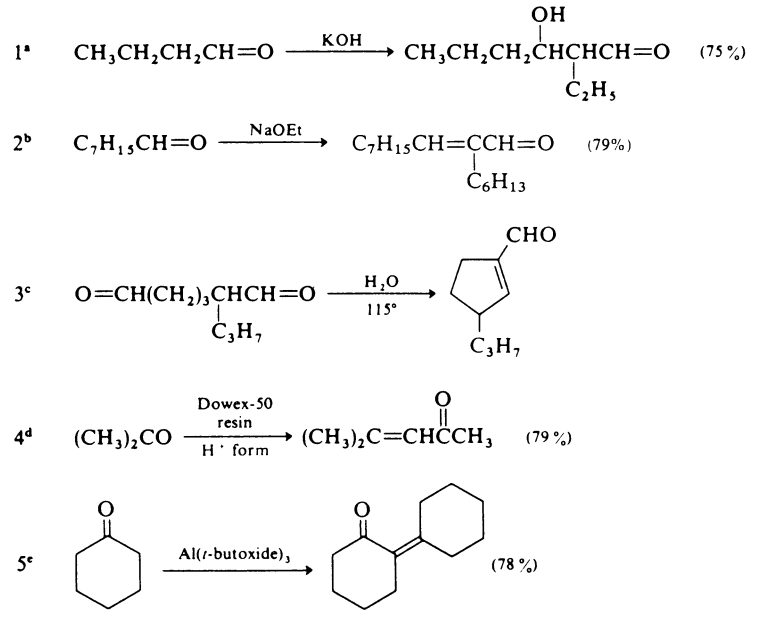
In general, the reactions in the addition phase of both the base-catalyzed and the acid-catalyzed condensations are readily reversible. The equilibrium constant for addition is usually unfavorable for acyclic ketones. The equilibrium constant for the dehydration phase, however, is usually favorable, largely because a conjugated α,β-unsaturated carbonyl system is formed. When the reaction conditions are sufficiently vigorous to cause dehydration, the overall reaction can go to completion even if the equilibrium constant for the addition phase is not favorable.

Intramolecular aldol condensations occur more readily than intermolecular ones. A particularly important example of the synthetic use of intramolecular condensations is in the Robinson annulation, a procedure that constructs a new six-membered ring from a ketone that has an enolizable hydrogen.[4,5] The stages

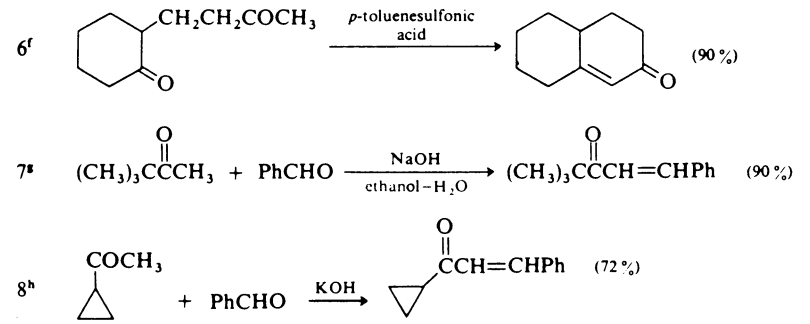
4. E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React.* **10**, 179 (1950); J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).
5. For more recent reviews of annulation reactions, see:
   a. R. E. Gawley, *Synthesis* 777 (1976).
   b. M. E. Jung, *Tetrahedron* **32**, 3 (1976).
   c. B. P. Mundy, *J. Chem. Ed.* **50**, 110 (1973).

Scheme 2.1. Examples of the

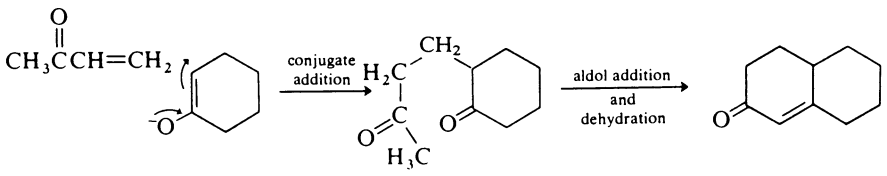
A. Aldehyde and Ketone Self-Condensation

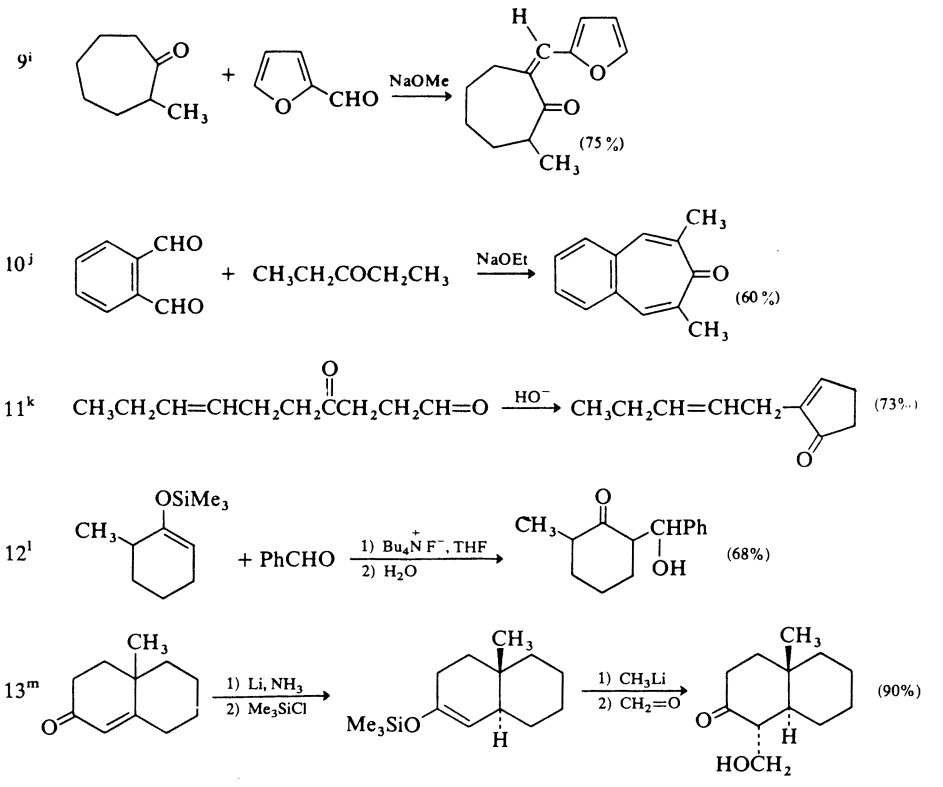


B. Mixed Condensations and Cyclizations



in which this alkylation–cyclization occurs are outlined below. The cyclization phase will be recognized as an intramolecular aldol condensation identical to that shown





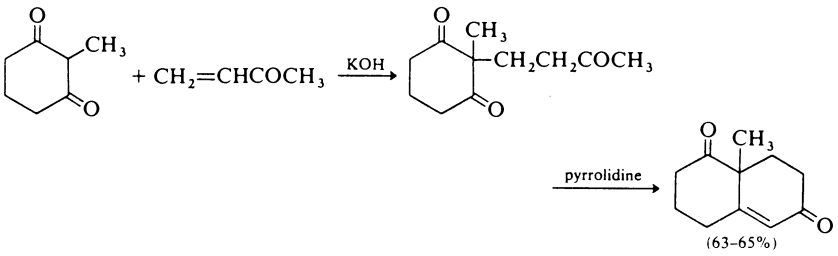
a. V. Grignard and A. Vesterman, *Bull. Chim. Soc. Fr.* **37**, 425 (1925).
b. F. J. Villani and F. F. Nord, *J. Am. Chem. Soc.* **69**, 2605 (1947).
c. J. English and G. W. Barber, *J. Am. Chem. Soc.* **71**, 3310 (1949).
d. N. B. Lorette, *J. Org. Chem.* **22**, 346 (1957).
e. W. Wayne and H. Adkins, *J. Am. Chem. Soc.* **62**, 3401 (1940).
f. D. J. Baisted and J. S. Whitehurst, *J. Chem. Soc.*, 4089 (1961).
g. G. A. Hill and G. Bramann, *Org. Synth.* **I**, 81 (1941).
h. S. C. Bunce, H. J. Dorsman, and F. D. Popp, *J. Chem. Soc.*, 303 (1963).
i. A. M. Islam and M. T. Zemaity, *J. Am. Chem. Soc.* **79**, 6023 (1957).
j. D. Meuche, H. Strauss, and E. Heilbronner, *Helv. Chim. Acta* **41**, 2220 (1958).
k. A. I. Meyers and N. Nazarenko, *J. Org. Chem.* **38**, 175 (1973).
l. R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimuzu, *J. Am. Chem. Soc.* **99**, 1265 (1977).
m. G. Stork and J. d'Angelo, *J. Am. Chem. Soc.* **96**, 7114 (1974).

in entry 6 of Scheme 2.1. This annulation procedure is an important method for the synthesis of cyclohexenones. Scheme 2.2 includes some examples of the Robinson annulation.

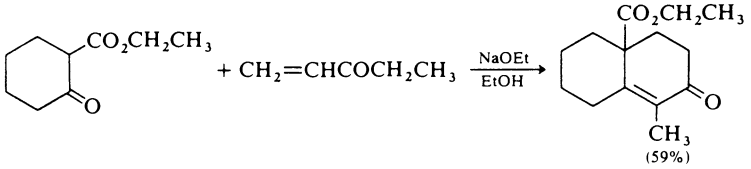
As we saw in Chapter 1, Michael additions to α,β-unsaturated ketones occur best when the nucleophile is only weakly basic. In entries 1 and 2 of Scheme 2.2, we note examples of Robinson annulation reactions in which the nucleophiles are derived by deprotonation of a β-diketone and a β-keto ester, respectively. The Michael acceptor is methyl vinyl ketone in entry 1 and is ethyl vinyl ketone in

Scheme 2.2. The Robinson Annulation Reaction

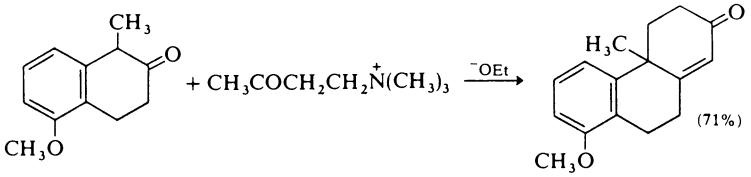
1[a]



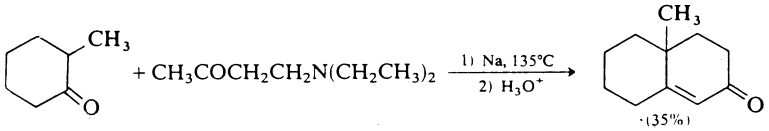
2[b]



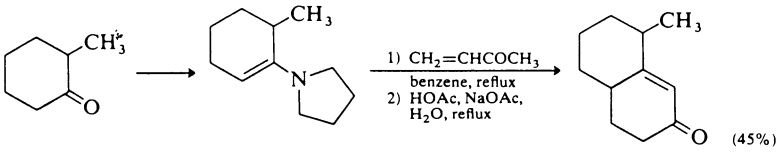
3[c]



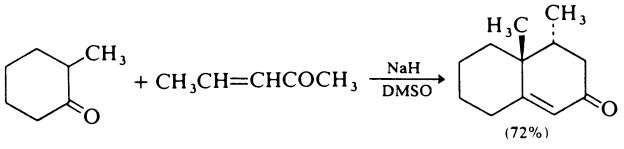
4[d]



5[e]



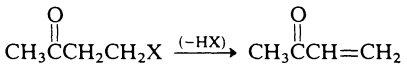
6[f]



a. S. Ramachandran and M. S. Newman, *Org. Synth.* **41**, 38 (1961).
b. D. L. Snitman, R. J. Himmelsbach, and D. S. Watt, *J. Org. Chem.* **43**, 4578 (1978).
c. J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).
d. M. Yanagita and K. Yamakawa, *J. Org. Chem.* **22**, 291 (1957).
e. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.* **85**, 207 (1963).
f. C. J. V. Scanio and R. M. Starrett, *J. Am. Chem. Soc.* **93**, 1539 (1971).

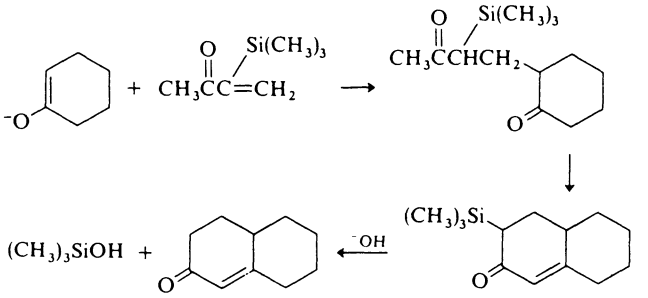
entry 2. The Robinson annulation product in entry 1 is known familiarly as the Wieland–Miescher ketone and has proven to be a popular starting material for the synthesis of a number of steroids and terpenes. When the cyclization leading to the Wieland–Miescher ketone is carried out using the optically active amino acid L-proline instead of pyrrolidine, the *S*-enantiomer of the product is obtained in high optical yield.[6] These reactions will be described in more stereochemical detail in Section 11.3. The use of similar asymmetric annulation reactions in the synthesis of optically active steroids has yielded impressive results.[7]

Early versions of the Robinson annulation did not use methyl vinyl ketone itself, but used instead compounds which could eliminate under the base-catalyzed reaction conditions to generate methyl vinyl ketone *in situ*. Entries 3 and 4 of Scheme 2.2 illustrate this approach. In more recent procedures methyl vinyl ketone is used directly.



Because the Michael addition step involves the thermodynamic enolate, Robinson annulation reactions are regioselective with unsymmetrical ketones. As entry 4 illustrates, the methyl group of 2-methylcyclohexanone appears at the ring junction in the annulated product. In order to achieve the opposite regioselectivity in annulation, recourse is taken to enamine methodology. Since the more stable pyrrolidine enamine of 2-methylcyclohexanone is the less substituted one (as discussed in Chapter 1, Section 1.9), annulation *via* the enamine occurs away from a 2-alkyl group. Entries 4 and 5 illustrate the complementary nature of annulation using enolates and enamines.

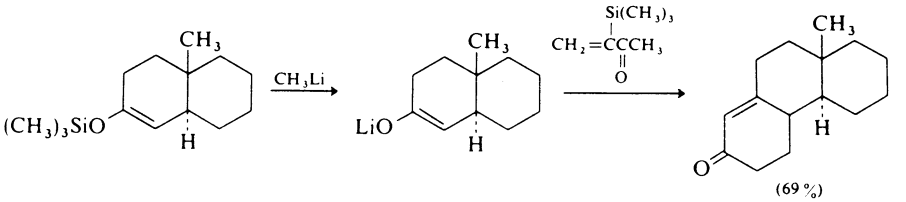
An alternative version of the Robinson annulation procedure involves the use of methyl 1-trimethylsilylvinyl ketone. The reaction follows the normal sequence of conjugate addition, aldol addition, and dehydration:



Ref. 8

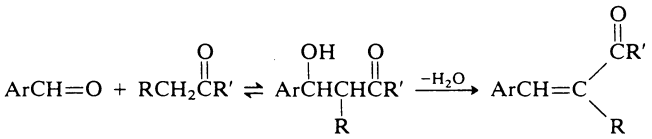
6. J. Gutzwiller, P. Buchschacher, and A. Fürst, *Synthesis* 167 (1977).
7. N. Cohen, *Acc. Chem. Res.* **9**, 412 (1976).
8. G. Stork and B. Ganem, *J. Am. Chem. Soc.* **95**, 6152 (1973); G. Stork and J. Singh, *J. Am. Chem. Soc.* **96**, 6181 (1974).

The role of the trimethylsilyl group is to stabilize the intermediate carbanion formed by conjugate addition. The silyl group is removed under conditions similar to those required for the dehydration; the removal occurs by nucleophilic attack on silicon resulting in displacement of the ketone. The advantage of the substituted methyl vinyl ketone is that it permits the annulation reaction to be carried out in aprotic solvents under conditions where enolate equilibration does not take place. The annulation of unsymmetrical ketones can therefore be controlled by using specific enolates generated by the methods described in Chapter 1.



Ref. 9

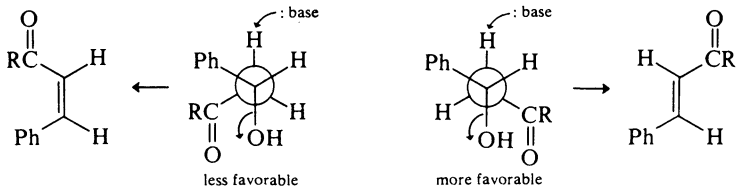
Returning now to intermolecular aldol condensations, we consider *mixed (or crossed) aldol condensations* between two different carbonyl compounds. To be useful as a method for construction of carbon–carbon bonds, there must be some basis for defining which carbonyl component will serve as the electrophile (acceptor carbonyl) and which is to serve as the enolate precursor. One of the most general of these mixed condensations involves the reaction of aromatic aldehydes with aliphatic ketones or aldehydes. An aromatic aldehyde cannot function as the nucleophilic species because, lacking an α-hydrogen atom, it is incapable of forming an enol or enolate. Dehydration is favored because it leads to a double bond conjugated with both the carbonyl group and the aromatic ring:



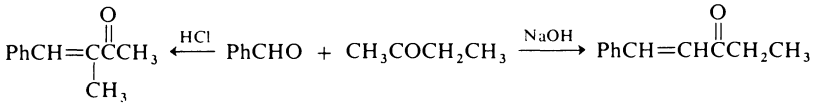
There are many examples of both acid- and base-catalyzed condensation reactions involving aromatic aldehydes. The name *Claisen–Schmidt condensation* is associated with this type of mixed aldol reaction. Entries 7–10 in Scheme 2.1 are a few of the hundreds of examples of this reaction that have been recorded.

There is a pronounced preference for the formation of *trans* double bonds in the Claisen–Schmidt condensation of methyl ketones. This stereoselectivity arises in the dehydration step. In the transition state for elimination to a *cis* double bond, an unfavorable interaction between the ketone substituent (R) and the phenyl group occurs. This unfavorable interaction is absent in the transition state for elimination to a *trans* double bond.

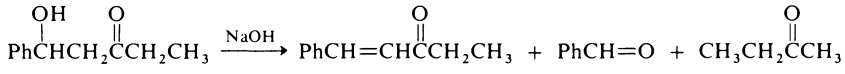
9. R. K. Boeckman, Jr., *J. Am. Chem. Soc.* **96**, 6179 (1974).

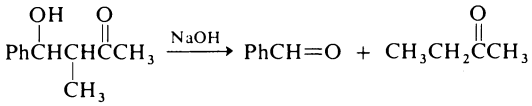


Additional insight into the factors affecting product structure was obtained by studies on the Claisen–Schmidt condensation of 2-butanone with benzaldehyde.[10]

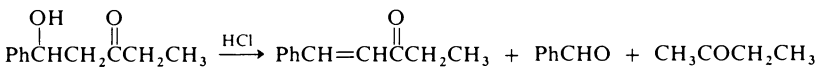


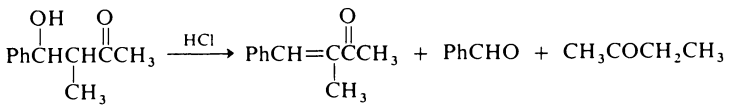
The results indicate how the interplay between the relative rates of the various reaction steps determines the identity of the reaction product. When catalyzed by base, 2-butanone reacts with benzaldehyde at the methyl group; under conditions of acid catalysis, the site of reaction is the methylene group. The reaction conditions do not permit the isolation of the intermediate ketols because the addition phase is rate-limiting, but these compounds have been prepared by an alternative route. They behave as shown in the following equations:





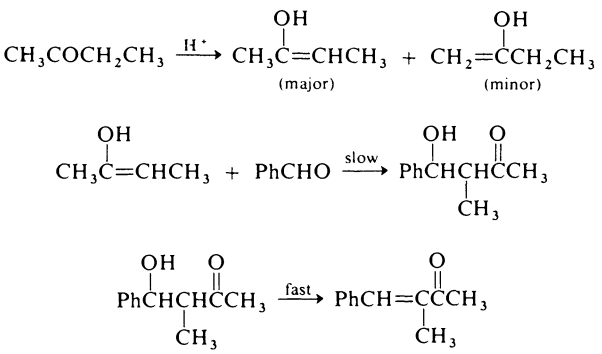
These results establish that base-catalyzed dehydration is slow relative to the reverse of the addition phase for the branched-chain isomer. The reason for selective formation of the straight-chain product under conditions of base catalysis is then apparent. In base the straight-chain ketol is the only productive addition intermediate. Acid treatment of each of the intermediates gives the dehydration product having the corresponding carbon skeleton, along with some of the cleavage products. Under conditions of acid catalysis, then, either intermediate can be dehydrated.





10. a. M. Stiles, D. Wolf, and G. V. Hudson, *J. Am. Chem. Soc.* **81**, 628 (1959).
b. D. S. Noyce and W. L. Reed, *J. Am. Chem. Soc.* **81**, 618, 620, 624 (1959).

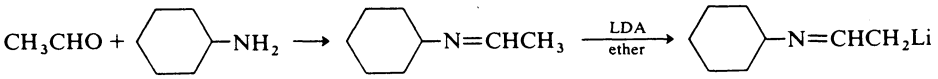
Under acid-catalyzed conditions, the addition phase is rate determining, and the relative amounts of the two dehydrated products are determined by the amounts of intermediates formed. The more substituted enol is favored, and the branched-chain isomer is therefore the major product in the acid-catalyzed reaction:



In any given system, the structure of the final product will depend upon the magnitude of the individual rate constants. In general, condensations of methyl ketones with aromatic aldehydes follow the pattern observed for 2-butanone; i.e., base catalysis favors the linear condensation product, while acid catalysis favors the branched product.

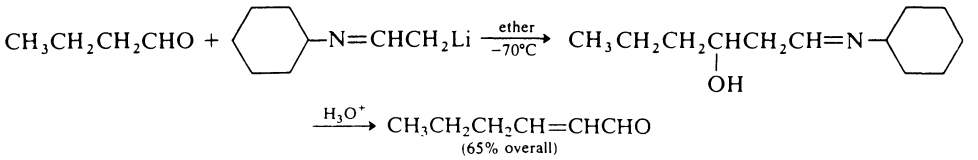
A more difficult mixed aldol condensation to bring about efficiently is one involving two carbonyl compounds, both of which can form enolate ions, especially if one (or both) are aldehydes. One procedure which has been devised to effect such condensations in a controlled manner utilizes metalloenamines as enolate equivalents (see Chapter 1, Section 1.9) and is referred to as a *directed aldol condensation.*[11] The method can be illustrated by considering the mixed aldol condensation of butyraldehyde and acetaldehyde with the objective of preparing 2-hexenal. It is easy to see that the proposed conversion will be accompanied by

self-condensation of each aldehyde as well as addition of the enolate of butyraldehyde to acetaldehyde. In the directed aldol condensation procedure, acetaldehyde is converted to its corresponding imine with cyclohexylamine. The imine is then

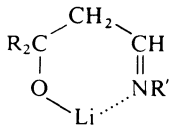


metallated. Addition of the acceptor carbonyl (butyraldehyde) to the metalloenamine gives an intermediate which on hydrolysis affords the desired product.

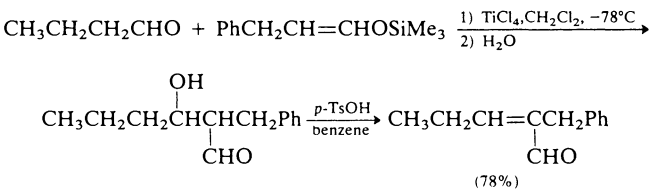
11. G. Wittig and H. Reiff, *Angew. Chem. Internat. Ed. Engl.* **7**, 7 (1968); H. Reiff, in *Newer Methods of Preparative Organic Chemistry*, Vol. VI, W. Foerst (ed.), Academic Press, New York (1971), pp. 48–66.



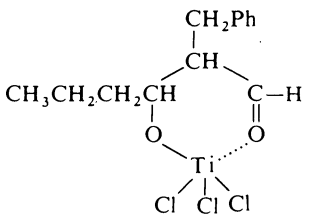
The success of the directed aldol condensation via metalloenamines arises from several factors. Most importantly, imines show little tendency to self-condense. Under basic conditions a C=N bond is less electrophilic than a C=O bond because nitrogen is less electronegative than oxygen. As mentioned earlier (Section 1.9), metalloenamines are more nucleophilic than enolate ions, so the addition phase of the process should be more favorable. It is also believed that the adduct of a metalloenamine and a carbonyl compound is strongly stabilized by chelation, increasing the equilibrium constant for the addition phase.



The prospect of chelation to a metal has been suggested as well in other mixed aldol condensations. Using its *O*-trimethylsilyl enol ether as an enol equivalent, 3-phenylpropanal undergoes directed aldol addition to butyraldehyde in the presence of titanium tetrachloride.[12]



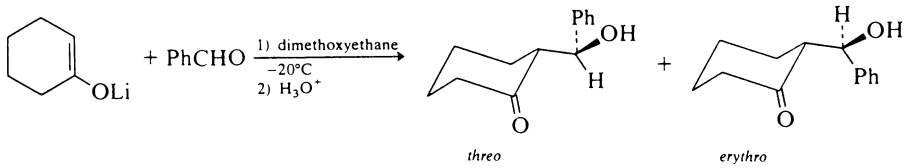
A titanium chelate of the type



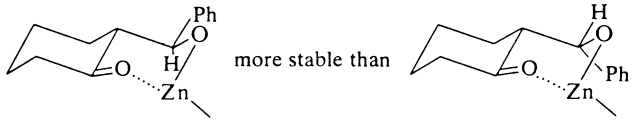
may be an intermediate.

12. T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.* **96**, 7503 (1974).

Addition of divalent metal salts ($MgBr_2$, $ZnCl_2$) as a means of displacing an unfavorable equilibrium in the addition phase by formation of a stable chelate has been studied.[13] While some increase in efficiency was observed, the most dramatic change was in the stereoselectivity of the aldol addition. When the lithium enolate of cyclohexanone was allowed to react with benzaldehyde, a 1 : 1 ratio of *threo* and *erythro* aldol products was obtained. Adding zinc chloride to the enolate first, then

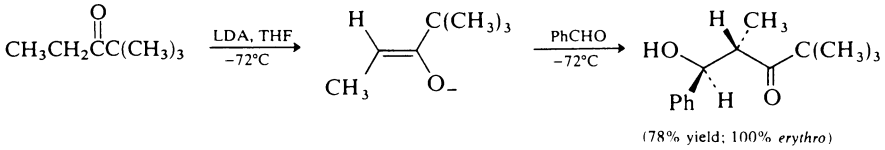


adding benzaldehyde, caused a change in the observed *threo/erythro* product ratio from 1 : 1 to 3 : 1. This change in stereoselectivity has been attributed to the greater stability of a chairlike zinc chelate when the phenyl group is equatorial than when it is axial.



The topic of the stereoselectivity of aldol condensation reactions has received much attention recently owing to efforts directed toward the total synthesis of macrolide antibiotics. The carbon backbone of many of these substances may be viewed as capable of being derived by combinations of several aldol additions. Because of the number of chiral centers, it is necessary that a high level of stereochemical control be achieved in the carbon–carbon bond-forming steps. Hence, a number of fundamental studies have been concerned with stereoselection in aldol addition reactions.

Using preformed lithium enolates, complete kinetic stereoselection has been achieved. The kinetic enolate of 2,2-dimethyl-3-pentanone is exclusively the *Z* isomer; it adds to benzaldehyde to give only the *erythro* aldol product.[14] Similar

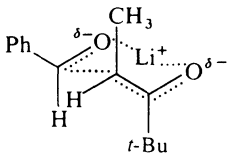


(78% yield; 100% *erythro*)

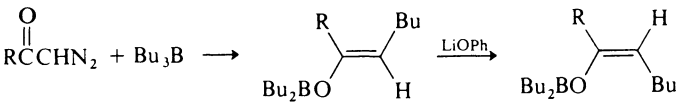
stereoselectivity was observed for other *Z* enolates derived from ketones which have a bulky substituent on the carbonyl group. The results were interpreted in

13. H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.* **95**, 3310 (1973).
14. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.* **45**, 1066 (1980).

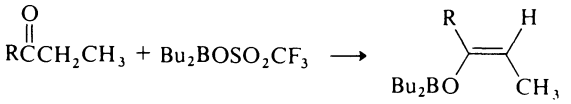
terms of the transition state shown. The essential elements which are considered to affect stereoselection are the chairlike geometry and the tendency for greatest separation of the phenyl and *tert*-butyl substituents.



Enol borinates show promise as enolate equivalents in stereoselective aldol additions. These compounds can be prepared by the reaction of diazoketones with trialkylboranes. Direct reaction gives the *E* enol borinate, which can be isomerized

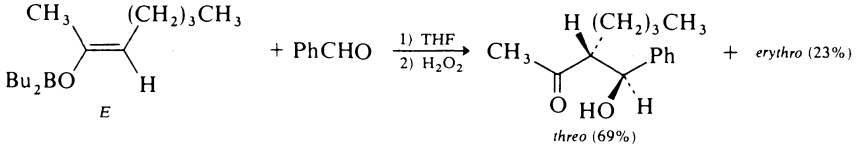


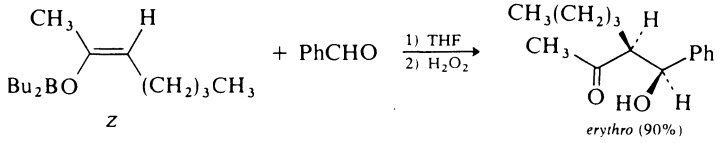
to the *Z* isomer by brief treatment with base.[15a] Alternatively, enol borinates are prepared by the reaction of ketones with dialkylboron triflates.[15b] Under conditions



of kinetic control the *Z*-enol borinates are formed in this process, sometimes with very high stereoselectivity.

Enol borinates react smoothly with aldehydes at room temperature. The *E*-enol borinates give about 3 : 1 diastereoselection favoring the *threo* aldol product, while the *Z*-isomer gives almost exclusively the *erythro* diastereomer.[15a] The factors





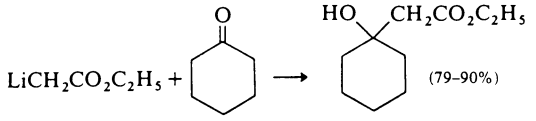
influencing stereoselection in these reactions are presumed to be similar to those which occur with lithium enolates. It has been suggested that the shorter boron–oxygen and boron–carbon distances, compared to lithium–oxygen and lithium–carbon, magnify the energy differences in the chairlike transition states to improve the stereoselectivity.[15b]

15. a. S. Masamune, S. Mori, D. Van Horn, and D. W. Brooks, *Tetrahedron Lett.* 1665 (1979).
b. D. A. Evans, E. Vogel, and J. V. Nelson, *J. Am. Chem. Soc.* **101**, 6120 (1979).

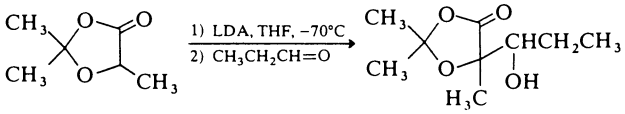
Scheme 2.3. Addition Reactions of Carbanions Derived from Esters, Carboxylic Acids, Amides, and Nitriles

1[a] $CH_3CO_2C_2H_5 + Ph_2CO \xrightarrow[2)\ NH_4Cl]{1)\ LiNH_2} Ph_2\overset{OH}{\overset{|}{C}}CH_2CO_2C_2H_5$ (75–84%)

2[b] $CH_3CO_2C_2H_5 + LiN[Si(CH_3)_3]_2 \rightarrow LiCH_2CO_2C_2H_5$

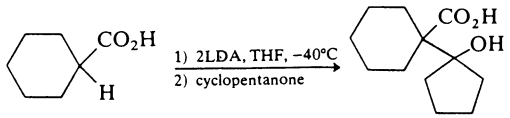


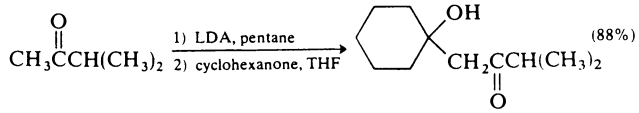
(79–90%)

3[c] 

(85%)

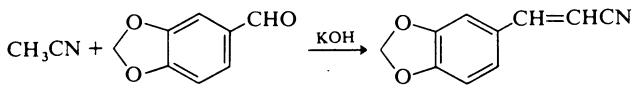
4[d] $(CH_3)_2CHCO_2H \xrightarrow[R_2NLi]{2\ mol} (CH_3)_2\overset{Li}{\overset{|}{C}}CO_2Li \xrightarrow{(CH_3CH_2)_2C=O} (CH_3CH_2)_2\overset{OH}{\overset{|}{C}}-\overset{CO_2H}{\overset{|}{C}}(CH_3)_2$ (77%)

5[e] 

6[f] 

(88%)

7[g] $CH_3CN \xrightarrow[2)\ (CH_3CH_2)_2C=O]{1)\ nBuLi,\ THF,\ -80°C} (CH_3CH_2)_2\overset{OH}{\overset{|}{C}}CH_2CN$ (68%)

8[h] 

(86%)

a. W. R. Dunnavant and C. R. Hauser, *Org. Synth.* **44**, 56 (1964).
b. M. W. Rathke, *Org. Synth.* **53**, 66 (1973).
c. C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. VanDerveer, *J. Org. Chem.* **45**, 3846 (1980).
d. G. W. Moersch and A. R. Burkett, *J. Org. Chem.* **36**, 1149 (1971).
e. A. P. Krapcho and E. G. E. Jahngen, Jr., *J. Org. Chem.* **39**, 1650 (1974).
f. R. P. Woodbury and M. W. Rathke, *J. Org. Chem.* **42**, 1688 (1977).
g. E. M. Kaiser and C. R. Hauser, *J. Org. Chem.* **33**, 3402 (1968).
h. S. A. DiBiase, B. A. Lipisko, A. Haag, R. A. Wolak, and G. W. Gokel, *J. Org. Chem.* **44**, 4640 (1979).

A variety of carbanionic species derived from carboxylic acids, esters, amides, and nitriles have been prepared and added to aldehydes and ketones. Usually, strong bases such as lithium diisopropylamide are used owing to the low level of

acidity of these substrates. Typical examples of some of these reactions are presented in Scheme 2.3.

2.2. Amine-Catalyzed Aldol Condensation Reactions

A number of preparatively useful reactions are variants of the mechanistic pattern established by the aldol condensation. One important group is a family of condensations that effect transformations quite similar to the aldol, but that are particularly effectively catalyzed by amines or buffer systems containing amines and the corresponding conjugate acid. These amine-catalyzed reactions are often referred to as *Knoevenagel condensations.*[16]

In several cases, it has been established that the amines do not function as simple bases but instead are involved in prior reaction with the carbonyl compounds as well. Kinetic evidence in support of such a mechanism in the condensation of aromatic aldehydes with nitromethane has been reported.[17] The fact that such condensations are often most effectively catalyzed when a weak acid is present in addition to the amine suggests that amines do not function as simple base catalysts. The reactive electrophile is probably the protonated form of the imine formed by condensation of the carbonyl compound and the amine. This iminium ion will be considerably more electrophilic than a carbonyl group because of the positive charge.

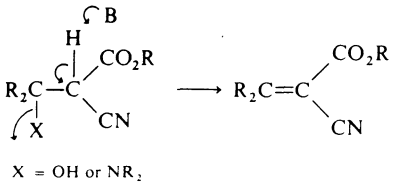
$$ArCH{=}O + C_4H_9NH_2 \rightleftarrows ArCH{=}NC_4H_9$$

$$ArCH{=}\overset{\overset{H^+}{\frown}}{N}C_4H_9 \;\underset{\frown}{\leftarrow}\; CH_2NO_2 \longrightarrow ArCH(CH_2NO_2)NHC_4H_9 \longrightarrow ArCH(\overset{\overset{H^+}{\frown}}{N}HC_4H_9)CH_2NO_2 \longrightarrow ArCH{=}CHNO_2$$

The main preparative application of the reaction has been condensation of ketones and aldehydes with easily enolizable compounds usually containing two activating groups. Malonic esters and cyanoacetic esters are the most common examples.[18] Usually, the product is the "dehydrated" compound, with the saturated intermediates being isolated only under especially mild conditions. Nitroalkanes are also effective nucleophilic substrates. The single, strongly electron-withdrawing nitro group sufficiently activates the α-hydrogens to permit formation of the nucleophilic nitronate anion under mildly basic conditions. A relatively highly acidic proton in the potential nucleophile is important for two reasons. First, weak bases, such as amines, can then provide a sufficient concentration of enolate for reaction, without causing deprotonation of the ketone or aldehyde. Self-condensation of the

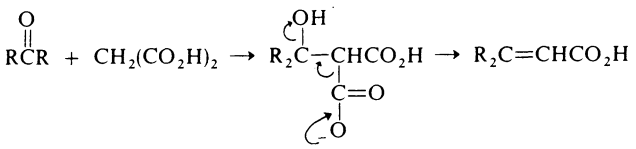
16. a. G. Jones, *Org. React.* **15**, 204 (1967).
    b. R. L. Reeves, in *The Chemistry of the Carbonyl Group*, S. Patai (ed.), Interscience, New York (1966), pp. 593–599.
17. T. I. Crowell and D. W. Peck, *J. Am. Chem. Soc.* **75**, 1075 (1953).
18. A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.* **63**, 3452 (1941).

carbonyl component is thus minimized. Second, the highly acidic proton facilitates the elimination step that drives the condensation to completion.

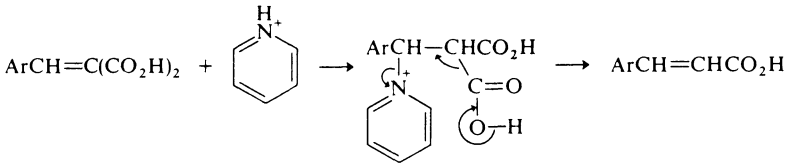


X = OH or NR_2

A closely related variation of the reaction uses cyanoacetic acid or malonic acid, as opposed to the corresponding esters, as the potential nucleophile. The mechanism of the addition phase of the reaction under these circumstances is similar to the previously discussed cases. The addition intermediates, however, are susceptible to decarboxylation. In many instances, the decarboxylation and elimination phases may occur as a single concerted process.[19] Many of the decarboxylative



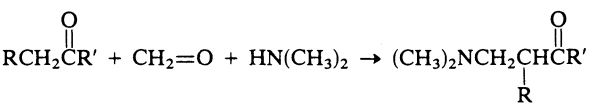
condensations have been carried out in pyridine, and it has been shown that pyridinium ion can catalyze the decarboxylation of arylidenemalonic acids.[20]



Scheme 2.4 provides a few examples of condensation reactions of the Knoevenagel type.

2.3. The Mannich Reaction

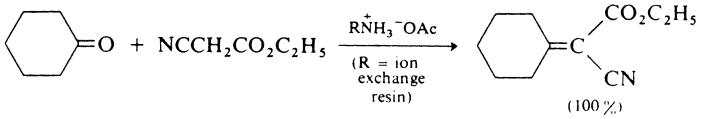
The *Mannich reaction* is very closely related to the Knoevenagel condensation reaction in that it involves iminium intermediates. The reaction, which is carried out in mildly acidic solution, effects α-alkylation of ketones and aldehydes with dialkylaminomethyl groups. The electrophilic species is the iminium ion derived



19. E. J. Corey, *J. Am. Chem. Soc.* **74**, 5897 (1952).
20. E. J. Corey and G. Fraenkel, *J. Am. Chem. Soc.* **75**, 1168 (1953).

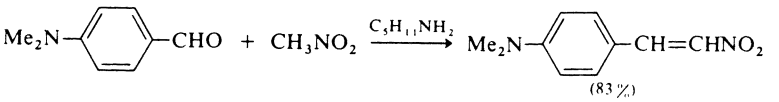
Scheme 2.4. Amine-Catalyzed Condensations of the Knoevenagel Type

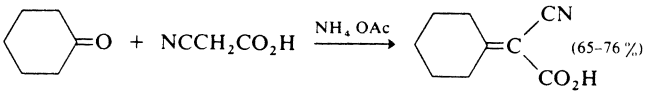
1[a] $CH_3CH_2CH_2CH{=}O + CH_3\overset{O}{\overset{\|}{C}}CH_2CO_2C_2H_5 \xrightarrow{\text{piperidine}} CH_3CH_2CH_2CH{=}C(\overset{O}{\overset{\|}{C}}CH_3)(CO_2C_2H_5)$ (81%)

2[b] 

3[c] $C_2H_5COCH_3 + N{\equiv}CCH_2CO_2C_2H_5 \xrightarrow{\beta\text{-alanine}} C_2H_5C(CH_3){=}C(CN)(CO_2C_2H_5)$ (81–87%)

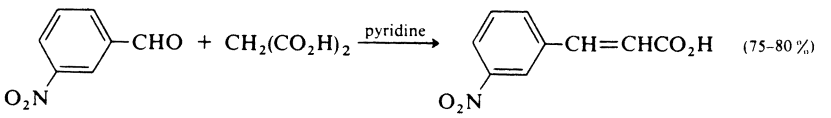
4[d] $CH_3(CH_2)_3CH(CH_2CH_3)CH{=}O + CH_2(CO_2C_2H_5)_2 \xrightarrow[RCO_2H]{\text{piperidine}} CH_3(CH_2)_3CH(CH_2CH_3)CH{=}C(CO_2C_2H_5)_2$ (87%)

5[e] 

6[f] 

7[g] $PhCH{=}O + CH_3CH_2CH(CO_2H)_2 \xrightarrow{\text{pyridine}} PhCH{=}C(CO_2H)(C_2H_5)$ (60%)

8[h] $CH_2{=}CHCH{=}O + CH_2(CO_2H)_2 \xrightarrow[60°C]{\text{pyridine}} CH_2{=}CHCH{=}CHCO_2H$ (42–46%)

9[i] 

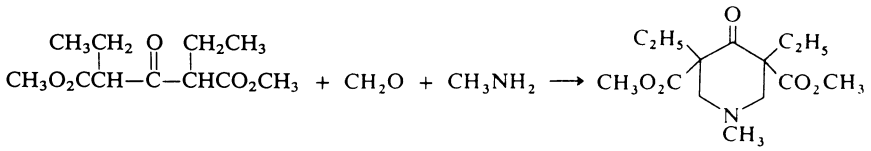
a. A. C. Cope and C. M. Hofmann, *J. Am. Chem. Soc.* **63**, 3456 (1941).
b. R. W. Hein, M. J. Astle, and J. R. Shelton, *J. Org. Chem.* **26**, 4874 (1961).
c. F. S. Prout, R. J. Hartman, E. P.-Y. Huang, C. J. Korpics, and G. R. Tichelaar, *Org. Synth.* **IV**, 93 (1963).
d. E. F. Pratt and E. Werble, *J. Am. Chem. Soc.* **72**, 4638 (1950).
e. D. E. Worrall and L. Cohen, *J. Am. Chem. Soc.* **66**, 842 (1944).
f. A. C. Cope, A. A. D'Addieco, D. E. Whyte, and S. A. Glickman, *Org. Synth.* **IV**, 234 (1963).
g. W. J. Gensler and E. Berman, *J. Am. Chem. Soc.* **80**, 4949 (1958).
h. P. J. Jessup, C. B. Petty, J. Roos, and L. E. Overman, *Org. Synth.* **59**, 1 (1979).
i. R. H. Wiley and N. R. Smith, *Org. Synth.* **IV**, 731 (1963).

from the amine and formaldehyde. The reaction is quite general for aldehydes and ketones having at least one enolizable hydrogen. For practical preparative purposes,

$$CH_2{=}O + HN(CH_3)_2 \rightleftharpoons HOCH_2N(CH_3)_2 \overset{H^+}{\rightleftharpoons} H_2O + CH_2{=}\overset{+}{N}(CH_3)_2$$

$$(CH_3)_2\overset{+}{N}{=}CH_2 + RCH{=}\overset{OH}{\overset{|}{C}}R' \rightarrow (CH_3)_2NCH_2\underset{R}{\overset{|}{C}}H\overset{O}{\overset{\|}{C}}R' + H^+$$

the reaction is limited to secondary amines, since dialkylation becomes a significant problem with primary amines. The dialkylation reaction, however, can be used advantageously in some ring closures.



Ref. 21

Entries 1 and 2 in Scheme 2.5 show the preparation of "Mannich bases" from ketones, formaldehyde, and dialkylamines according to the classical procedure. Alternatively, formaldehyde equivalents may be used, such as *bis*-(dimethylamino)methane (entry 3). On treatment with trifluoroacetic acid, this aminal generates the iminium trifluoracetate as the reactive electrophile.

$$(CH_3)_2NCH_2N(CH_3)_2 + 2CF_3CO_2H \rightarrow (CH_3)_2\overset{+}{N}{=}CH_2 + H_2\overset{+}{N}(CH_3)_2 + 2CF_3CO_2^-$$

A procedure in which the iminium salt shown, *N,N*-dimethyl(methylene) ammonium trifluoroacetate, is isolated and added separately to an enolate ion allows Mannich bases to be prepared by routes other than those involving acidic media. This procedure is exemplified by entry 4. *N,N*-Dimethyl(methylene) ammonium iodide[22] is commercially available as "Eschenmoser's salt" and is sufficiently electrophilic so as to react directly with enol silyl ethers in neutral media.[23] Ketone enolates have been converted to Mannich bases with Eschenmoser's salt (entry 5).

The importance of the Mannich reaction stems from the synthetic utility of the resulting aminoketones. Thermal decomposition of the amines or the derived quaternary salts leads to α-methylene ketones. The decomposition of the quaternary salts is particularly facile, and they can be used as *in situ* sources of many α,β-unsaturated carbonyl compounds. These are useful synthetic intermediates, for

$$(CH_3)_2CH\underset{CH_2N(CH_3)_2}{\overset{|}{C}}HCH{=}O \overset{\Delta}{\rightarrow} (CH_3)_2CH\overset{CH_2}{\overset{\|}{C}}CH{=}O$$

Ref. 24

21. C. Mannich and P. Schumann, *Chem. Ber.* **69**, 2299 (1936).
22. J. Schreiber, H. Maag, N. Hashimoto, and A. Eschenmoser, *Angew. Chem. Internat. Ed. Engl.* **10**, 330 (1971).
23. S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Am. Chem. Soc.* **98**, 6715 (1976).
24. C. S. Marvel, R. L. Myers, and J. H. Saunders, *J. Am. Chem. Soc.* **70**, 1694 (1948).

example, in Michael additions (Chapter 1), Robinson annulation reactions (entries 3 and 4 of Scheme 2.2), and certain hydroboration procedures for carbon–carbon bond formation (Chapter 4). Entries 8 and 9 in Scheme 2.5 illustrate two of the ways in which Mannich bases can be used to construct carbon skeletons by Michael addition reactions.

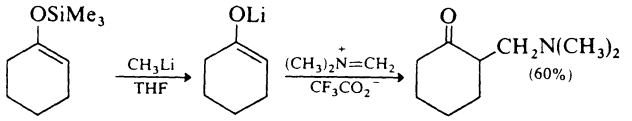
Scheme 2.5. Synthesis and Utilization of Mannich Bases

1[a] $PhCOCH_3 + CH_2O + (CH_3)_2\overset{+}{N}H_2Cl^- \rightarrow PhCOCH_2CH_2\overset{H}{\overset{+}{N}}(CH_3)_2Cl^-$ (70%)

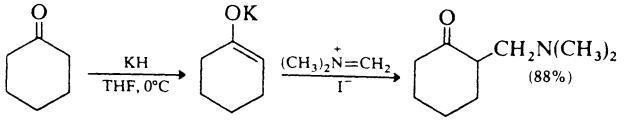
2[b] $CH_3COCH_3 + CH_2O + (CH_3CH_2)_2\overset{+}{N}H_2Cl^- \rightarrow CH_3COCH_2CH_2CH_2\overset{H}{\overset{+}{N}}(C_2H_5)_2Cl^-$ (66–75%)

3[c] $(CH_3)_2CHCOCH_3 + [(CH_3)_2N]_2CH_2 \xrightarrow{CF_3CO_2H} (CH_3)_2CHCOCH_2CH_2N(CH_3)_2$

4[d]

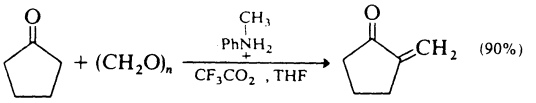


5[e]

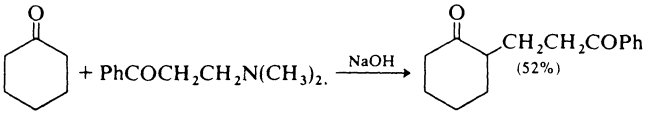


6[f] $CH_3CH_2CH_2CH{=}O + CH_2O + (CH_3)_2\overset{+}{N}H_2Cl^- \xrightarrow[2)\ \text{distill}]{1)\ 60°C,\ 6\ hr} CH_2{=}\underset{\displaystyle CH_2CH_3}{\underset{|}{C}}CH{=}O$ (73%)

7[g]



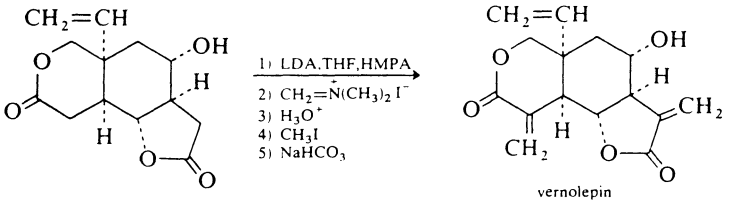
8[h]



9[i] $PhCOCH_2CH_2N(CH_3)_2 + KCN \rightarrow PhCOCH_2CH_2CN$ (67%)

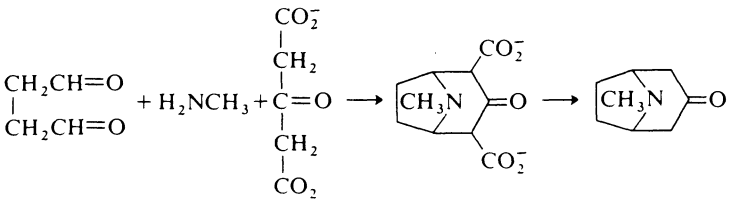
a. C. E. Maxwell, *Org. Synth.* **III**, 305 (1955).
b. A. L. Wilds, R. M. Nowak, and K. E. McCaleb, *Org. Synth.* **IV**, 281 (1963).
c. M. Gaudry, Y. Jasor, and T. B. Khac, *Org. Synth.* **59**, 153, (1979).
d. N. L. Holy and Y. F. Wang, *J. Am. Chem. Soc.* **99**, 944 (1977).
e. J. L. Roberts, P. S. Borromeo, and C. D. Poulter, *Tetrahedron Lett.*, 1621 (1977).
f. C. S. Marvel, R. L. Myers, and J. H. Saunders, *J. Am. Chem. Soc.* **70**, 1694 (1948).
g. J. L. Gras, *Tetrahedron Lett.*, 2111, 2955 (1978).
h. A. C. Cope and E. C. Hermann, *J. Am. Chem. Soc.* **72**, 3405 (1950).
i. E. B. Knott, *J. Chem. Soc.*, 1190 (1947).

α-Methylene lactones provide the biologically important functionality in a large number of tumor-inhibitory natural products.[25] The reaction of ester enolates with dimethyl(methylene)ammonium trifluoroacetate,[26] or with Eschenmoser's salt,[27] has been demonstrated to be an effective approach in the synthesis of vernolepin, a compound with anti-leukemic activity.[28,29]



vernolepin

Mannich reactions, or at least some close mechanistic analogs, are important in the biosynthesis of many nitrogen-containing molecules. As a result, the Mannich reaction has played an important role in the total synthesis of such compounds, especially in synthesis patterned after the mode of biosynthesis, i.e., *biogenetic-type synthesis*. The earliest example of the use of the Mannich reaction in this context was the successful synthesis of tropinone, a derivative of the alkaloid tropine, by Sir Robert Robinson in 1917.



Ref. 30

2.4. Acylation of Carbanions. The Claisen, Dieckmann, and Related Condensation Reactions

The most generally used carbonyl compounds for the *acylation* of enolate ions are esters. Here, nucleophilic addition of the anion to the carbonyl group is followed by loss of alkoxide from the tetrahedral intermediate. A classic example of this type of reaction is the *Claisen condensation*—the base-catalyzed self-condensation

25. S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.* **14**, 1147 (1971).
26. N. L. Holy and Y. F. Wang, *J. Am. Chem. Soc.* **99**, 499 (1977).
27. J. L. Roberts, P. S. Borromes, and C. D. Poulter, *Tetrahedron Lett.*, 1621 (1977).
28. S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, *J. Am. Chem. Soc.* **99**, 6066 (1977).
29. For a review of methods for the synthesis of α-methylene lactones, see R. B. Gammill, C. A. Wilson, and T. A. Bryson, *Synthetic Comm.* **5**, 245 (1975).
30. R. Robinson, *J. Chem. Soc.*, 762 (1917).

of esters.[31] Ethyl acetoacetate, for example, is prepared by Claisen condensation of ethyl acetate. All of the steps except the last one are readily reversible. The pK_a

$$CH_3CO_2CH_2CH_3 + CH_3CH_2O^- \rightleftharpoons {}^-CH_2CO_2CH_2CH_3 + CH_3CH_2OH$$

$$CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3 + {}^-CH_2CO_2CH_2CH_3 \rightleftharpoons CH_3\overset{\overset{O^-}{|}}{C}(CH_2CO_2CH_2CH_3)OCH_2CH_3$$

$$CH_3\overset{\overset{O^-}{|}}{C}(CH_2CO_2CH_2CH_3)OCH_2CH_3 \rightleftharpoons CH_3\overset{\overset{O}{\|}}{C}CH_2CO_2CH_2CH_3 + CH_3CH_2O^-$$

$$CH_3\overset{\overset{O}{\|}}{C}CH_2CO_2CH_2CH_3 + CH_3CH_2O^- \rightarrow CH_3\overset{\overset{O}{\|}}{C}\underline{C}HCO_2CH_2CH_3 + CH_3CH_2OH$$

of ethyl acetoacetate is very much lower than any of the other species present. Ethyl acetoacetate is also much more acidic than ethanol, so the equilibrium constant for the last step is highly favorable and the overall reaction is driven essentially to completion when at least one mole of base is used. The neutral form of the β-keto ester product is obtained after acidification of the reaction mixture.

$$2\ CH_3CO_2CH_2CH_3 + \underset{\text{stronger base}}{CH_3CH_2O^-} \rightarrow \underset{\text{weaker base}}{CH_3\overset{\overset{O}{\|}}{C}\underline{C}HCO_2CH_2CH_3} + 2\ CH_3CH_2OH$$

As a practical matter, the alkoxide used as catalyst must be the same as the alcohol portion of the ester to prevent formation of product mixtures by ester-interchange reactions. Because the final irreversible proton transfer cannot occur when α-disubstituted esters are employed, these compounds do not condense when alkoxide ions are used as catalysts. This limitation can be overcome by the use of a very strong base that converts the starting ester essentially completely to its enolate. One procedure employs triphenylmethylsodium for this purpose (entry 2, Scheme 2.6).

The intramolecular version of ester condensation is often referred to as *Dieckmann condensation*.[32] It is an important tool for the closure of five- and six-membered rings during synthetic sequences, and has occasionally been employed for formation of larger rings. Entries 3–7 in Scheme 2.6 are illustrative.

Modern workers have often chosen sodium hydride and a small amount of alcohol as the catalyst system. It is probable that the effective catalyst is actually the sodium alkoxide formed by reaction of the alcohol released in the condensation with sodium hydride.

$$R'OH + NaH \rightarrow R'ONa + H_2$$

The sodium alkoxide is also no doubt the active catalyst in reactions in which sodium metal is present. The alkoxide is formed by reaction between metallic

31. C. R. Hauser and B. E. Hudson, Jr., *Org. React.* **1**, 266 (1942).
32. J. P. Schaefer and J. J. Bloomfield, *Org. React.* **15**, 1 (1967).

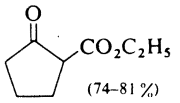
Scheme 2.6. Acylation of

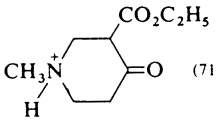
A. Intermolecular Ester Condensations

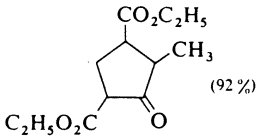
1[a] $CH_3(CH_2)_3CO_2C_2H_5 \xrightarrow{NaOEt} CH_3(CH_2)_3COCHCO_2C_2H_5$ (77%)
$CH_2CH_2CH_3$

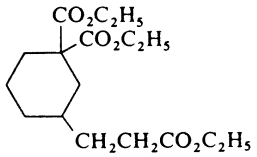
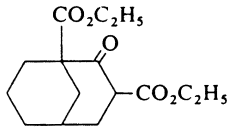
2[b] $CH_3CH_2CHCO_2C_2H_5 \xrightarrow{Ph_3C^-Na^+} CH_3CH_2CHC(=O)-CCO_2C_2H_5$ (63%)
CH_3 CH_3 CH_2CH_3 CH_3

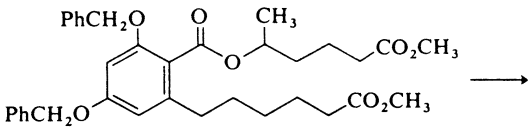
B. Cyclization of Diesters

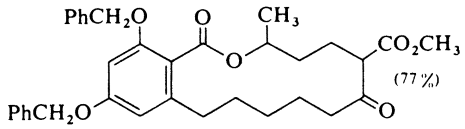
3[c] $C_2H_5O_2C(CH_2)_4CO_2C_2H_5 \xrightarrow{Na,\ toluene}$  (74–81%)

4[d] $CH_3-N(CH_2CH_2CO_2C_2H_5)(CH_2CH_2CO_2C_2H_5) \xrightarrow[benzene]{NaOEt} \xrightarrow{HCl}$  (71%)

5[e] $C_2H_5O_2CCH_2CH_2CH(CO_2C_2H_5)CHCH_3(CO_2C_2H_5) \xrightarrow{NaH}$  (92%)

6[f]  $\xrightarrow{NaH}$  (21%)

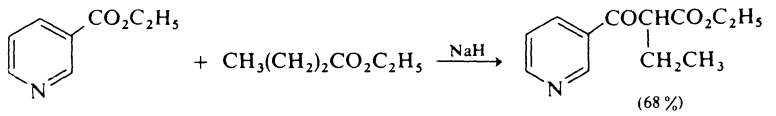
7[g] 

$\xrightarrow[\text{dilute solution}]{[(CH_3)_3Si]_2NNa}$  (77%)

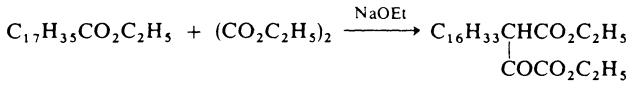
C. Mixed Ester Condensations

8[h] $(CH_2CO_2C_2H_5)_2 + (CO_2C_2H_5)_2 \xrightarrow{NaOEt} CH(COCO_2C_2H_5)(CH_2CO_2C_2H_5)CHCO_2C_2H_5$ (86–91%)

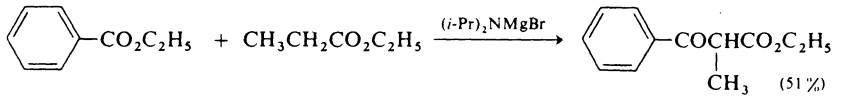
9[i]



10[j]

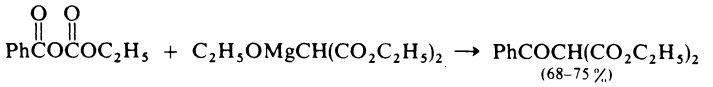


11[k]

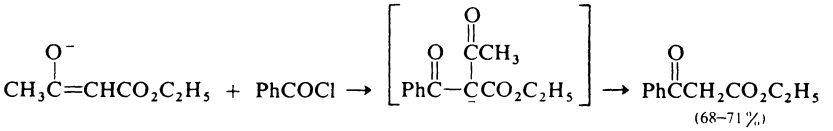


D. Acylation with Anhydrides and Acyl Halides

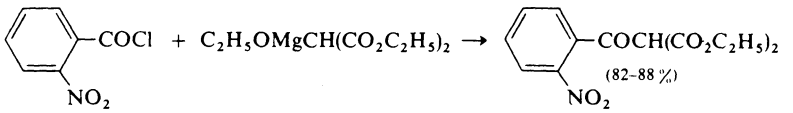
12[l]



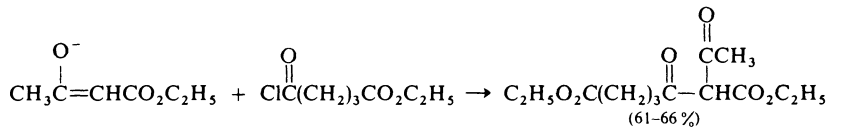
13[m]



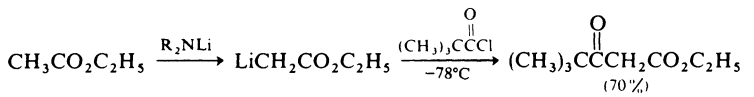
14[n]



15[o]

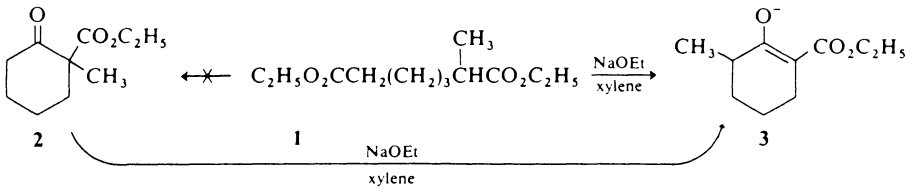


16[p]



a. R. R. Briese and S. M. McElvain, *J. Am. Chem. Soc.* **55**, 1697 (1933).
b. B. E. Hudson, Jr., and C. R. Hauser, *J. Am. Chem. Soc.* **63**, 3156 (1941).
c. P. S. Pinkney, *Org. Synth.* **II**, 116 (1943).
d. E. A. Prill and S. M. McElvain, *J. Am. Chem. Soc.* **55**, 1233 (1933).
e. M. S. Newman and J. L. McPherson, *J. Org. Chem.* **19**, 1717 (1954).
f. J. P. Ferris and N. C. Miller, *J. Am. Chem. Soc.* **85**, 1325 (1963).
g. R. N. Hurd and D. H. Shah, *J. Org. Chem.* **38**, 390 (1973).
h. E. M. Bottorff and L. L. Moore, *Org. Synth.* **44**, 67 (1964).
i. F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.* **72**, 1352 (1950).
j. D. E. Floyd and S. E. Miller, *Org. Synth.* **IV**, 141 (1963).
k. E. E. Royals and D. G. Turpin, *J. Am. Chem. Soc.* **76**, 5452 (1954).
l. J. A. Price and D. S. Tarbell, *Org. Synth.* **IV**, 285 (1963).
m. J. M. Straley and A. C. Adams, *Org. Synth.* **IV**, 415 (1963).
n. G. A. Reynolds and C. R. Hauser, *Org. Synth.* **IV**, 708 (1963).
o. M. Guha and D. Nasipuri, *Org. Synth.* **42**, 41 (1962).
p. M. W. Rathke and J. Deitch, *Tetrahedron Lett.*, 2953 (1971).

sodium and the alcohol liberated as the condensation proceeds. The driving force for the reaction is the formation of a stable enolate system. Since the reaction is easily reversible, it is governed by thermodynamic control, and in situations where more than one enolate is possible, the product derived from the more stable one will be formed. An example of this effect is the cyclization of the diester **1**.[33] Only **3** is formed, because **2** cannot be converted to a stable enolate. If **2**, synthesized by another means, is subjected to conditions of the cyclization, it is isomerized to **3** by way of the reversible condensation mechanism:



Successful mixed condensations of esters are subject to the same general restrictions as outlined in the consideration of mixed aldol condensations. One carbonyl compound must act preferentially as the acceptor and the other as the nucleophile. To compete with self-condensation of aliphatic esters, the carbonyl acceptor must be relatively electrophilic. The systems that have been commonly employed are esters of aromatic acids, formate esters, and oxalate esters. In each instance, these esters contain groups that are electron withdrawing relative to alkyl and do not possess enolizable hydrogens. They are therefore good electrophiles, but cannot function as the nucleophile. Some examples are shown in Section C of Scheme 2.6.

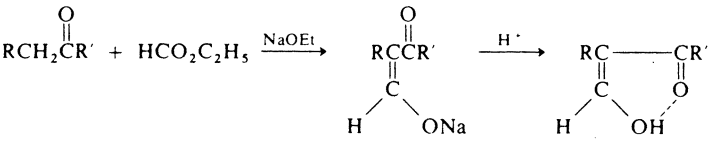
The preparation of diethyl benzoylmalonate (entry 12) represents the use of an acid anhydride, which is much more reactive than an ester, as the acylating agent. The reaction must be carried out in nonnucleophilic solvents to prevent solvolysis of the anhydride from competing with the desired reaction. Other limitations on the use of highly reactive acylating agents, such as acid anhydrides and acid chlorides, in reactions with enolates derive from the fact that O-acylation may be the dominant reaction. The magnesium salt of diethyl malonate (entries 12 and 14) has proved to be a satisfactory reagent in these reactions, in part because it is soluble in nonnucleophilic solvents such as ether. Low temperatures permit successful acylation of lithium enolates with acid chlorides (entry 16).

The acylation of enolates derived from ketones with esters is an important tool for enhancing reactivity and selectivity in synthetic modification of ketones. We saw in Chapter 1 that it is often difficult to *alkylate* simple ketone enolates efficiently. *Acylation*, however, occurs readily under the usual conditions. Examples

33. N. S. Vul'fson and V. I. Zaretskii, *J. Gen. Chem. USSR* **29**, 2704 (1959).

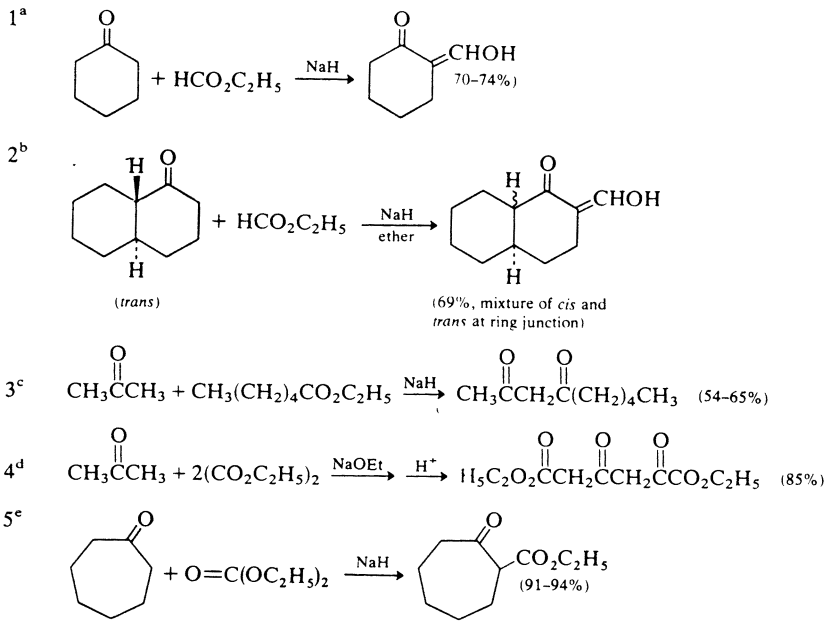
of the acylation of ketones by reaction of their enolates with esters are shown in Scheme 2.7. The products of these reactions are β-diketones, β-keto aldehydes, or β-keto esters, depending on the acylating agent used. These products, all of which contain a β-dicarbonyl unit, *can* be alkylated efficiently. Synthetic advantage has been taken of this fact, as we shall see shortly.

The most common transformation involving acylation of ketone enolates is their *formylation* by reaction with ethyl formate.



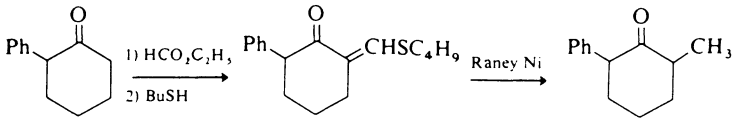
Since the β-ketoaldehydes that result from acidification exist with the formyl group extensively enolized, the compounds are often referred to as *hydroxymethylene derivatives*. The formation of the product is governed by thermodynamic control; therefore, the dominant product expected from unsymmetrical ketones can be

Scheme 2.7. Acylation of Ketones with Esters



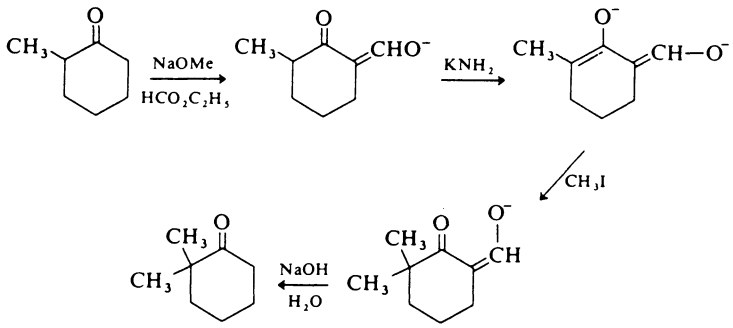
a. C. Ainsworth, *Org. Synth.* **IV**, 536 (1963).
b. P. H. Lewis, S. Middleton, M. J. Rosser, and L. E. Stock, *Aust. J. Chem.* **32**, 1123 (1979).
c. N. Green and F. B. La Forge, *J. Am. Chem. Soc.* **70**, 2287 (1948); F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.* **72**, 1352 (1950).
d. E. R. Riegel and F. Zwilgmeyer, *Org. Synth.* **II**, 126 (1943).
e. A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, *Org. Synth.* **47**, 20 (1967).

predicted on the basis of considerations of relative stability. Once formed, hydroxymethylene compounds have several synthetic uses. A hydroxymethylene group can be converted to methyl via reaction with a mercaptan followed by reduction.[34]



Aluminum hydride reduction of sodium enolates of hydroxymethylene ketones gives hydroxymethyl ketones.[35]

A sequence for directing an alkylation to a monosubstituted site has been developed; the sequence involves a dianion intermediate[36]:



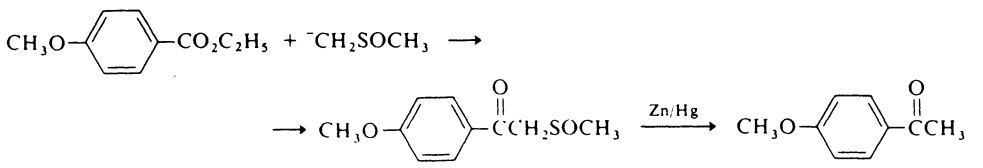
On the other hand, if an unsymmetrical ketone is to be alkylated at the site where acylation would be favored, the hydroxymethylene derivative can be directly subjected to alkylation. Condensation with ethyl carbonate or diethyl oxalate before alkylation can also serve the purpose of increasing reactivity at the α position of a ketone. The resulting β-keto esters are readily alkylated by the procedures described in the previous chapter.

Related synthetic intermediates are the β-keto sulfoxides, which are prepared by acylation of dimethyl sulfoxide anion with esters[37]:

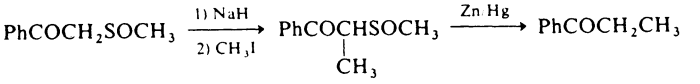
$$\underset{\text{O}}{\overset{\|}{\text{RCOR}'}} + {}^{-}\text{CH}_2\underset{\text{O}}{\overset{\|}{\text{S}}}\text{CH}_3 \rightleftharpoons \text{RC}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{HS}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{H}_3 + \text{R}'\text{OH}$$

Mechanistically, this reaction is similar to an ester condensation and results in the formation of a quite stable carbanion. These substances are of general synthetic

34. a. R. E. Ireland and J. A. Marshall, *J. Org. Chem.* **27**, 1615 (1962).
b. J. D. Metzger, M. W. Baker, and R. J. Morris, *J. Org. Chem.* **37**, 789 (1972).
35. E. J. Corey and D. E. Cane, *J. Org. Chem.* **36**, 3070 (1971).
36. S. Boatman, T. M. Harris, and C. R. Hauser, *Org. Synth.* **48**, 40 (1968).
37. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **87**, 1345 (1965); H. D. Becker, G. J. Mikol, and G. A. Russel, *J. Am. Chem. Soc.* **85**, 3410 (1963).



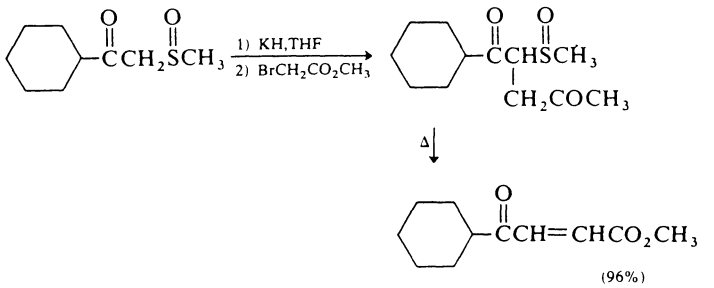
Ref. 38a



Ref. 38b

utility because the molecule can be reductively cleaved with removal of the methylsulfinyl substituent. Thus, a two-step sequence involving condensation and reduction converts esters to methyl ketones. If an alkylation step is included, higher ketones can be prepared. Dimethyl sulfone can be subjected to a similar sequence of reactions.[39]

Alkylation of β-keto sulfoxides gives intermediates which can undergo thermal elimination to form α,β-unsaturated ketones[40]:



(96%)

(The thermal elimination of sulfoxides will be discussed in Chapter 7.)

2.5. The Wittig and Related Carbonyl Olefination Reactions

Phosphorus ylides are an important group of nucleophilic carbon species. An ylide is a molecule that has a contributing Lewis structure with opposite charges on adjacent atoms when these atoms have octets of electrons. While this definition is broad enough to include a number of other classes of compounds, we will restrict the following discussion to ylides in which a negative charge is on carbon. The synthetic applications of ylides are particularly significant when the positively charged atom is a second-row element, such as phosphorus or sulfur.

38. a. G. A. Russell and G. J. Mikol, *J. Am. Chem. Soc.* **88**, 5498 (1966).
b. P. G. Gassman and G. D. Richmond, *J. Org. Chem.* **31**, 2355 (1966).
39. a. H. O. House and J. K. Larson, *J. Org. Chem.* **33**, 61 (1968).
b. For a review of sulfone chemistry, see P. D. Magnus, *Tetrahedron* **33**, 2019 (1977).
40. P. A. Bartlett, *J. Am. Chem. Soc.* **98**, 3305 (1976).

Phosphorus ylides are usually stable, albeit highly reactive, compounds and can be represented by two limiting Lewis structures. These are sometimes referred to as the *ylide* and *ylene* form. Using $(CH_3)_3PCH_2$ (trimethylphosphonium methylide) as an example, these two forms can be illustrated as follows:

$$\underset{\text{ylide}}{(CH_3)_3\overset{+}{P}-CH_2^-} \leftrightarrow \underset{\text{ylene}}{(CH_3)_3P=CH_2}$$

The stability of phosphorus ylides is ascribed to resonance between the two Lewis structures in which the ylene form implies electron donation into phosphorus 3*d* orbitals. Recent careful ^1H, ^{13}C, and ^{31}P nmr spectroscopic studies of trimethylphosphonium methylide, however, are more consistent with the dipolar ylide structures having an sp^2-hybridized carbon and sp^3-hybridized phosphorus and suggest only a minor contribution from the ylene structure.[41] Although ylides had been known for many years, their synthetic potential was not appreciated until G. Wittig and his associates at the University of Heidelberg established their utility in olefin synthesis.[42] The reaction of a phosphorus ylide with an aldehyde or ketone provides a means of introducing a carbon–carbon double bond in place of a carbon–oxygen double bond, as shown by the equation:

$$R_3\overset{+}{P}-\overset{-}{C}R'_2 + R''_2C=O \rightarrow R''_2C=CR'_2 + R_3P=O$$

The mechanism originally proposed is one of nucleophilic addition of the ylide carbon to the carbonyl group to yield a dipolar intermediate (a betaine), followed by elimination of phosphine oxide. The elimination might be concerted, or it might take place via a four-membered oxaphosphetane intermediate.[43] Alternatively, this oxaphosphetane may be formed directly by a cycloaddition reaction of the ylide and the carbonyl compound, completely bypassing the betaine as an intermediate.[44] The formation of oxaphosphetanes at low temperature, and their fragmentation on warming, has been clearly demonstrated, while the evidence for authentic betaine intermediates has been questioned.[45]

$$R_3\overset{+}{P}-\overset{-}{C}R'_2 + R''_2C=O \longrightarrow \left[\begin{array}{l} \rightarrow R_3\overset{+}{P}-CR'_2 \\ \qquad\quad | \\ \qquad \overset{-}{O}-CR''_2 \\ \text{(betaine intermediate)} \\ \qquad\quad \downarrow \\ \rightarrow R_3P-CR'_2 \\ \qquad\quad | \\ \qquad O-CR''_2 \end{array}\right] \rightarrow R_3P=O + R''_2C=CR'_2$$

(oxaphosphetane intermediate)

41. H. Schmidbaur, W. Buchner, and D. Schentzow, *Chem. Ber.* **106**, 1251 (1973).
42. For a general review of the Wittig reaction, see A. Maercker, *Org. React.* **14**, 270 (1965).
43. C. Trindle, J.-T. Hwang, and F. A. Carey, *J. Org. Chem.* **38**, 2664 (1973).
44. a. E. Vedejs and K. A. J. Snoble, *J. Am. Chem. Soc.* **95**, 5778 (1973).
b. For a theoretical study, see R. Holler and H. Lischkea, *J. Am. Chem. Soc.* **102**, 4632 (1980).
45. E. Vedejs, G. P. Meier, and K. A. J. Snoble, *J. Am. Chem. Soc.* **103**, 2823 (1981).

Phosphorus ylides are usually prepared by deprotonation of phosphonium salts. The phosphonium salts most commonly employed are alkyltriphenylphosphonium halides prepared by the reaction of triphenylphosphine and alkyl halides:

$$Ph_3P + RCH_2X \rightarrow Ph_3\overset{+}{P}-CH_2R\ X^-$$
$$X = I, Br, \text{ or } Cl$$

The alkyl halide must be one (primary or secondary) which is reactive toward S_N2 displacement. Alkyltriphenylphosphonium halides are only weakly acidic. Deprotonation can be carried out with organolithium reagents; *n*-butyllithium in tetrahydrofuran is frequently used. Deprotonation using the sodium salt of dimethyl sulfoxide in dimethyl sulfoxide as the solvent is probably the most popular means of converting phosphonium salts to ylides.[46] The ylide once formed is not normally isolated, but is treated directly with the carbonyl compound. Ylides of this type, where R is hydrogen, alkyl, or aryl, are quite reactive toward aldehydes and ketones.

$$Ph_3\overset{+}{P}CH_2R \xrightarrow[DMSO]{NaH} Ph_3P{=}CHR$$

β-Ketophosphonium salts are considerably more acidic than alkylphosphonium salts and can be converted to ylides with relatively weak bases. The resulting ylides are stabilized by enolate resonance and are substantially less reactive. Vigorous conditions are often required to bring about their reaction with ketones. Modifications of the Wittig reaction to be discussed in succeeding sections are often more convenient for synthesis of olefins bearing electron-withdrawing substituents.

$$\overset{O}{\overset{\|}{RC}}-\overset{-}{C}H-\overset{+}{P}R'_3 \leftrightarrow \overset{O^-}{\overset{|}{RC}}{=}CH-\overset{+}{P}R'_3 \leftrightarrow \overset{O}{\overset{\|}{RC}}-CH{=}PR'_3$$

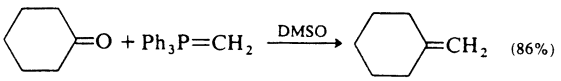
The stereoselectivity of Wittig olefination reactions is variable and depends strongly on the nature of the ylide—whether it is a "stabilized ylide" or an "unstabilized" one—and on how the ylide is prepared—whether it exists as a "salt-free" solution of the ylide or as an ylide–lithium halide complex.

The customary generalization is that unstabilized ylides react with aldehydes to give predominantly *Z*-alkenes (*cis*), while stabilized ylides give predominantly *E*-alkenes (*trans*).[47] Unstabilized ylides include the typical alkylidenetriphenylphosphoranes shown in entries 1–5 of Scheme 2.8. Their tendency to form *Z*-alkenes can be very high, especially when conditions are chosen so that lithium salts are not present in the reaction medium. Sodium amide (entry 3) and the sodium salt of hexamethyldisilazane (entry 5) are convenient strong bases for the preparation of salt-free solutions of ylides. When ethylidenetriphenylphosphorane is prepared from ethyltriphenylphosphonium iodide and *n*-butyllithium (entry 4), the high

46. R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.* **28**, 1128 (1963).
47. M. Schlosser, *Top. Stereochem.* **5**, 1 (1970).

Scheme 2.8. The Wittig Reaction

1[a] $Ph_3\overset{+}{P}CH_3\ I^- \xrightarrow[DMSO]{NaCH_2S(O)CH_3} Ph_3P{=}CH_2$



2[b] $Ph_3\overset{+}{P}CH_2CH_2CH_2CH_2CH_3\ Br^- \xrightarrow[DMSO]{n\text{-}BuLi} Ph_3P{=}CHCH_2CH_2CH_2CH_3$

$CH_3\overset{O}{\overset{\|}{C}}CH_3 + Ph_3P{=}CHCH_2CH_2CH_2CH_3 \xrightarrow{DMSO} (CH_3)_2C{=}CHCH_2CH_2CH_2CH_3$ (56%)

3[c] $CH_3CH_2\overset{+}{P}Ph_3\ Br^- \xrightarrow[NH_3]{NaNH_2} CH_3CH{=}PPh_3$

$C_6H_5CHO + CH_3CH{=}PPh_3 \xrightarrow[benzene]{} C_6H_5CH{=}CHCH_3$ (98% yield; 87% *cis*)

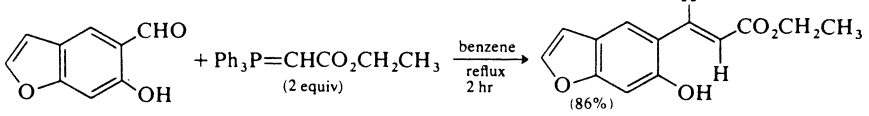
4[c] $CH_3CH_2\overset{+}{P}Ph_3\ I^- \xrightarrow{n\text{-}BuLi} CH_3CH{=}PPh_3$

$C_6H_5CHO + CH_3CH{=}PPh_3 \xrightarrow[benzene]{LiI} C_6H_5CH{=}CHCH_3$ (76% yield; 58% *cis*)

5[d] $CH_3CH_2CH_2CH_2CH_2\overset{+}{P}Ph_3\ Br^- \xrightarrow[THF]{Na^+N(SiMe_3)_2} CH_3CH_2CH_2CH_2CH{=}PPh_3$

$HC\overset{O}{\overset{\|}{C}}(CH_2)_7CH_2OAc + CH_3CH_2CH_2CH_2CH{=}PPh_3 \rightarrow CH_3(CH_2)_3CH{=}CH(CH_2)_7CH_2OAc$ (79% yield; 98% *cis*)

6[e] $Ph_3\overset{+}{P}CH_2CO_2CH_2CH_3\ Br^- \xrightarrow[H_2O]{NaOH} Ph_3P{=}CHCO_2CH_2CH_3$ (stable, isolable ylide)

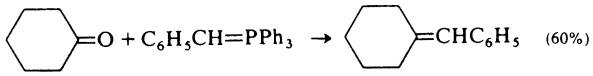


7[f] $C_6H_5CHO + Ph_3P{=}CHCO_2CH_2CH_3 \xrightarrow{EtOH} C_6H_5CH{=}CHCO_2CH_2CH_3$ (77% yield; only *trans*)

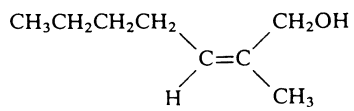
8[g] $C_6H_5CH_2\overset{+}{P}Ph_3\ Cl^- \xrightarrow[ether]{PhLi} C_6H_5CH{=}PPh_3$

$C_6H_5CHO + C_6H_5CH{=}PPh_3 \rightarrow C_6H_5CH{=}CHC_6H_5$ (82% yield; 70% *trans*)

9[f]



10[b] $CH_3CH_2CH_2CH_2CHO + CH_3CH{=}PPh_3 \xrightarrow[3)\ CH_2O,\ 25°C]{1)\ LiBr,\ THF,\ -78°C;\ 2)\ BuLi}$



a. R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.* **28**, 1128 (1963).
b. U. T. Bhalerao and H. Rapoport, *J. Am. Chem. Soc.* **93**, 4835 (1971).
c. M. Schlosser and K. F. Christmann, *Justus Liebig's, Ann. Chem.* **708**, 1 (1967).
d. H. J. Bestmann, K. H. Koschatzky, and O. Vostrowsky, *Chem. Ber.* **112**, 1923 (1979).
e. Y. Y. Liu, E. Thom, and A. A. Liebman, *J. Heterocycl. Chem.* **16**, 799 (1979).
f. G. Wittig and W. Haag, *Chem Ber.* **88**, 1654 (1955).
g. G. Wittig and U. Schöllkopf, *Chem Ber.* **87**, 1318 (1954).

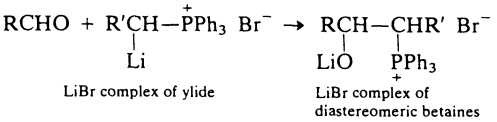
stereoselectivity is lost and the Z/E ratio is only 58:42. Lithium iodide, produced by deprotonation of the phosphonium salt, possesses significant solubility in benzene and affects the stereoselectivity of Wittig reactions.

Stabilized ylides are those which bear a carbanion-stabilizing substituent on the negatively charged carbon of the ylide. Stabilized ylides such as (carboethoxymethylidene)triphenylphosphorane (entries 6 and 7) react with aldehydes to give exclusively *trans*-alkenes. Stabilized ylides react sluggishly or not at all with ketones.

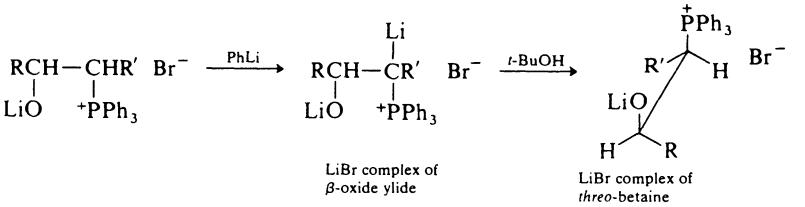
Benzylidenetriphenylphosphorane (entries 8 and 9) occupies a borderline position between stabilized and nonstabilized ylides. It will react with both aldehydes and ketones. Mixtures of *cis*- and *trans*-stilbene result from the reaction of benzylidenetriphenylphosphorane with benzaldehyde.

Inasmuch as there remain important unanswered questions about the mechanism of the Wittig olefination reaction we will not attempt a detailed rationalization of its stereoselectivity. Indeed, as has been pointed out in a thoughtful article on this subject, "there is probably no single unifying mechanism for all Wittig reactions."[45] The empirical generalization concerning the preference for formation of *cis*-alkenes from nonstabilized ylides under salt-free conditions and *trans*-alkenes from stabilized ylides serves as a good rule of thumb. A mechanistic explanation based on reversible betaine formation has been offered.[47]

The reaction of nonstabilized ylides with aldehydes can be induced to yield *trans*-alkenes with high stereoselectivity by a procedure known as the *Schlosser modification* of the Wittig reaction.[48] In this procedure, the ylide is generated as a lithium halide complex and allowed to react with an aldehyde at low temperature, presumably forming a mixture of diastereomeric betaine–lithium halide complexes. At the temperatures under which the addition is carried out, fragmentation to an alkene and triphenylphosphine oxide does not occur. This complex is then treated

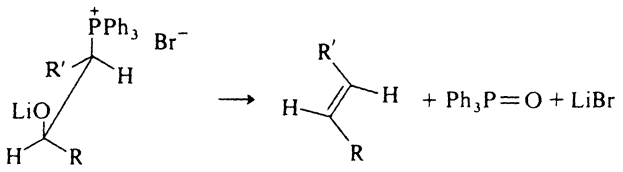


with an equivalent of strong base such as phenyllithium to form a β-oxido ylide. Addition of *tert*-butyl alcohol protonates the β-oxido ylide stereoselectively to give

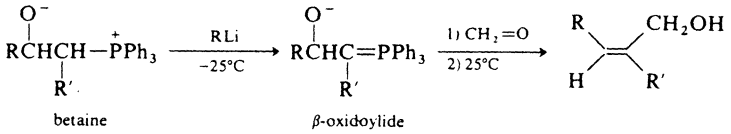


the more stable *threo*-betaine (as a lithium halide complex). Warming the solution causes the *threo*-betaine-lithium halide complex to fragment to give *trans*-alkene.

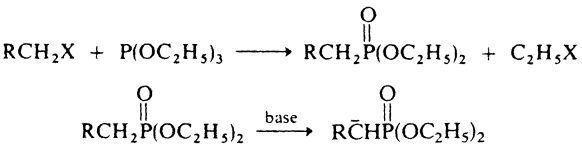
48. M. Schlosser, and K.-F. Christmann, *Justus Liebig's Ann. Chem.* **708**, 1 (1967); M. Schlosser, K.-F. Christmann, and A. Piskala, *Chem. Ber.* **103**, 2814 (1970).



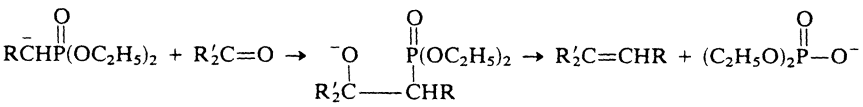
A useful extension of this method is one in which the β-oxido ylide intermediate, instead of being protonated, is allowed to react with formaldehyde. The β-oxido ylide and formaldehyde react to give, on warming, an allylic alcohol. Entry 10 in Scheme 2.8 is an example of this reaction. The reaction is valuable for the stereoselective synthesis of Z-allylic alcohols from aldehydes.[49]



An important complement to Wittig olefination is found in the reaction of phosphonate carbanions with carbonyl compounds.[50] Phosphonate carbanions are generated by treating alkylphosphonic esters with bases such as sodium hydride, *n*-butyllithium, or lithium ethoxide. The alkylphosphonic esters are made by the reaction of an alkyl halide, preferably primary, with a phosphite ester. Phosphonate



carbanions are more nucleophilic than an analogous ylide and, when R is a carbanion-stabilizing substituent, react readily with aldehydes and ketones to give alkenes. The reaction exhibits a strong preference for the formation of *trans*-alkenes.



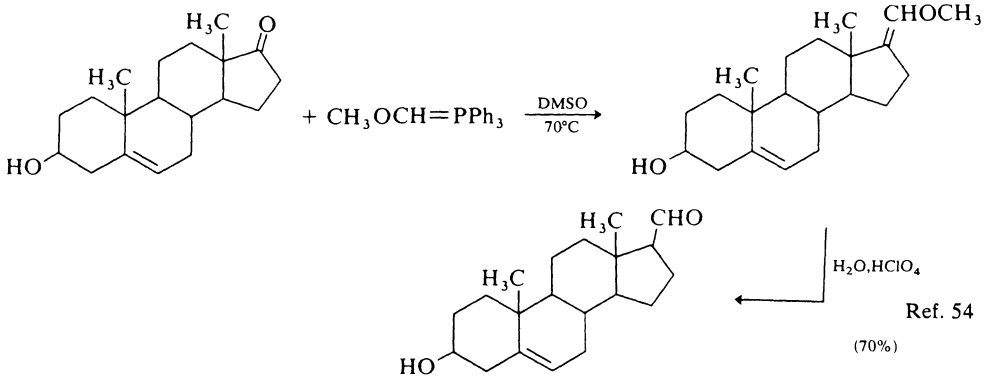
When R is a simple alkyl group, addition of the phosphonate carbanion to the carbonyl compound occurs but the intermediate does not undergo elimination.[51] Since the reaction sequence results in the conversion of an aldehyde or ketone to an alkene, as does the Wittig reaction, but works well when electron-withdrawing

49. E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.* **92**, 226 (1970); E. J. Corey, H. Yamamoto, D. K. Herron, and K. Achiwa, *J. Am. Chem. Soc.* **92**, 6635 (1970); E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.* **92**, 6636 (1970); E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.* **92**, 6637 (1970); E. J. Corey, J. I. Shulman, and H. Yamamoto, *Tetrahedron Lett.*, 447 (1970).
50. For reviews, see J. Boutagy and R. Thomas, *Chem. Rev.* **74**, 87 (1974); W. S. Wadsworth, Jr., *Org. React.* **25**, 73 (1977).
51. E. J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.* **88**, 5654 (1966).

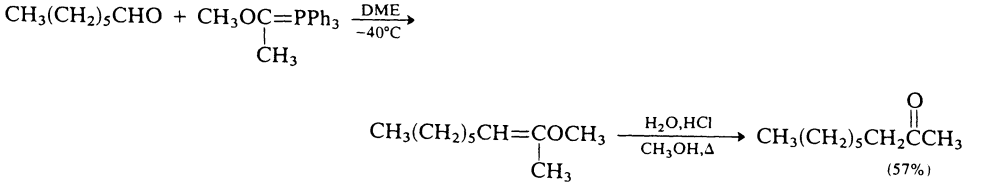
substituents are at the reactive site while the Wittig reaction does not, olefination through the use of phosphonate carbanions plays a significant role in organic synthesis. Scheme 2.9 lists some olefination reactions employing phosphonate carbanions.

Intramolecular olefinations based on ketophosphonate cyclizations carried out under conditions of high dilution have been utilized in macrocycle synthesis (entries 6 and 7, Scheme 2.9).

The synthetic utility of carbonyl olefination reactions can be expanded beyond alkene synthesis through the use of functionalized ylides and functionalized phosphonate carbanions. Thus, methoxymethylene[52] and phenoxymethylene[53] ylides lead to vinyl ethers which can be readily hydrolyzed to aldehydes.



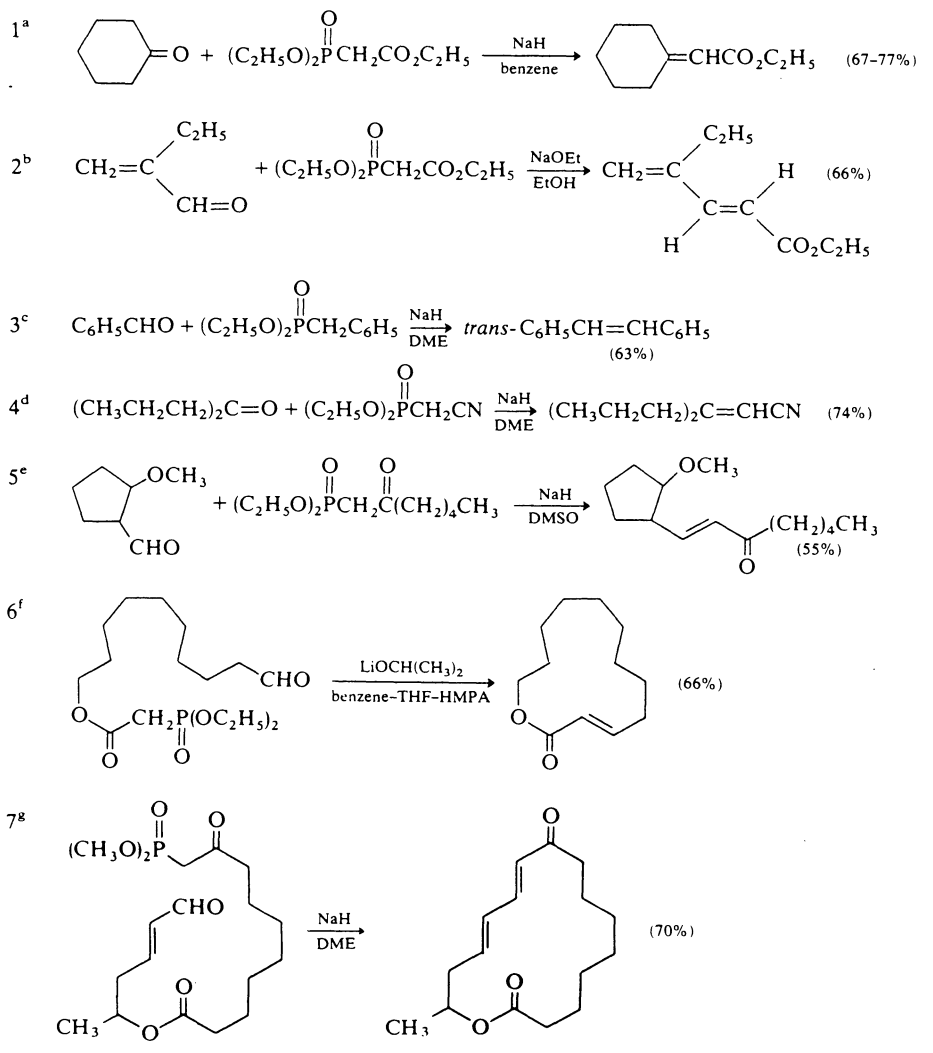
Methyl ketones have been prepared by an analogous reaction.



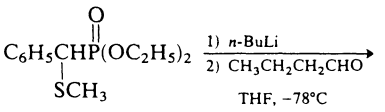
Similarly, vinyl thioethers may be prepared using the appropriately functionalized phosphonate carbanion. Although vinyl thioethers are normally more difficult to hydrolyze to carbonyl compounds than are enol ethers, a number of methods are available which permit this conversion.[56]

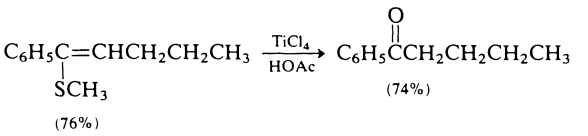
52. S. G. Levine, *J. Am. Chem. Soc.* **80**, 6150 (1958).
53. G. Wittig, W. Boll, and K. H. Kruck, *Chem. Ber.* **95**, 2514 (1962).
54. S. Danishefsky, K. Nagasawa, and N. Wang, *J. Org. Chem.* **40**, 1989 (1975).
55. D. R. Coulsen, *Tetrahedron Lett.*, 3323 (1964).
56. These methods are reviewed by B.-T. Grobel and D. Seebach, *Synthesis*, 357 (1977).

Scheme 2.9. Carbonyl Olefination Using Phosphonate Carbanions



a. W. S. Wadsworth, Jr. and W. D. Emmons, *Org. Synth.* **45**, 44 (1965).
b. R. J. Sundberg, P. A. Buckowick, and F. O. Holcombe, *J. Org. Chem.* **32**, 2938 (1967).
c. W. S. Wadsworth, Jr. and W. D. Emmons, *J. Am. Chem. Soc.* **83**, 1733 (1961).
d. J. A. Marshall, C. P. Hagan, and G. A. Flynn, *J. Org. Chem.* **40**, 1162 (1975).
e. N. Finch, J. J. Fitt, and I. H. S. Hsu, *J. Org. Chem.* **40**, 206 (1975).
f. G. Stork and E. Nakamura, *J. Org. Chem.* **44**, 4010 (1979).
g. K. C. Nicolaou, S. P. Seitz, M. R. Pavia, and N. A. Petasis, *J. Org. Chem.* **44**, 4010 (1979).

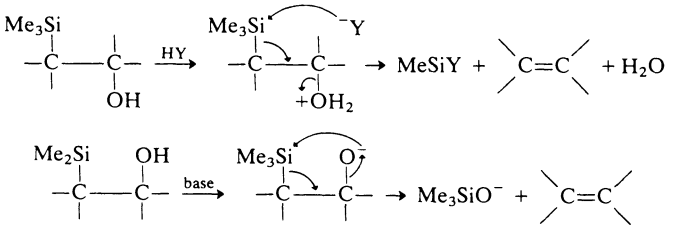




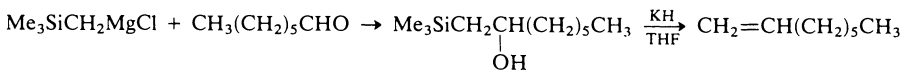
Ref. 57

2.6. Carbonyl Olefination Using α-Trimethylsilyl-Substituted Organolithium Reagents

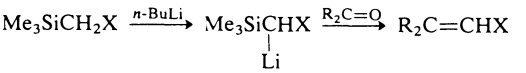
β-Hydroxyalkyltrimethylsilanes are converted smoothly to alkenes in either acidic or basic solution.[58] These elimination reactions provide the basis for a wide



variety of transformations which begin with the nucleophilic addition of a trimethylsilyl-substituted organometallic reagent to an aldehyde or ketone. In the simplest examples of this process, addition of the Grignard reagent of chloromethyltrimethylsilane to an aldehyde or ketone leads to a methylenation method which is a useful alternative to the Wittig reaction.[59]



Organolithium reagents of the type $Me_3SiCH(Li)X$, where X is a carbanion-stabilizing substituent, can be prepared by deprotonation of Me_3SiCH_2X with *n*-butyllithium. These reagents react with aldehydes and ketones to give heteroatom-substituted olefins directly. No additional elimination step is necessary since fragmentation of the intermediate occurs spontaneously under the reaction conditions. Examples of the preparation of functionally substituted alkenes using α-trimethylsilyl-substituted organolithium reagents are presented in Scheme 2.10.



57. M. Mikolajczyk, S. Grezejsczak, A. Chefczynaska, and A. Zatoski, *J. Org. Chem.* **44**, 2967 (1979).
58. P. F. Hudrlik and D. Peterson, *J. Am. Chem. Soc.* **97**, 1464 (1975).
59. D. J. Peterson, *J. Org. Chem.* **33**, 780 (1968).

Scheme 2.10. Carbonyl Olefination Using Trimethylsilyl-substituted Organolithium Reagents

1[a] $Me_3SiCHCO_2C_2H_5$ (Li) + cyclohexanone → $=CHCO_2C_2H_5$ (94%)

2[b] $Me_3SiCHCO_2Li$ (Li) + cyclopentanone → $=CHCO_2H$ (84%)

3[c] $Me_3SiCHCN$ (Li) + $C_6H_5CH=CHCHO$ → $C_6H_5CH=CHCH=CHCN$ (95%)

4[d] $Me_3SiCHSC_6H_5$ (Li) + $(CH_3)_3CCCH_3$ (O) → $C_6H_5SCH=C(CH_3)C(CH_3)_3$ (55%)

5[e] $Me_3SiCHSC_6H_5$ (Li, O) + $C_6H_5CH=CHCHO$ → $C_6H_5CH=CHCH=CHSC_6H_5$ (O) (70%)

6[f] 2-lithio-2-trimethylsilyl-1,3-dithiane + CH_3CH_2CHO → $CH_3CH_2CH=$ dithiane (75%)

7[d] $Me_3SiCHP(OC_2H_5)_2$ (Li, O) + $(CH_3)_2CHCHO$ → $(CH_3)_2CHCH=CHP(OC_2H_5)_2$ (O) (92%)

8[g] $Me_3SiC(SeC_6H_5)_2$ (Li) + C_6H_5CHO → $C_6H_5CH=C(SeC_6H_5)_2$ (75%)

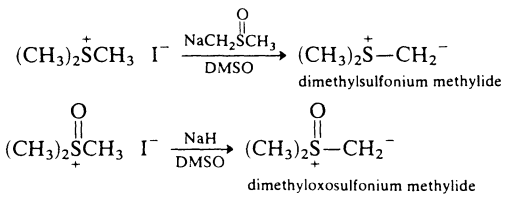
a. K. Shimoji, H. Taguchi, K. Oshima, H. Yamanoto, and H. Nozaki, *J. Am. Chem. Soc.* **96**, 1620 (1974).
b. P. A. Grieco, C. L. J. Wang, and S. D. Burke, *J. Chem. Soc. Chem. Commun.*, 537 (1975).
c. I. Matsuda, S. Murata, and Y. Ishii, *J. Chem. Soc. Perkin Trans. 1*, 26 (1979).
d. F. A. Carey and A. S. Court, *J. Org. Chem.* **37**, 939 (1972).
e. F. A. Carey and O. Hernandez, *J. Org. Chem.* **38**, 2670 (1973).
f. D. Seebach, M. Kolb, and B.-T. Grobel, *Chem Ber.* **106**, 2277 (1973).
g. B.-T. Grobel and D. Seebach, *Chem Ber.* **110**, 852 (1977).

2.7. Sulfur Ylides and Related Species as Nucleophiles[60]

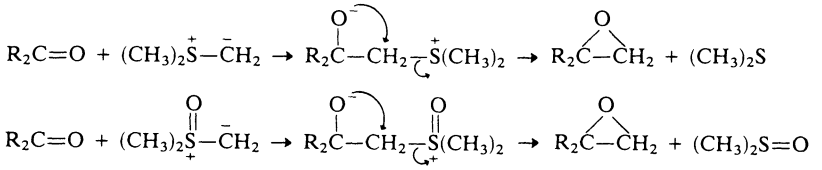
Next to phosphorus ylides in importance as synthetic reagents are sulfur ylides, especially dimethylsulfonium methylide and dimethyloxosulfonium methylide.[61] These sulfur ylides are prepared by deprotonation of the appropriate sulfonium

60. a. B. M. Trost and L. S. Melvin, Jr., *Sulfur Ylides*, Academic Press, New York (1975).
b. E. Block, *Reactions of Organosulfur Compounds*, Academic Press, New York (1978).
61. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **87**, 1353 (1965).

salts, both of which are commercially available.

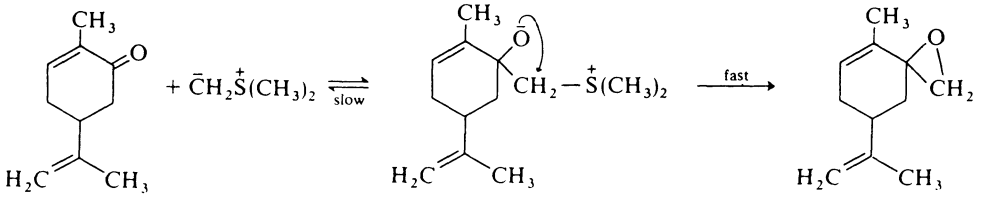


There is an important difference between the reactions of these sulfur ylides and the analogous phosphorus ylides with carbonyl compounds. Whereas phosphorus ylides react with aldehydes and ketones to yield alkenes, dimethylsulfonium methylide and dimethyloxosulfonium methylide yield epoxides. Instead of a four-center elimination in the zwitterionic intermediate, intramolecular nucleophilic displacement by oxygen occurs.



Examples of the use of dimethylsulfonium methylide and dimethyloxosulfonium methylide in the preparation of epoxides by methylene transfer are listed in Scheme 2.11. Entries 1–4 illustrate epoxide formation with simple aldehydes and ketones. Dimethylsulfonium methylide is both more reactive and less stable than dimethyloxosulfonium methylide so it is generated and used at a lower temperature.

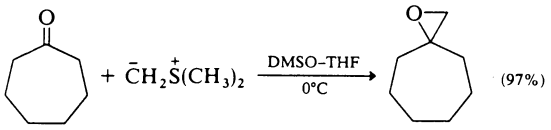
A sharp distinction between the two ylides emerges in their reactions with α,β-unsaturated carbonyl groups. Dimethylsulfonium methylide yields epoxides, while dimethyloxosulfonium methylide reacts by conjugate addition to give cyclopropanes (entries 5 and 6). It appears that the reason for the difference in their behavior lies in the relative rates of the two reactions available to the betaine intermediate: (a) reversal to starting materials and (b) intramolecular nucleophilic displacement.[62] Presumably, the addition to the carbonyl group is faster than conjugate addition. Dimethylsulfonium methylide reacts with carvone (entry 5) in the normal fashion to give epoxide. Dimethyloxosulfonium methylide is a less basic,



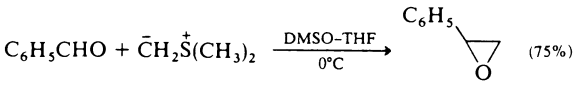
62. C. R. Johnson, C. W. Schroeck, and J. R. Shanklin, *J. Am. Chem. Soc.* **95**, 7424 (1973).

Scheme 2.11. Reactions

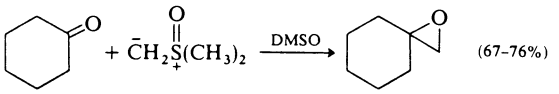
1[a]



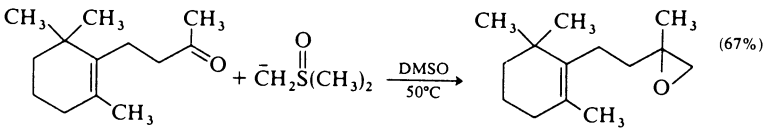
2[a]



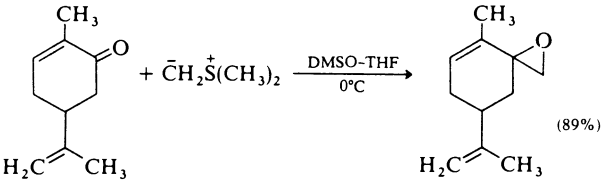
3[b]



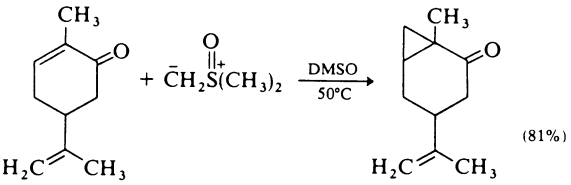
4[c]



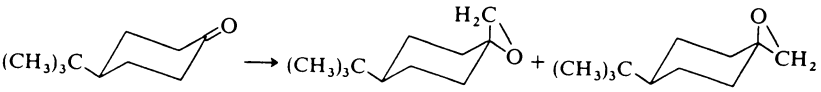
5[a]



6[a]



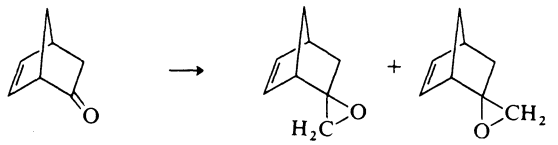
7[a]



ylide: $\bar{C}H_2\overset{+}{S}(CH_3)_2$	THF, 0°C	83%	17%
ylide: $\bar{C}H_2\overset{O}{\overset{\|}{S}}(CH_3)_2$	THF, 65°C	not formed	only product

more highly stabilized ylide and its addition to the carbonyl group is significantly more reversible. The reverse of the addition step is faster than intramolecular nucleophilic displacement in the intermediate. Consequently, nucleophilic addition

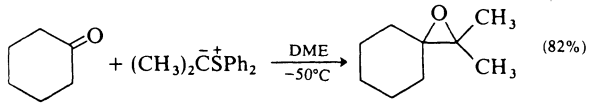
8[d]



ylide: $\bar{C}H_2\overset{+}{S}(CH_3)_2$ —DMSO-THF, 0°C→ 6% 94%

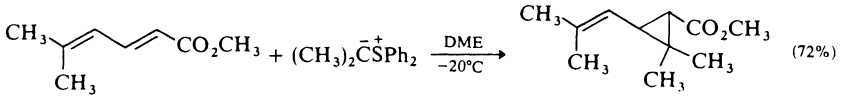
ylide: $\bar{C}H_2\overset{O}{\overset{\|}{S}}(CH_3)_2$ —DMSO, 60°C→ 65% 27%

9[e]



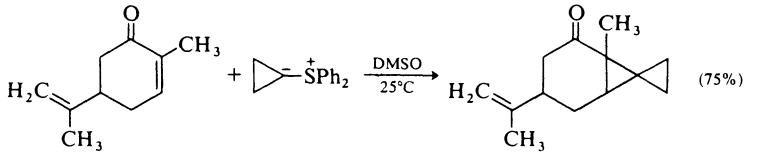
(82%)

10[f]



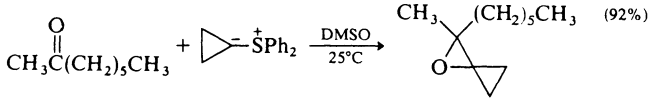
(72%)

11[g]



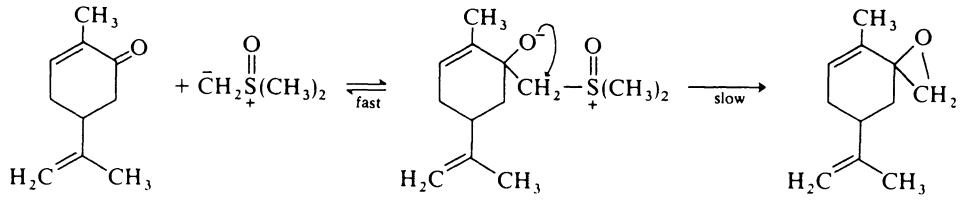
(75%)

12[h]

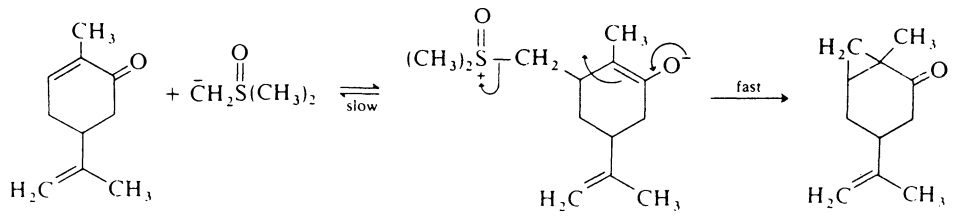


(92%)

a. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **87**, 1353 (1965).
b. E. J. Corey and M. Chaykovsky, *Org. Synth.* **49**, 78 (1969).
c. M. G. Franchebond, O. Shimomura, R. K. Hill, and F. H. Johnson, *Tetrahedron Lett.* 3951 (1969).
d. R. S. Bly, C. M. Du Bose, Jr., and G. B. Konizer, *J. Org. Chem.* **33**, 2188 (1968).
e. E. J. Corey, M. Jautelat, and W. Oppolzer, *Tetrahedron Lett.* 2325 (1967).
f. E. J. Corey and M. Jautelat, *J. Am. Chem. Soc.* **89**, 3112 (1967).
g. B. M. Trost and M. H. Bogdanowicz, *J. Am. Chem. Soc.* **95**, 5307 (1973).
h. B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.* **95**, 5311 (1973).

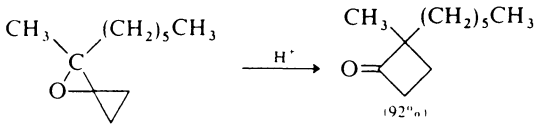


of the ylide to the carbon–carbon double bond occurs to give an intermediate enolate ion in which nucleophilic attack by carbon gives the cyclopropane-containing product.

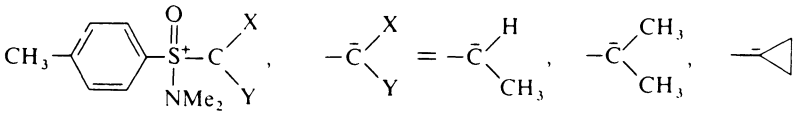


Another difference between dimethylsulfonium methylide and dimethyloxosulfonium methylide has to do with the stereoselectivity of epoxide formation. Dimethylsulfonium methylide tends to add to ketones from the less-hindered side while dimethyloxosulfonium methylide tends to give the more stable epoxide (entries 7 and 8). It may be presumed that the stereoselectivity of epoxide formation is influenced by the reversibility of the addition step with dimethylsulfonium methylide giving the product of kinetically controlled addition and dimethyloxosulfonium ylide the product of thermodynamically controlled addition.[62]

A limited number of ylides are available which allow the transfer of more complex alkylidene units, such as an isopropylidene group (entries 9 and 10) or a cyclopropylidene group (entries 11 and 12). The oxaspiropentanes formed by reaction of aldehydes and ketones with diphenylsulfonium cyclopropylide are useful intermediates in a number of transformations such as acid-catalyzed isomerization to cyclobutanones.[63]



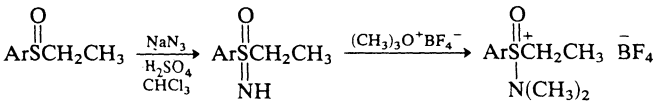
Aside from the methylide and cyclopropylide, however, conditions for generating and using sulfonium ylides are rather exacting and the ylides tend to be stable only at low temperature. Another class of reagents, based on ylides and carbanions derived from alkyl sulfoximines, offer greater versatility in bringing about alkylidene transfer reactions.[64] Thus, (dimethylamino)-*p*-tolyloxosulfonium ylides react with aldehydes and ketones to yield epoxides and with α,β-unsaturated carbonyl compounds to give cyclopropanes. A variety of alkylidene groups have been transferred

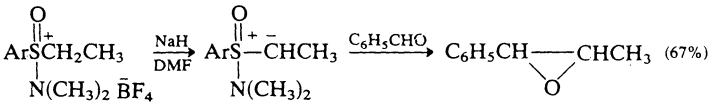


63. B. M. Trost and M. H. Bogdanowicz, *J. Am. Chem. Soc.* **95**, 5321 (1973).
64. C. R. Johnson, *Acc. Chem. Res.* **6**, 341 (1973).

and, since the ylides are chiral, they have been utilized in asymmetric synthesis for the preparation of enantiomerically enriched epoxides and cyclopropanes.[65]

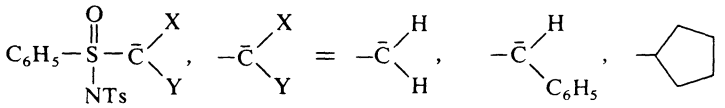
The preparation and use of this class of ylides can be illustrated by the sequence



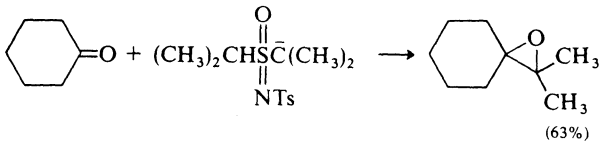


Ar = *p*-$CH_3C_6H_4$—

A similar pattern of reactivity was demonstrated for carbanions formed by deprotonation of *S*-alkyl-*N*-*p*-toluenesulfonyl-*S*-phenylsulfoximines.[66] Anions of dialkylsul-



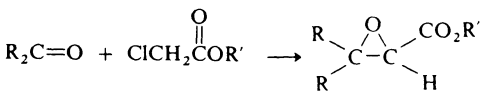
foximines provide convenient reagents for alkylidene transfer. When both alkyl substituents on sulfur are the same, regioselectivity of deprotonation is not an issue.



Ref. 66

2.8. Nucleophilic Addition–Cyclization

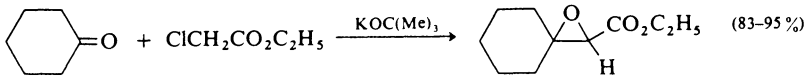
The pattern of nucleophilic addition at a carbonyl group followed by intramolecular nucleophilic displacement of a leaving group present in the nucleophile can also be recognized in a much older synthetic technique, the *Darzens reaction* (glycidic ester synthesis).[67]

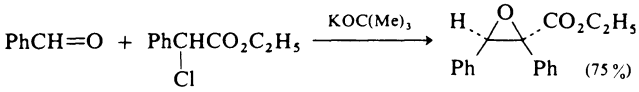


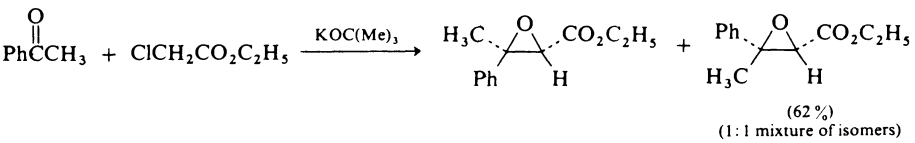
The first step is an addition of the enolate derived from an α-halo ester to the carbonyl compound. The alkoxide oxygen then effects nucleophilic attack on the

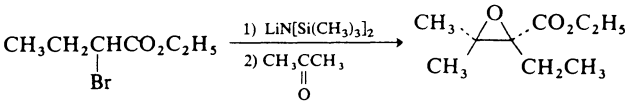
65. C. R. Johnson and E. R. Janiga, *J. Am. Chem. Soc.* **95**, 7673 (1973).
66. C. R. Johnson, R. A. Kirchoff, R. J. Reischer, and G. F. Katekar, *J. Am. Chem. Soc.* **95**, 4287 (1973).
67. M. S. Newman and B. J. Magerlein, *Org. React.* **5**, 413 (1951).

Scheme 2.12. Darzens Condensation Reactions

1[a] 

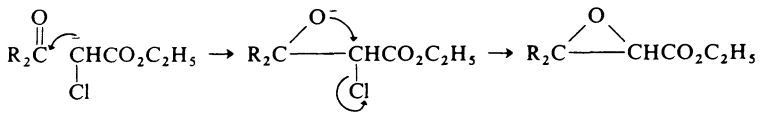
2[b] 

3[c] 

4[d] 

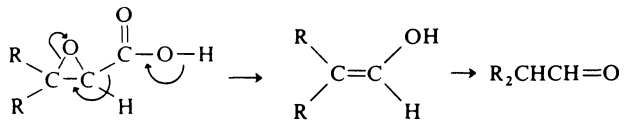
a. R. H. Hunt, L. J. Chinn, and W. S. Johnson, *Org. Synth.* **IV**, 459 (1963).
b. H. E. Zimmerman and L. Ahramjian, *J. Am. Chem. Soc.* **82**, 5459 (1960).
c. F. W. Bachelor and R. K. Bansal, *J. Org. Chem.* **34**, 3600 (1969).
d. R. F. Borch, *Tetrahedron Lett.*, 3761 (1972).

carbon–halogen bond, forming an α,β-epoxy ester called a glycidic ester. the reaction is not very stereoselective, so a mixture of isomers is usually formed from



unsymmetrical ketones.[68] Scheme 2.12 gives some typical examples of the Darzens reactions.

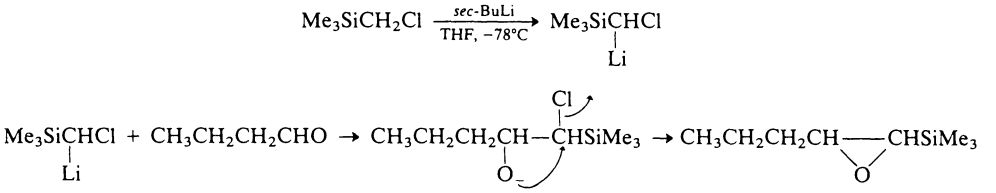
The epoxy esters formed in the Darzens condensation have been used in the synthesis of ketones and aldehydes. The acids formed by saponification of the esters



undergo thermal decarboxylation to give an aldehyde or ketone by way of the corresponding enol.

68. F. W. Bachelor and R. K. Bansal, *J. Org. Chem.* **34**, 3600 (1969).

Epoxysilanes may be prepared by a variant of this approach. Lithiation of chloromethyltrimethylsilane with *sec*-butyllithium gives an α-chloro carbanion which affords epoxysilanes on reaction with aldehydes and ketones.[69]



General References

Aldol Condensation

A. T. Nielsen and W. J. Houlihan, *Org. React.* **16**, 1 (1968).
T. Mukaiyama, *Org. React.* **28**, 203 (1982).

Annulation Reactions

R. E. Gawley, *Synthesis*, 777 (1976).
M. E. Jung, *Tetrahedron* **32**, 3 (1976).

Mannich Reaction

F. F. Blicke, *Org. React.* **1**, 303 (1942).

Wittig Reaction

A. Maercker, *Org. React.* **14**, 270 (1965); A. W. Johnson, *Ylide Chemistry*, Academic Press, New York (1966).

Phosphonate Carbanions

W. S. Wadsworth, Jr., *Org. React.* **25**, 73 (1977); J. Boutagy and R. Thomas, *Chem. Rev.* **74**, 87 (1974).

Sulfur Ylides

B. M. Trost and L. S. Melvin, Jr., *Sulfur Ylides*, Academic Press, New York (1975).

69. C. Burford, F. Cooke, E. Ehlinger, and P. D. Magnus, *J. Am. Chem. Soc.* **99**, 4536 (1977).

Problems

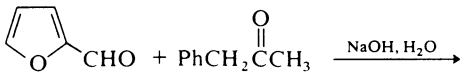
References for these problems are found on page 620.

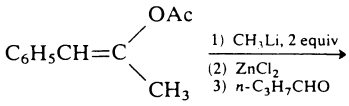
1. Predict the product formed in each of the following reactions:

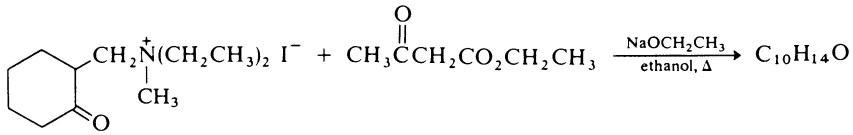
(a) γ-butyrolactone + ethyl oxalate $\xrightarrow[2)\ H^+]{1)\ NaOCH_2CH_3}$

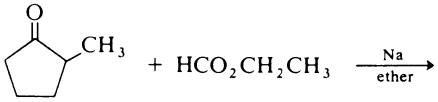
(b) 4-bromobenzaldehyde + ethyl cyanoacetate $\xrightarrow[\text{piperidine}]{\text{ethanol}}$

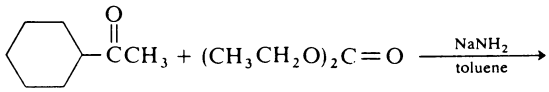
(c) $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[3)\ H_2O]{1)\ LiN(iPr)_2,\ 2)\ CH_3CH_2CHO}$

(d)  $\xrightarrow{NaOH,\ H_2O}$

(e) 

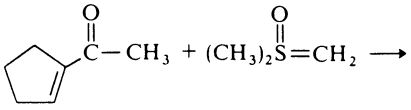
(f) 

(g) 

(h) 

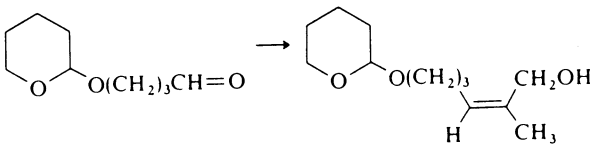
(i) $C_6H_5\overset{O}{\overset{\|}{C}}CH_3 + (CH_3CH_2O)_2\overset{O}{\overset{\|}{P}}CH_2CN \xrightarrow[THF]{NaH}$

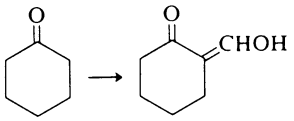
(j) $CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2CO_2CH_2CH_3 \xrightarrow[xylene]{NaOCH_3}$

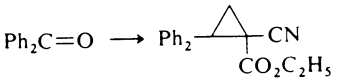
(k) 

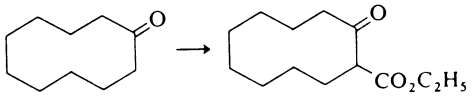
Indicate reaction conditions or a series of reactions that could effect each of the following synthetic conversions:

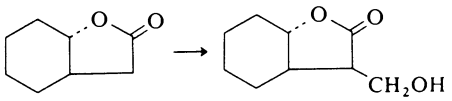
(a) $CH_3CO_2C(CH_3)_3 \rightarrow (CH_3)_2\overset{OH}{\overset{|}{C}}CH_2CO_2C(CH_3)_3$

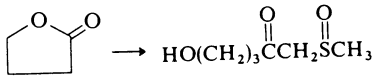
(b) 

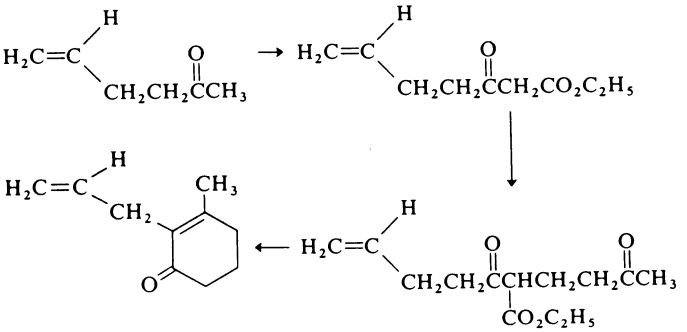
(c) 

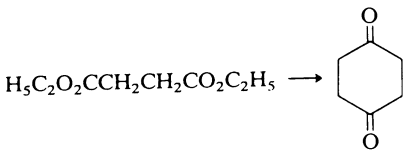
(d) 

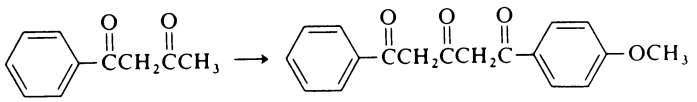
(e) 

(f) 

(g) 

(h) 

(i) 

(j) 

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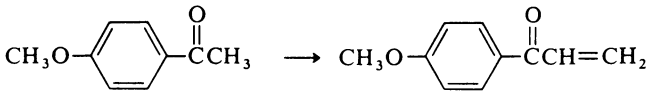

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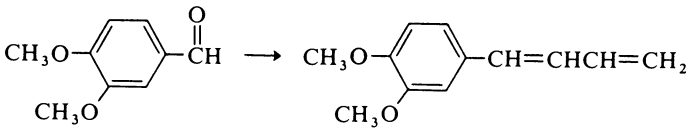

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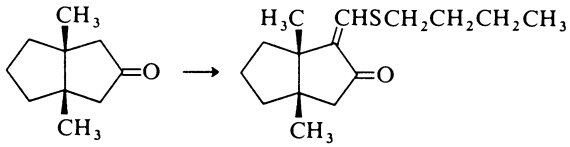
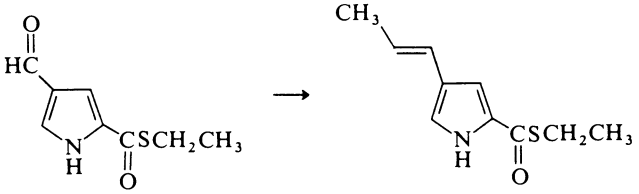


(n)



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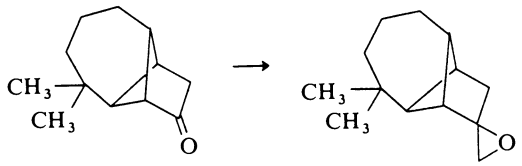

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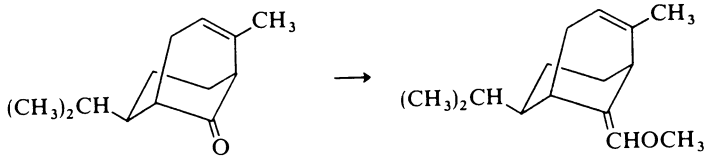

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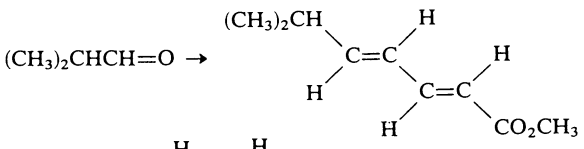

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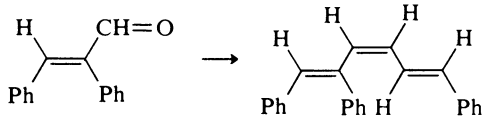

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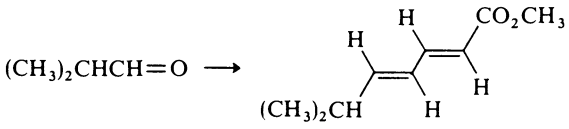
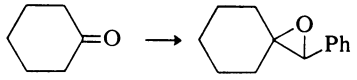
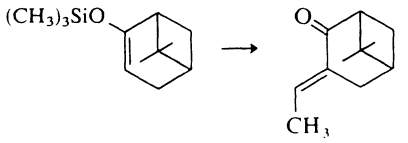
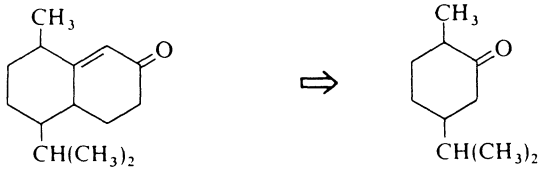


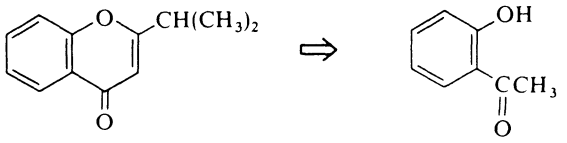
(t)

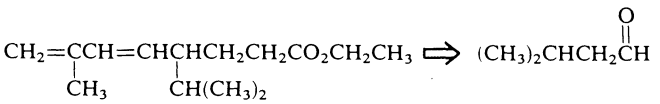


(u) 

3. Step-by-step retrosynthetic analysis of each of the target molecules reveals that they can be efficiently prepared in a few steps from the starting material shown on the right. Show a retrosynthetic analysis and suggest reagents and conditions for carrying out the desired synthesis.

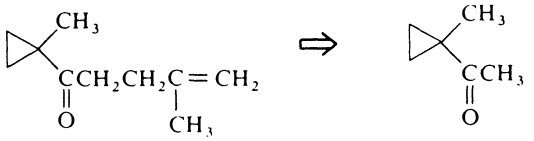
(a) 

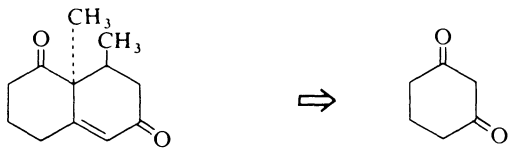
(b) 

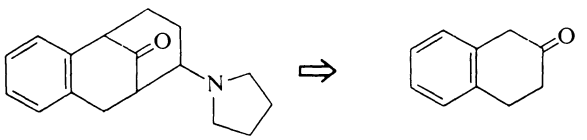
(c) 

Hint: See Chapter 1, problem 8h.

(d) 

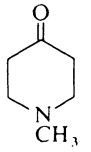
(e) 

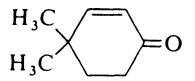
(f) 

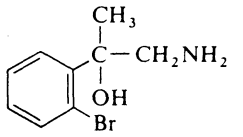
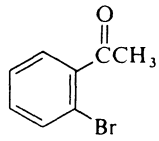
(g) 

(h) $Ph_2C{=}CHCH{=}O \Rightarrow Ph_2C{=}O$

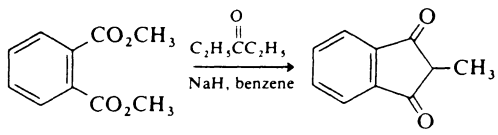
(i) $CH_3CH_2\underset{\underset{CH_2}{\|}}{C}CH{=}CHCO_2C_2H_5 \Rightarrow CH_3CH_2CH_2CH{=}O,\ ClCH_2CO_2C_2H_5$

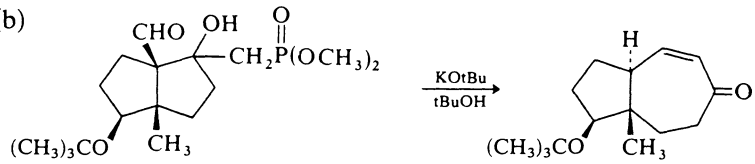
(j)  $\Rightarrow CH_3NH_2,\ CH_2{=}CHCO_2C_2H_5$

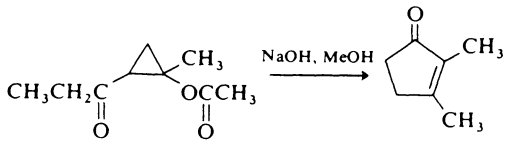
(k)  $\Rightarrow (CH_3)_2CHCH{=}O,\ CH_2{=}CH\overset{\overset{O}{\|}}{C}CH_3$

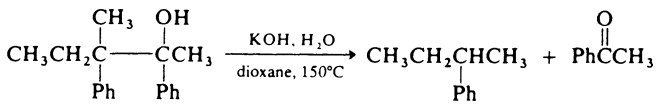
(l)  $\Rightarrow$ 

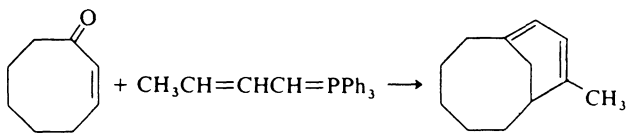
4. Offer a mechanism for each of the following transformations:

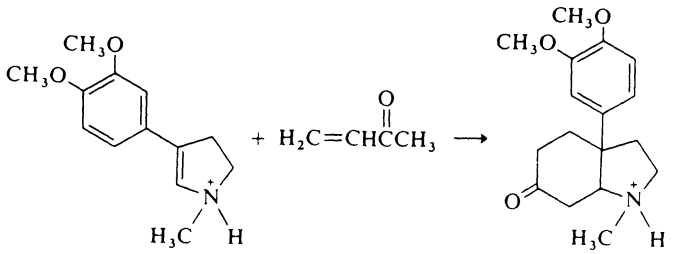
(a) 

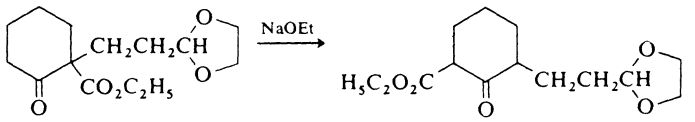
(b) 

(c) 

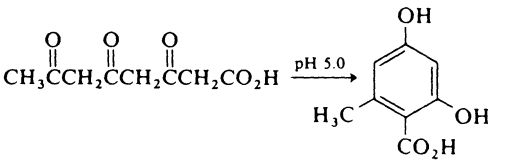
(d) 

(e) 

(f) 

(g) 

5. Tetraacetic acid (or a biological equivalent) has been suggested as an intermediate in the biosynthesis of phenolic natural products. Its synthesis has been described, as has its ready conversion to orsellinic acid. Suggest a mechanism for formation of orsellinic acid under the conditions specified:

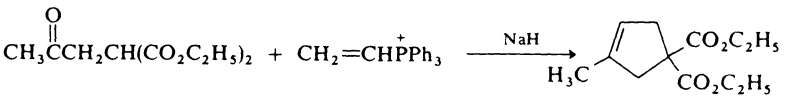


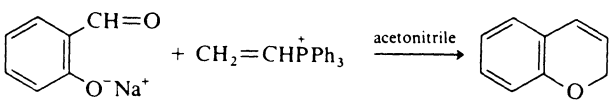
orsellinic acid

6. (a) A stereospecific method for deoxygenating epoxides to alkenes involves reaction of the epoxide with the diphenylphosphide ion, followed by methyl iodide. The method results in overall inversion of the alkene stereochemistry. Thus, *cis*-cyclooctene epoxide gives *trans*-cyclooctene. Propose a mechanism for this process and discuss the relationship of the reaction to the Wittig reaction.

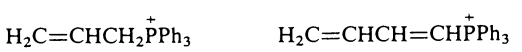
   (b) Reaction of the epoxide of *E*-4-octene (*trans*-2,3-di-*n*-propyloxirane) with trimethylsilylpotassium affords *Z*-4-octene as the only alkene in 93% yield. Suggest a reasonable mechanism for this reaction.

7. (a) A fairly general method for ring closure that involves vinyltriphenylphosphonium halides has been developed. Two examples are shown. Comment on the mechanism of the reaction and suggest two additional types of rings that could be synthesized, using vinyltriphenylphosphonium salts.

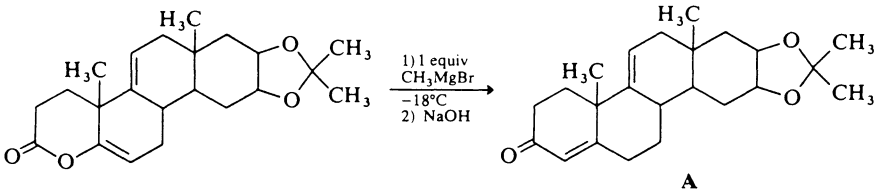




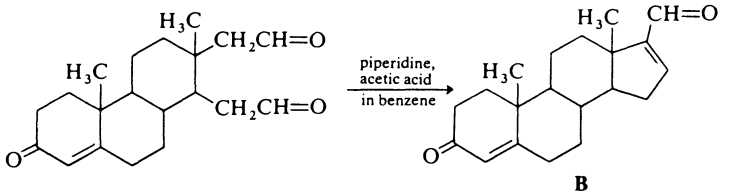
(b) The two phosphonium salts shown have both been used in syntheses of cyclohexadienes. Suggest appropriate coreactants and catalysts that would be expected to lead to cyclohexadienes.



8. Compounds **A** and **B** are key intermediates in one total synthesis of cholesterol. Rationalize their formation by the routes shown:

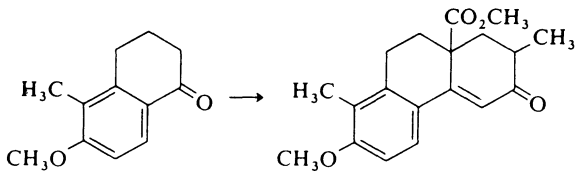


A



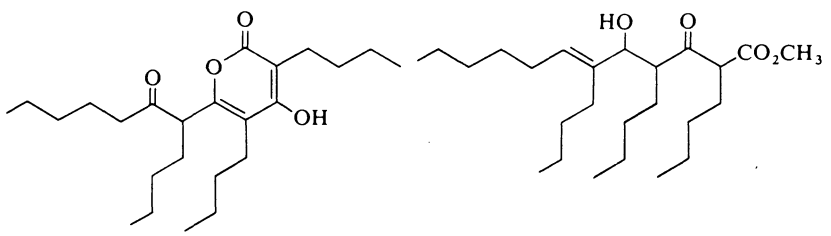
B

9. The first few steps of the synthesis of the alkaloid conessine produce **D** from **C**. Suggest a sequence of reactions for effecting this conversion:



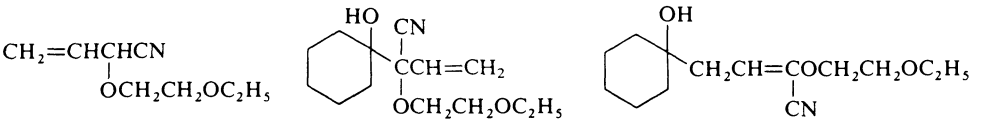
C **D**

10. A substance known as elastase is a primary cause of arthritis, various inflammations, pulmonary emphysema, and pancreatitis. Elastase activity can be inhibited by a compound known as elasnin, obtained from the culture broth of a particular microorganism. The structure of elasnin is shown. A synthesis of elasnin has been reported which utilizes Compound **E** as a key intermediate. Suggest a synthesis of Compound **E** from methyl hexanoate and hexanal.



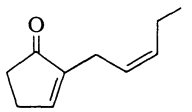
Elasnin Compound **E**

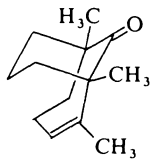
11. Treatment of compound **F** with lithium diisopropylamide followed by cyclohexanone gives either **G** or **H**. **G** is formed if the aldehyde is added at −78°C, whereas **H** is formed if the aldehyde is added at 0°C. Furthermore, treatment of **G** with lithium diisopropylamide at 0°C gives **H**. Explain these results.



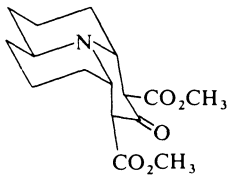
F **G** **H**

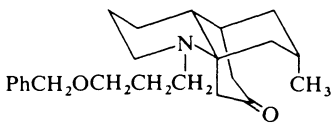
12. Dissect the following molecules into potential precursors by locating all bond connections which could be made by aldol-type condensations. Suggest the structure for potential precursors and conditions for performing the desired condensation.

(a) 

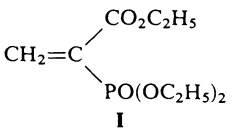
(b) 

13. Mannich condensations permit one-step reactions to form the following substances from substantially less complex starting materials. By retrosynthetic analysis identify a potential starting material which could give rise to the product shown in a single-step under Mannich reaction conditions.

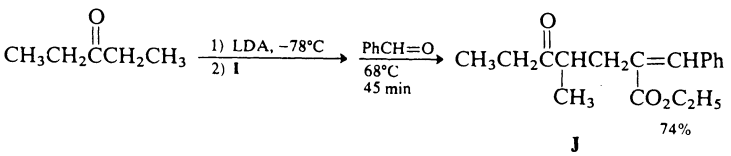
(a) 

(b) 

14. (a) The reagent **I** has found use in constructing rather complex molecules from simple precursors; for example, the enolate of 3-pentanone, treated first with **I**, then with benzaldehyde, gives **J** as a 2 : 1 mixture of stereoisomers. Explain the mechanism by which this synthesis occurs.

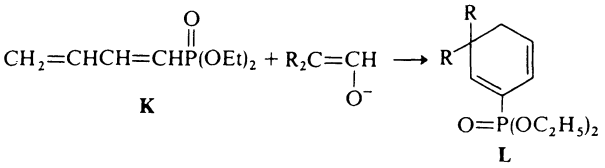


I



J

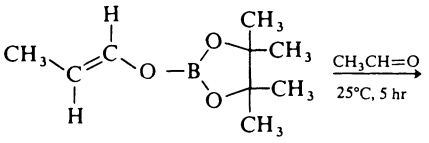
(b) The reagent **K** converts enolates of aldehydes into the cyclohexadienyl phosphonates **L**. What is the mechanism of this reaction? What alternative product might have been expected?



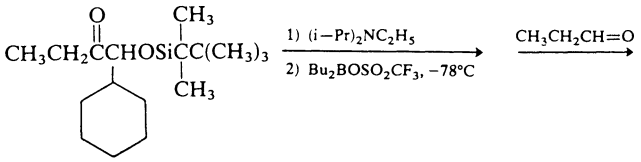
K **L**

15. Indicate whether the aldol condensation reactions shown below would be expected to exhibit high stereoselectivity. If high stereoselectivity is to be expected, show the relative configuration which is to be expected for the predominant product.

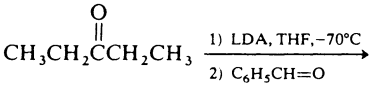
(a)



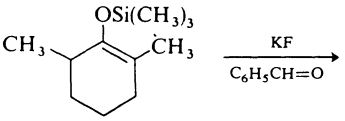
(b)



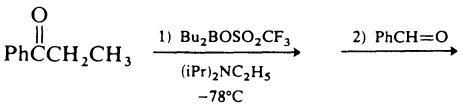
(c)



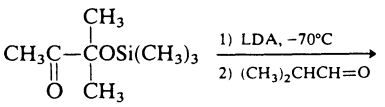
(d)



(e)



(f)



3

Functional Group Interconversion by Nucleophilic Substitution

The first two chapters have dealt with formation of new carbon bonds by processes in which carbon is the nucleophilic atom. The reactions considered in Chapter 1 involve attack by carbon nucleophiles at sp^3 centers, while those discussed in Chapter 2 involved reaction at sp^2 centers, primarily carbonyl groups. In this chapter we turn our attention to noncarbon nucleophiles. Nucleophilic substitution both at sp^3 and sp^2 centers is used in a variety of synthetic operations, particularly in the interconversion of functional groups. The mechanistic aspects of these reactions are treated more fully in Part A, Chapters 5 and 8.

3.1. Conversion of Alcohols to Alkylating Agents

3.1.1. Sulfonate Esters

The preparation of sulfonate esters from alcohols is an effective way of introducing a reactive leaving group onto an alkyl chain. The reaction is very general and complications arise only if the resulting sulfonate ester is sufficiently reactive to require special precautions. *p*-Toluenesulfonate (tosylate) and methanesulfonate (mesylate) esters are the most frequently used groups in preparative work, but the more reactive trifluoromethanesulfonates are useful when a very good leaving group is required. The usual method for introducing tosyl or mesyl

groups is to stir the alcohol with the sulfonyl chloride in pyridine at 0–25°C.[1] A useful alternative for preparing mesylates from alcohols is a rapid reaction carried out at 0°C using triethylamine as a base.[2] Under these conditions the reaction probably proceeds through a sulfene intermediate.[3] Use of the lithium salt of the

$$CH_3SO_2Cl + (C_2H_5)_3N \rightarrow CH_2{=}SO_2 + (C_2H_5)_3\overset{+}{N}H\ Cl^-$$

$$ROH + CH_2{=}SO_2 \rightarrow ROS(=O)(=O)CH_3$$

alcohol is also a valuable method in that it avoids possible secondary reaction of the product sulfonates with excess amine.[4] Trifluoromethanesulfonates of alkyl and

$$ROLi + ClSO_2\text{-}C_6H_4\text{-}CH_3 \longrightarrow ROSO_2\text{-}C_6H_4\text{-}CH_3$$

allylic alcohols can be prepared by reaction with trifluoromethanesulfonic anhydride in halogenated solvents in the presence of pyridine at 0°C.[5] Since the preparation

$$ROH + (CF_3SO_2)_2O \xrightarrow[\text{pyridine}]{0°C} ROSO_2CF_3$$

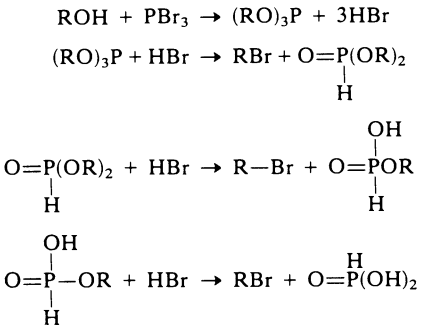
of sulfonate esters does not disturb the C—O bond, problems of rearrangement or racemization do not arise in the ester formation step itself. However, sensitive sulfonate esters, such as allylic systems, may be subject to ionization reactions once formed, so that appropriate care must be taken. Tertiary alkyl toluenesulfonates are neither prepared as readily nor are they as stable as those from primary and secondary alcohols. Usually a tertiary alcohol is observed to be converted to an alkene on attempted preparation of its tosylate ester.

3.1.2. Halides

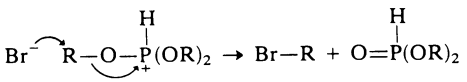
The prominent role of alkyl halides in formation of carbon–carbon bonds by nucleophilic substitution was evident in Chapter 1. The most common precursor of alkyl halides is the corresponding alcohol and a variety of procedures for converting alcohols to halides have been developed. The choice of an appropriate reagent is usually dictated by the sensitivity of the alcohol and any other functional groups contained in the molecule. Simple primary alcohols can be converted to bromides with hot concentrated hydrobromic acid.[6] Similarly, chlorides can be formed by reaction of simple primary alcohols with hydrochloric acid–zinc chloride

1. R. S. Tipson, *J. Org. Chem.* **9**, 235 (1944).
2. R. K. Crossland and K. L. Servis, *J. Org. Chem.* **35**, 3195 (1970).
3. W. E. Truce and J. R. Norell, *J. Am. Chem. Soc.* **85**, 3231 (1963); J. F. King and T. W. S. Lee, *J. Am. Chem. Soc.* **91**, 6524 (1969).
4. H. C. Brown, R. Bernheimer, C. J. Kim, and S. E. Scheppele, *J. Am. Chem. Soc.* **89**, 370 (1967).
5. C. D. Beard, K. Baum, and V. Grakauskas, *J. Org. Chem.* **38**, 3673 (1973).
6. E. E. Reid, J. R. Ruhoff, and R. E. Burnett, *Org. Synth.* **II**, 246 (1943).

(Lucas reagent).[7] These reactions proceed by an S_N2 mechanism and elimination and rearrangements are not ordinarily troublesome. Concentrated hydrogen halides convert tertiary alcohols to halides *via* S_N1 processes. These reactions are preparatively useful when the intermediate carbonium ion is unlikely to give rise to any rearranged products.[8] Another general method for converting alcohols to halides involves reactions with various halides of nonmetallic elements. The classical reagents such as thionyl chloride, phosphorus trichloride or phosphorus tribromide, are suitable for alcohols which are neither acid-sensitive nor prone to any structural rearrangement. The mechanisms for the reactions with phosphorus halides can be illustrated by considering the reaction with phosphorus tribromide. Initial attack on phosphorus tribromide by the alcohol forms a trialkyl phosphite ester by successive displacements of bromide. The reaction stops at this stage if it is run in the presence of an amine which neutralizes the hydrogen bromide that is formed.[9] Introduction of the bromide on the alkyl group then occurs by reaction of hydrogen bromide with the phosphite ester. Each carbon–bromine bond is formed by a



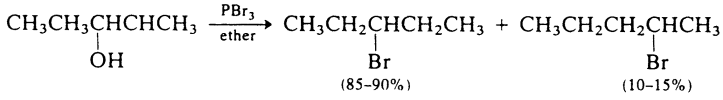
back-side displacement. The driving force for cleavage of the C—O bond is the formation of a phosphoryl bond. The degree of stereospecificity decreases for the



third displacement step, as can be recognized by occurrence of some racemization in the reactions of chiral secondary alcohols.[10] The occurrence of rearrangement of alkyl groups during the conversion of alcohols to alkyl halides parallels the stereochemical behavior. For example, conversion of optically active 2-butanol to 2-butyl bromide with PBr_3 is accompanied by 10–13% racemization.[11] A small amount (1.5%) of *t*-butyl bromide is also formed.[12] The extent of ionization and

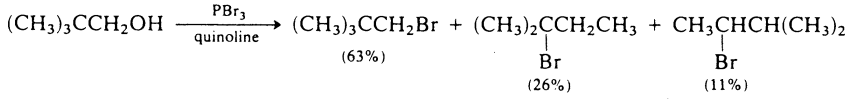
7. J. E. Copenhaver and A. M. Whaley, *Org. Synth.* **I**, 142 (1941).
8. J. F. Norris and A. W. Olmsted, *Org. Synth.* **I**, 144 (1941); H. C. Brown and M. H. Rei, *J. Org. Chem.* **31**, 1090 (1966).
9. A. H. Ford-Moore and B. J. Perry, *Org. Synth.* **IV**, 955 (1963).
10. H. R. Hudson, *Synthesis*, 112 (1969).
11. D. G. Goodwin and H. R. Hudson, *J. Chem. Soc.* **B**, 1333 (1968).
12. E. J. Coulson, W. Gerrard, and H. R. Hudson, *J. Chem. Soc.*, 2364 (1965).

rearrangement increases with increasing chain length and branching. Sterically



Ref. 13

hindered substrates such as neopentyl alcohol give rise to larger amounts of rearranged products.[14]



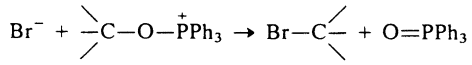
A compound formed from triphenylphosphine and bromine also converts alcohols to bromides, and it is especially useful for secondary alcohols and other systems in which migration and rearrangement might occur when using other phosphorus reagents.[15] The active reagent in the PPh_3–Br_2 system is a pentavalent

$$PPh_3 + Br_2 \rightarrow Br_2PPh_3$$

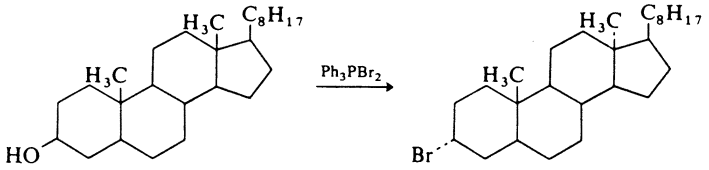
$$Br_2PPh_3 + ROH \rightarrow RO\overset{+}{P}Ph_3\ Br^- + HBr$$

$$Br^- + RO\overset{+}{P}Ph_3 \rightarrow RBr + O{=}PPh_3$$

phosphorus compound. The alcohol displaces a bromide ion from this pentavalent adduct, giving an ionic phosphonium intermediate. These species can be isolated in some instances.[16] The phosphonium intermediate then undergoes nucleophilic attack by bromide ion, with displacement of triphenylphosphine oxide. The strength of the P=O bond formed in this step provides much of the driving force for the reaction. Since the initial adduct is formed in a reaction that does not involve a bond directly to carbon, and the second step proceeds by back-side displacement



on this carbon, the stereochemical course of the reaction for saturated secondary halides is inversion of configuration. Triphenylphosphine dichloride exhibits similar reactivity towards alcohols and has been used to prepare chlorides.[18]



Ref. 17

13. J. Cason and J. S. Correia, *J. Org. Chem.* **26**, 3645 (1961).
14. H. R. Hudson, *J. Chem. Soc.*, 664 (1968).
15. G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Am. Chem. Soc.* **86**, 964 (1964).
16. J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.* **30**, 2635 (1965).
17. D. Levy and R. Stevenson, *J. Org. Chem.* **30**, 3469 (1965).
18. L. Horner, H. Oediger, and H. Hoffmann, *Justus Liebig's Ann. der Chemie* **626**, 26 (1959).

A useful method for preparation of chlorides from alcohols is based on the reaction of triphenylphosphine with carbon tetrachloride[19a] or hexachloroacetone.[19b] In each instance a chlorophosphonium ion is formed by a reaction between the phosphine and halogen source.[19c] The chlorophosphonium ion then

$$Ph_3P + CCl_4 \rightarrow Ph_3\overset{+}{P}-Cl + {}^{-}CCl_3$$

$$Ph_3P + Cl_3C\overset{O}{\overset{\|}{C}}CCl_3 \rightarrow Ph_3\overset{+}{P}-Cl + {}^{-}CCl_2\overset{O}{\overset{\|}{C}}CCl_3$$

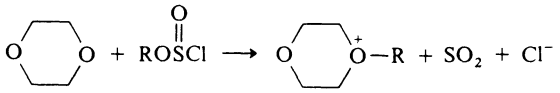
reacts with the alcohol to give an alkoxyphosphonium ion which provides a reactive phosphorus–oxygen bond which is susceptible to nucleophilic attack by chloride ion with formation of triphenylphosphine oxide.

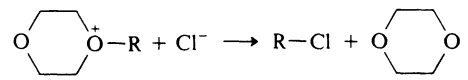
$$Ph_3\overset{+}{P}-Cl + ROH \rightarrow Ph_3\overset{+}{P}-OR + HCl$$

$$Ph_3\overset{+}{P}-OR + Cl^{-} \rightarrow Ph_3P{=}O + R-Cl$$

Thionyl chloride, $SOCl_2$, is frequently used for preparation of chlorides from alcohols. There are two mechanisms by which thionyl chloride reacts with alcohols. In nucleophilic solvents such as dioxane, net retention of configuration is possible because of participation by the solvent.[20] In the absence of such solvents net

$$ROH + SOCl_2 \rightarrow R\overset{O}{\overset{\|}{O}}SCl + HCl$$





inversion is likely to occur via a mechanism involving nucleophilic attack by chloride on an intermediate alkyl chlorosulfite.

$$ROH + SOCl_2 \rightarrow R\overset{O}{\overset{\|}{O}}SCl + HCl$$

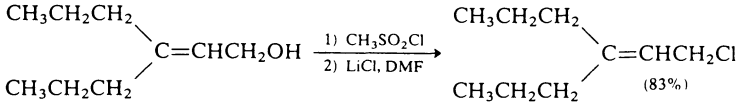
$$Cl^{-} \curvearrowright R-O\overset{O}{\overset{\|}{S}}-Cl \rightarrow R-Cl + SO_2 + Cl^{-}$$

If the possibility of racemization or rearrangement is not a concern, reaction of thionyl chloride with alcohols can be catalyzed by zinc chloride.[21]

A very mild method which is particularly useful for systems that are prone to allylic rearrangement involves prior conversion of the alcohol to the tosylate

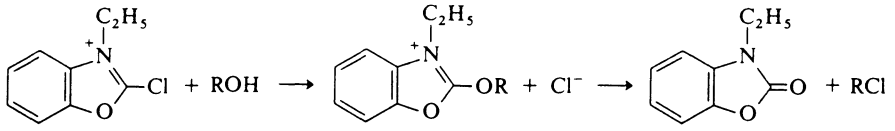
19. a. J. B. Lee and T. J. Nolan, *Can. J. Chem.* **44**, 1331 (1966).
    b. R. M. Magid, O. S. Fruchey, W. L. Johnson, and T. G. Allen, *J. Org. Chem.* **44**, 359 (1979).
    c. R. Appel, *Angew. Chem. Int. Ed. Engl.* **14**, 801 (1975).
20. E. S. Lewis and C. E. Boozer, *J. Am. Chem. Soc.* **74**, 308 (1952).
21. T. G. Squires, W. W. Schmidt, and C. S. McCandlish, Jr., *J. Org. Chem.* **40**, 134 (1975).

followed by nucleophilic displacement by a chloride or bromide ion. Another very



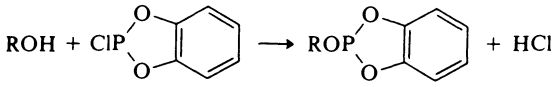
Ref. 22

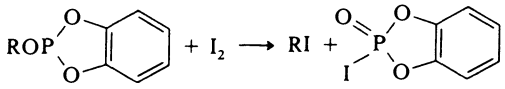
mild reagent for converting alcohol to chlorides is the heterocyclic cation 2-chloro-3-ethylbenzoxazolium.[23] The alcohol adds to the electrophilic heterocyclic ring,



displacing chloride. The activated alkoxy group is subject to nucleophilic displacement on carbon, forming the alkyl chloride and the stable product, 3-ethylbenzoxazolone. The reaction proceeds at 0°C in the presence of triethylamine and a chloride ion source such as tetraethylammonium chloride. Use of tetraethylammonium bromide leads to formation of the corresponding bromide.[24]

Iodides can be made smoothly from tosylates or bromides by reaction with sodium iodide in acetone.[25] There are also several procedures based on phosphorus reagents which are mechanistically related to those discussed for bromides and chloride. One procedure involves preparation of a cyclic phosphite ester from the alcohol and *o*-phenylenephosphorochloridite. Treatment of the cyclic phosphite with iodine then generates the alkyl iodide.[26] An alkoxyphosphonium intermediate is involved.





A related procedure involves heating the alcohol with an adduct formed from triphenyl phosphite and methyl iodide.[27] In this instance a reactive alkoxyphosphonium intermediate is formed by displacement of a phenoxy group at phosphorus.

$$CH_3I + (PhO)_3P \rightarrow CH_3\overset{+}{P}(OPh)_3 + I^-$$

$$ROH + CH_3\overset{+}{P}(OPh)_3 \rightarrow RO\overset{+}{P}(OPh)_2 + PhOH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3$$

22. E. W. Collington and A. I. Meyers, *J. Org. Chem.* **36**, 3044 (1971).
23. T. Mukaiyama, S. Shoda, and Y. Watanabe, *Chem. Lett.*, 383 (1977).
24. N. A. Porter, J. D. Byers, A. E. Ali, and T. E. Eling, *J. Am. Chem. Soc.* **102**, 1183 (1980).
25. D. T. Longone, *J. Org. Chem.* **28**, 1770 (1963).
26. E. J. Corey and J. E. Anderson, *J. Org. Chem.* **32**, 4160 (1967).
27. J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.* **35**, 2319, 2868 (1970).

$$I^- + RO\overset{+}{P}(OPh)_2 \rightarrow RI + O{=}P(OPh)_2$$
$$\qquad\quad | \qquad\qquad\qquad\qquad\quad |$$
$$\qquad\quad CH_3 \qquad\qquad\qquad\quad CH_3$$

Iodides can also be prepared from alcohols by a procedure which has been shown to result in clean inversion of stereochemistry in cyclic systems. The reagents used are triphenylphosphine, diethyl azodicarboxylate, and methyl iodide.[28] Again an alkoxyphosphonium ion is the key intermediate.

$$Ph_3P + ROH + C_2H_5O_2CN{=}NCO_2C_2H_5 \rightarrow Ph_3\overset{+}{P}OR + C_2H_5O_2C\overset{-}{N}NHCO_2C_2H_5$$

$$C_2H_5O_2\overset{-}{N}NHCO_2C_2H_5 + CH_3I \rightarrow C_2H_5O_2C\underset{\displaystyle CH_3}{\underset{|}{N}}NHCO_2C_2H_5 + I^-$$

$$Ph_3\overset{+}{P}OR + I^- \rightarrow RI + Ph_3P{=}O$$

The role of the diethyl azodicarboxylate is to activate the triphenylphosphine toward nucleophilic attack by the alcohol. In the course of the reaction the N=N double bond is reduced and alkylated. As will be discussed subsequently, other types of nucleophiles can be introduced via the same activated intermediates.

Trimethylsilyl ethers of alcohols are converted to iodides by reaction with trimethylsilyl iodide.[29] This transformation can be carried out by *in situ* generation

$$ROSi(CH_3)_3 + (CH_3)_3SiI \rightarrow RI + (CH_3)_3SiOSi(CH_3)_3$$

of trimethylsilyl iodide from trimethylsilyl chloride and sodium iodide.[30] The silyl ethers are easily prepared from alcohols by reaction with trimethylsilyl chloride in pyridine. The method appears to be quite general and good yields have been reported for primary, secondary, tertiary, and benzylic alcohols. Secondary systems react with predominant inversion of configuration.

$$S\text{-}CH_3\underset{\displaystyle OSi(CH_3)_3}{\underset{|}{C}H}(CH_2)_5CH_3 \xrightarrow{(CH_3)_3SiI} R\text{-}CH_3\underset{\displaystyle I}{\underset{|}{C}H}(CH_2)_5CH_3$$

(89% optical purity) Ref. 30

Scheme 3.1 summarizes some examples of the various alcohol to halide conversions that have been discussed.

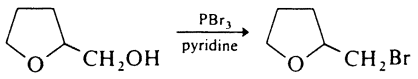
3.2. Introduction of Functional Groups by Nucleophilic Substitution at Saturated Carbon

The mechanistic aspects of nucleophilic substitution reactions were treated in detail in Chapter 5, Part A. That mechanistic basis has contributed to the development of nucleophilic substitution reactions as important synthetic processes. The S_N2 mechanism, because of its predictable stereochemistry and avoidance of

28. H. Loibner and E. Zbiral, *Helv. Chim. Acta* **59**, 2100 (1976).
29. M. E. Jung and P. L. Ornstein, *Tetrahedron Lett.*, 2659 (1977).
30. T. Morita, S. Yoshida, Y. Okamoto, and H. Sakurai, *Synthesis*, 379 (1979).

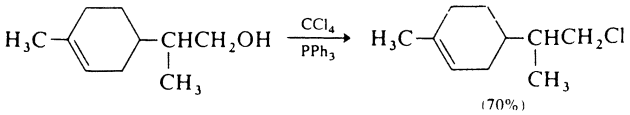
Scheme 3.1. Preparation of Alkyl Halides

1[a] $(CH_3)_2CHCH_2OH \xrightarrow{PBr_3} (CH_3)_2CHCH_2Br$ (55–60%)

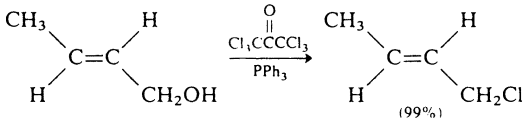
2[b] 

(53–61%)

3[c] $(CH_3)_3CCH_2OH \xrightarrow[PPh_3]{Cl_2} (CH_3)_3CCH_2Cl$ (92%)

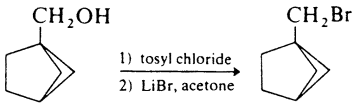
4[d] 

(70%)

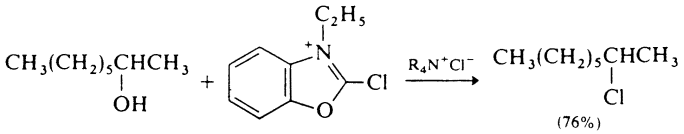
5[e] 

(99%)

6[f] $Ph_2C{=}CHCH_2CH_2OH \xrightarrow[2)\ LiBr]{1)\ \text{tosyl chloride}} Ph_2C{=}CHCH_2CH_2Br$ (89%)

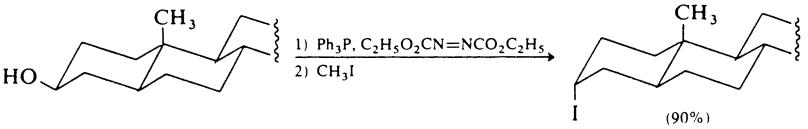
7[g] 

(94%)

8[h] 

(76%)

9[i] $(CH_3)_2NCH_2CH_2OH \xrightarrow{SOCl_2} (CH_3)_2\overset{+}{N}HCH_2CH_2Cl\ Cl^-$ (90%)

10[j] 

(90%)

11[k] $PhCH{=}CHCH_2OH \xrightarrow{Ph_3PBr_2} PhCH{=}CHCH_2Br$ (60–70%)

a. C. R. Noller and R. Dinsmore, *Org. Synth.* **II**, 358 (1943).
b. L. H. Smith, *Org. Synth.* **III**, 793 (1955).
c. G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Am. Chem. Soc.* **86**, 964 (1964).
d. B. D. MacKenzie, M. M. Angelo, and J. Wolinsky, *J. Org. Chem.* **44**, 4042 (1979).
e. R. M. Magid, O. S. Fruchy, W. L. Johnson, and T. G. Allen, *J. Org. Chem.* **44**, 359 (1979).
f. M. E. H. Howden, A. Maercker, J. Burdon, and J. D. Roberts, *J. Am. Chem. Soc.* **88**, 1732 (1966).
g. K. B. Wiberg and B. R. Lowry, *J. Am. Chem. Soc.* **85**, 3188 (1963).
h. T. Mukaiyama, S. Shoda, and Y. Watanabe, *Chem. Lett.*, 383 (1977).
i. L. A. R. Hall, V. C. Stephens, and J. H. Burckhalter, *Org. Synth.* **IV**, 333 (1963).
j. H. Loibner and E. Zbiral, *Helv. Chim. Acta* **59**, 2100 (1976).
k. J. P. Schaefer, J. G. Higgins, and P. K. Shenoy, *Org. Synth.* **V**, 249 (1973).

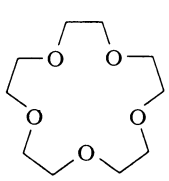
carbonium ion intermediates and the resulting possibilities for elimination and rearrangements, is the most desirable type of substitution process from a synthetic point of view. This section will discuss the role of the S_N2 reaction in preparation of a number of functional group types, but first it is desirable to review the important role that solvent plays in S_N2 reactions. The knowledgeable manipulation of solvent and related medium effects has led to significant improvement of many synthetic procedures which proceed by the S_N2 mechanism.

3.2.1. General Solvent Effects

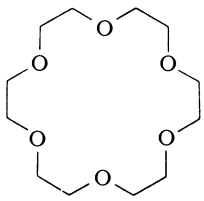
The objective in designing the reaction conditions for a preparative nucleophilic substitution is to enhance the mutual reactivity of the leaving group and nucleophile so that the desired substitution occurs at a convenient rate and without deleterious competition from other possible reactions. The reactivity of the leaving group is determined, for the most part, by the choice of the substrate for substitution. The general reactivity order $RSO_3^- > I^- > Br^- > Cl^-$ pertains to most S_N2 processes. (See Section 5.6, Part A for more complete data.) Mesylates, tosylates, iodides and bromides are all widely used synthetically but chlorides usually react rather slowly, except in especially reactive cases such as allyl and benzyl systems. The particular nucleophile to be used is normally governed by the synthetic objective. Optimization of nucleophilicity therefore must be achieved by choice of the reaction conditions, particularly the solvent. Several generalizations about solvents can be made. Hydrocarbons and ethers are usually unsuitable solvents for salts. Acetone and acetonitrile are somewhat more polar but still only a few ionic compounds have high solubility. Solubility can be considerably improved by using the anion in the form of a tetralkylammonium salt. Alcohols are generally reasonably good solvents for salts but the nucleophilicity of anions is relatively low in alcohols because of extensive solvation. The polar aprotic solvents, particularly dimethylformamide and dimethylsulfoxide, are good solvents for salts and, by virtue of selective cation solvation, anionic nucleophiles usually show high reactivity in these solvents. The high water solubility of these solvents and their high boiling points can be causes of product isolation and purification difficulties, however. Hexamethylphosphoric triamide, *N*,*N*-diethylacetamide, and *N*-methylpyrrolidinone are other examples of useful polar aprotic solvents.[31] In addition to enhancing reactivity, polar aprotic solvents affect the order of reactivity of nucleophilic anions. In dimethylformamide the halides are all of comparable nucleophilicity with $Cl^- > Br^- > I^-$,[32] whereas in hydroxylic solvents the order is $I^- > Br^- > Cl^-$ and the differences in reactivity are much greater.[33]

31. A. F. Sowinski and G. M. Whitesides, *J. Org. Chem.* **44**, 2369 (1979).
32. W. M. Weaver and J. D. Hutchinson, *J. Am. Chem. Soc.* **86**, 261 (1964).
33. R. G. Pearson and J. Songstad, *J. Org. Chem.* **32**, 2899 (1967).

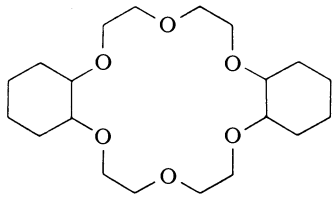
Two recent developments which have been extensively applied in nucleophilic substitution processes have been the use of the "crown ethers" as complexing agents and the use of "phase transfer" catalysts. The crown ethers are a family of cyclic polyethers, three examples of which are shown below:



15-crown-5



18-crown-6



dicyclohexano-18-crown-6

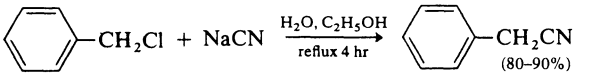
The first number designates the ring size and the second the number of oxygen atoms in the ring. These materials have specific cation complexing properties and give rise to catalytic effects which are of importance in preparative nucleophilic substitution. By complexing the cation in the cavity of the crown ether, these compounds act as solubilizing agents and many ionic salts which are insoluble in organic solvents are dissolved in the presence of crown ethers. Once dissolved in aprotic solvents of low polarity, the anions are highly reactive as nucleophiles since they are weakly solvated and tight ion-pairing is precluded by the complexation of the cation by the crown ether. As a result, nucleophilicity reaches or exceeds that observed in aprotic polar solvents.

The second general area which has had a great influence on nucleophilic substitution processes has been the development of phase transfer catalysts. The phase transfer catalysts are ionic substances, usually quaternary ammonium or phosphonium salts, in which the size of the hydrocarbon groups in the cation is large enough to convey good solubility of the salt in organic solvents. In other words, the cation must be highly lipophilic. The mechanism by which nucleophilic reactivity is enhanced by phase transfer catalysts depends upon a solvent effect. The conditions for phase transfer processes involve use of a two-phase system. The organic substrate is dissolved in a water-insoluble organic solvent such as a hydrocarbon or halogenated hydrocarbon. The ionic nucleophile is dissolved in water. Even with vigorous mixing, such systems show little tendency to react since the nucleophile and substrate remain separated in the aqueous and organic phases, respectively. The situation changes when a phase transfer catalyst is added. When the alkyl groups of the catalyst are sufficiently large as to confer solubility in the organic phase, the cations carry nucleophilic anions from the water phase into the organic phase to maintain electroneutrality. As a result, a situation similar to crown ether catalysis results. The anions are not strongly solvated in the organic phase. Many of the preparative transformations to be discussed in the succeeding sections have been carried out with catalysis by crown ethers or phase transfer agents. The results described further illustrate the magnitude of the resulting solvent effects. These catalytic procedures become useful synthetically when the reactivity under other conditions is inconveniently slow or inefficient for some other reason.

3.2.2. Nitriles

The replacement of a halide or tosylate by cyanide ion, extending the carbon chain by one atom and providing an entry into the family of carboxylic acid derivatives, has been a reaction of synthetic importance since the earliest days of organic chemistry.

The classical conditions for preparing aliphatic nitriles involve heating the halide with a cyanide salt in aqueous alcohol solution.



Ref. 34

$$ClCH_2CH_2CH_2Br + KCN \xrightarrow[\text{reflux 1.5 hr}]{H_2O,\ C_2H_5OH} \underset{(40\text{–}50\%)}{ClCH_2CH_2CH_2CN}$$

Ref. 35

When the solvent is changed to DMSO the reaction with primary chlorides is completed in 1 hr or less at temperatures of 120–140°C.[36] Phase transfer catalysis by hexadecyltributylphosphonium bromide converts a two-phase system containing 1-chlorooctane and aqueous potassium cyanide to octyl cyanide in 95% yield in 2 hr at 105°C.[37]

$$CH_3CH_2CH_2CH_2Cl \xrightarrow[\substack{\text{DMSO}\\ 90\text{–}160^\circ C}]{\text{NaCN}} \underset{(93\%)}{CH_3CH_2CH_2CH_2CN}$$

Ref. 36b

$$CH_3(CH_2)_6CH_2Cl \xrightarrow[\substack{H_2O,\ \text{decane}\\ CH_3(CH_2)_{15}P^+(CH_2CH_2CH_2CH_3)_3\\ 105^\circ,\ 2\ \text{hr}}]{\text{NaCN}} \underset{(95\%)}{CH_3(CH_2)_6CH_2CN}$$

Ref. 37b

Catalysis by 18-crown-6 of the reaction of solid potassium cyanide with halides in acetonitrile has been studied using a variety of chlorides and bromides.[38,39] With primary bromides yields were high and reaction times were 15–30 hr at reflux (83°C). Interestingly, in this system chlorides are more reactive than bromides and have reaction time of only about 2 hr. Secondary halides react considerably more slowly and yields drop to 50–60%, because of competing elimination. Tertiary halides do not react successfully since elimination processes dominate. A good example of the utility of these nonaqueous conditions is the preparation of trimethylsilyl cyanide from the hydrolytically sensitive trimethylsilyl chloride.[39]

$$(CH_3)_3SiCl \xrightarrow[\substack{18\text{-crown-6}\\ CH_2Cl_2\\ 40^\circ C,\ 24\ \text{hr}}]{\text{KCN}} \underset{(45\%)}{(CH_3)_3SiCN}$$

Ref. 39

34. R. Adams and A. F. Thal, *Org. Synth.* **I**, 101 (1932).
35. C. F. H. Allen, *Org. Synth.* **I**, 150 (1932).
36. a. L. Friedman and H. Shechter, *J. Org. Chem.* **25**, 877 (1960).
b. R. A. Smiley and C. Arnold, *J. Org. Chem.* **25**, 257 (1960).
37. C. M. Starks, *J. Am. Chem. Soc.* **93**, 195 (1971); C. M. Starks and R. M. Owens, *J. Am. Chem. Soc.* **95**, 3613 (1973).
38. F. L. Cook, C. W. Bowers, and C. L. Liotta, *J. Org. Chem.* **39**, 3416 (1974).
39. J. W. Zubrick, B. I. Dunbar, and H. D. Durst, *Tetrahedron Lett.*, 71 (1975).

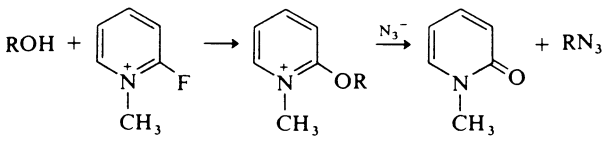
3.2.3. Azides

Azides are useful intermediates for synthesis of various kinds of nitrogen-containing functional groups. They undergo cycloaddition reactions as will be discussed in Section 7.1.5 and can also easily be reduced to primary amines. Azido groups are usually introduced into aliphatic molecules by nucleophilic substitution. The reaction is somewhat slow, even in aprotic dipolar solvents.[40] The most reliable procedures involve heating the appropriate halide with sodium azide in dimethyl sulfoxide[41] or dimethylformamide.[42] Alkyl azides can be prepared by reaction of sodium azide with iodides using high-boiling alcohols as the solvent.[43] Phase transfer

$$CH_3(CH_2)_3CH_2I + NaN_3 \xrightarrow[H_2O]{CH_3CH_2OCH_2CH_2OCH_2CH_2OH} \underset{(84\%)}{CH_3(CH_2)_3CH_2N_3} \qquad \text{Ref. 43}$$

catalysis of substitution reactions involving the azide ion have been observed using polyethylene glycols[44] and methyltrioctylammonium chloride.[45]

There are also useful procedures for preparation of azides directly from alcohols. Activation of alcohols with 2-fluoro-1-methylpyridinium iodide, followed by reaction with lithium azide, gives good yields of alkyl azides.[46] These conditions



lead to predominant inversion for secondary alcohols. Diphenylphosphoryl azide reacts with alcohols in the presence of the triphenylphosphine–diethyl azodicarboxylate combination.[47] Hydrazoic acid, HN_3, can also serve as the azide ion source

$$ROH + Ph_3P + C_2H_5O_2CN{=}NCO_2C_2H_5 \rightarrow \overset{+}{R}O\overset{+}{P}Ph_3 + C_2H_5O_2C\overset{-}{N}NHCO_2C_2H_5$$

under these activating conditions.[48] The mechanism of the alcohol activation process under these conditions was discussed in connection with the synthesis of halides.

$$\overset{+}{R}O\overset{+}{P}Ph_3 + N_3^- \rightarrow RN_3 + Ph_3P{=}O$$

3.2.4. Alkylation of Amines and Amides

The alkylation of neutral amines by halides is one of the oldest known organic reactions. The process is complicated from a synthetic point of view in that it can

40. M. E. C. Biffin, J. Miller, and D. B. Paul, in *The Chemistry of the Azido Group*, S. Patai (ed.), Interscience, New York (1971), Chap. 2.
41. R. Goutarel, A. Cave, L. Tan, and M. Leboeuf, *Bull. Soc. Chim. France*, 646 (1962).
42. E. J. Reist, R. R. Spencer, B. R. Baker, and L. Goodman, *Chem. Ind. (London)*, 1794 (1962).
43. E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.* **22**, 238 (1957).
44. H. Lehmkuhl, F. Rabet, and K. Ha..schild, *Synthesis*, 184 (1977).
45. W. P. Reeves and M. L. Bahr, *Synthesis*, 823 (1976).
46. K. Hojo, S. Kobayashi, K. Soai, S. Ikeda, and T. Mukaiyama, *Chem. Lett.*, 635 (1977).
47. B. Lal, B. N. Pramanik, M. S. Manhas, and A. K. Bose, *Tetrahedron Lett.*, 1977 (1977).
48. J. Schweng and E. Zbiral, *Justus Liebig's Ann. der Chem.*, 1089 (1978); H. Loibner and E. Zbiral, *Helv. Chim. Acta.* **59**, 2100 (1976).

proceed to give a quaternary ammonium salt in the presence of excess alkylating agent. Even in the presence of stoichiometric amounts of halide or tosylate, the

$$RNH_2 + R'{-}X \rightarrow \overset{+H}{\underset{H}{R\overset{}{N}}}R' + X^-$$

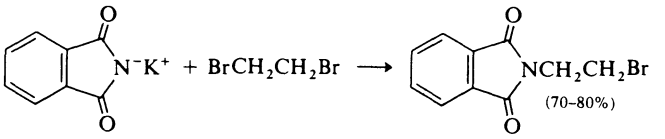
$$\overset{+H}{\underset{H}{R\overset{}{N}}}R' + RNH_2 \rightleftharpoons \underset{H}{RNR'} + \overset{+}{R}NH_3$$

$$\underset{H}{RNR'} + R'{-}X \rightarrow \underset{H}{\overset{+}{R}NR'_2} + X^-$$

$$\underset{H}{\overset{+}{R}NR'_2} + RNH_2 \rightleftharpoons RNR'_2 + \overset{+}{R}NH_3$$

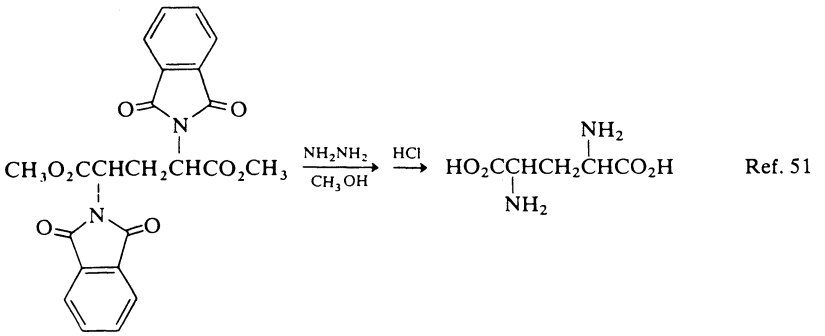
$$RNR'_2 + R'{-}X \rightarrow \overset{+}{R}NR'_3 + X^-$$

equilibria between protonated product and neutral starting amine are fast so that a mixture of products is usually obtained. For this reason, when monoalkylation of an amine is desired it is usually carried out by a reductive alkylation using an aldehyde as the alkyl group source, as will be discussed in Chapter 5. On the other hand, if complete alkylation to the quaternary salt is desired, use of excess halide and the presence of a base to neutralize the liberated acid will result in complete reaction. Amides, in contrast to amines, are only weakly nucleophilic and react very slowly with halides. The situation changes on going to the anions of amides. The classical Gabriel procedure using phthalimide is illustrative.[49]



Ref. 50

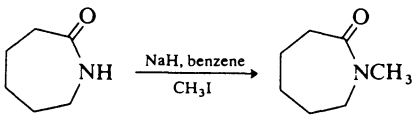
The enhanced acidity of the NH group in phthalimide permits formation of an anion which is readily alkylated by alkyl halides or tosylates. The alkylated amine can be liberated by reaction of the substituted phthalimide with hydrazine.



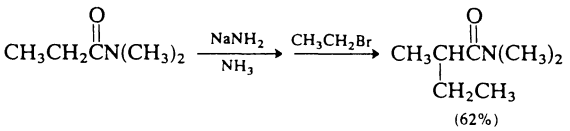
Ref. 51

49. M. S. Gibson and R. N. Bradshaw, *Angew. Chem. Int. Ed. Engl.* **7**, 919 (1968).
50. P. L. Salzberg and J. V. Supniewski, *Org. Synth.* **I**, 114 (1932).
51. J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.* **72**, 2786 (1950).

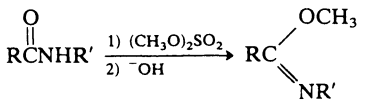
Secondary amides can be alkylated by using sodium hydride for proton abstraction followed by reaction with alkyl halides.[52] Under strongly basic conditions



tertiary amides form the amide enolate which undergoes carbon alkylation.[53] Sodium amide and lithium dialkylamides have been used for the deprotonation.



Neutral tertiary and secondary amides combine with very reactive alkylating agents, such as triethyloxonium fluoroborate, to give O-alkylation.[54] This reaction takes place more slowly, but still at a useful rate, with tosylates and with dimethyl sulfate. Treatment of the resulting salts with base yields a general route to the iminoethers:



Entry 8, Scheme 3.2 is a specific example of this reaction.

3.2.5. Oxygen Nucleophiles

The oxygen nucleophiles which are of primary interest in synthesis are the hydroxide ion (or water), alkoxide ions and carboxylate anions. The products of substitution, respectively, are, of course, alcohols, ethers, and esters.

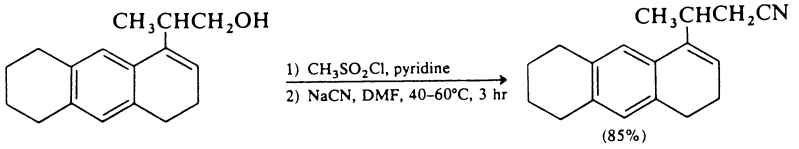
More frequently than not, a given alcohol is more easily obtained than the corresponding halides so the halide-to-alcohol transformation is not a very frequent one for synthetic purposes. When it is synthetically advantageous, the main problem is that of adjusting reaction conditions to avoid competing elimination. The hydrolysis of benzyl halides to the corresponding alcohols proceeds in good yields.[55] This

52. a. W. S. Fones, *J. Org. Chem.* **14**, 1099 (1949).
    b. R. M. Moriarty, *J. Org. Chem.* **29**, 2748 (1964).
53. a. H. L. Needles and R. E. Whitfield, *J. Org. Chem.* **31**, 989 (1966).
    b. B. M. Trost and R. A. Kunz, *J. Org. Chem.* **39**, 2475 (1974).
    c. P. G. Gassman and B. L. Fox, *J. Org. Chem.* **31**, 982 (1966).
54. L. Weintraub, S. R. Oles, and N. Kalish, *J. Org. Chem.* **33**, 1679 (1968); H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.* **154**, 83 (1939).
55. J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newbery, and A. D. Self, *J. Chem. Soc.*, 103 (1942).

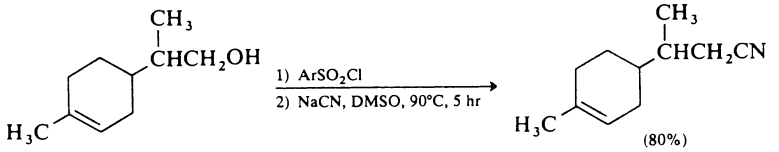
Scheme 3.2. Transformation of Functional Groups by Nucleophilic Substitution

A. Nitriles

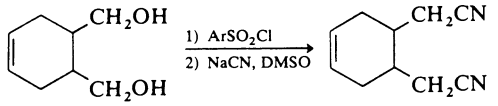
1a



2[b]



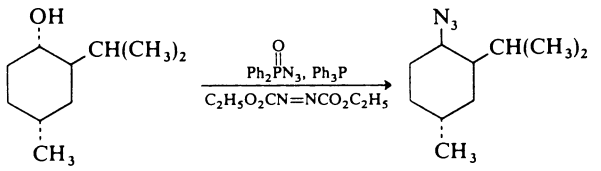
3[c]



B. Azides

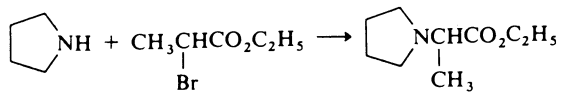
4[d] $CH_3CH_2CH_2CH_2Br + NaN_3 \xrightarrow[H_2O,\ 100°C,\ 6\ hr]{R_4\overset{+}{N}Cl^-} CH_3CH_2CH_2CH_2N_3$ (97%)

5[e]

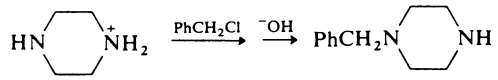


C. Amines and Amides

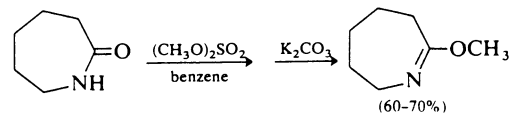
6[f]



7[g]



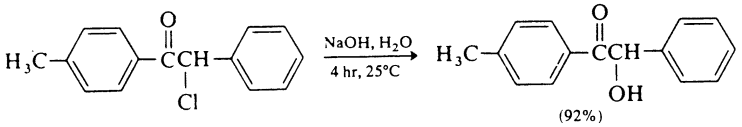
8[h]



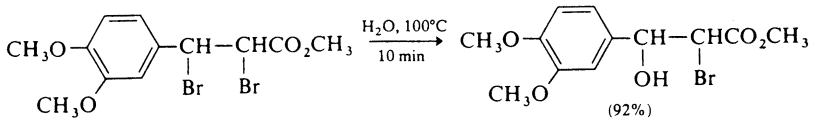
Scheme 3.2—*continued*

D. Hydrolysis of Alkyl Halides

9[i]

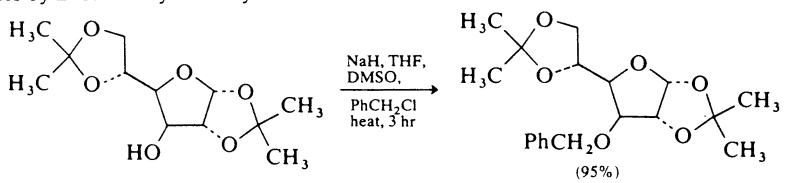


10[j]

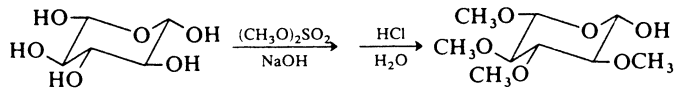


E. Ethers by Base-Catalyzed Alkylation

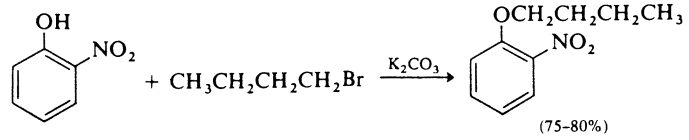
11[k]



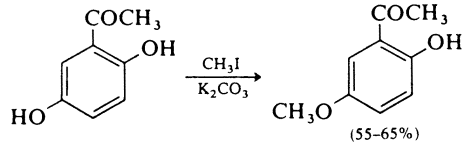
12[l]



13[m]

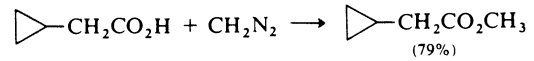


14[n]

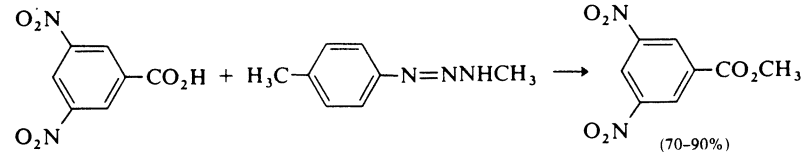


F. Esterification by Diazoalkanes and Triazenes

15[o]

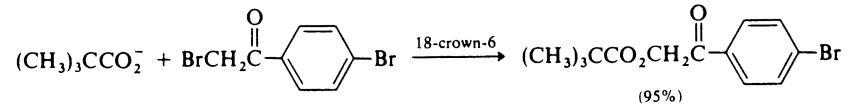


16[p]



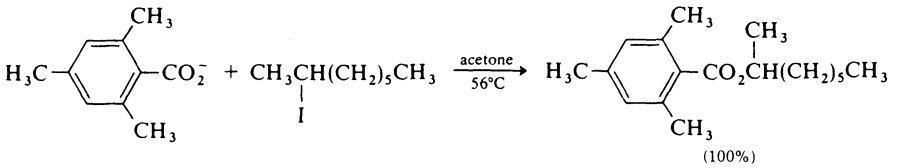
G. Esterification by Nucleophilic Substitution with Carboxylate Salts

17[q]



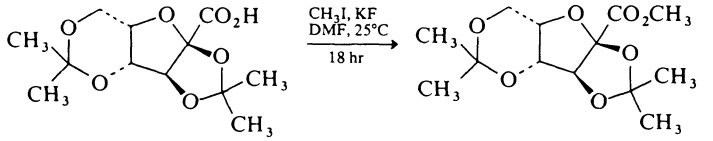
Scheme 3.2—*continued*

18[r]



(100%)

19[s]



(84%)

H. Phosphorus Nucleophiles

20[t] $Ph_3P + BrCH_2CH_2OPh \rightarrow Ph_3\overset{+}{P}CH_2CH_2OPh\ Br^-$

21[u] $[(CH_3)_2CHO]_3P + CH_3I \rightarrow [(CH_3)_2CHO]_2\overset{O}{\overset{\|}{P}}CH_3 + (CH_3)_2CHI$

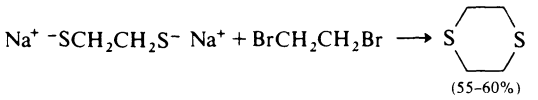
(85–90%)

I. Sulfur Nucleophiles

22[v] $CH_3(CH_2)_{10}CH_2Br + S{=}C(NH_2)_2 \xrightarrow[H_2O]{NaOH} CH_3(CH_2)_{10}CH_2SH$

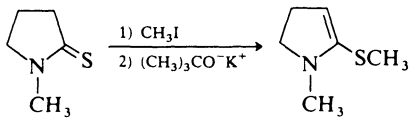
(80%)

23[w]



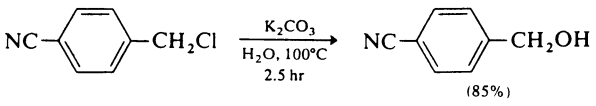
(55–60%)

24[x]



(62%)

a. M. S. Newman and S. Otsuka, *J. Org. Chem.* **23**, 797 (1958).
b. B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy, *J. Am. Chem. Soc.* **92**, 336 (1970).
c. J. J. Bloomfield and P. V. Fennessey, *Tetrahedron Lett.*, 2273 (1964).
d. W. P. Reeves and M. L. Bahr, *Synthesis*, 823 (1976).
e. B. Lal, B. N. Pramanik, M. S. Manhas, and A. K. Bose, *Tetrahedron Lett.*, 1977 (1977).
f. R. B. Moffett, *Org. Synth.* **IV**, 466 (1963).
g. J. C. Craig and R. J. Young, *Org. Synth.* **V**, 88 (1973).
h. R. E. Benson and T. L. Cairns, *Org. Synth.* **IV**, 588 (1963).
i. R. N. McDonald and P. A. Schwab, *J. Am. Chem. Soc.* **85**, 4004 (1963).
j. E. Adler and K. J. Bjorkquist, *Acta Chem. Scand.* **5**, 241 (1951).
k. C. H. Heathcock, C. T. White, J. J. Morrison, and D. VanDerveer, *J. Org. Chem.* **46**, 1296 (1981).
l. E. S. West and R. F. Holden, *Org. Synth.* **III**, 800 (1955).
m. C. F. H. Allen and J. W. Gates, Jr., *Org. Synth.* **III**, 140 (1955).
n. G. N. Vyas and N. M. Shah, *Org. Synth.* **IV**, 836 (1963).
o. L. I. Smith and S. McKenzie, Jr., *J. Org. Chem.* **15**, 74 (1950); A. I. Vogel, *Practical Organic Chemistry*, third edition, Wiley (1956), p. 973.
p. E. H. White, A. A. Baum, and D. E. Eitel, *Org. Synth.* **V**, 797 (1973).
q. H. D. Durst, *Tetrahedron Lett.*, 2421 (1974).
r. G. G. Moore, T. A. Foglia, and T. J. McGahan, *J. Org. Chem.* **44**, 2425 (1979).
s. C. H. Heathcock, C. T. White, J. Morrison, and D. VanDerveer, *J. Org. Chem.* **46**, 1296 (1981).
t. E. E. Schweizer and R. D. Bach, *Org. Synth.* **V**, 1145 (1973).
u. A. H. Ford-Moore and B. J. Perry, *Org. Synth.* **IV**, 325 (1963).
v. G. G. Urquhart, J. W. Gates, Jr., and R. Connor, *Org. Synth.* **III**, 363 (1965).
w. R. G. Gillis and A. B. Lacey, *Org. Synth.* **IV**, 396 (1963).
x. R. Gompper and W. Elser, *Org. Synth.* **V**, 780 (1973).



can be a useful synthetic transformation since benzyl halides are available either by side-chain bromination or chlorination or by the chloromethylation reaction (Section 8.1.3).

Ether formation from alkoxides and alkylating reagents is a reaction of general synthetic importance. The conversion of phenols to methoxy aromatics, for example, is a very common reaction, with methyl iodide or dimethyl sulfate usually being the alkylating agent. This reaction proceeds in the presence of a weak base, for example, Na_2CO_3, since the phenolic hydroxylic group is acidic. Under these conditions excellent yields are obtained from primary halides, sulfonates, and sulfates. The conjugate bases of alcohols are considerably more basic than phenoxides and therefore β-elimination of the alkyl halide becomes more of a problem. Fortunately the most commonly encountered ethers are methyl and benzyl ethers. The corresponding halides are incapable of β-elimination and are especially reactive toward substitution, so yields are usually excellent. Entries 11–14 in Scheme 3.2 are some typical examples of ether preparations.

Two methods for converting carboxylic acids to esters fall into the mechanistic pattern under discussion in this section. One of these methods is the reaction of carboxylic acids with diazo compounds, especially diazomethane. The second is alkylation of carboxylate anions by halides or sulfonates. The esterification of carboxylic acids with diazomethane is a very quick and clean reaction. The alkylating agent is the extremely reactive methyldiazonium ion which is generated by protonation of diazomethane. The reacting intermediate is probably best described as an ion pair which reacts virtually instantaneously to give the ester and molecular nitrogen. This reaction has been used innumerable times for the preparation of

$$RCO_2H + CH_2N_2 \rightarrow [RCO_2^- \; CH_3\overset{+}{N}_2] \rightarrow RCO_2CH_3 + N_2$$

methyl esters and is a very general reaction. The toxicity of diazoalkanes and some of its precursors is a drawback to this reaction. One possible alternative is the use of alkyltriazenes as reactive alkylating agents.[56] Alkyltriazenes are readily prepared from primary amines and aryldiazonium salts.[57] The triazenes, on being

$$RCO_2H + Ar{-}N{=}NNHR' \rightleftharpoons Ar{-}\overset{+}{\underset{H}{\underset{|}{N}}}{-}N{=}N{-}R' \; {}^{-}O_2CR \rightarrow RCO_2R' + ArNH_2 + N_2$$

protonated, generate a reactive alkylating agent which is equivalent, if not identical, to the alkyldiazonium ions generated from diazoalkanes.

56. E. H. White, H. Maskill, D. J. Woodcock, and M. A. Schroeder, *Tetrahedron Lett.*, 1713 (1969).
57. E. H. White and H. Scherrer, *Tetrahedron Lett.*, 758 (1961).

Especially for large-scale work, esters may be more safely and efficiently prepared by reaction of carboxylate salts with alkyl bromides, iodides or tosylates. The carboxylate anion is not a particularly reactive nucleophile so reaction proceeds best in polar aprotic solvents[58] or with crown ether catalysis.[59] Acetone has also been found to be a good solvent for reactions with alkyl iodides.[60] Carboxylate alkylation procedures have been particularly advantageous for preparation of hindered esters which can be relatively difficult to prepare by the acid-catalyzed esterification reactions to be discussed in Section 3.4. Sections F and G of Scheme 3.2 give some specific examples of ester alkylation by both diazoalkanes and other alkylating agents.

3.2.6. Sulfur Nucleophiles

Anions derived from thiols are very nucleophilic and can easily be alkylated by halides. Alcohol solvents are usually used. Phase transfer catalysis is observed,[61]

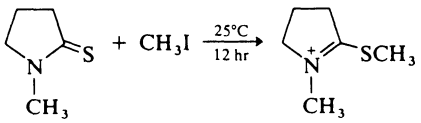
$$CH_3S^-Na^+ + ClCH_2CH_2OH \xrightarrow{C_2H_5OH} \underset{(75\text{-}80\%)}{CH_3SCH_2CH_2OH} \qquad \text{Ref. 62}$$

$$PhS^-Na^+ + CH_2{=}CHCHCl \rightarrow \underset{(50\%)}{CH_2{=}CHCHSPh} \qquad \text{Ref. 63}$$

as would be expected, but is usually unnecessary for preparative success, because of the high inherent nucleophilicity of thiolate anions. Nucleophilicity tends to increase with polarizability. Polarizability increases with increasing atomic number so that sulfur atoms are more nucleophilic than oxygen atoms in a comparable structural environment.

Neutral sulfur compounds are also good nucleophiles. Sulfides and thioamides readily form salts with methyl iodide, for example. Even sulfoxides, where

$$(CH_3)_2S + CH_3I \xrightarrow[12\text{-}16\text{ hr}]{25^\circ C} (CH_3)_3\overset{+}{S}\,I^- \qquad \text{Ref. 64}$$



Ref. 65

58. P. E. Pfeffer, T. A. Foglia, P. A. Barr, I. Schmeltz, and L. S. Silbert, *Tetrahedron Lett.*, 4063 (1972); J. E. Shaw, D. C. Kunerth, and J. J. Sherry, *Tetrahedron Lett.*, 689 (1973); J. Grundy, B. G. James, and G. Pattenden, *Tetrahedron Lett.*, 757 (1972).
59. C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez, and K. Smith, *Tetrahedron Lett.*, 2417 (1974).
60. G. G. Moore, T. A. Foglia, and T. J. McGahan, *J. Org. Chem.* **44**, 2425 (1979).
61. A. W. Herriott and D. Picker, *J. Am. Chem. Soc.* **97**, 2345 (1975).
62. W. Windus and P. R. Shildneck, *Org. Synth.* **II**, 345 (1943).
63. W. E. Parham and S. H. Groen, *J. Org. Chem.* **30**, 728 (1965).
64. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **87**, 1353 (1965).
65. R. Gompper and W. Elser, *Org. Synth.* **V**, 780 (1973).

nucleophilicity is decreased by the additional oxygen, can be alkylated by methyl iodide. These sulfonium and sulfoxonium salts have useful synthetic application as discussed in Chapter 2.

$$(CH_3)_2S{=}O + CH_3I \xrightarrow[72\ hr]{25°C} (CH_3)_3\overset{+}{S}{=}O\ I^- \qquad \text{Ref. 66}$$

3.2.7. Phosphorus Nucleophiles

Both neutral and anionic phosphorus compounds are good nucleophiles toward alkyl halides. Examples of these reactions were already encountered in Chapter 2 in connection with the preparation of the valuable phosphorane and phosphonate intermediates for Wittig-type reactions:

$$Ph_3P + CH_3Br \xrightarrow[2\ days]{room\ temp} Ph_3\overset{+}{P}CH_3\,Br^- \qquad \text{Ref. 67}$$

$$[(CH_3)_2CHO]_3P + CH_3I \rightarrow [(CH_3)_2CHO]_2\overset{O}{\overset{\|}{P}}CH_3 + (CH_3)_2CHI \qquad \text{Ref. 68}$$

The reaction with phosphite esters is known as the Michaelis–Arbuzov reaction and proceeds through an unstable trialkoxyphosphonium ion intermediate. The

$$R'{-}X + P(OR)_3 \rightarrow (RO)_2\overset{+}{P}(R')-O-R\ \ ^-X \rightarrow (RO)_2\overset{O}{\overset{\|}{P}}R' + RX$$

second step in the sequence is another example of the great tendency of alkoxyphosphonium ions to react with nucleophiles to break the O—C bond, resulting in formation of a phosphoryl bond.

The reaction of α-bromoketones with phosphines and phosphites can take a competitive course in which phosphorus attacks at bromine. In protic solvents the enolate intermediate is protonated so that the overall course of the reaction is dehalogenation of the ketone[69]:

$$R_3P + BrCH_2\overset{O}{\overset{\|}{C}}R' \rightarrow R_3\overset{+}{P}Br + H_2C{=}\overset{O^-}{\overset{|}{C}}R'$$

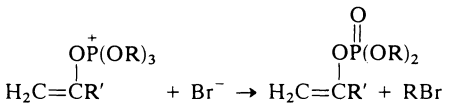
$$R_3\overset{+}{P}Br + H_2C{=}\overset{O^-}{\overset{|}{C}}R' \rightarrow H_2C{=}\overset{O\overset{+}{P}R_3}{\overset{|}{C}}R' + Br^-$$

or

$$R_3\overset{+}{P}Br + H_2C{=}\overset{O^-}{\overset{|}{C}}R' + ROH \rightarrow R_3P{=}O + CH_3\overset{O}{\overset{\|}{C}}R' + RBr$$

66. R. Kuhn and H. Trischmann, *Justus Liebig's Ann. der Chem.* **611**, 117 (1958).
67. G. Wittig and U. Schoellkopf, *Org. Synth.* **V**, 751 (1973).
68. A. H. Ford-Moore and B. J. Perry, *Org. Synth.* **IV**, 325 (1963).
69. N. Kreutzkamp and H. Kayser, *Chem. Ber.* **89**, 1614 (1956).

When the phosphorus compound is a phosphite ester the stable product is an enol phosphate.[70]

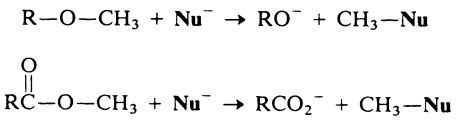


3.2.8. Summary of Nucleophilic Substitution at Saturated Carbon

In the preceding sections some of the nucleophilic substitution reactions at sp^3 carbons which are most valuable for synthesis have been outlined. These reactions all fit into the general mechanistic patterns that were discussed in Chapter 5, Part A. Thus the order of reactivity of alkylating groups is benzyl > allyl ~ methyl > secondary. Tertiary alkylating agents generally will not react satisfactorily. The reactivity of leaving groups is sulfonate > iodide > bromide > chloride. Steric hindrance can greatly decrease the rate of reaction in nucleophilic substitution. Thus projected steps involving nucleophilic substitution must be carefully evaluated for potential steric problems. Because of their high reactivity toward nucleophilic substitution, α-haloesters, α-haloketones, α-halonitriles, and α-haloethers are all especially favorable substrates for reactions of the type considered in the preceding sections. Scheme 3.2 gives some representative nucleophilic substitutions drawn from the *Organic Syntheses* series and recent synthetic efforts.

3.3. Nucleophilic Cleavage of Carbon–Oxygen Bonds in Ethers and Esters

The cleavage by nucleophilic substitution of carbon–oxygen bonds in ethers or in esters is frequently a desirable synthetic transformation. The objective may



be to remove a temporary blocking group or in the case of esters, for example, to liberate a carboxylate group under nonhydrolytic conditions. The classical ether cleavage reactions involving concentrated hydrogen halides are much too strenuous for most polyfunctionalized molecules. Fortunately, several much milder reagents have been developed for effecting these transformations. These reagents include

70. I. J. Borowitz and H. Parnes, *J. Org. Chem.* **32**, 3560 (1967).

boron tribromide,[71] trimethylsilyl iodide,[72] and boron trifluoride in the presence of thiols.[73]

The mechanism for ether cleavage with boron tribromide involves attack of bromide ion on an adduct formed from the ether and the electrophilic boron reagent. The cleavage step can occur by either an S_N2- or S_N1-type process,

$$R{-}O{-}R + BBr_3 \rightarrow R{-}\overset{+}{O}(^{-}BBr_3){-}R$$

$$R{-}\overset{+}{O}(^{-}BBr_3){-}R \overset{\curvearrowleft Br^-}{\rightarrow} R{-}O{-}BBr_2 + RBr + Br^-$$

$$R{-}O{-}BBr_2 + 3H_2O \rightarrow ROH + B(OH)_3 + 2HBr$$

depending on the nature of the alkyl group. Generally good yields are observed, especially for methyl ethers. Trimethylsilyl iodide cleaves methyl ethers in a period of a few hours at room temperature.[72] Benzyl and *t*-butyl systems are cleaved very rapidly, whereas secondary systems react over 10–50 hr. The reaction presumably proceeds via an initially formed oxonium ion intermediate. The direction of cleavage

$$R{-}O{-}R + (CH_3)_3SiI \rightarrow R{-}\overset{+}{O}(Si(CH_3)_3){-}R + I^-$$

$$R{-}\overset{+}{O}(Si(CH_3)_3){-}R + I^- \rightarrow R{-}O{-}Si(CH_3)_3 + RI$$

in unsymmetrical ethers is determined by the relative ease of O—R bond breaking by either S_N2 (methyl, etc.) or S_N1 (*t*-butyl, etc.) processes. Because trimethylsilyl iodide is rather expensive and is also difficult to store and handle, alternative procedures which generate the reagent *in situ* from other sources have been reported. In the presence of an ether, the cleavage reaction proceeds as the trimethylsilyl iodide is generated.

$$(CH_3)_3SiCl + NaI \xrightarrow{CH_3CN} (CH_3)_3SiI + NaCl \qquad \text{Ref. 74}$$

$$PhSi(CH_3)_3 + I_2 \rightarrow (CH_3)_3SiI + PhI \qquad \text{Ref. 75}$$

Trimethylsilyl iodide also effects rapid cleavage of esters. The first products formed are trimethylsilyl esters but these are hydrolyzed on exposure to water.[76]

71. J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron* **24**, 2289 (1968).
72. M. E. Jung and M. A. Lyster, *J. Org. Chem.* **42**, 3761 (1977).
73. M. Node, H. Hori, and E. Fujita, *J. Chem. Soc. Perkin Trans. 1*, 2237 (1976); K. Fuji, K. Ichikawa, M. Node, and E. Fujita, *J. Org. Chem.* **44**, 1661 (1979).
74. T. Morita, Y. Okamoto, and H. Sakurai, *J. Chem. Soc. Chem. Commun.*, 874 (1978); G. A. Olah, S. C. Narang, B. G. B. Gupta, and R. Malhotra, *Synthesis*, 61 (1979).
75. T. L. Ho and G. A. Olah, *Synthesis*, 417 (1977); R. A. Benkeser, E. C. Mozdzen, and C. L. Muth, *J. Org. Chem.* **44**, 2185 (1979).
76. T. L. Ho and G. A. Olah, *Angew. Chem. Int. Ed. Engl.* **15**, 774 (1976); M. E. Jung and M. A. Lyster, *J. Am. Chem. Soc.* **99**, 968 (1977).

$$RCO{-}R' + (CH_3)_3SiI \rightarrow R\overset{+}{C}O{-}R' + I^-$$

$$R\overset{+}{C}O{-}R' + I^- \rightarrow RCOSi(CH_3)_3 + R'I$$

$$RCOSi(CH_3)_3 + H_2O \rightarrow RCO_2H + (CH_3)_3SiOH$$

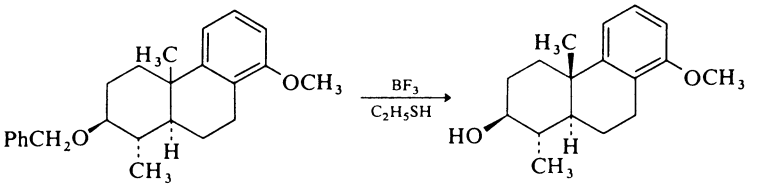
Benzyl, methyl, and *t*-butyl esters are rapidly cleaved, but secondary esters react more slowly. In the case of the *t*-butyl esters, the initial silylation is followed by a rapid ionization to the *t*-butyl cation.

The boron trifluoride–alkyl thiol combination of reagents also operates on the principal of nucleophilic attack on an oxonium complex of the ether.[77] The transition

$$R{-}O{-}R + BF_3 \rightarrow R{-}\overset{+}{O}(BF_3^-){-}R$$

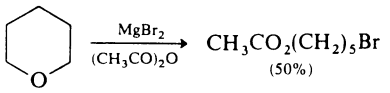
$$R{-}\overset{+}{O}(BF_3^-){-}R + R'SH \rightarrow ROBF_3^- + RSR' + H^+$$

state for the reaction must involve substantial ionization since it is found that benzyl ethers are cleaved in preference to methyl ethers.



Ref. 77

Ether cleavage has also been observed in reactions with Lewis acids and acetic anhydride. Lewis acids which have been used in this context include BF_3,[78] $FeCl_3$,[79]



Ref. 80

and $MgBr_2$.[80] Mechanistic investigations have pointed to acylium ions, generated from the anhydride and Lewis acid as the reactive electrophile:

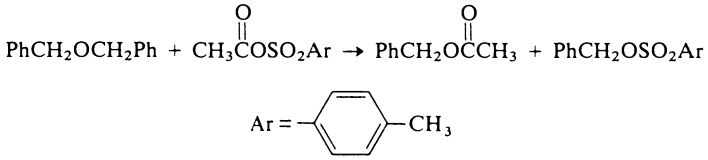
$$(RCO)_2O + MX_n \rightarrow RC{\equiv}\overset{+}{O} + [MX_nO_2CR]^-$$

$$RC{\equiv}\overset{+}{O} + R'{-}O{-}R' \rightarrow R'{-}\overset{+}{O}(R{-}C{=}O){-}R'$$

$$R'{-}\overset{+}{O}(R{-}C{=}O){-}R' + X^- \rightarrow R'{-}X + RCO_2R'$$

77. K. Fuji, K. Ichikawa, M. Node, and E. Fujita, *J. Org. Chem.* **44**, 1661 (1979).
78. C. R. Narayanan and K. N. Iyer, *J. Org. Chem.* **30**, 1734 (1965).
79. B. Ganem and V. R. Small, Jr., *J. Org. Chem.* **39**, 3728 (1974).
80. D. J. Goldsmith, E. Kennedy, and R. G. Campbell, *J. Org. Chem.* **40**, 3571 (1975).

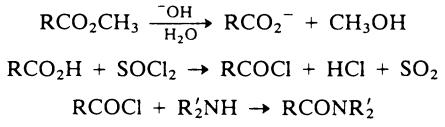
Mixed sulfonic–acetic anhydrides convert ethers to esters.[81] Here the mixed anhydride serves as the source of the acylium ion.



Scheme 3.3 gives some specific examples of ether-cleaving reactions.

3.4. Synthetic Interconversion of Carboxylic Acid Derivatives

The classes of compounds which are conveniently considered together as derivatives of carboxylic acids include the carboxylic acid anhydrides, acid chlorides, esters, and amides. In the case of simple aliphatic and aromatic acids, synthetic transformations among these derivatives is usually a straightforward matter involving such fundamental reactions as ester saponification, formation of acid chlorides, and the reaction of amines with acid anhydrides or acid chlorides. When a multistep



synthesis is being undertaken with other sensitive functional groups present in the molecule, milder reagents and conditions may be necessary. As a result, many alternative methods for effecting interconversion of the carboxylic acid derivatives have been developed and some of these will be considered in the succeeding sections.

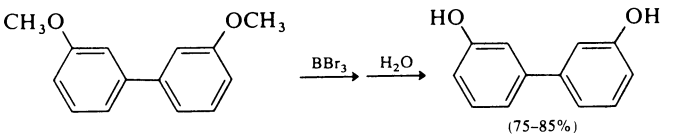
3.4.1. Preparation of Reactive Reagents for Acylation

The traditional method for transforming carboxylic acids into reactive acylating agents capable of converting alcohols to esters or amines to amides is the formation of an acid chloride. Molecules devoid of acid-sensitive functional groups can be converted to the acid chloride with thionyl chloride or phosphorus pentachloride. When milder conditions are necessary, the reaction of the acid or its sodium salt with oxalyl chloride, usually in a hydrocarbon solvent, provides the acid chloride under essentially neutral conditions.

81. M. H. Karger and Y. Mazur, *J. Org. Chem.* **36**, 532 (1971).

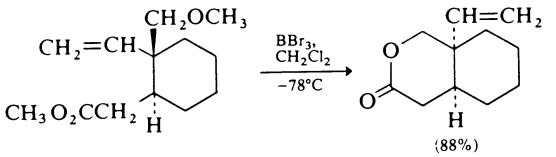
Scheme 3.3. Cleavage of Ethers and Esters

1[a]



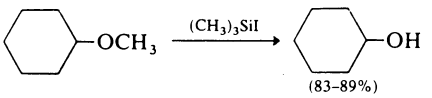
(75–85%)

2[b]



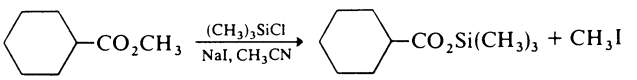
(88%)

3[c]



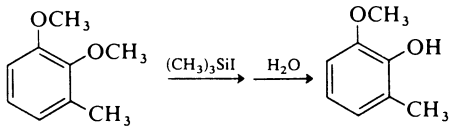
(83–89%)

4[d]

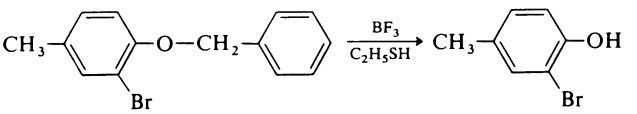


(86%)

5[e]

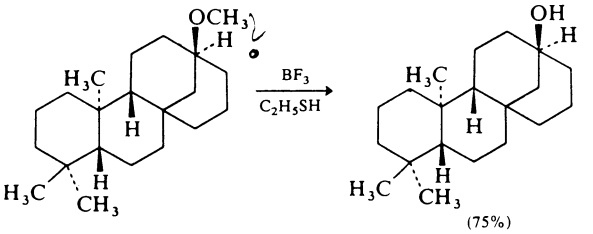


6[f]



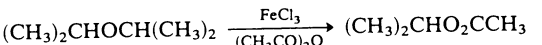
(90%)

7[g]



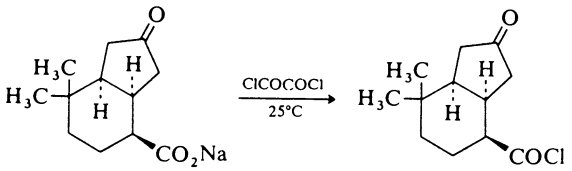
(75%)

8[h]



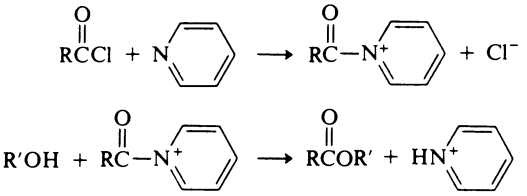
(83%)

a. J. F. W. McOmie and D. E. West, *Org. Synth.* **V**, 412 (1973).
b. P. A. Grieco, K. Hiroi, J. J. Reap, and J. A. Noguez, *J. Org. Chem.* **40**, 1450 (1975).
c. M. E. Jung and M. A. Lyster, *Org. Synth.* **59**, 35 (1980).
d. T. Morita, Y. Okamoto, and H. Sakurai, *J. Chem. Soc. Chem. Commun.*, 874 (1978).
e. E. H. Vickery, L. F. Pahler, and E. J. Eisenbraun, *J. Org. Chem.* **44**, 4444 (1979).
f. K. Fuji, K. Ichikawa, M. Node, and E. Fujita, *J. Org. Chem.* **44**, 1661 (1979).
g. M. Nobe, H. Hori, and E. Fujita, *J. Chem. Soc. Perkin Trans. 1*, 2237 (1976).
h. B. Ganem and V. R. Small, Jr., *J. Org. Chem.* **39**, 3728 (1974).



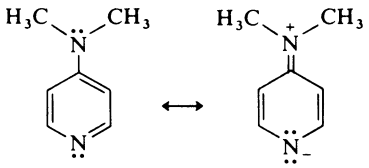
Ref. 82

Acid chlorides are highly reactive acylating agents and react very rapidly with amines. For alcohols, preparative procedures often call for use of pyridine as a catalyst. Pyridine-catalyzed acylations probably usually involve initial acylation of pyridine followed by reaction with the alcohol. Pyridine is a better nucleophile



than neutral alcohols, but once the cationic acylpyridinium ion is formed the carbonyl carbon becomes more susceptible to nucleophilic attack.[83]

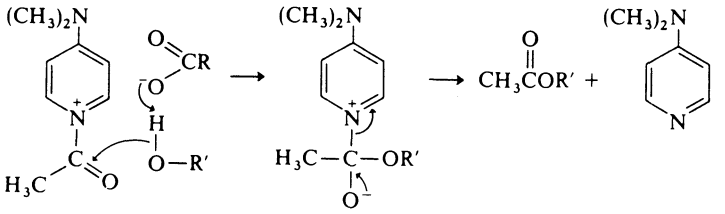
An even stronger catalytic effect is obtained when 4-dimethylaminopyridine is used as a nucleophilic catalyst.[84] The dimethylamino function acts as an electron donor substituent, increasing both the nucleophilicity and basicity of the pyridine nitrogen. The inclusion of dimethylaminopyridine to the extent of 5–20 mol % in



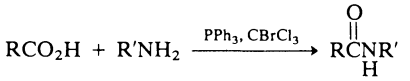
acylations by acid anhydrides and acid chlorides increases acylation rates by up to four orders of magnitude and permits successful acylation of tertiary and other hindered alcohols.

The mechanism of catalysis by dimethylaminopyridine is considered to involve an *N*-acylpyridinium ion. However, the identity of the anion also affects the reactivity so that a complete formulation requires attention to the ion pair characteristics of the acylpyridinium ion. Interestingly, in the presence of 4-dimethylaminopyridine, acetic anhydride is a more reactive acylating agent than acetyl chloride. This is a reversal of their normal reactivity. This reversal can be explained if the counterion acetate, a stronger base than chloride, is involved in deprotonating the alcohol.[84]

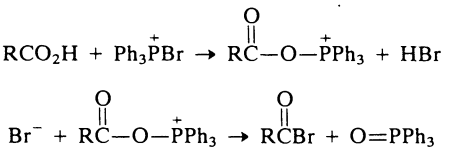
82. M. Miyano and C. R. Dorn, *J. Org. Chem.* **37**, 268 (1972).
83. A. R. Fersht and W. P. Jencks, *J. Am. Chem. Soc.* **92**, 5432, 5442 (1970).
84. G. Hofle, W. Steglich, and H. Vorbruggen, *Angew. Chem. Intern. Ed. Engl.* **17**, 569 (1978); E. Guibe-Jampel, G. Le Corre, and M. Wakselman, *Tetrahedron Lett.*, 1157 (1979).



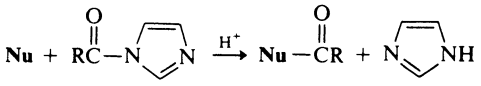
There are other activation procedures which generate acyl halides *in situ* in the presence of the nucleophile. Refluxing a carboxylic acid, triphenylphosphine, bromotrichloromethane, and an amine gives rise to the corresponding amide.[85] This



reaction presumably proceeds via the acid bromide since it is known that triphenylphosphine and carbon tetrachloride convert acids to the corresponding acid chloride.[86] Similarly, carboxylic acids react with the triphenylphosphine–bromide adduct to give acyl bromides.[87] These reactions are mechanistically analogous to the alcohol to halide conversions which were disucssed in Section 3.1.2.



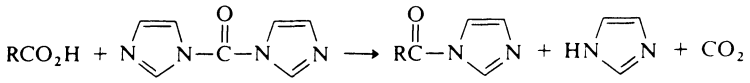
In addition to acid chlorides and acid bromides there are a number of milder and more selective acylating agents which can be readily prepared from carboxylic acids. Imidazolides, the *N*-acyl derivatives of imidazole, are examples.[88] The reactivity of imidazolides as acylating reagents is based on the relative weakness of this particular type of amide bond because of the aromatic character of imidazole. Unlike normal amides, the resonance donation from the nitrogen to the carbonyl oxygen is weak. As a result the carbonyl group is susceptible to nucleophile attack. The



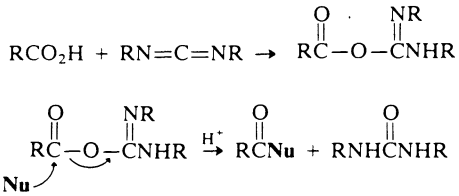
reactivity of the imidazolides is also enhanced if protonation occurs on the other imidazole nitrogen. The imidazole ring functions much the same as the pyridine ring in pyridine-catalyzed acylation. Imidazolides are, however, isolable substances and can be prepared directly from the carboxylic acid by reaction with carbonyldi-

85. L. E. Barstow and V. J. Hruby, *J. Org. Chem.* **36**, 1305 (1971).
86. J. B. Lee, *J. Am. Chem. Soc.* **88**, 3440 (1966).
87. H. J. Bestmann and L. Mott, *Justus Liebig's Ann. der Chem.* **693**, 132 (1966).
88. H. A. Staab and W. Rohr, *Newer Methods Prep. Org. Chem.* **5**, 61 (1968).

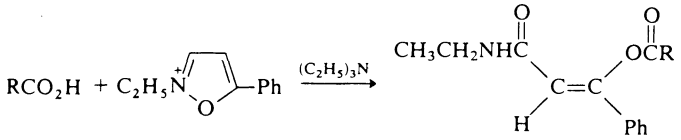
imidazole. Imidazolides react with alcohols on heating to give esters and react at room temperature with amines to give amides. Imidazolides are particularly appropriate for acylation of acid-sensitive materials.



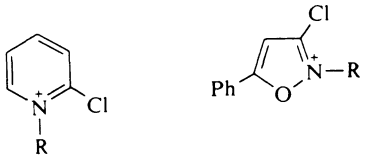
Cyclohexylcarbodiimide is another example of a reagent which converts carboxylic acids directly to reactive acylating agents. This substance has been particularly widely applied for the acylation step in the synthesis of polypeptides from amino acids but the method of activation is also applicable to other problems.[89] Carboxylic acids react with carbodiimides to give an acyl isourea. The acyl group is highly reactive in this environment because the cleavage of the acyl–oxygen bond converts the carbon–nitrogen double bond of the isourea to a more stable carbon–oxygen double bond.[90] A somewhat similar mechanistic principle also applies in



the reaction of carboxylic acids with isoxazolium salts.[91] The mechanism of carboxyl activation by these reagents is the topic of problem 13. 2-Chloropyridinium[92] and

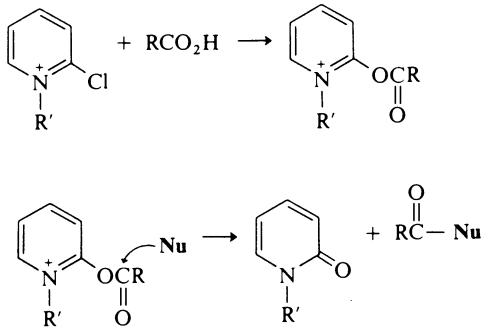


3-chloroisoxazolium[93] cations also activate carboxyl groups for nucleophilic attack. In each instance the halide is displaced from the heterocycle by the carboxylate

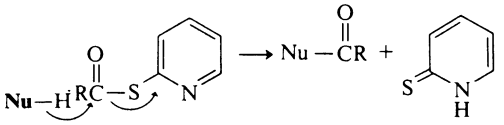


89. F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.* **67**, 107 (1967). A. Hassner and V. Alexanian, Tetrahedron Lett., 4475 (1978).
90. D. F. DeTar and R. Silverstein, *J. Am. Chem. Soc.* **88**, 1013, 1020 (1966); D. F. DeTar, R. Silverstein, and F. F. Rogers, Jr., *J. Am. Chem. Soc.* **88**, 1024 (1966).
91. R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.* **83**, 1007 (1961).
92. T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, *Chem. Lett.*, 1045 (1975).
93. K. Tomita, S. Sugai, T. Kobayashi, and T. Murakami, *Chem. Pharm. Bull.* **27**, 2398 (1979).

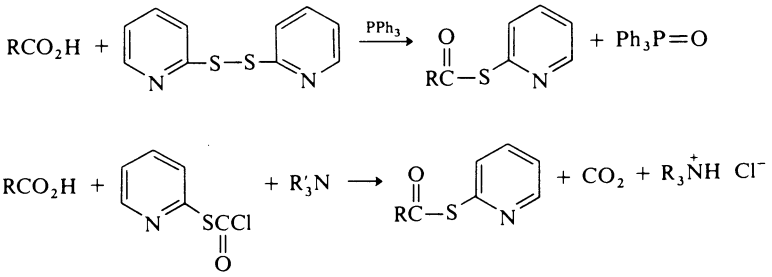
group. The acyl group is then very reactive to nucleophilic attack, with the heterocyclic ring being converted to an amide-like structure in each case. The positive charge initially present on the heterocyclic ring, of course, greatly accelerates both the initial substitution step and the subsequent acylation.



Carboxylic acid esters of thiols are considerably more reactive as acylating reagents than are the esters of simple alcohols. Particularly reactive are esters of pyridine-2-thiol since there is an additional driving force—the formation of the more stable pyridine-2-thione tautomer.



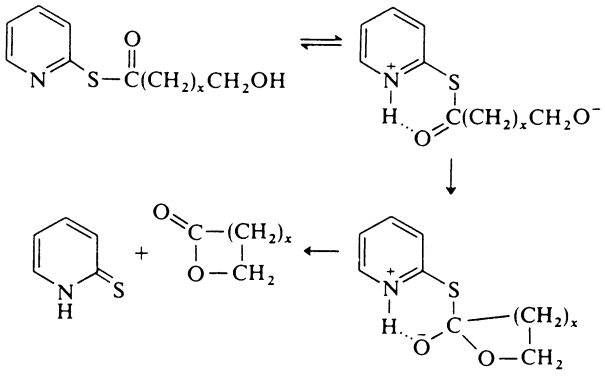
These esters can be prepared by reaction of the carboxylic acid with 2,2′-dipyridyl disulfide and triphenylphosphine[94] or directly from the acid and 2-pyridyl thiochloroformate.[95]



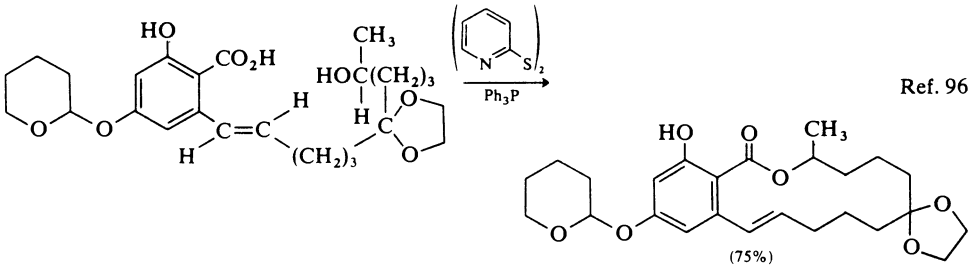
The 2-pyridyl and related 2-imidazoyl disulfides have found a special use in the closure of large lactone rings.[96] This type of structural feature is encountered

94. T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, 1901 (1970).
95. E. J. Corey and D. A. Clark, *Tetrahedron Lett.*, 2875 (1979).
96. E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.* **96**, 5614 (1974); K. C. Nicolaou, *Tetrahedron* **33**, 683 (1977).

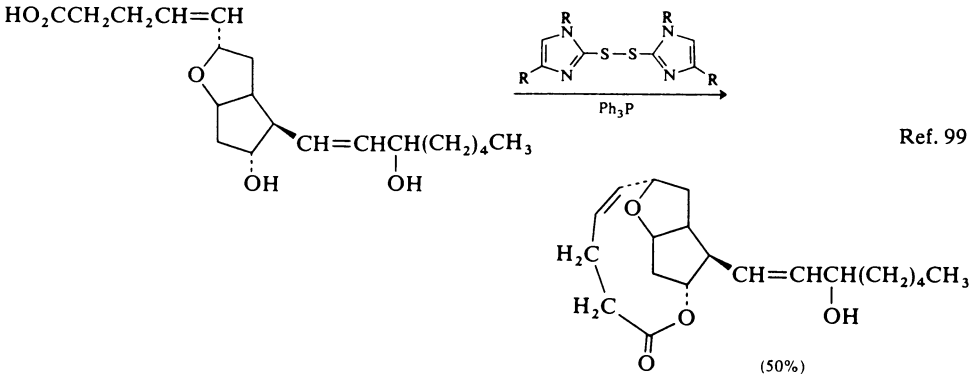
in a number of antibiotics which, because of the presence of numerous other sensitive functional groups, require mild conditions for cyclization. It has been proposed that the pyridyl and imidazoyl thioesters function by a mechanism in which the heterocyclic nitrogen also acts as a base, deprotonating the alcohol group. This provides the possibility for a cyclic transition state in which hydrogen bonding



enhances the reactivity of the carbonyl group.[97,98] Quite remarkable yields of lactones are achieved by this method.



Ref. 96



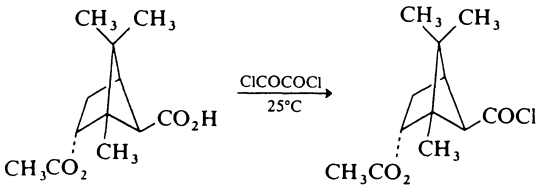
Ref. 99

97. E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., *J. Am. Chem. Soc.* **97**, 654 (1975).
98. E. J. Corey, D. J. Brunelle, and P. J. Stork, *Tetrahedron Lett.*, 3405 (1976).
99. E. J. Corey, H. L. Pearce, I. Szekely, and M. Ishiguro, *Tetrahedron Lett.*, 1023 (1978).

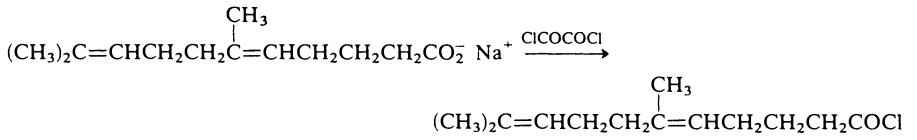
Scheme 3.4 gives some typical examples of preparation of reactive acylating reagents from carboxylic acids as well as the subsequent conversion of the acid derivatives to esters and amides.

Scheme 3.4. Preparation and Reactions of Active Acylating Agents

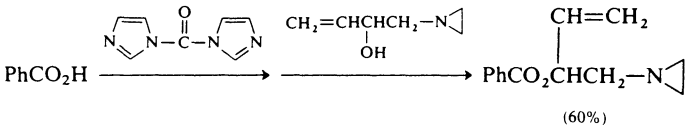
1[a]



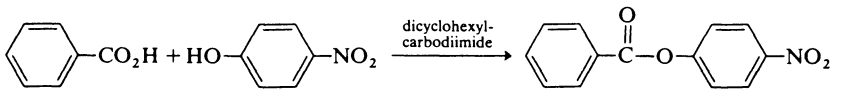
2[b]



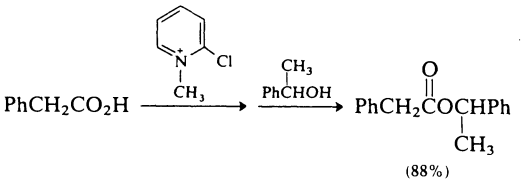
3[c]



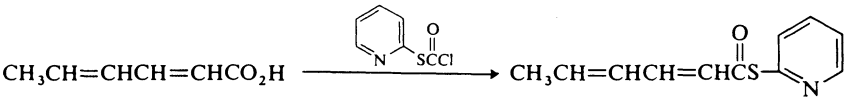
4[d]



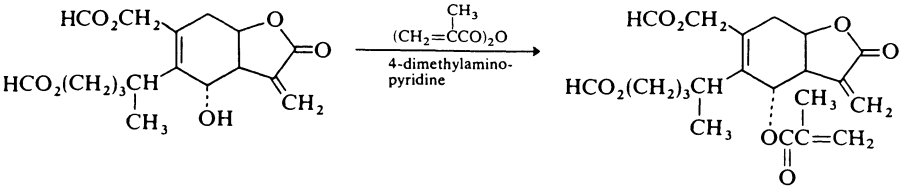
5[e]



6[f]



7[g]



a. J. Meinwald, J. C. Shelton, G. L. Buchanan, and A. Courtain, *J. Org. Chem.* **33**, 99 (1968).
b. U. T. Bhalerao, J. J. Plattner, and H. Rapaport, *J. Am. Chem. Soc.* **92**, 3429 (1970).
c. H. A. Staab and W. Rohr, *Chem. Ber.* **95**, 1298 (1962).
d. S. Neelakantan, R. Padmasani, and T. R. Seshadri, *Tetrahedron* **21**, 3531 (1965).
e. T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, *Chem. Lett.*, 1045 (1975).
f. E. J. Corey and D. A. Clark, *Tetrahedron Lett.*, 2875 (1979).
g. P. A. Grieco, T. Oguri, S. Gilman, and G. DeTitta, *J. Am. Chem. Soc.* **100**, 1616 (1978).

3.4.2. Preparation of Esters

As mentioned in the preceding section one of the most general methods of synthesis of esters is by reaction of alcohols with an acid chloride or other activated carboxylic acid derivative. Section 3.2.5 included a discussion of two other important methods, namely, reactions with diazoalkanes and reactions of carboxylate salts with alkyl halides or sulfonate esters. There remains to be mentioned the acid-catalyzed reaction of carboxylic acids with alcohols, which is frequently referred to as Fischer esterification:

$$RCO_2H + R'OH \xrightarrow{H^+} RCO_2R' + H_2O$$

This is an equilibrium process and there are two techniques which are used to drive the reaction to completion. One is to use a large excess of the alcohol. This is feasible for simple and relatively inexpensive alcohols. The second method is to drive the reaction forward by irreversible removal of water. Azeotropic removal of water is one simple method for doing this. Entries 1–4 in Scheme 3.5 are examples of acid-catalyzed esterifications. Entry 5 is the preparation of a diester starting with an anhydride. This is a closely related reaction in which the initial opening of the anhydride ring is followed by an acid-catalyzed esterification.

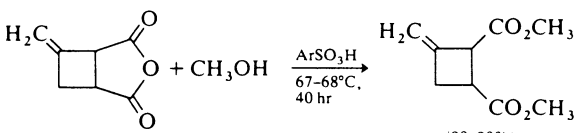
Scheme 3.5. Acid-Catalyzed Esterification

1[a] $CH_3CO_2H + HOCH_2CH_2CH_2Cl \xrightarrow[\text{benzene, azeotropic removal of water}]{ArSO_3H} CH_3CO_2CH_2CH_2CH_2Cl$ (93%–95%)

2[b] $HO_2CC{\equiv}CCO_2H + CH_3OH \xrightarrow[25°C,\ 4\ days]{H_2SO_4} CH_3O_2CC{\equiv}CCO_2CH_3$ (72–88%)

3[c] $CH_3CH{=}CHCO_2H + CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_3 \xrightarrow[\text{benzene, azeotropic removal of water}]{H_2SO_4} CH_3CH{=}CHCO_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_3$ (85–90%)

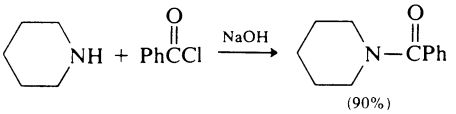
4[d] $PhCH(OH)CO_2H + C_2H_5OH \xrightarrow[78°C,\ 5\ hr]{HCl} PhCH(OH)CO_2C_2H_5$ (82–86%)

5[e]  (80–90%)

a. C. F. H. Allen and F. W. Spangler, *Org. Synth.* **III**, 203 (1955).
b. E. H. Huntress, T. E. Lesslie, and J. Bornstein, *Org. Synth.* **IV**, 329 (1963).
c. J. Munch-Petersen, *Org. Synth.* **V**, 762 (1973).
d. E. L. Eliel, M. T. Fisk, and T. Prosser, *Org. Synth.* **IV**, 169 (1963).
e. H. B. Stevenson, H. N. Cripps, and J. K. Williams, *Org. Synth.* **V**, 459 (1973).

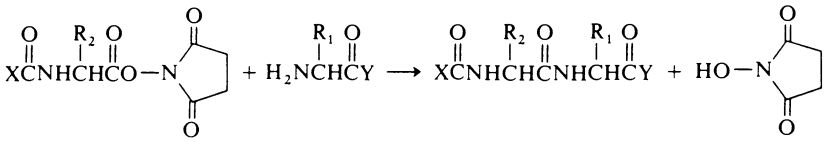
3.4.3. Preparation of Amides

By far the most common method for preparation of amides is the reaction of ammonia or a primary or secondary amine with one of the reactive acylating reagents described in Section 3.4.1. When acyl halides are used, some provision for neutralizing the hydrogen halide is necessary since it will otherwise tie up some of the reagent amine as the corresponding salt. Acid anhydrides give rapid acylation of most amines and are convenient if available. The Schotten–Baumann conditions involving shaking an amine with excess anhydride or acid chloride and an alkaline aqueous solution is a very satisfactory method for preparation of simple amides.



Ref. 100

A great deal of work has been done on the *in situ* activation of carboxylic acids toward nucleophilic substitution by amines. This type of reaction forms the backbone of the methods for synthesis of peptides and proteins. Among the methods for carboxylate activation which have achieved importance in peptide synthesis that were mentioned in Section 3.4.1 are the carbodiimide and isoxazolium methods. Since amines are better nucleophiles than alcohols, the leaving group in a potential acylation reagent need not be as reactive as is necessary for alcohols. The *p*-nitrophenyl[101] and 2,4,5-trichlorophenyl[102] esters of amino acids are sufficiently reactive toward amines to be useful in peptide synthesis. Acyl derivatives of *N*-hydroxysuccinimide are also useful for synthesis of peptides and other types of amides.[103] Like the *p*-nitrophenyl esters, the acylated *N*-hydroxysuccinimides can be isolated and purified, but rapidly react with free amino groups. The *N*-hydroxysuccinimide that is liberated is easily removed because of its solubility in dilute



base. The relative stability of the anion of *N*-hydroxysuccinimide is also responsible for the acyl derivative being reactive toward nucleophilic attack by an amino group.

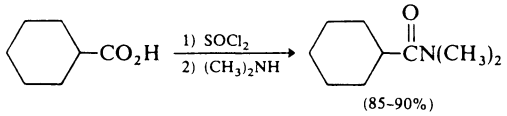
The preparation of amides directly from alkyl esters is feasible but can be troublesome. Reaction between most esters and simple amines proceeds to give amides but is inconveniently slow for most preparative purposes. Entries 4 and 5 in Scheme 3.6 are successful examples. The reactivity of ethyl cyanoacetate (entry 4)

100. C. S. Marvel and W. A. Lazier, *Org. Synth.* **I**, 99 (1941).
101. M. Bodanszky and V. DuVigneaud, *J. Am. Chem. Soc.* **81**, 5688 (1959).
102. J. Pless and R. A. Boissonnas, *Helv. Chim. Acta* **46**, 1609 (1963).
103. G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Am. Chem. Soc.* **86**, 1839 (1964).

Scheme 3.6. Synthesis of Amides

A. From Acid Chlorides and Anhydrides

1[a] $(CH_3)_2CHCO_2H \xrightarrow[2)\ NH_3]{1)\ SOCl_2} (CH_3)_2CHCNH_2$ (70%)

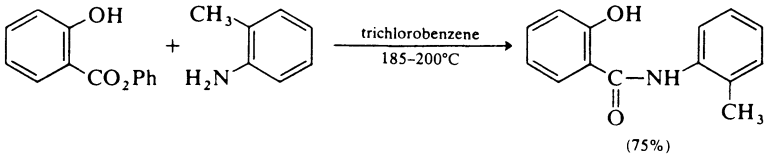
2[b] 

(85–90%)

3[c] $(CH_3CO)_2O + H_2NCH_2CO_2H \rightarrow CH_3CNCH_2CO_2H$ (90%)

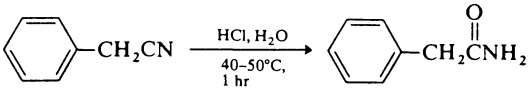
B. From Esters

4[d] $NCCH_2CO_2C_2H_5 \xrightarrow{NH_4OH} NCCH_2CNH_2$

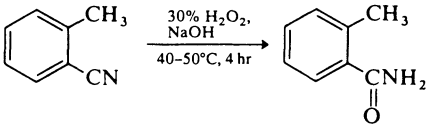
5[e] 

(75%)

C. From Nitriles

6[f] 

(80%)

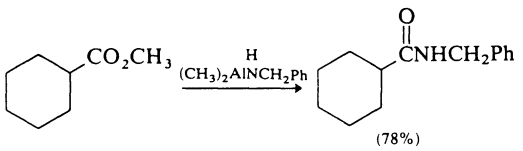
7[g] 

(90%)

a. R. E. Kent and S. M. McElvain, *Org. Synth.* **III**, 490 (1955).
b. A. C. Cope and E. Ciganek, *Org. Synth.* **IV**, 339 (1963).
c. R. M. Herbst and D. Shemin, *Org. Synth.* **II**, 11 (1943).
d. B. B. Corson, R. W. Scott, and C. E. Vose, *Org. Synth.* **I**, 179 (1941).
e. C. F. H. Allen and J. Van Allan, *Org. Synth.* **III**, 765 (1955).
f. W. Wenner, *Org. Synth.* **IV**, 760 (1963).
g. C. R. Noller, *Org. Synth.* **II**, 586 (1943).

is higher than for unsubstituted aliphatic compounds because of the activating effect of the cyano group.

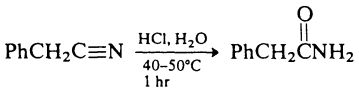
A promising new method for converting esters to amides involves aluminum amides which can be prepared from trimethylaluminum and ammonia or an amine. These reagents convert esters directly to amides at room temperature. The driving



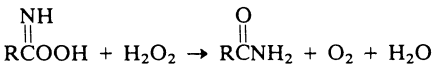
Ref. 104

force for this reaction is the strength of the aluminum–oxygen bond relative to the aluminum–nitrogen bond. Trialkyltin amides and *tetrakis*-(dimethylamino)titanium show similar reactivity.[105]

The cyano group is at the carboxylic acid oxidation level so nitriles are potential precursors of primary amides. Partial hydrolysis is sometimes possible.[106] A milder



procedure involves the reaction of a nitrile with an alkaline solution of hydrogen peroxide.[107] The strongly nucleophilic hydrogen peroxide adds to the nitrile and the resulting adduct gives the amide. There are several possible mechanisms for the subsequent decomposition of the peroxycarboximidic acid adduct.[108] In all the



mechanisms the hydrogen peroxide is converted to oxygen and water, leaving the organic substrate hydrolyzed, but at the same oxidation level. Scheme 3.6 illustrates some of the methods which are available for synthesis of amides from carboxylic acids, esters, and nitriles.

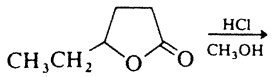
Problems

(*References for these problems are found on page* 622.)

1. Give the products which would be expected to be formed under the specified reaction conditions. Be sure to specify all aspects of stereochemistry.

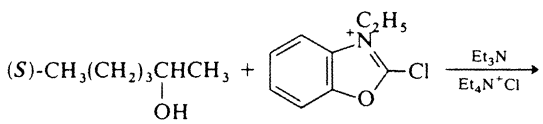
104. A. Basha, M. Lipton, and S. M. Weinreb, *Tetrahedron Lett.*, 4171 (1977).
105. G. Chandra, T. A. George, and M. F. Lappert, *J. Chem. Soc. C*, 2565 (1969).
106. W. Wenner, *Org. Synth.* **IV**, 760 (1963).
107. C. R. Noller, *Org. Synth.* **II**, 586 (1943); J. S. Buck and W. S. Ide, *Org. Synth.* **II**, 44 (1943).
108. K. B. Wiberg, *J. Am. Chem. Soc.* **75**, 3961 (1953); **77**, 2519 (1955); J. E. McIsaac, Jr., R. E. Ball, and E. J. Behrman, *J. Org. Chem.* **36**, 3048 (1971).

(a)

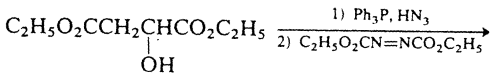


(b) $CH_3(CH_2)_4CH_2OH + ClCH_2OCH_3 \xrightarrow[CH_2Cl_2]{CH_3CH_2N(i\text{-}Pr)_2}$

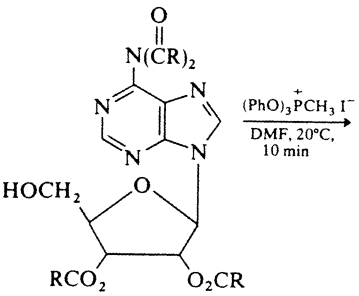
(c)



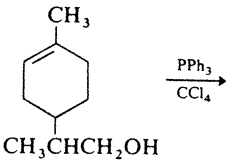
(d)



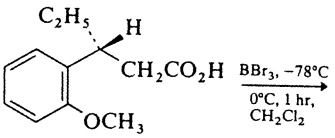
(e)



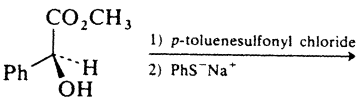
(f)



(g)

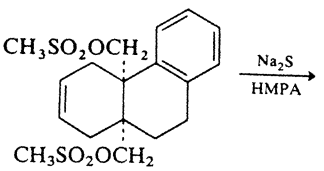


(h)

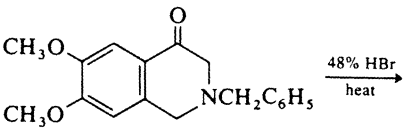


(i) $(C_6H_5)_2CHBr + P(OCH_3)_3 \rightarrow$

(j)



(k)

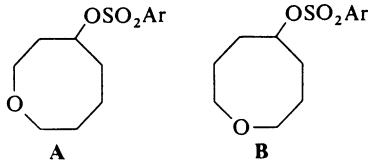


2. When (*R*)-(−)-5-hexen-2-ol was treated with triphenylphosphine in refluxing carbon tetrachloride, (+)-5-chloro-1-hexene was obtained. Conversion of (*R*)-(−)-5-hexen-2-ol to its *p*-bromobenzenesulfonate ester and subsequent reaction with lithium chloride gave (+)-5-chloro-1-hexene. Reaction of (*S*)-(+)-5-hexen-2-ol with phosphorus pentachloride in ether gave (−)-5-chloro-1-hexene.
   (a) Write chemical equations for each of the reactions described above and specify whether each one proceeds with net retention of configuration or inversion of configuration.
   (b) What is the sign of rotation of (*R*)-5-chloro-1-hexene?
3. A careful investigation of the extent of isomeric products formed by reaction of several alcohols with thionyl chloride has been reported. The product compositions for several of the alcohols are given below. Show how each of the rearranged products arises and discuss the structural features which promote isomerization.

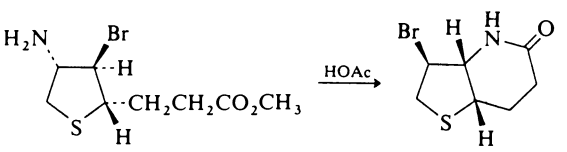
$$\text{ROH} \xrightarrow[100°\text{C}]{\text{SOCl}_2} \text{RCl}$$

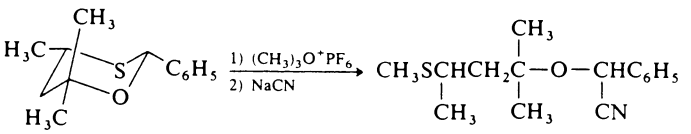
R	% unrearranged RCl	Structure and amount of rearranged RCl
$CH_3CH_2CH_2CH_2-$	100	
$(CH_3)_2CHCH_2-$	99.7	$CH_3CH_2\underset{\displaystyle Cl}{\underset{\vert}{C}}HCH_3$ (0.3%)
$(CH_3)_2CHCH_2CH_2-$	100	
$CH_3CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2-$	78	$CH_3\underset{\displaystyle Cl}{\underset{\vert}{C}}HCH_2CH_2CH_3$ (1%), $CH_3CH_2\underset{\displaystyle Cl}{\underset{\vert}{C}}HCH_2CH_3$ (11%), $CH_3CH_2\underset{\displaystyle Cl}{\underset{\vert}{C}}(CH_3)_2$ (10%)
$(CH_3)_3CCH_2-$	2	$CH_3CH_2\underset{\displaystyle Cl}{\underset{\vert}{C}}(CH_3)_2$ (98%)
$CH_3CH_2CH_2\underset{\displaystyle \vert}{C}HCH_3$	98	$CH_3CH_2\underset{\displaystyle Cl}{\underset{\vert}{C}}HCH_2CH_3$ (2%)
$CH_3CH_2\underset{\displaystyle \vert}{C}HCH_2CH_3$	90	$CH_3CH_2CH_2\underset{\displaystyle Cl}{\underset{\vert}{C}}HCH_3$ (10%)
$(CH_3)_2CH\underset{\displaystyle \vert}{C}HCH_3$	5	$CH_3CH\underset{\displaystyle Cl}{\underset{\vert}{C}}(CH_3)_2$ (95%)

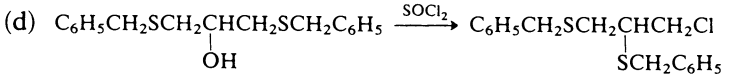
4. Give a reaction mechanism which will explain the following observations and transformations.
   (a) Kinetic measurements reveal that solvolytic displacement is about 5×10^5 faster for **B** than for **A**.

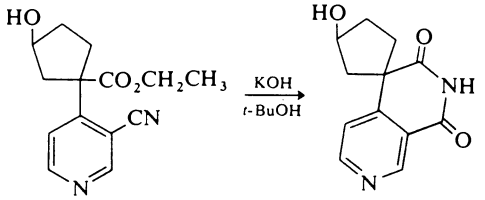


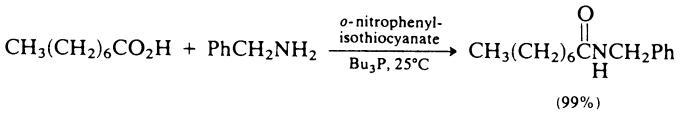
A **B**

(b) 

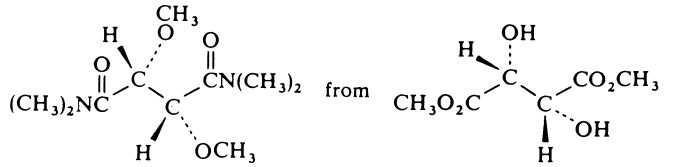
(c) 

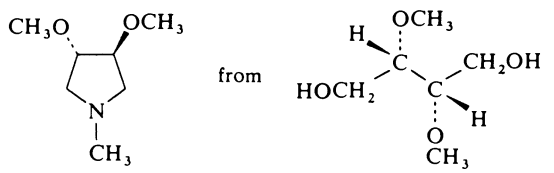
(d) 

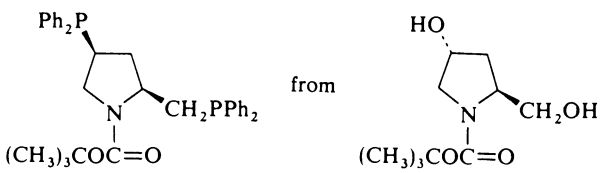
(e) 

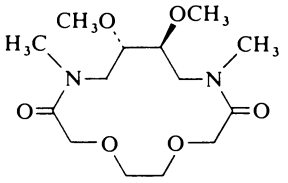
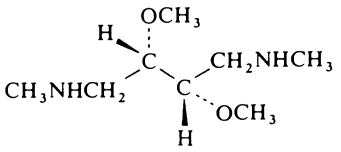
(f) 

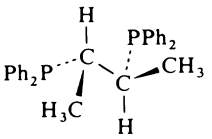
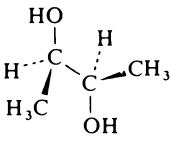
5. Substances such as carbohydrates, amino acids, and other small molecules available from natural sources are valuable starting materials for the synthesis of stereochemically defined substances. Suggest a sequence of reactions which could effect the following transformations, taking particular care to ensure that the product would be obtained stereochemically pure.

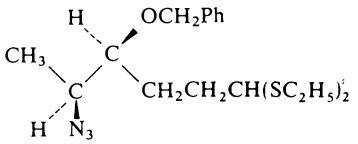
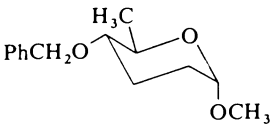
(a) 

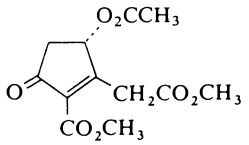
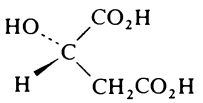
(b) 

(c) 

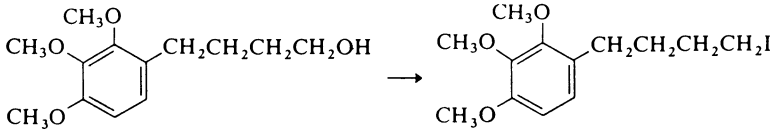
(d)  from 

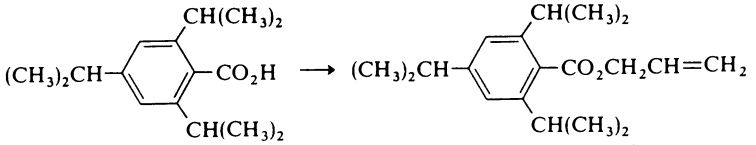
(e)  from 

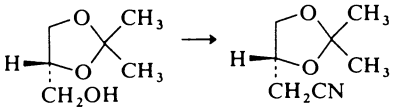
(f)  from 

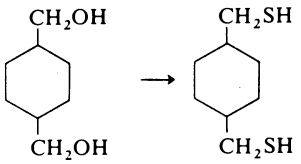
(g)  from 

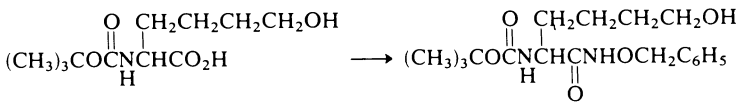
6. Suggest reagents and reaction conditions which could be expected to effect the following conversions.

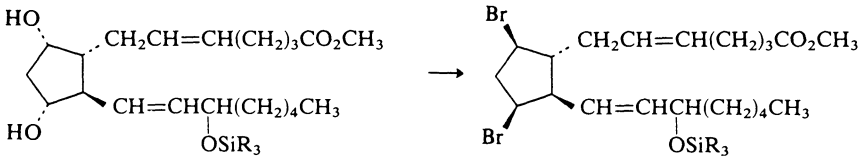
(a) 

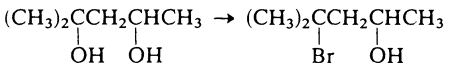
(b) 

(c) 

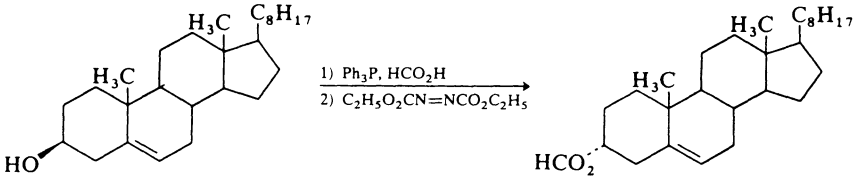
(d)  (more than one step is required)

(e) 

(f) 

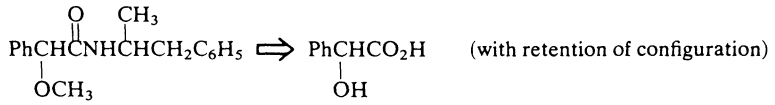
(g) 

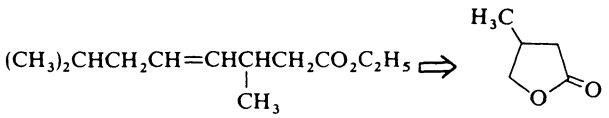
7. A procedure for inverting the configuration of alcohols has been developed and demonstrated using cholesterol as a substrate

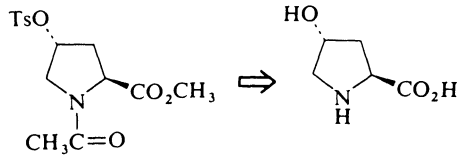


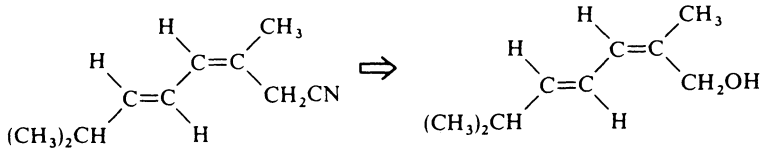
Show the details of the mechanism of the key step which converts cholesterol to the inverted formate ester.

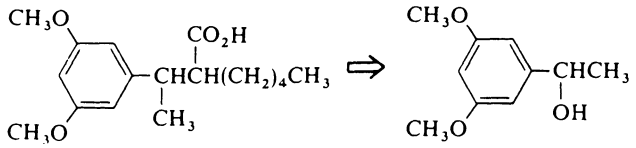
8. Short synthetic sequences have been used to accomplish conversion of the material at the right to that on the left. Suggest appropriate methods. No more than three separate steps should be required.

(a)  (with retention of configuration)

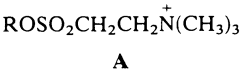
(b) 

(c) 

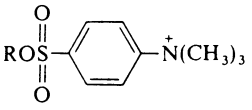
(d) 

(e) 

9. It has been found that triphenylphosphine oxide reacts with trifluoromethylsulfonic anhydride to give an ionic substance with the composition of a simple 1 : 1 adduct. When this substance is added to a solution containing a carboxylic acid, followed by addition of an amine, amides are formed in good yield. Similarly, esters are formed by treating carboxylic acids first with the reagent and then with an alcohol. What is a likely structure for this ionic substance and how can it effect the activation of the carboxylic acids?
10. Sulfonate esters having quaternary nitrogen substituents, such as **A** and **B**, show exceptionally high reactivity towards nucleophilic displacement reactions. Discuss factors which might contribute to the reactivity of these substances.

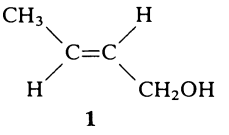


A

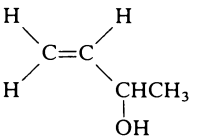


B

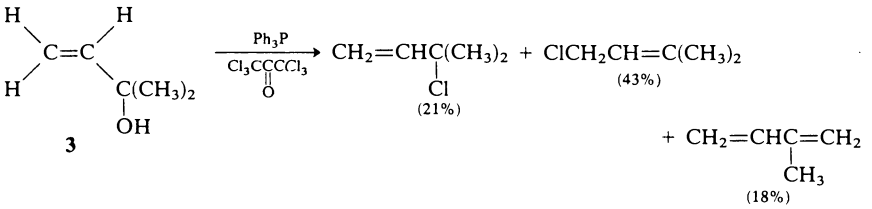
11. The scope of the reaction of triphenylphosphine-hexachloroacetone with allylic alcohols has been studied. Primary and some secondary alcohols such as **1** and **2** give good yields of unrearranged halides. Certain other alcohols, such as **3** and **4** give more complex mixtures. Discuss structural features which are probably important in determining how cleanly a given alcohol is converted to halide.



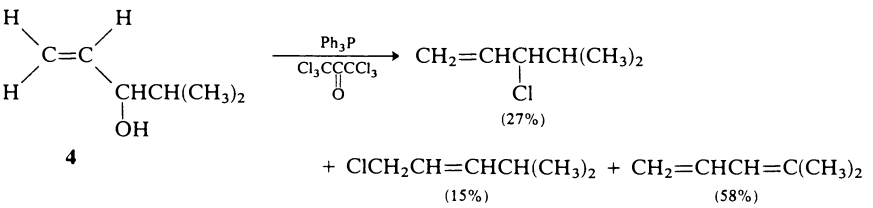
1



2



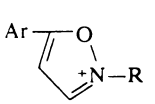
3



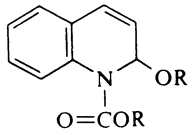
4

12. Alcohols react with hexachloroacetone in the presence of dimethylformamide to give alkyl trichloroacetates in high yield. Primary alcohols react fastest. Tertiary alcohols do not react. Suggest a reasonable mechanism for this reaction.

13. Two heterocyclic ring systems which have found some use in the formation of amides under mild conditions are *N*-alkyl-5-arylisoxazolium salts (structure **A**) and *N*-acyloxy-2-alkoxydihydroisoquinolines (structure **B**).

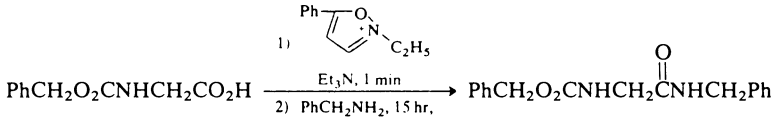


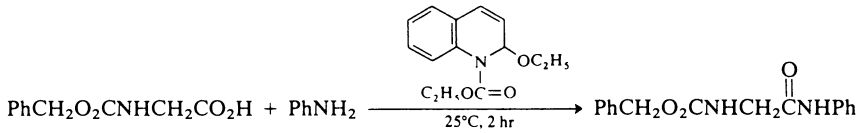
A



B

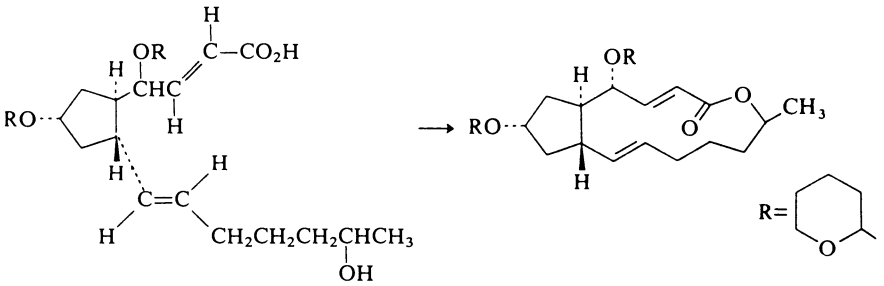
A typical set of reactions conditions is indicated below for each reagent. Consider mechanisms by which these heterocyclic molecules might function to activate the carboxylic acid group under these conditions, and outline the mechanisms you consider to be most likely.



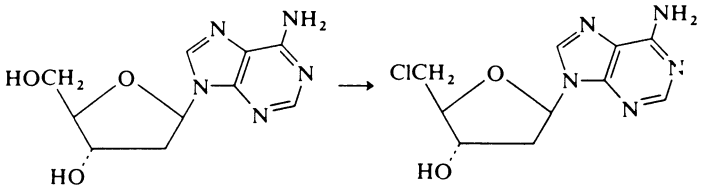


14. Either because of potential interferences with other functional groups present in the molecule or because of special structural features, the following reactions would require especially careful selection of reagents and reaction conditions. Identify the special requirements of each substrate and suggest appropriate conditions for effecting the desired transformation.

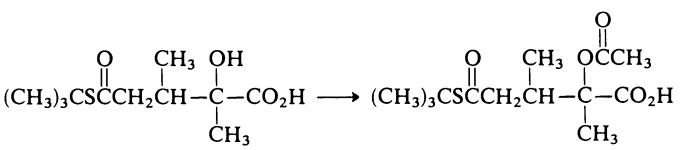
(a)

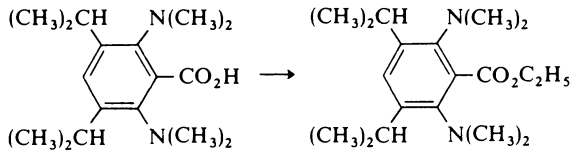


(b)

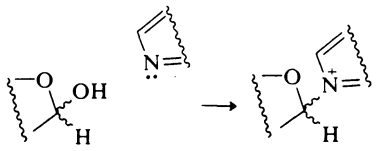


(c)

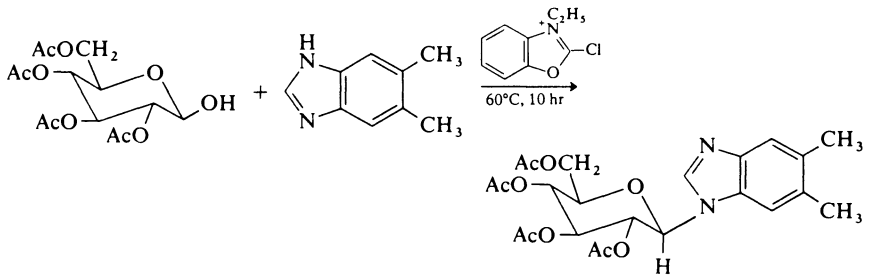


(d) 

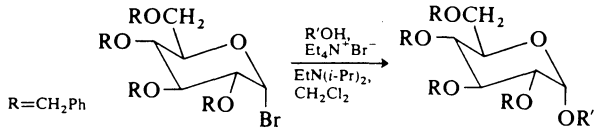
15. The preparation of nucleosides by reaction of carbohydrates and heterocyclic bases is fundamental to the study of the important biological activity of such substances. Several methods have been developed for accomplishing this reaction.



Application of 2-chloro-3-ethylbenzoxazolium chloride to this problem has been investigated using 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranose as the carbohydrate derivative. Good yields were observed and, furthermore, the process was stereoselective, giving the β-nucleoside. Suggest a mechanism and explain the stereochemistry.



16. A route to α-glycosides has been described in which 2,3,4,6-tetra-*O*-benzyl-α-*D*-glucopyranosyl bromide is treated with an alcohol and tetraethylammonium bromide and diisopropylethylamine in dichloromethane.



Suggest an explanation for the stereochemical course of this reaction.

4

Electrophilic Additions to Carbon–Carbon Multiple Bonds

One of the most general and useful reactions of alkenes and acetylenes for synthetic purposes is the addition of electrophilic reagents. This chapter is restricted to reactions which proceed through polar intermediates or transition states. Several other classes of addition reactions of alkenes are of importance and these are discussed elsewhere. Nucleophilic additions to electrophilic alkenes were covered in Chapter 1 and cycloadditions involving concerted mechanisms will be encountered in Chapter 7. Many of the free-radical addition reactions of alkenes are considered in Chapter 12 of Part A.

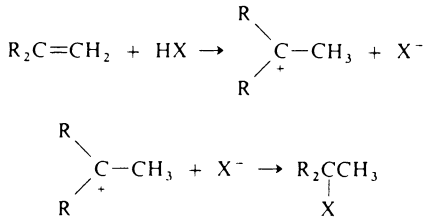
4.1. Addition of Hydrogen Halides

Hydrogen chloride and hydrogen bromide add to olefins to give addition products. Many years ago, it was noted that addition usually takes place to give the product in which the halogen atom is attached to the more substituted end of the olefin. This type of behavior was sufficiently general that the name *Markownikoff's rule* was given to the statement generalizing this observed mode

$$R_2C{=}CH_2 + HX \rightarrow R_2\underset{\displaystyle X}{\underset{|}{C}}CH_3$$

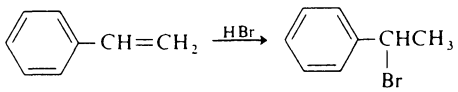
$$R_2C{=}CHR' + HX \rightarrow R_2\underset{\displaystyle X}{\underset{|}{C}}CH_2R$$

of addition. A very rudimentary picture of the mechanism of addition reveals the mechanistic foundation of Markownikoff's rule. The first step in the addition involves protonation of the olefin or the formation of a transition state involving partial protonation of the carbon–carbon double bond. In the example above,

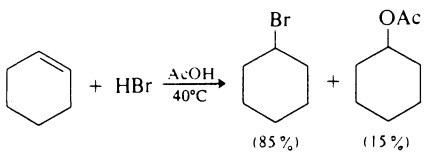


addition of a proton can lead to either a tertiary or a primary carbonium ion. The relative stability of the two possible intermediates favors formation of the more substituted carbonium ion. Addition is completed when the carbonium ion and halide ion react to give product. A more complete discussion of the mechanism of ionic addition of hydrogen halides to alkene is given in Part A, Chapter 6. In particular, the question of whether or not a discrete carbonium ion is always involved is considered there.

The general terms *regioselective* and *regiospecific* have been introduced to describe addition reactions that proceed selectively or exclusively in one direction with unsymmetrical alkenes.[1] Markownikoff's rule then describes a general case of regioselectivity that operates because of the stabilizing effect of alkyl and aryl groups on carbonium ion centers.



In nucleophilic solvents, products that arise from reaction of the solvent with the intermediate may be encountered. For example, reaction of cyclohexene with hydrogen bromide in acetic acid gives cyclohexyl acetate as well as cyclohexyl bromide. This result is readily understood as resulting from acetic acid and bromide ion acting as competing nucleophiles.



Ref. 2

1. A. Hassner, *J. Org. Chem.* **33**, 2684 (1968).
2. R. C. Fahey and R. A. Smith, *J. Am. Chem. Soc.* **86**, 5035 (1964).

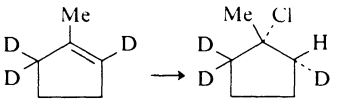
Because of the involvement of carbonium ion intermediates, carbon skeleton rearrangement is a possibility. Reaction of *t*-butylethylene with hydrogen chloride in acetic acid gives both rearranged and unrearranged chloride.[3] The rearranged acetate may also be formed, but it is unstable under the reaction conditions, being converted to the rearranged chloride.

$$(CH_3)_3CCH{=}CH_2 \xrightarrow[HCl]{AcOH} \underset{\substack{|\\ Cl\\ (35\text{–}40\%)}}{(CH_3)_3CCHCH_3} + \underset{\substack{|\\ Cl\\ (40\text{–}50\%)}}{(CH_3)_2CCH(CH_3)_2} +$$

$$\uparrow$$

$$\underset{\substack{|\\ OAc\\ (15\text{–}20\%)}}{(CH_3)_3CCHCH_3} + \left[\underset{\substack{|\\ OAc}}{(CH_3)_2CCH(CH_3)_2}\right]$$

The stereochemistry of the addition of hydrogen halides to a variety of alkenes has been investigated. The stereochemistry is dependent on the alkene structure and also on the reaction solvent and temperature. The addition of hydrogen chloride to 1-methylcyclopentene, for example, is entirely *anti* in nitromethane at 25°C.[4]



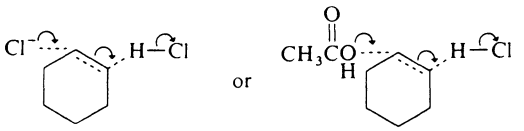
Addition of hydrogen bromide to cyclohexene and *cis*- and *trans*-2-butene also takes place by *anti* addition.[5] 1,2-Dimethylcyclohexene is an example of an alkene for which the stereochemistry of hydrogen chloride addition is solvent and temperature dependent. At −78°C in dichloromethane 88% of the product is the result of *syn* addition, whereas at 0°C in ether 95% of the product results from *anti* addition.[6] *Syn* addition is particularly common with olefins having a phenyl substituent. Table 4.1 lists examples of several olefins for which the stereochemistry of addition of hydrogen chloride or hydrogen bromide has been studied.

The stereochemistry of the addition depends upon the details of the addition mechanism. Two general mechanisms have been encountered for alkenes. The addition can proceed through an ion pair intermediate:

$$RCH{=}CH_2 + HCl \longrightarrow \underset{\substack{+\\ Cl^-}}{RCHCH_3} \longrightarrow \underset{\substack{|\\ Cl}}{RCHCH_3}$$

Most alkenes, however, react via a transition state that involves the alkene, hydrogen halide, and a third species, either solvent or halide ion. This termolecular mechanism is generally pictured as involving nucleophilic attack on an alkene–hydrogen halide complex and thus bypassing a discrete carbonium ion:

3. R. C. Fahey and C. A. McPherson, *J. Am. Chem. Soc.* **91**, 3865 (1969).
4. Y. Pocker and K. D. Stevens, *J. Am. Chem. Soc.* **91**, 4205 (1969).
5. D. J. Pasto, G. R. Meyer, and S. Kang, *J. Am. Chem. Soc.* **91**, 2163 (1969).
6. K. B. Becker and C. A. Grob, *Synthesis*, 789 (1973).



The ion pair mechanism would not be expected to be stereospecific, since the carbonium ion intermediate permits loss of the stereochemistry relative to the initial olefin. It might be expected that the ion pair mechanism could lead to a preference for *syn* addition, since at the instant of formation of the ion pair, the halide ion is necessarily on the same side of the multiple bond from which hydrogen was added. On the other hand, the termolecular mechanism would be expected to give *anti* addition. Concerted attack by the nucleophile would occur at the face opposite from proton addition:

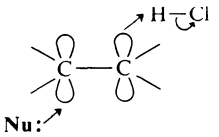


Table 4.1 Stereochemistry of Addition of Hydrogen Halides to Olefins

Olefin	Hydrogen halide	Stereochemistry	Ref.
1,2-Dimethylcyclohexene	HBr	*anti*	a
1,2-Dimethylcyclohexene	HCl	solvent- and temperature-dependent	a
Cyclohexene	HBr	*anti*	b
cis-2-Butene	DBr	*anti*	c
trans-2-Butene	DBr	*anti*	c
1,2-Dimethylcyclopentene	HBr	*anti*	d
1-Methylcyclopentene	HCl	*anti*	e
Norbornene	HBr	*syn* and rearrangement	f
Norbornene	HCl	*syn* and rearrangement	g
trans-1-Phenylpropene	HBr	*syn* (9 : 1)	h
cis-1-Phenylpropene	HBr	*syn* (8 : 1)	h
Bicyclo[3.1.0]hex-2-ene	DCl	*syn*	i
1-Phenyl-4-*t*-butylcyclohexene	DCl	*syn*	j

a. G. S. Hammond and T. D. Nevitt, *J. Am. Chem. Soc.* **76**, 4121 (1954); R. C. Fahey and C. A. McPherson, *J. Am. Chem. Soc.* **93**, 2445 (1971); K. B. Becker and C. A. Grob, *Synthesis*, 789 (1973).
b. R. C. Fahey and R. A. Smith, *J. Am. Chem. Soc.* **86**, 5035 (1964).
c. D. J. Pasto, G. R. Meyer, and B. Lepeska, *J. Am. Chem. Soc.* **96**, 1858 (1974).
d. G. S. Hammond and C. H. Collins, *J. Am. Chem. Soc.* **82**, 4323 (1960).
e. Y. Pocker and K. D. Stevens, *J. Am. Chem. Soc.* **91**, 4205 (1969).
f. H. Kwart and J. L. Nyce, *J. Am. Chem. Soc.* **86**, 2601 (1964).
g. J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *J. Am. Chem. Soc.* **88**, 4922 (1966).
h. M. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.* **85**, 3645 (1963).
i. P. K. Freeman, F. A. Raymond, and M. F. Grostic, *J. Org. Chem.* **32**, 24 (1967).
j. K. D. Berlin, R. O. Lyerla, D. E. Gibbs, and J. P. Devlin, *Chem. Commun.*, 1246 (1970).

Part A, Section 6.1, contains more discussion of the structural features which affect the competition between the two possible mechanisms. In general, *syn* addition is most likely to be observed with alkenes which can be protonated to give relatively stable carbonium ions.

4.2. Hydration and Other Acid-Catalyzed Additions

In addition to halide ions, various other nucleophilic species can be added to olefinic bonds under acidic conditions. A fundamental example is the hydration of olefins in aqueous systems:

$$R_2C{=}CH_2 + H^+ \longrightarrow R_2\overset{+}{C}CH_3 \xrightarrow{H_2O} R_2\underset{{}^+OH_2}{C}CH_3 \xrightarrow{-H^+} R_2\underset{OH}{C}CH_3$$

Addition of a proton occurs to give the more substituted carbonium ion, so that addition occurs regioselectively and in accordance with Markownikoff's rule. A more detailed discussion of the reaction mechanism is given in Part A, Section 6.2. The reaction is occasionally applied to the synthesis of tertiary alcohols:

$$(CH_3)_2C{=}CHCH_2CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[H_2O]{H_2SO_4} (CH_3)_2\underset{OH}{C}CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3 \qquad \text{Ref. 7}$$

Because of the strongly acidic and rather vigorous reaction conditions required to effect hydration of most alkenes, the reaction is applicable only to molecules that have no other very sensitive functional groups. Also, because of the involvement of cationic intermediates, rearrangements can occur in systems where a more stable cation would result by aryl, alkyl, or hydrogen migration. A much milder procedure for alkene hydration is discussed in the next section.

Additions of nucleophilic solvents such as alcohols and carboxylic acids can be effected by use of strong acid catalysts[8]:

$$(CH_3)_2C{=}CH_2 + MeOH \xrightarrow{HBF_4} (CH_3)_3COCH_3$$

$$CH_3CH{=}CH_2 + CH_3CO_2H \xrightarrow{HBF_4} (CH_3)_2CHOCOCH_3$$

Trifluoroacetic acid is a sufficiently strong acid to react with olefins under relatively mild conditions.[9] The addition is regiospecific in the direction predicted

7. J. Meinwald, *J. Am. Chem. Soc.* **77**, 1617 (1955).
8. R. D. Morin and A. E. Bearse, *Ind. Eng. Chem.* **43**, 1596 (1951); D. T. Dalgleish, D. C. Nonhebel, and P. L. Pauson, *J. Chem. Soc. C*, 1174 (1971).
9. P. E. Peterson, R. J. Bopp, D. M. Chevli, E. L. Curran, D. E. Dillard, and R. J. Kamat, *J. Am. Chem. Soc.* **89**, 5902 (1967).

by Markownikoff's rule. The reaction is catalyzed by sulfuric acid, and ring strain

$$ClCH_2CH_2CH_2CH{=}CH_2 \xrightarrow[\Delta]{CF_3CO_2H} ClCH_2CH_2CH_2\underset{\displaystyle O_2CCF_3}{\underset{|}{C}}HCH_3$$

enhances olefin reactivity. Norbornene undergoes rapid addition at 0°C.[10] Again, rearrangement can occur in substrates which form a carbonium ion that can be stabilized by migration.[11]

$$(CH_3)_3CCH{=}CH_2 \xrightarrow{CF_3CO_2H} (CH_3)_2\overset{+}{C}-CH(CH_3)_2 \longrightarrow (CH_3)_2\underset{\displaystyle O_2CCF_3}{\underset{|}{C}}-CH(CH_3)_2$$

4.3. Oxymercuration

The addition reactions which were discussed in Sections 4.1 and 4.2 are initiated by interaction of a proton with the alkene, which then permits nucleophilic attack on the double bond. The role of the initial electrophile can be played by metal ions as well. Mercuric ion is the electrophile in several synthetically valuable procedures.[12] The most commonly used reagent is mercuric acetate, but trifluoroacetate or nitrate salts are preferable in some applications. A general mechanism depicts a mercurinium ion as the first intermediate.[13] Such species can be detected by physical measurements when alkenes react with mercuric ion in nonnucleophilic solvents.[14] Depending on the structure of the particular alkene the mercurinium ion may be predominantly bridged or open. The addition is completed by attack of a nucleophile. The nucleophiles which react satisfactorily for synthetic

$$RCH{=}CH_2 + Hg(II) \rightarrow RCH\overset{\displaystyle 2+}{\underset{\displaystyle Hg}{\diagup\!\!\diagdown}}CH_2 \quad \text{or} \quad R\overset{+}{C}H-\underset{\displaystyle Hg}{\underset{|}{C}}H_2 \xrightarrow{Nu^-} RCHCH_2-Hg^+ \;\; (Nu)$$

purposes include water, alcohols, carboxylate ions, hydroperoxides, amines, and nitriles. Scheme 4.1 includes examples of these reactions. After the addition step is complete the mercury atom is reductively removed, usually by sodium borohydride. As shown in Scheme 4.1, the net result of the reaction is the addition of hydrogen and the nucleophile to the alkene. The regioselectivity is excellent

10. H. C. Brown, J. H. Kawakami, and K.-T. Liu, *J. Am. Chem. Soc.* **92**, 5536 (1970).
11. V. J. Shiner, Jr., R. D. Fisher, and W. Dowd, *J. Am. Chem. Soc.* **91**, 7748 (1969).
12. R. C. Larock, *Angew. Chem. Int. Ed. Engl.* **17**, 27 (1978); W. Kitching, *Organomet. Chem. Rev.* **3**, 61 (1968).

13a. S. J. Cristol, J. S. Perry, Jr., and R. S. Beckley, *J. Org. Chem.* **41**, 1912 (1976).
b. D. J. Pasto and J. A. Gontarz, *J. Am. Chem. Soc.* **93**, 6902 (1971).

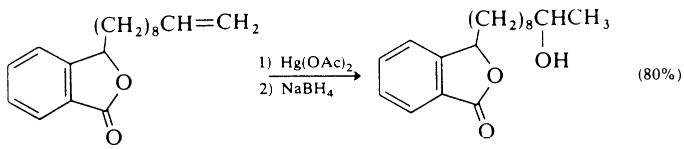
14. G. A. Olah and P. R. Clifford, *J. Am. Chem. Soc.* **95**, 6067 (1973); G. A. Olah and S. H. Yu, *J. Org. Chem.* **40**, 3638 (1975).

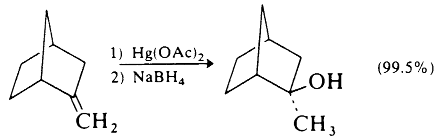
Scheme 4.1. Synthesis via Mercuration

Alcohols

1[a] $(CH_3)_3CCH{=}CH_2 \xrightarrow[\text{2) NaBH}_4]{\text{1) Hg(OAc)}_2} (CH_3)_3CCH(OH)CH_3 + (CH_3)_3CCH_2CH_2OH$

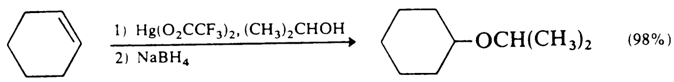
(97%) (3%)

2[b] 

3[c] 

Ethers

4[d] $CH_3(CH_2)_3CH{=}CH_2 \xrightarrow[\text{2) NaBH}_4]{\text{1) Hg(OAc)}_2\text{, CH}_3\text{OH}} CH_3(CH_2)_3CH(OCH_3)CH_3$ (90%)

5[d] 

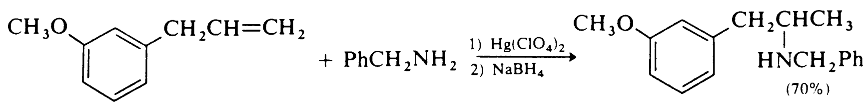
Amides

6[e] $CH_3(CH_2)_3CH{=}CH_2 \xrightarrow[\text{2) NaBH}_4\text{, H}_2\text{O}]{\text{1) Hg(NO}_3)_2\text{, CH}_3\text{CN}} CH_3CH_2CH_2CH_2CH(HNCOCH_3)CH_3$ (92%)

Peroxides

7[f] $CH_3(CH_2)_4CH{=}CHCH_3 \xrightarrow[\text{2) NaBH}_4]{\text{1) Hg(OAc)}_2\text{, } t\text{-BuOOH}} CH_3(CH_2)_4CH(OOH)CH_2CH_3$ (40%)

Amines

8[g] 

a. H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.* **35**, 1844 (1970).
b. H. L. Wehrmeister and D. E. Robertson, *J. Org. Chem.* **33**, 4173 (1968).
c. H. C. Brown and W. J. Hammar, *J. Am. Chem. Soc.* **89**, 1524 (1967).
d. H. C. Brown and M.-H. Rei, *J. Am. Chem. Soc.* **91**, 5646 (1969).
e. H. C. Brown and J. T. Kurek, *J. Am. Chem. Soc.* **91**, 5647 (1969).
f. D. H. Ballard and A. J. Bloodworth, *J. Chem. Soc. C*, 945 (1971).
g. R. C. Griffith, R. J. Gentile, T. A. Davidson, and F. L. Scott, *J. Org. Chem.* **44**, 3580 (1979).

and is in the same sense as is observed for proton-catalyzed additions, but because of the milder conditions the mercuration procedures are often synthetically advantageous.[15]

15. H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.* **35**, 1844 (1970).

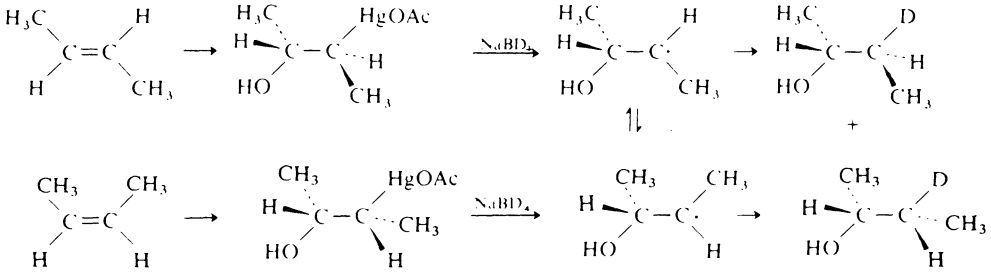
The mechanism of the reductive replacement of mercury by hydrogen using sodium borohydride as the reductant involves a free-radical intermediate generated by decomposition of an intermediate alkylmercury hydride.[16] The evidence for this

$$RHgX + NaBH_4 \rightarrow RHgH$$

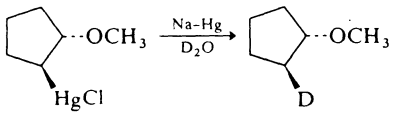
$$RHgH \rightarrow R\cdot + Hg^{(I)}H$$

$$R\cdot + RHgH \rightarrow RH + Hg^{(0)} + R\cdot$$

mechanism includes the fact that the course of the reaction can be diverted by oxygen, an efficient radical scavenger. Also, the stereochemistry of the reduction, as studied by using $NaBD_4$ as the reducing agent, is consistent with a radical intermediate.[17] For example, a 50:50 mixture of *erythro*- and *threo*-3-deuterio-2-butanol is obtained by oxymercuration of either *cis*- or *trans*-2-butene, followed by reduction with $NaBD_4$. Furthermore, the cyclization products that are charac-



teristic of a free-radical intermediate are observed when hex-5-enylmercury compounds are reduced with sodium borohydride.[18] An alternate reagent for demercuration is sodium amalgam in a protic solvent. Here the evidence is that free radicals are not involved and that the mercury is replaced with complete retention of configuration.[19]



The stereochemistry of oxymercuration has been examined in a number of systems. Conformationally biased systems such as 4-*t*-butylcyclohexene and 4-*t*-butyl-1-methylcyclohexene give exclusively the product of *anti* addition which is consistent with a mercurinium ion intermediate.[13b,20] This is normally the preferred

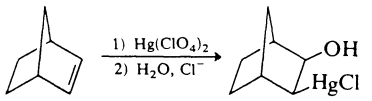
16. C. L. Hill and G. M. Whitesides, *J. Am. Chem. Soc.* **96**, 870 (1974).
17. D. J. Pasto and J. A. Gontarz, *J. Am. Chem. Soc.* **91**, 719 (1969); G. A. Gray and W. R. Jackson, *J. Am. Chem. Soc.* **91**, 6205 (1969).
18. R. P. Quirk and R. E. Lea, *J. Am. Chem. Soc.* **98**, 5973 (1976).
19. F. R. Jensen, J. J. Miller, S. J. Cristol, and R. S. Beckley, *J. Org. Chem.* **37**, 4341 (1972); R. P. Quirk, *J. Org. Chem.* **37**, 3554 (1972); W. Kitching, A. R. Atkins, G. Wickham, and V. Alberts, *J. Org. Chem.* **46**, 563 (1981).
20. H. C. Brown, G. J. Lynch, W. J. Hammar, and L. C. Liu, *J. Org. Chem.* **44**, 1910 (1979).

Table 4.2. Relative Reactivity of Some Alkenes in Oxymercuration[a]

1-Pentene	6.6
2-Methyl-1-pentene	48
Cis-2-pentene	0.56
Trans-2-pentene	0.17
2-Methyl-2-pentene	1.24

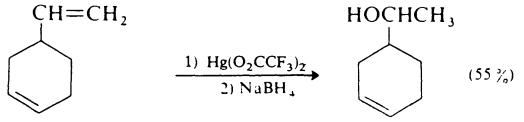
a. Relative to cyclohexene; Data from H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.* **37**, 1937 (1972).

stereochemistry, but with hindered or strained alkenes where the transition state for *anti* addition is disfavored, a *syn* mode of addition is accessible.[21] Norbornene, for example, in which an *anti* addition is opposed by both steric (difficulty of *endo* approach) and torsional (prohibition of an *anti*periplanar transition state) factors, reacts entirely by *syn–exo* addition.



Ref. 22

The reactivity of alkenes toward mercuration varies over a considerable range and is governed by a combination of steric and electronic factors.[23] Terminal double bonds are more reactive than internal ones. Disubstituted terminal olefins, however, are more reactive than monosubstituted cases, as would be expected for electrophilic attack. The differences in relative reactivities are large enough that selectivity can be achieved in certain dienes. Relative reactivity data for some pentene derivatives are given in Table 4.2.



Ref. 23b

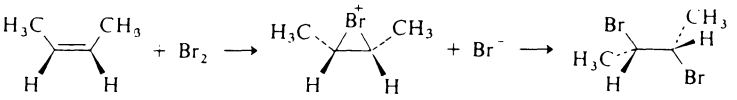
4.4. Addition of Halogens to Alkenes

The addition of chlorine and bromine to alkenes is a very general reaction. Considerable insight has been gained into the mechanism of halogen addition

21. W. L. Waters, T. G. Traylor, and A. Factor, *J. Org. Chem.* **38**, 2306 (1973).
22. T. G. Traylor and A. W. Baker, *Tetrahedron Lett.*, No. 19, 14 (1959).
23a. H. C. Brown and P. J. Geoghegan, *J. Org. Chem.* **37**, 1937 (1972).
b. H. C. Brown, P. J. Geoghegan, Jr., G. J. Lynch, and J. T. Kurek, *J. Org. Chem.* **37**, 1941 (1972).

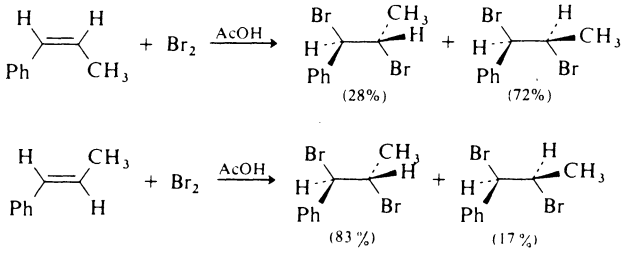
$$RCH{=}CHR + X_2 \rightarrow \underset{X}{\overset{|}{RCH}}-\underset{X}{\overset{|}{CHR}}$$

reactions by studies on the stereochemistry of the reaction. Most types of alkenes are known to add bromine in a highly stereospecific manner, giving the products of *anti* addition. Among the olefins that are known to undergo *anti* addition are maleic and fumaric acid, *cis*-2-butene, *trans*-2-butene, and a number of cycloalkenes.[24] Cyclic, positively charged bromonium-ion intermediates offer an attractive explanation for the observed stereospecificity. The bridging bromine atom



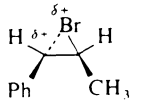
prevents rotation around the bond linking the olefinic carbon atoms, and normal backside nucleophilic opening of the ring by bromide can lead to the observed *anti* addition. Physical evidence for the existence of bromonium ions has been obtained from nmr measurements.[25] A bromonium-ion salt (counterion, Br_3^-) has been isolated from the reaction of bromine with the very hindered alkene adamantylideneadamantane.[26]

Substantial amounts of *syn* addition have been observed for *cis*-1-phenylpropene (27–80% *syn* addition), *trans*-1-phenylpropene (17–29% *syn* addition), and *cis*-stilbene (up to 90% *syn* addition in polar solvents). A common feature of the compounds that give extensive *syn* addition is the presence of a



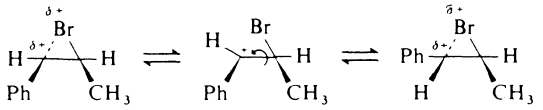
Ref. 24

phenyl ring on at least one of the olefinic carbons. The substituent is believed to be responsible for the loss of stereospecificity. The presence of a phenyl substituent diminishes the necessity for strong bromonium-ion bridging, since it can effectively stabilize the charge deficiency at the benzyl carbon. Weakened, unsymmetrical bridging can be depicted as follows:

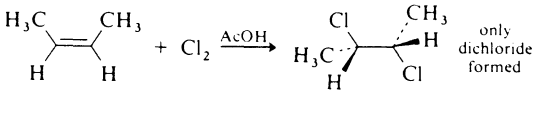


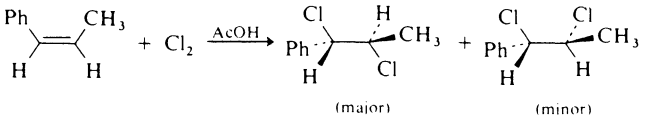
24. J. H. Rolston and K. Yates, *J. Am. Chem. Soc.* **91**, 1469, 1477 (1969).
25. G. A. Olah, J. M. Bollinger, and J. Brinich, *J. Am. Chem. Soc.* **90**, 2587 (1968); G. A. Olah, P. Schilling, P. W. Westerman, and H. C. Lin, *J. Am. Chem. Soc.* **96**, 3581 (1974).
26. J. Strating, J. H. Wieringa, and H. Wynberg, *Chem. Commun.* 907 (1969).

The intermediate has carbonium character at the phenyl-substituted carbon. The effect of this diminished bridging is to increase the rate of rotation around the central C–C bond. If such rotation takes place, *anti* stereospecificity is, of course, lost.



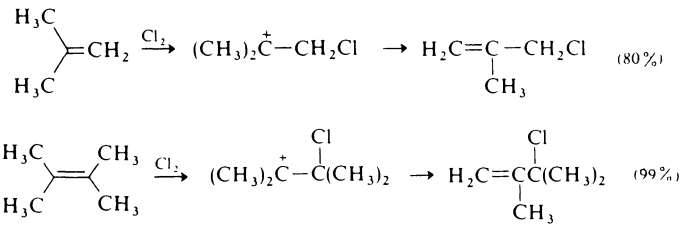
Although chlorination of aliphatic olefins gives largely *anti* addition, *syn* addition is often dominant for phenyl-substituted olefins.[27] These results again





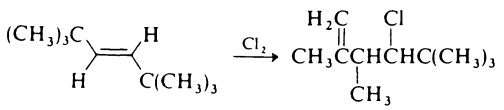
reflect a difference in the extent of bridging in the intermediates. With aliphatic olefins, there is strong bridging with resulting high *anti* stereospecificity. Phenyl substitution leads to increased carbonium-ion character at the benzylic site, and the addition is far less stereospecific, showing a preference for *syn* addition. Because of its smaller polarizability, chlorine is less effective than bromine at bridging in any particular olefin, and bromination therefore generally shows a higher degree of stereospecific addition than chlorination.[28]

Chlorination can be accompanied by reactions that are characteristic of carbonium-ion intermediates. Branched olefins can give products that are the result of elimination of a proton from a cationic intermediate.

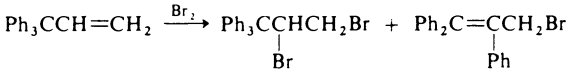


Skeletal rearrangement has also been observed but only in systems that are very prone toward migration:

27a. M. L. Poutsma, *J. Am. Chem. Soc.* **87**, 2161, 2172 (1965).
b. R. C. Fahey, *J. Am. Chem. Soc.* **88**, 4681 (1966); R. C. Fahey and C. Shubert, *J. Am. Chem. Soc.* **87**, 5172 (1965).
28. R. J. Abraham and J. R. Monasterios, *J. Chem. Soc. Perkin Trans. 1*, 1446 (1973).



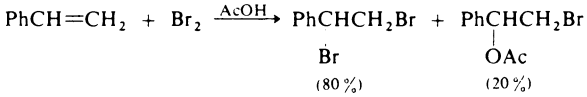
Ref. 29



Ref. 30

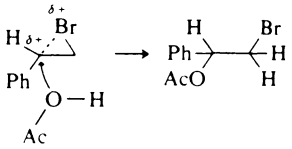
Since halogenation involves electrophilic attack on the olefin, substituent groups that increase the electron density increase the rate of reaction, whereas electron-withdrawing substituents have the opposite effect. Bromination of simple alkenes is extremely fast, and a trend toward increasing reactivity with increasing alkyl substitution is evident. Specific rate data are tabulated and discussed in Part A, Section 6.3.

In nucleophilic solvents, the solvent can compete with halide ion for the positively charged intermediate. For example, the bromination of styrene in acetic acid leads to substantial amounts of the acetoxybromo derivative:



Ref. 31

The acetoxy group is introduced exclusively at the benzylic carbon. This is in accord with the picture of the intermediate bromonium ion as a weakly bridged species. If the C–Br bonds were of equal strength, preferential attack at the least hindered carbon would be anticipated. The addition of bromide salts to the reaction mixture

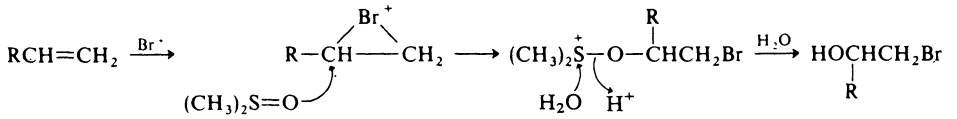


diminishes the amount of acetoxy compound formed by tipping the competition between acetic acid and bromide ion for the electrophilic site in favor of the bromide ion by a concentration effect.

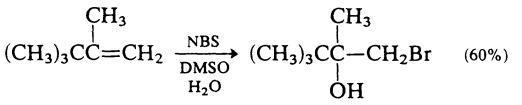
From a synthetic point of view, the participation of water in brominations, leading to bromohydrins, is probably the most important example of nucleophilic participation by solvent. In the case of an unsymmetrical bromonium ion, the water molecule will react at the carbon atom with the most pronounced carbonium ion character. If it is desired to favor introduction of water, it is clear that the concentration of the competing bromide ion should be kept as low as possible. One method for accomplishing this is to use *N*-bromosuccinimide as the bromine source. High

29. M. L. Poutsma, *J. Am. Chem. Soc.* **87**, 4285 (1965).
30. R. O. C. Norman and C. B. Thomas, *J. Chem. Soc. B*, 598 (1967).
31. J. H. Rolston and K. Yates, *J. Am. Chem. Soc.* **91**, 1469 (1969).

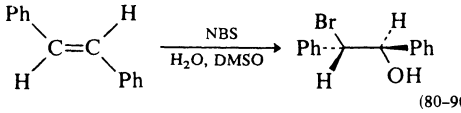
yields of bromohydrins are realized under such conditions.[32] Dimethyl sulfoxide is a particularly effective solvent for the reaction.[33] The reaction exhibits a high degree of stereospecificity with predominant *anti* addition. As in brominations, a bridged bromonium ion is invoked to explain the *anti* stereospecificity. For the reaction in



dimethyl sulfoxide, it has been shown that the initial nucleophilic attack is by the sulfoxide oxygen, which subsequently reacts with water to give the bromohydrin. In accord with the Markownikoff rule, the hydroxyl group is introduced at the carbon best able to support positive charge.

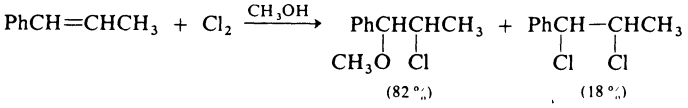


(60%) Ref. 33

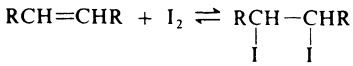


(80–90%) Ref. 34

Chlorinations in nucleophilic solvents can also lead to solvent incorporation, as for example in the chlorination of phenylpropene in methanol:[28,35]



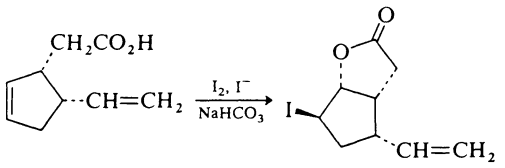
Addition of iodine to olefins can be accomplished by a photochemically initiated reaction. Elimination of iodine is catalyzed by excess iodine radicals, but the diiodo



compounds can be obtained if unreacted iodine is removed.[36] The diiodo compounds are very sensitive to light and have not been used very often in synthesis. Iodine, however, is a synthetically important electrophile for effecting intramolecular additions to alkenes, particularly in the iodolactonization reaction. Treatment of car-

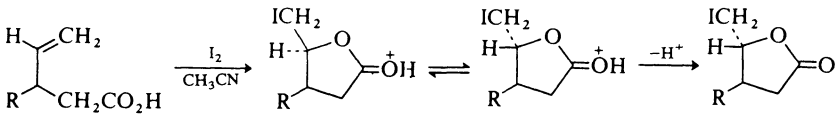
32. A. J. Sisti and M. Meyers, *J. Org. Chem.* **38**, 4431 (1973); C. O. Guss and R. Rosenthal, *J. Am. Chem. Soc.* **77**, 2549 (1955).
33. D. R. Dalton, V. P. Dutta, and D. C. Jones, *J. Am. Chem. Soc.* **90**, 5498 (1968).
34. A. W. Langman and D. R. Dalton, *Org. Synth.* **59**, 16 (1979).
35. M. L. Poutsma and J. L. Kartch, *J. Am. Chem. Soc.* **89**, 6595 (1967).
36. P. S. Skell and R. R. Pavlis, *J. Am. Chem. Soc.* **86**, 2956 (1964); R. L. Ayres, C. J. Michejda, and E. P. Rack, *J. Am. Chem. Soc.* **93**, 1389 (1971).

boxylic acids having carbon–carbon double bonds placed to permit intramolecular reaction results in formation of iodolactones.[37] The reaction shows a preference for formation of five-membered rings over six-membered[38] ones and is a strictly stereospecific *anti* addition when carried out under basic conditions. The *anti*



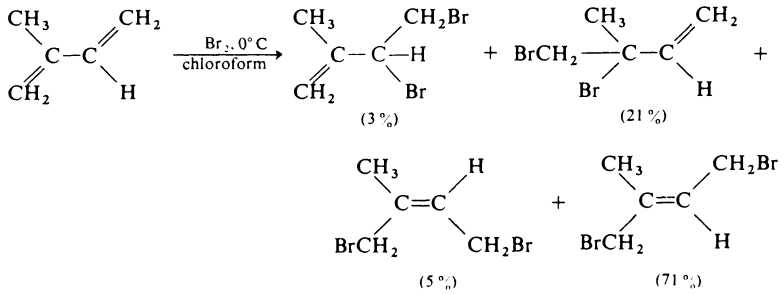
Ref. 39

addition is kinetically controlled and involves irreversible backside opening of an iodonium ion intermediate by the carboxylate nucleophile. When the reaction is carried out under nonbasic conditions the addition becomes reversible and is thermodynamically controlled.[40] The iodolactonization reaction has been a very



useful tool for establishing stereochemistry relative to an existing carboxylate group, particularly in cyclic systems.

Conjugated dienes often give mixtures of halogen-addition products. The case of isoprene can serve as an example.[41] The first two products are products of "1,2 addition," i.e., both halogens are introduced at adjacent carbons, whereas the other two are "1,4 addition" products, the bromine atoms having been added at the extremities of the conjugate system. Electrophilic attack by bromine on a conjugated diene generates an intermediate with the character of an allylic cation. The stability of the allylic system presumably diminishes the requirements for strong bromine



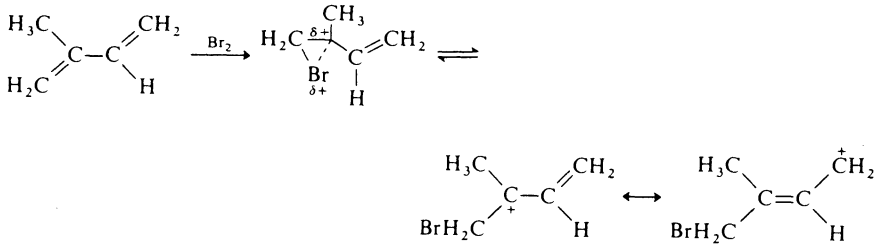
bridging. Nucleophilic attack by bromide ion can occur at either of the positive centers in the allylic system, leading to the mixture of 1,2- and 1,4-addition products.

37. M. D. Dowle and D. I. Davies, *Chem. Soc. Rev.*, **8**, 171 (1979).
38. S. Ranganathan, D. Ranganathan, and A. K. Mehrota, *Tetrahedron* **33**, 807 (1977).
39. L. A. Paquette, G. D. Crouse, and A. K. Sharma, *J. Am. Chem. Soc.* **102**, 3972 (1980).
40. P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.* **100**, 3950 (1978).
41. V. L. Heasley, C. L. Frye, R. T. Gore, Jr., and P. S. Wilday, *J. Org. Chem.* **33**, 2342 (1968).

Scheme 4.2. Other Sources of Positive Halogen

A. Chlorinating Agents	Synthetic Applications[a]
Sodium hypochlorite solution	Formation of chlorohydrins from olefins.
N-Chlorosuccinimide	Chlorination with solvent participation and cyclization.
Antimony pentachloride	Controlled chlorination of acetylenes.
B. Brominating Agents	
Pyridinium hydrotribromide (pyridinium hydrobromide perbromide)	Substitute for bromine when increased selectivity or mild reaction conditions are required
Dioxane–bromine complex	Same as for pyridinium hydrotribromide.
N-Bromosuccinimide	Substitute for bromine when low Br^- concentration is required.
2,4,4,6-Tetrabromocyclohexadienone	Selective bromination of polyolefins and cyclization induced by Br^+.

a. For specific examples consult M. Fieser and L. F. Fieser, *Reagents for Organic Synthesis*, Vols. 1–8, John Wiley and Sons, New York (1979).

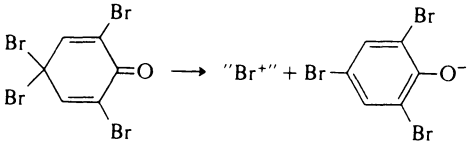


Both 1,2 and 1,4 addition occur in the chlorination and bromination of butadiene. Both reactions give mixtures containing slightly more of the 1,2-addition product than the 1,4-addition product.[42]

The halogens are not the only source of electrophilic halogen atoms and for some synthetic purposes other "positive halogen" compounds may be useful sources of the necessary electrophile. The utility of *N*-bromosuccinimide in formation of bromohydrins was mentioned earlier. Others which have been recommended for specific purposes are illustrated in Scheme 4.2. Pyridinium hydrotribromide (pyridinium hydrobromide perbromide) and dioxane–bromine complex are examples of complexes of bromine in which the reactivity is somewhat attenuated, resulting in increased selectivity. *N*-Chlorosuccinimide and *N*-bromosuccincimide transfer electrophilic halogen with the succinimide anion acting as the leaving group. This anion is subsequently protonated to give the nonnucleophilic succinimide. These reagents therefore favor nucleophilic additions by solvent and intramolecular cyclizations since there is no competition from a nucleophilic anion. In tetrabromocyclohexadienone, the leaving group is 2,4,6-tribromophenoxide ion. This

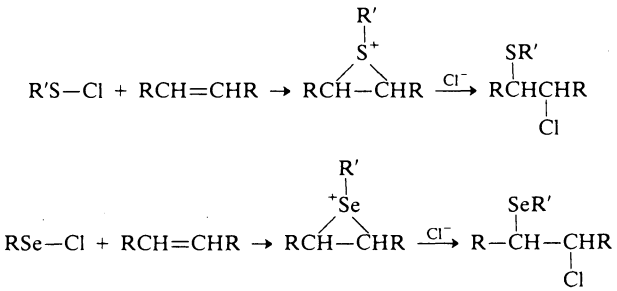
42. M. L. Poutsma, *J. Org. Chem.* **31**, 4167 (1966); V. L. Heasley and S. K. Taylor, *J. Org. Chem.* **34**, 2779 (1969).

reagent is a very mild and selective source of electrophilic bromine.



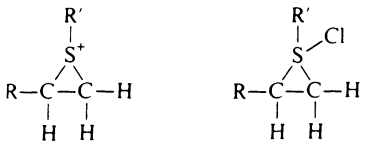
4.5. Electrophilic Sulfur and Selenium Reagents

Sulfur and selenium compounds in which the sulfur and selenium atoms are bound to more electronegative elements can react with alkenes to give addition products. The mechanism is similar to that in halogenation with a cyclic cationic intermediate being involved. In many synthetic applications the sulfur and selenium



substituent is subsequently removed by elimination as will be discussed in Chapter 7. Ease of access is therefore the primary factor in choice of the addition reagents. The arylsulfenyl halides are the most commonly used of the sulfur reagents. A variety of selenium reagents have been employed. Scheme 4.3 give some examples of reactive sulfur and selenium electrophiles.

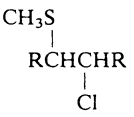
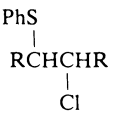
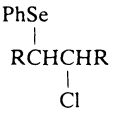
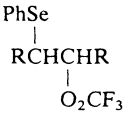
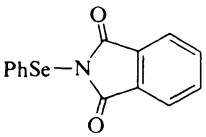
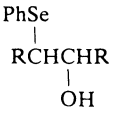
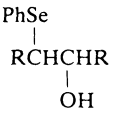
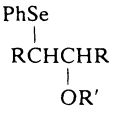
Mechanistic studies have been most complete with the sulfenyl halides.[43] The reaction shows moderate sensitivity to alkene structure with electron-releasing groups accelerating the reaction. The addition can occur in the Markownikoff or anti-Markownikoff sense depending upon the structure of the alkene and the electrophile.[44] These results can be understood by focusing attention on the addition intermediate, which may range from a sulfonium intermediate to a less electrophilic cyclic chlorosulfurane:



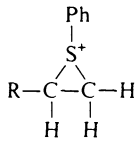
43. W. A. Smit, N. S. Zefirov, I. V. Bodrikov, and M. Z. Krimer, *Acc. Chem. Res.* **12**, 282 (1979).
44. W. H. Mueller and P. E. Butler, *J. Am. Chem. Soc.* **90**, 2075 (1968).

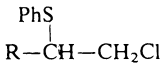
For R′ = Ph or CH_3 the intermediate species is fairly stable and ease of approach by the nucleophile is the major factor in determining the direction of ring opening. In this case the product has the anti-Markownikoff orientation.

Scheme 4.3. Sulfur and Selenium Reagents for Electrophilic Addition

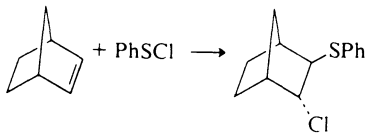
	Reagent	Product
1[a,b]	CH_3SCl	
2[a]	PhSCl	
3[c]	PhSeCl	
4[d]	$PhSeO_2CCF_3$	
5[e]		
6[f]	$PhSeO_2H$, H_3PO_2	
7[g]	PhSeCN, Cu(II), R′OH	

a. W. M. Mueller and P. E. Butler, *J. Am. Chem. Soc.* **90**, 2075 (1968).
b. W. A. Thaler, *J. Org. Chem.* **34**, 871 (1969).
c. K. B. Sharpless and R. F. Lauer, *J. Org. Chem.* **39**, 429 (1974); D. Liotta and G. Zima, *Tetrahedron Lett.* 4977 (1978).
d. H. J. Reich, *J. Org. Chem.* **39**, 428 (1974).
e. K. C. Nicolaou, D. A. Claremon, W. E. Barnette, and S. P. Seitz, *J. Am. Chem. Soc.* **101**, 3704 (1979).
f. D. Labar, A. Krief, and L. Hevesi, *Tetrahedron Lett.* 3967 (1978).
g. A. Toshimitsu, T. Aoai, S. Uemura, and M. Okano, *J. Org. Chem.* **45**, 1953 (1980).



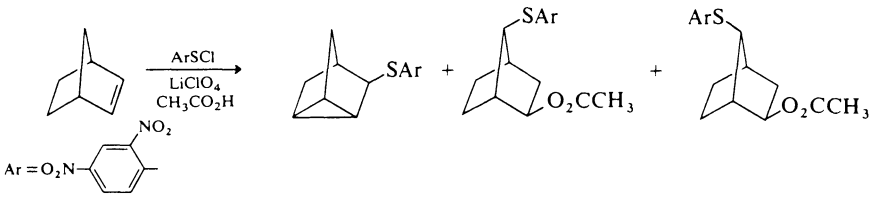


The stereospecific *trans* addition to norbornene is a particularly interesting reaction. Neither carbonium ion rearrangements nor the *syn* addition seen with many other electrophilic reagents is observed. These results, which are indicative



Ref. 43

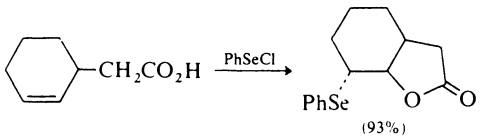
of a quite stable intermediate which reacts only by nucleophilic attack, are drastically changed if nonnucleophilic salts, e.g., $LiClO_4$, are added to the reaction medium. In the presence of the perchlorate salts structural rearrangements characteristic of a more reactive intermediate are observed. The mechanistic interpretation of



Ref. 45

these results suggests that a relatively unreactive intermediate, perhaps the chlorosulfurane, is the intermediate under the usual reaction conditions and that the added salt gives rise to a more reactive species closer in character to the episulfonium ion structure. For selenenyl halides[46] these addition reactions show high Markownikoff regioselectivity with the selenium species acting as the electrophile. The reaction is, however, readily reversible and can give rise to the isomeric product easily.[47]

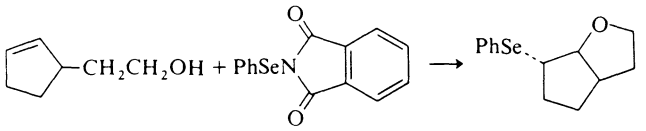
The electrophilic selenium reagents are very effective in promoting cyclization of unsaturated molecules containing nucleophilic sites. Unsaturated carboxylic acids, for example, give selenolactones and this has been termed *selenolactonization*.[48] Phenylsulfenyl chloride induces similar cyclization as well. Use of *N*-phenylselenophthalimide (Entry 5, Scheme 4.3) permits this cyclization to be extended



45. N. S. Zefirov, N. K. Sadovaja, A. M. Maggerramov, I. V. Bodrikov, and V. E. Kasrtashov, *Tetrahedron* **31**, 2949 (1975).
46. D. Liotta and G. Zima, *Tetrahedron Lett.* 4977 (1978).
47. S. Raucher, *J. Org. Chem.* **42**, 2950 (1977).
48. K. C. Nicolaou, S. P. Seitz, W. J. Sipio, and J. F. Blount, *J. Am. Chem. Soc.* **101**, 3884 (1979).

to the formation of 14- and 16-membered lactone rings.[49] The advantage of the reagent in this particular application is the low nucleophilicity of the phthalimide anion which does not compete with the remote internal nucleophile.

The reaction of phenylselenenyl chloride or *N*-phenylselenophthalimide with unsaturated alcohols leads to cyclization and formation of β-phenylselenenyl ethers.[49,50]



Reaction of alcoholic solutions of alkenes with potassium selenocyanate and cupric chlorides gives β-selenocyanato ethers.[51]

$$\text{RCH=CHR} + {}^{-}\text{SeCN} + \text{Cu(II)} \xrightarrow{\text{ROH}} \underset{\text{R'O}}{\overset{\text{SeCN}}{\text{RCHCHR}}}$$

This reaction proceeds by the oxidative generation of an electrophilic species, probably N≡C—Se—Cl, which could be formed as a result of oxidation by Cu(II).

$$2\text{CuCl}_2 + {}^{-}\text{SeC}{\equiv}\text{N} \rightarrow 2\text{CuCl} + \text{Cl—SeC}{\equiv}\text{N} + \text{Cl}^{-}$$

This reagent then gives a cyclic selenium ion intermediate which captures the solvent as nucleophile, leading to product. The thiocyanate ion behaves similarly under these reaction conditions.[52]

4.6. Addition of Other Electrophilic Reagents

Many small halogen-containing molecules react with alkenes to give addition products by mechanisms similar to halogenation. Scheme 4.4 lists some examples of such electrophilic reagents. A cationic intermediate is generated by a reaction which transfers the positive portion of the reagent to the alkene. Bridging in the intermediate may be symmetrical or unsymmetrical, depending on the ability of the carbon atoms to accommodate positive charge. The direction of opening of the bridged intermediate is usually governed by electronic factors. That is, the addition is completed by attack of the nucleophile at the more positive carbon atom of the

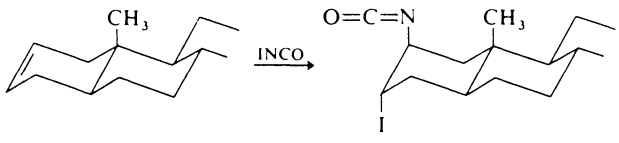
49. K. C. Nicolaou, D. A. Claremon, W. E. Barnette, and S. P. Seitz, *J. Am. Chem. Soc.* **101**, 3704 (1979).
50. K. C. Nicolaou, R. L. Magolda, W. J. Sipio, W. E. Barnette, Z. Lysenko, and M. M. Joullie, *J. Am. Chem. Soc.* **102**, 3784 (1980).
51. A. Toshimitsu, Y. Kozawa, S. Uemura, and M. Okano, *J. Chem. Soc. Perkin Trans. 1*, 1273 (1978).
52. A. Onoe, S. Uemura, and M. Okano, *Bull. Chem. Soc. Japan* **47**, 2818 (1974).

Scheme 4.4. Addition Reactions of Other Electrophilic Reagents

	Reagent	Preparation	Product
1[a]	I—N=C=O	$AgCNO$, I_2	RCH(I)—CHR(NCO)
2[b]	Br—N=$\overset{+}{N}$=N^-	HN_3, Br_2	RCH(Br)—CHR(N_3)
3[c]	I—N=$\overset{+}{N}$=N^-	NaN_3, ICl	RCH(I)—CHR(N_3)
4[d]	I—S—C≡N	$(NCS)_2$, I_2	RCH(I)—CHR(S—C≡N)
5[e]	I—ONO_2	$AgNO_3$, ICl	RCH(I)—CHR(ONO_2)
6[f]	O=N—Cl		RC(=NOH)—CHR(Cl)
7[g]	O=N—O_2CH	$(CH_3)_2CHCH_2CH_2ONO$, HCO_2H	RC(=NOH)—CHR(O_2CH)
8[h]	Cl—SCN	$Pb(SCN)_2$, Cl_2	RCH(Cl)—CHR(SCN)
9[i]	N≡CS—SC≡N	$Pb(SCN)_2$, Br_2	RCH(N≡CS)—CHR(SC≡N) and RCH(N≡CS)—CHR(N=C=S)

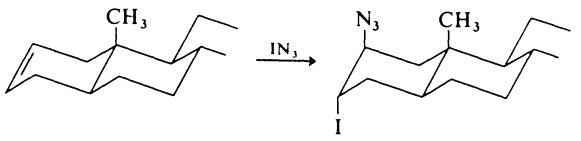
a. A. Hassner, R. P. Hoblitt, C. Heathcock, J. E. Kropp, and M. Lorber, *J. Am. Chem. Soc.* **92**, 1326 (1970); A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.* **32**, 540 (1967).
b. A. Hassner, F. P. Boerwinkle, and A. B. Levy, *J. Am. Chem. Soc.* **92**, 4879 (1970).
c. F. W. Fowler, A. Hassner, and L. A. Levy, *J. Am. Chem. Soc.* **89**, 2077 (1967).
d. R. J. Maxwell and L. S. Silbert, *Tetrahedron Lett.* 4991 (1978).
e. J. W. Lown and A. V. Joshua, *J. Chem. Soc. Perkin Trans. 1*, 2680 (1973).
f. J. Meinwald, Y. C. Meinwald, and T. N. Baker, III, *J. Am. Chem. Soc.* **86**, 4074 (1967).
g. H. C. Hamann and D. Swern, *J. Am. Chem. Soc.* **90**, 6481 (1968).
h. R. G. Guy and I. Pearson, *J. Chem. Soc. Perkin Trans. 1*, 281 (1973); *J. Chem. Soc. Perkin Trans. 2*, 1359 (1973).
i. R. J. Maxwell, L. S. Silbert, and J. R. Russell, *J. Org. Chem.* **42**, 1510 (1977).

bridged intermediate. The orientation of the addition reaction therefore follows Markownikoff's rule. The usual stereochemistry of the addition reaction is *anti*, again because of the involvement of bridged intermediates. In cyclohexene systems, preference for diaxial addition is noted with these reagents.



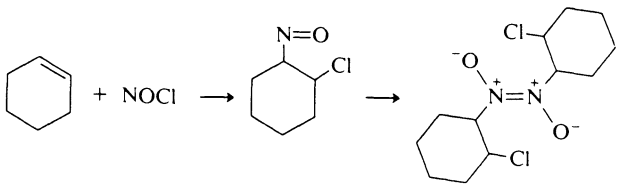
Ref. 53

53. A. Hassner and C. Heathcock, *J. Org. Chem.* **30**, 1748 (1965).

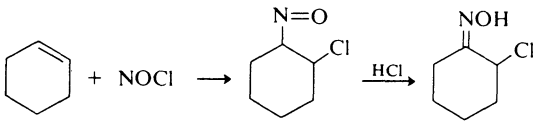


Ref. 54

Beyond these general characteristics of electrophilic addition, certain of the reagents shown in Scheme 4.4 exhibit special features which should be noted. The addition of nitrosyl chloride or nitrosyl formate to alkenes is accompanied by subsequent reactions if the nitroso group is not tertiary. The nitroso compound may dimerize or rearrange to the more stable oxime tautomer.



Ref. 55



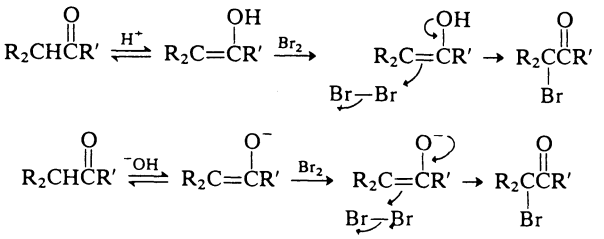
Ref. 56

In the case of thiocyanogen chloride and thiocyanogen, the formal electrophile is $N{\equiv}C{-}S^{+}$. The presumed intermediate is a sulfur-bridged species. The thiocyanate anion is an ambident nucleophile and both carbon–sulfur and carbon–nitrogen bond formation can be observed, depending upon the solvent (see Entry 9, Scheme 4.4).

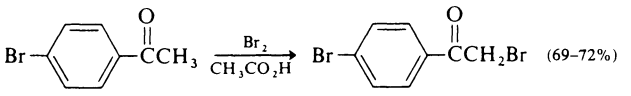
4.7. Electrophilic Substitution Alpha to Carbonyl Groups

Although the reaction of ketones and other carbonyl compounds with electrophiles such as bromine is formally a substitution process, it is mechanistically closely related to electrophilic additions to alkenes. The enol or enolate derived from the carbonyl compound is the reactive species, and the initial attack is similar to the electrophilic attack on alkenes. The reaction is completed by restoration of the carbonyl bond, rather than by addition of a nucleophile. The acid- and base-catalyzed halogenation of ketones, which were discussed briefly in Part A, Chapter 7, are the best-studied examples of the reaction. The most common preparative

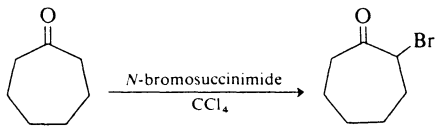
54. A. Hassner and F. Boerwinkle, *J. Am. Chem. Soc.* **90**, 216 (1968).
55. B. W. Ponder, T. E. Walton, and W. J. Pollock, *J. Org. Chem.* **33**, 3957 (1968).
56. M. Ohno, N. Naruse, S. Torimitsu, and M. Okamoto, *Bull. Chem. Soc. Japan* **39**, 1119 (1966).



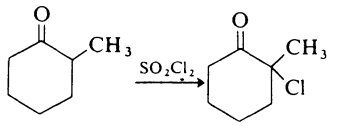
procedures involve use of the halogen, usually bromine, in acetic acid. Other available halogenating agents include *N*-bromosuccinimide, tetrabromocyclohexadienone, and sulfuryl chloride:



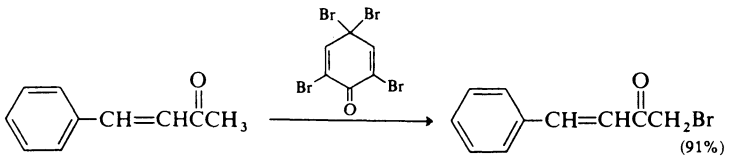
Ref. 57



Ref. 58



Ref. 59



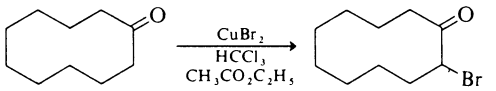
Ref. 60

Since the reactions involving bromine or chlorine evolve hydrogen halide, they are autocatalytic. In reactions with *N*-bromosuccinimide or tetrabromocyclohexadienone no hydrogen bromide is formed, so this method may be preferable in the case of acid-sensitive compounds.

As was pointed out in Part A, Section 7.3, under many conditions halogenation is fast, relative to enolization. When this is true, the position of substitution in unsymmetrical ketones is governed by the relative rates of formation of the isomeric enols. In general, mixtures are formed with unsymmetrical ketones. The presence of a halogen substituent decreases the rate of enolization and retards the rate of introduction of a second halogen on carbon. Monohalogenation can therefore usually be carried out satisfactorily in acidic solution. Base-catalyzed halogenation

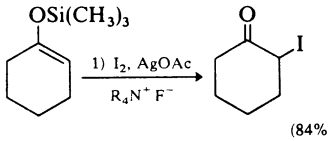
57. W. D. Langley, *Org. Synth.* **1**, 122 (1932).
58. E. J. Corey, *J. Am. Chem. Soc.* **75**, 2301 (1954).
59. E. W. Warnhoff, D. G. Martin, and W. S. Johnson, *Org. Synth.* **IV**, 162 (1963).
60. V. Calo, L. Lopez, G. Pesce, and P. E. Todesco, *Tetrahedron* **29**, 1625 (1973).

tends to proceed to polyhalogenated products. The use of cupric chloride and cupric bromide[61] in solvents such as chloroform has also proven to be an efficient method for monohalogenation of ketones.

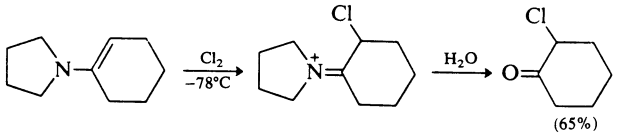


Ref. 62

In addition to direct halogenation of ketones, reactions with more reactive ketone derivatives such as silyl enol ethers[63] and enamines[64] have advantages in certain cases.

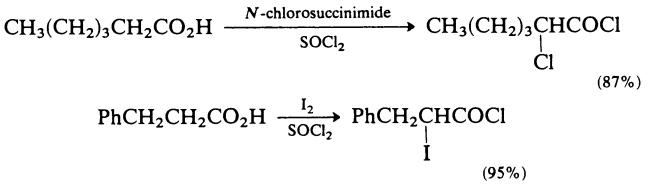


Ref. 63



Ref. 64

A final example of an α-halogenation reaction which has synthetic utility is the α-halogenation of acid chlorides. The mechanism is presumed to be similar to ketone halogenation and to proceed through an enol. This transformation can be effected in thionyl chloride as solvent to give α-chloro, α-bromo, or α-iodo acid chlorides, using, respectively, *N*-chlorosuccinimide, *N*-bromosuccinimide, and molecular iodine as the halogenation agent.[65] Because the thionyl chloride rapidly converts carboxylic acids to acid chlorides, the acid can be used as the starting material.



The α-sulfenylation[66] and α-selenation[67] of carbonyl compounds have become very important reactions since these derivatives can subsequently be oxidized to

61. E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.* **28**, 630 (1963); E. M. Kosower and G.-S. Wu, *J. Org. Chem.* **28**, 633 (1963).
62. D. P. Bauer and R. S. Macomber, *J. Org. Chem.* **40**, 1990 (1975).
63. G. M. Rubottom and R. C. Mott, *J. Org. Chem.* **44**, 1731 (1979).
64. W. Seufert and F. Effenberger, *Chem. Ber.* **112**, 1670 (1979).
65. D. N. Harpp, L. Q. Bao, C. J. Black, J. G. Gleason, and R. A. Smith, *J. Org. Chem.* **40**, 3420 (1975).
66. B. M. Trost, *Chem. Rev.* **78**, 363 (1978).
67. H. J. Reich, *Acc. Chem. Res.* **12**, 22 (1979); H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.* **97**, 5434 (1975).

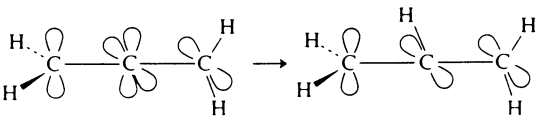
sulfoxides and selenoxides. The sulfoxides and selenoxides readily undergo elimination (see Section 6.3, Chapter 7), generating the corresponding α,β-unsaturated carbonyl compounds. Sulfenylations and selenations are usually carried out under conditions where the enolate of the carbonyl compound is the reactive species. Scheme 4.5 gives some specific examples of these types of reactions. The most general procedure involves generating an enolate by deprotonation, or by one of the alternative methods, followed by reaction with the sulfenylation or selenation reagent. Disulfides are the most common sulfenylation reagents, whereas diselenides or selenyl halides are used for selenation. As entries 6 and 7 indicate, the selenation of ketones can also be effected by reactions of enol acetates or enol silyl ethers. If a specific enolate is generated by one of the methods described in Chapter 1, the position of sulfenylation or selenation can be controlled.[68]

4.8. Additions to Allenes and Alkynes

Both allenes and alkynes require special consideration with regard to mechanisms of electrophilic addition. The attack by a proton on allene can conceivably lead to the allyl cation or the 2-propenyl cation:

$$^{+}CH_2{-}CH{=}CH_2 \xleftarrow{H^+} CH_2{=}C{=}CH_2 \xrightarrow{H^+} CH_3{-}\overset{+}{C}{=}CH_2$$

An immediate presumption that the more stable allyl ion will be formed ignores the stereoelectronic facets of the reaction. Protonation at the center carbon without rotation of the terminal methylene groups leads to a primary carbonium ion



unstabilized by resonance since the remaining π bond is orthogonal to the empty p orbital. Direct formation of an allyl cation therefore involves a more complex process than protonation.

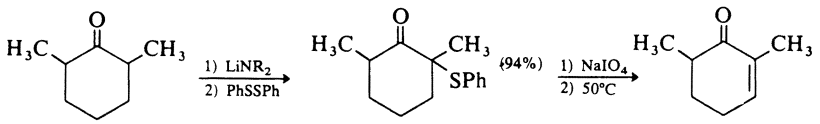
The addition of HCl, HBr, and HI to allene has been studied in some detail.[69] In each case, the halogen is found at the center carbon in the product with protonation at the terminal carbon. The initial product also undergoes some addition, giving rise to 2,2-dihalopropanes. Dimers are also formed, but we will not consider these.

$$CH_2{=}C{=}CH_2 + HX \rightarrow \underset{\displaystyle X}{\overset{\displaystyle |}{CH_3C}}{=}CH_2 + H_3C\underset{\displaystyle X}{\overset{\displaystyle X}{\overset{\displaystyle |}{\underset{\displaystyle |}{C}}}}CH_3$$

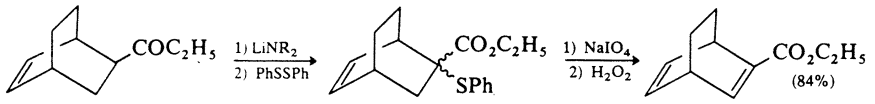
68. P. G. Gassman, D. P. Gilbert, and S. M. Cole, *J. Org. Chem. Soc.* **42**, 3233 (1977).
69. K. Griesbaum, W. Naegele, and G. G. Wanless, *J. Am. Chem. Soc.* **87**, 3151 (1965).

Scheme 4.5. α-Sulfenylation and α-Selenenylation of Carbonyl Compounds

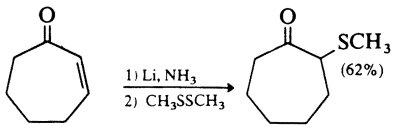
1[a]



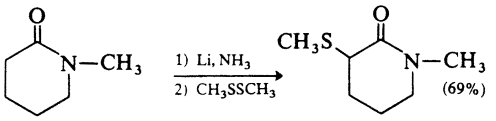
2[a]



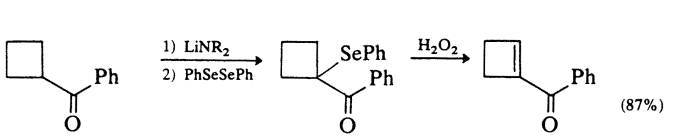
3[b]



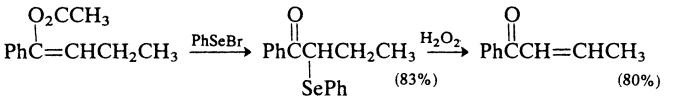
4[c]



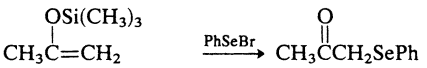
5[d]



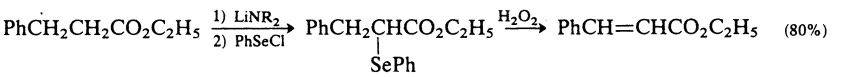
6[e]



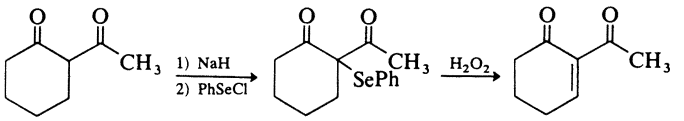
7[f]



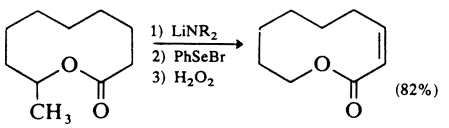
8[e]



9[g]

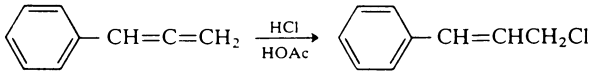


10[h]



a. B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.* **98**, 4887 (1976).
b. P. G. Gassman, D. P. Gilbert, and S. M. Cole, *J. Org. Chem.* **42**, 3233 (1977).
c. P. G. Gassman and R. J. Balchunis, *J. Org. Chem.* **42**, 3236 (1977).
d. H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.* **97**, 5434 (1975).
e. H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.* **95**, 5813 (1973).
f. I. Ryu, S. Murai, I. Niwa, and N. Sonoda, *Synthesis*, 874 (1977).
g. J. M. Renga and H. J. Reich, *Org. Synth.* **59**, 58 (1979).
h. T. Wakamatsu, K. Akasaka, and Y. Ban, *J. Org. Chem.* **44**, 2008 (1979).

The presence of a phenyl group results in the formation of products from protonation at the center carbon[70]:



Two alkyl groups, as in 1,1-dimethylallene, have the same effect[71]:

$$(CH_3)_2C{=}C{=}CH_2 \rightarrow (CH_3)_2C{=}CHCH_2Cl$$

These substituent effects are presumably due to stabilization of the cation that is generated by protonation at the center carbon. Even if the allylic conjugation is not effective in the transition state, the aryl and alkyl substituents can stabilize the charge that develops at the terminal carbon. Allenes are not nearly as widely available as alkenes and acetylenes and the uses that have been made of these materials in synthesis, at least to date, have been restricted.

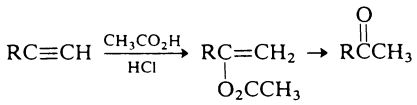
Acetylenes, though not as accessible as alkenes, have a number of important uses in synthesis. In general, alkynes are somewhat less reactive than alkenes toward comparable electrophiles. A major contribution to this difference in reactivity is the substantially higher energy of the vinyl cation intermediate formed by electrophilic attack on an alkyne as opposed to an alkyl carbonium ion generated from an alkene. This energy difference is roughly 10 kcal/mol, depending specifically on the electrophile X^+ and the particular system under study.[72] Table 4.3 summarizes

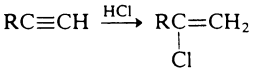
$$RC{\equiv}CH \xrightarrow{X^+} R\overset{+}{C}{=}CH{-}X$$

$$RCH{=}CH_2 \xrightarrow{X^+} R\overset{+}{C}H{-}CH_2{-}X$$

some data that provide an insight into the relative reactivity of alkenes versus alkynes. A more complete discussion of mechanistic aspects of addition to alkynes can be found in Section 6.5, Part A.

Acid-catalyzed additions to alkynes follow the Markownikoff rule. The initial addition products are not always stable, however. Addition of acetic acid, for example, results in the formation of enol acetates, which are easily converted to the corresponding carbonyl compound[73]:





70. T. Okuyama, K. Izawa, and T. Fueno, *J. Am. Chem. Soc.* **95**, 6749 (1973).
71. T. L. Jacobs and R. N. Johnson, *J. Am. Chem.* **82**, 6397 (1960).
72. K. Yates, G. H. Schmid, T. W. Regulski, D. G. Garratt, H. W. Leung, and R. McDonald, *J. Am. Chem. Soc.* **95**, 160 (1973).
73. R. C. Fahey and D.-J. Lee, *J. Am. Chem. Soc.* **90**, 2124 (1968).

Table 4.3. Relative Reactivity of Alkenes and Alkynes[a]

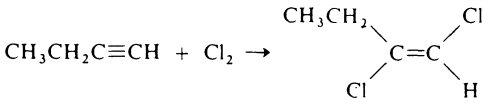
	Ratio of second-order rate constants (alkene/alkyne)		
	Bromination, acetic acid	Chlorination, acetic acid	Acid-catalyzed hydration, water
$CH_3CH_2CH_2CH_2CH{=}CH_2$ $CH_3CH_2CH_2CH_2C{\equiv}CH$	1.8×10^5	5.3×10^5	3.6
trans-$CH_3CH_2CH{=}CHCH_2CH_3$ $CH_3CH_2C{\equiv}CCH_2CH_3$	3.4×10^5	$\sim 1 \times 10^5$	16.6
$PhCH{=}CH_2$ $PhC{\equiv}CH$	2.6×10^3	7.2×10^2	0.65

a. From data tabulated in Ref. 72.

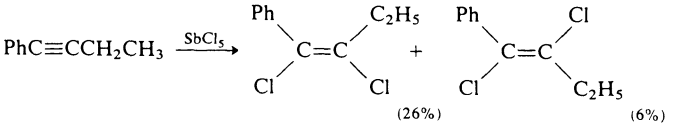
In aqueous solution, enols are formed and rapidly converted to the carbonyl compound.

The most synthetically valuable method for converting acetylenes to ketones is by mercuric-ion-catalyzed hydration. Terminal alkynes give methyl ketones in good yields. Unsymmetrical internal alkynes give a mixture of two possible ketones in the absence of some special stabilizing feature. Scheme 4.6 gives some examples of acetylene hydrations.

Addition of chlorine to alkynes is slow in the absence of light. When the addition reaction is initiated by light, the major product when butyne is in large excess is *trans*-1,2-dichlorobutene[74]:



The requirement for photoinitiation indicates that a radical-chain mechanism must be involved. Chlorination of 1-pentyne carried out in a gas phase reactor at higher temperatures and with higher chlorine:alkyne ratios gives both the *trans* dichloroalkene and the saturated tetrachloro compound derived from addition of a second mole of chlorine.[75] Fair yields of dichloroalkenes, predominantly the *cis* dihalide, can be obtained from acetylenes by reaction with antimony pentachloride[76]:

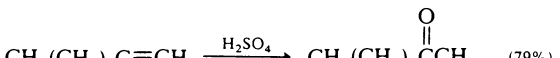


Bromination of alkynes occurs *via* an electrophilic mechanism. A bridged intermediate is postulated for alkyl substituted acetylenes, while vinyl cations are

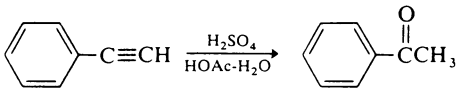
74. M. L. Poutsma and J. L. Kartch, *Tetrahedron* **22**, 2167 (1966).
75. A. T. Morse and L. C. Leitch, *Can. J. Chem.* **33**, 6 (1955).
76. S. Uemura, A. Onoe, and M. Okano, *J. Chem. Soc. Chem. Commun.* 145 (1976).

Scheme 4.6. Ketones by Hydration of Alkynes

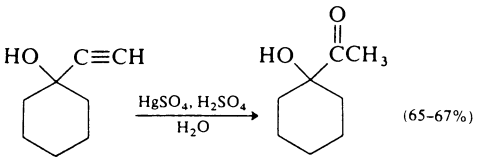
1[a]



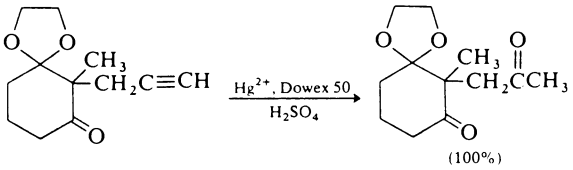
2[b]



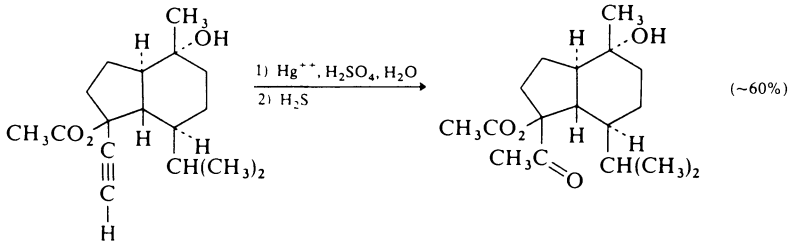
3[c]



4[d]

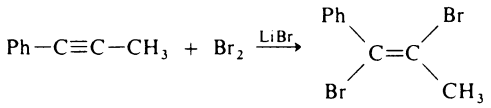


5[e]



a. R. J. Thomas, K. N. Campbell, and G. F. Hennion, *J. Am. Chem. Soc.* **60**, 718 (1938).
b. R. W. Bott, C. Eaborn, and D. R. M. Walton, *J. Chem. Soc.* 384 (1965).
c. G. N. Stacy and R. A. Mikulec, *Org. Synth.* **IV**, 13 (1963).
d. W. G. Dauben and D. J. Hart, *J. Org. Chem.* **42**, 3787 (1977).
e. D. Caine and F. N. Tuller, *J. Org. Chem.* **38**, 3663 (1973).

suggested for aryl-substituted examples.[77] Bromination of 1-phenylpropyne in acetic acid gives the *trans* dibromo adduct as the major product, but significant amounts of the *cis* isomer and products derived from incorporation of acetic acid are also observed. Addition of LiBr, however, makes the *trans* dibromo compound the overwhelming product[78]:



77. G. H. Schmid, A. Modro, and K. Yates, *J. Org. Chem.* **45**, 665 (1980).
78. J. A. Pincock and K. Yates, *J. Am. Chem. Soc.* **90**, 5643 (1968).

Among the most useful synthetic reactions of acetylenes are those initiated by addition of boron hydrides and aluminum hydrides to triple bonds. These reactions are discussed in Sections 4.9.4 and 4.9.5.

4.9. Hydroboration

4.9.1. Synthesis of Organoboranes

Borane, BH_3, is an avid electron pair acceptor because only a sextet of valence electrons is present at boron in the monomeric molecule. The pure material exists as a dimer. In aprotic solvents which act as electron pair donors such as ethers, tertiary amines, and sulfides, diborane forms stable Lewis acid–Lewis base

$$B_2H_6 \rightleftharpoons 2BH_3 \overset{2R_2O}{\rightleftharpoons} 2\,R_2\overset{+}{O}-\overset{-}{B}H_3$$

complexes. Borane adds very rapidly to most alkenes. This reaction, which is known as hydroboration, has been extensively developed, largely through the work of H. C. Brown and his associates, into the basis for a variety of useful synthetic operations.[79]

$$3RCH{=}CH_2 + BH_3 \rightarrow B(CH_2CH_2R)_3$$

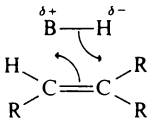
Diborane can be generated *in situ* from sodium borohydride and boron trifluoride. Solutions in tetrahydrofuran are commercially available. An alternative commercially available reagent is the borane–dimethyl sulfide complex:

$$H_3\overset{-}{B}-\overset{+}{S}(CH_3)_2$$

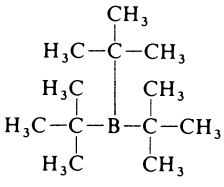
It is more amenable to storage over extended periods than diborane and exhibits comparable reactivity toward alkenes.[80]

Studies with many alkenes have shown that the addition of the B–H bond is highly selective both with respect to orientation (regioselectivity) and with respect to the stereochemistry of addition. The boron becomes bonded primarily to the *less substituted* carbon atom of the olefin. A combination of steric and electronic effects work together in favoring this orientation. Boron is less electronegative than hydrogen. The hydroboration reaction shows a weakly negative ρ value (-0.5) with a series of substituted styrenes, indicating some development of positive charge at the transition state.[81] This positive charge is best accommodated by the more highly substituted end of the multiple bond. Markownikoff's rule is thus followed in the

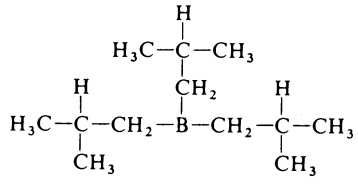
79. H. C. Brown, *Organic Synthesis via Boranes*, John Wiley and Sons, New York (1975).
80. L. M. Braun, R. A. Braun, H. R. Crissman, M. Opperman, and R. M. Adams, *J. Org. Chem.* **36**, 2388 (1971); C. F. Lane, *J. Org. Chem.* **39**, 1437 (1974).
81. L. C. Vishwakarma and A. Fry, *J. Org. Chem.* **45**, 5306 (1980).



addition, but, in contrast to the common examples of addition of acids to olefins, the hydrogen is *not* the electrophilic position in the attacking reagent. Steric factors also favor addition of the boron atom to the less substituted end of the multiple bond. In the final trialkylborane, considerable steric interferences develop if the alkyl chains are highly branched. These unfavorable steric effects are minimized by addition of the boron to the less substituted carbon. With electronic and steric



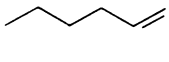
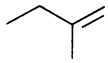
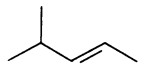
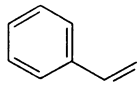
severe nonbonded repulsions



nonbonded repulsions reduced

effects operating in the same direction, the hydroboration reaction shows high and predictable regioselectivity. Except in the case of very sterically hindered alkenes, the reaction with borane proceeds rapidly to the trialkylborane stage by successive reaction of all three B–H bonds. Table 4.4 provides several examples of systems

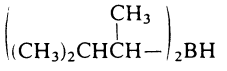
Table 4.4. Regioselectivity of Diborane and Alkylboranes toward Representative Alkenes

	Percent of Boron Added at Less Substituted Carbon Alkenes			
Hydroborating reagent	 1-Hexene	 2-Methyl-1-butene	 4-Methyl-2-pentene	 Styrene
Diborane[a]	94	99	57	80
Chloroborane–dimethyl sulfide[b]	99.2	99.9	—	93
Disiamylborane[a]	99	—	97	98
Thexylborane[c]	94	—	66	95
Thexylchloroborane–dimethyl sulfide[d]	99	99	97	99
9-BBN[e]	99.9	99.8*	99.8	98.5

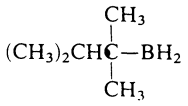
* data for 2-methyl-1-pentene

a. G. Zweifel and H. C. Brown, *Org. React.* **13**, 1 (1963).
b. H. C. Brown, N. Ravindran, and S. U. Kulkarni, *J. Org. Chem.* **44**, 2417 (1979).
c. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.* **82**, 4708 (1960).
d. H. C. Brown, J. A. Sikorski, S. U. Kulkarni, and H. D. Lee, *J. Org. Chem.* **45**, 4540 (1980).
e. H. C. Brown, E. F. Knights, and C. G. Scouten, *J. Am. Chem. Soc.* **96**, 7765 (1974).

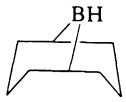
in which the regioselectivity of the addition has been measured. Included in the table are some mono- and dialkylboranes which show even higher regioselectivity than diborane itself. Certain of the names that are widely used in the literature for alkylboranes are nonsystematic. The structures of the three most commonly encountered alkylborane reagents are shown below:



disiamylborane
bis-(3-methyl-2-butyl)borane

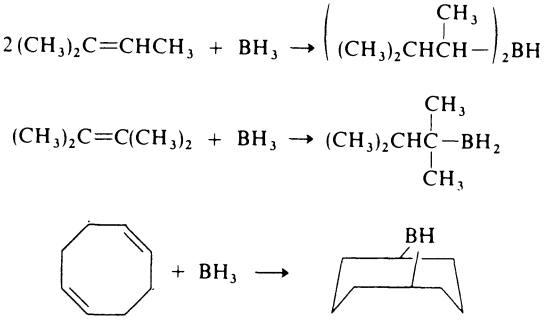


thexylborane
1,1,2-trimethylpropylborane



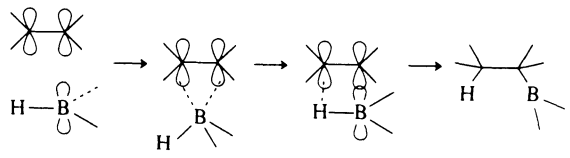
9-BBN
9-borabicyclo[3.3.1]nonane

These reagents are prepared by hydroboration of the appropriate alkene using control of stoichiometry to terminate the hydroboration at the desired stage.



Further changes in reactivity and regioselectivity can be achieved by use of chloroalkylboranes[81] and by use of the dimethyl sulfide complexes of the alkylboranes[80] as is indicated by the data in Table 4.4.

The hydroboration reaction is also highly specific with regard to the stereochemistry of addition. The addition occurs stereospecifically *syn* through a four-center transition state with essentially simultaneous bonding to boron and hydrogen. Both the new C–B and C–H bonds are therefore formed from the same side of the multiple bond. In molecular orbital terms, the addition reaction is viewed as taking place by interaction of the olefin π orbital with the empty p orbital on trivalent boron. Formation of the carbon–boron bond is accompanied by concerted rupture of a B–H bond[82]:



82. D. J. Pasto, B. Lepeska, and T.-C. Cheng, *J. Am. Chem. Soc.* **94**, 6083 (1972); P. R. Jones, *J. Org. Chem.* **37**, 1886 (1972); S. Nagase, K. N. Ray, and K. Morokuma, *J. Am. Chem. Soc.* **102**, 4536 (1980).

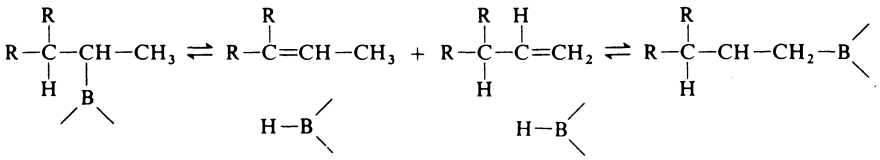
Table 4.5. Stereoselectivity of Hydroboration of Cyclic Alkenes[a]

Hydroborating reagent	Product composition[a]								
	3-Methylcyclopentene			3-Methylcyclohexene				7,7-Dimethylnorbornene	
	Trans-2	*Cis*-3	*Trans*-3	*Cis*-2	*Trans*-2	*Cis*-3	*Trans*-3	*Exo*	*Endo*
Borane	45	55		16	34	18	32	22	78[c]
Disiamylborane	40	60		18	30	27	25	—	—
9-BBN	25	50	25	0	20	40	40	3	97

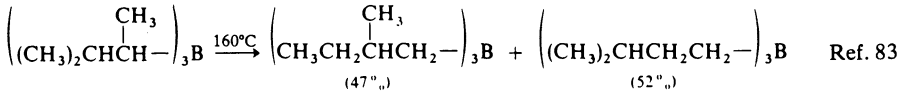
a. Product composition refers to methylcycloalkanol formed by subsequent oxidation.
b. Data from H. C. Brown, R. Liotta, and L. Brener, *J. Am. Chem. Soc.* **99**, 3427 (1977), except where noted otherwise.
c. H. C. Brown, J. H. Kawakami, and K.-T. Liu, *J. Am. Chem. Soc.* **95**, 2209 (1973).

As is true for most reagents, there is a preference for approach from the less hindered side of the molecule. Since diborane is a relatively small molecule, there is little selectivity in the avenue of approach to unhindered molecules. Table 4.5 gives some data comparing the stereochemistry of approach to three representative cyclic alkenes. The results show a trend away from the more sterically congested isomer which is revealed by the decreasing proportion of 2-substituted product. Only with the quite hindered 7,7-dimethylnorbornane, however, does the selectivity exerted by steric approach control become high. Scheme 4.7 (entries 2 and 3) provides additional examples of the preference for *syn* addition from the less hindered side of cyclic molecules.

Hydroboration is thermally reversible. At 160°C and above, B–H moieties are eliminated from alkylboranes, but in this temperature range the equilibrium is still in favor of the addition. These reversible additions lead to migration of boron to the least substituted carbon atom by a series of elimination and additions. Migration

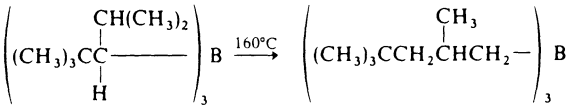


cannot occur past a quaternary carbon, however, since the required elimination is blocked. Some examples of thermal isomerizations of boranes are shown below:

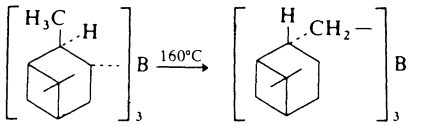


Ref. 83

83. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.* **88**, 1433 (1966).



Ref. 83



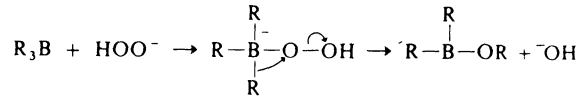
Ref. 84

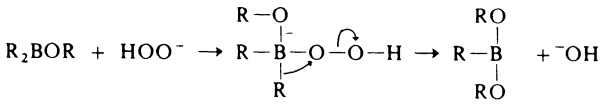
$$CH_3(CH_2)_{13}CH{=}CH(CH_2)_{13}CH_3 \xrightarrow[2)\ 80°C,\ 14\ hr]{1)\ B_2H_6} [CH_3(CH_2)_{28}]_3B$$

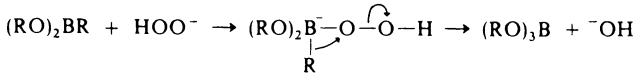
Ref. 85

4.9.2. Reactions of Organoboranes

The organoboranes formed by hydroboration or isomerization are of interest in organic synthesis because of the subsequent reactions which they undergo. The initial work showed that the boron atom could be replaced by hydroxyl groups, amino groups, and halogen atoms. The addition–replacement sequence can thereby accomplish conversion of alkenes to a variety of other types of organic compounds. The most widely used reaction of organoboranes is the oxidation to alcohols. Alkaline aqueous hydrogen peroxide is the reagent used to effect the oxidation. The mechanism is as outlined.







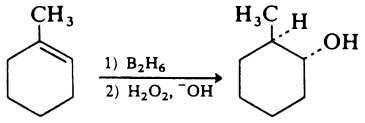
The R–O–B bonds are hydrolyzed during the oxidation, resulting in generation of the alcohol. It will be noted that the oxidation mechanism involves a series of B-to-O migrations of the alkyl groups, which migrate with their bonding electrons. The overall stereochemical outcome of the oxidation involves replacement of a C–B bond with retention of configuration. In combination with the orientation effects previously described, this result allows the structure and stereochemistry of

84. G. Zweifel and H. C. Brown, *J. Am. Chem. Soc.* **86**, 393 (1964).
85. K. Maruyama, K. Terada, and Y. Yamamoto, *J. Org. Chem.* **45**, 737 (1980).

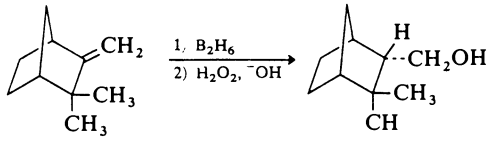
Scheme 4.7. Alcohols, Ketones,

A. Alcohols

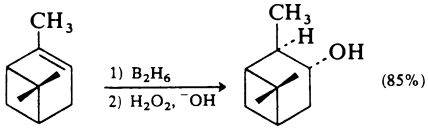
1[a]



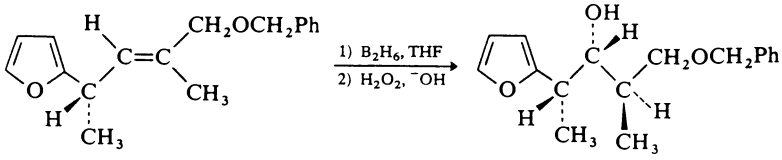
2[b]



3[c]

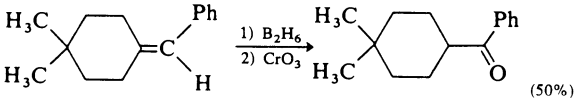


4[d]

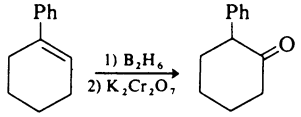


B. Ketones

5[e]



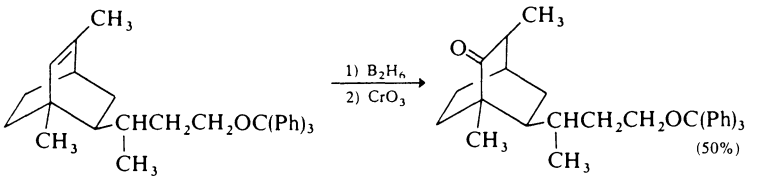
alcohols produced by the hydroboration–oxidation sequence to be predicted with confidence. Several examples are shown in Scheme 4.7. Conditions that permit oxidation of organoboranes to alcohols using molecular oxygen[86] or amine oxides[87] as oxidants have been discovered. More vigorous oxidizing agents effect replacement of boron and oxidation of the substituted carbon atom, permitting the synthesis of ketones.[88]



The boron atom can also be replaced by an NH_2 group.[89] The reagents that effect this conversion are chloramine or hydroxylamine-*O*-sulfonic acid. The

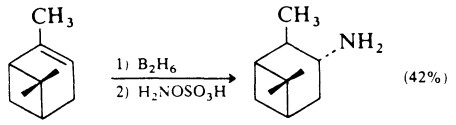
86. H. C. Brown, M. M. Midland, and G. W. Kabalka, *J. Am. Chem. Soc.* **93**, 1024 (1971).
87. G. W. Kabalka and H. C. Hedgecock, Jr., *J. Org. Chem.* **40**, 1776 (1975).
88. H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.* **83**, 2951 (1961).
89. M. W. Rathke, N. Inoue, K. R. Varma, and H. C. Brown, *J. Am. Chem. Soc.* **88**, 2870 (1966).

6[f]

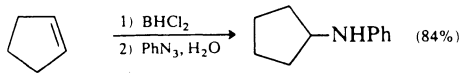


C. Amines

7[g]

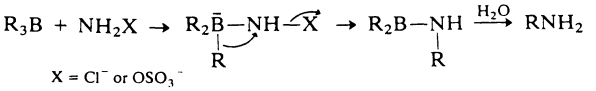


8[h]



a. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.* **83**, 2544 (1961).
b. R. Dulou, Y. Chretien-Bessiere, *Bull. Soc. Chim. France*, 1362 (1959).
c. G. Zweifel and H. C. Brown, *Org. Synth.* **52**, 59 (1972).
d. G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.* **101**, 259 (1979).
e. W. B. Farnham, *J. Am. Chem. Soc.* **94**, 6857 (1972).
f. R. N. Mirrington, and K. J. Schmalzl, *J. Org. Chem.* **37**, 2871 (1972).
g. M. W. Rathke and A. A. Millard, *Org. Synth.* **58**, 32 (1978).
h. H. C. Brown, M. M. Midland, and A. B. Levy, *J. Am. Chem. Soc.* **95**, 2394 (1973).

mechanisms of these reactions are very similar to that of the hydrogen peroxide oxidation of organoboranes. The nitrogen-containing reagents react as nucleophiles by adding to the boron, and rearrangement with expulsion of chloride ion or sulfate ion follows. The amine is freed by hydrolysis of the B–N bonds. Secondary amines



are formed by reaction of trisubstituted boranes with alkyl or aryl azides. The most efficient boranes to use for this purpose are monoalkyldichloroboranes, which are generated by reaction of an alkene with $BHCl_2 \cdot Et_2O$.[90] The entire sequence of steps and the mechanism of the final stages are summarized by the equations below:

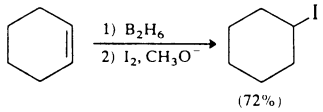
90. H. C. Brown, M. M. Midland, and A. B. Levy, *J. Am. Chem. Soc.* **95**, 2394 (1973).

$$BHCl_2{\cdot}Et_2O + RCH{=}CH_2 \rightarrow RCH_2CH_2BCl_2$$

$$RCH_2CH_2BCl_2 + R'{-}N_3 \rightarrow Cl_2\bar{B}{-}\underset{\underset{RCH_2CH_2}{|}}{\overset{\overset{R'}{|}}{N}}{-}\overset{+}{N}{\equiv}N \rightarrow Cl_2BN(R')CH_2CH_2R$$

$$Cl_2BN(R')CH_2CH_2R \xrightarrow{H_2O} R'NHCH_2CH_2R$$

Organoborane intermediates can also be used to synthesize alkyl halides. Replacement of the boron by iodine is rapid in the presence of base.[91] The best yields are obtained using sodium methoxide in methanol.[92] If less basic conditions are required, the use of iodine monochloride and sodium acetate as the base gives good yields.[93] A similar process using bromine and sodium hydroxide affords



Ref. 92

$$PhCO_2(CH_2)_3CH{=}CH_2 \xrightarrow[2)\ ICl]{1)\ B_2H_6} \underset{(88\%)}{PhCO_2(CH_2)_3CH_2CH_2I}$$

Ref. 93

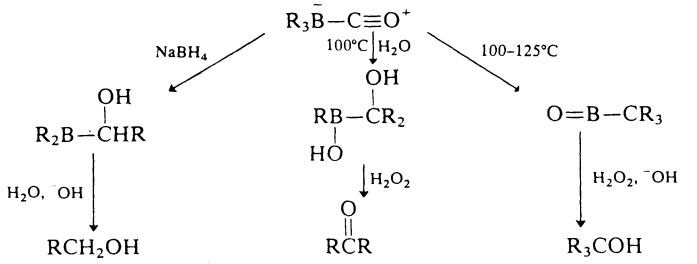
bromides in good yields.[94] It should be noted that since the halogen atom replaces the boron atom, the regioselectivity of these reactions is opposite to that observed by direct addition of the hydrogen halide. Terminal olefins give primary halides.

$$RCH{=}CH_2 \xrightarrow[2)\ Br_2, NaOH]{1)\ B_2H_6} RCH_2CH_2Br$$

4.9.3. Formation of Carbon–Carbon Bonds via Organoboranes

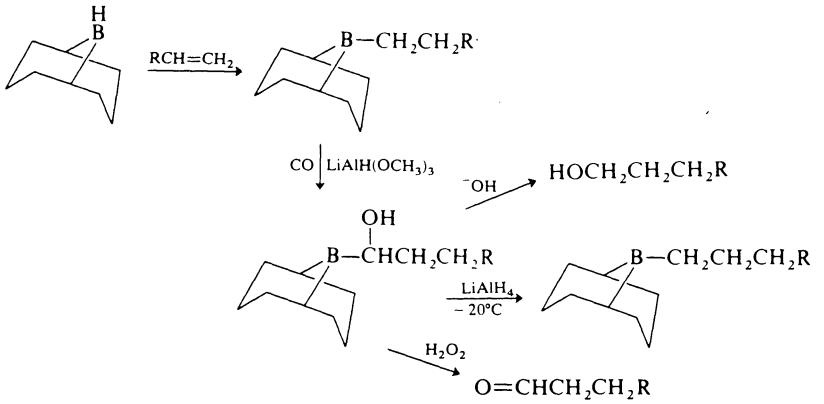
The reactions of organoboranes that have been discussed up to this point are valuable methods for introducing functionality into alkenes. The discovery that carbon monoxide reacts with organoboranes under mild conditions has led to the development of procedures which permit formation of new carbon–carbon bonds with the final products being primary alcohols, ketones, or tertiary alcohols.[95] The adduct of carbon monoxide and trialkylboranes undergo boron-to-carbon migration of the alkyl groups. By control of the conditions during rearrangements, the reaction can be stopped after one, two, or three migrations.

91. H. C. Brown, M. W. Rathke, and M. M. Rogic, *J. Am. Chem. Soc.* **90**, 5038 (1968).
92. N. R. deLue and H. C. Brown, *Synthesis*, **114** (1976).
93. G. W. Kabalka and E. E. Gooch, III, *J. Org. Chem.* **45**, 3578 (1980).
94. H. C. Brown and C. F. Lane, *J. Am. Chem. Soc.* **92**, 6660 (1970).
95. H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.* **89**, 2737 (1967).



If the organoborane is heated with carbon monoxide at 100–125°C, all groups migrate and a tertiary alcohol is obtained after oxidation. The presence of water in the carbonylation reaction mixture causes the reaction to cease after migration of two alkyl groups from boron to carbon. Oxidation of the reaction mixture at this stage gives dialkyl ketones.[96] Primary alcohols are obtained when the carbonylation stage of the reaction is carried out in the presence of sodium borohydride or lithium borohydride.[97] The hydride reducing agent reduces the product of the first migration step and hydrolysis gives a primary alcohol.

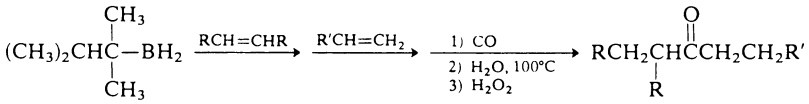
It should be noted that in the synthesis of primary alcohols only one of the three alkyl groups in the organoborane is converted to product. This disadvantage can be overcome by using a dialkylborane, particularly 9-BBN, in the initial hydroboration. The monomigration product can also be worked up under mildly oxidative conditions to give aldehydes.[98] The carbonylated intermediate can



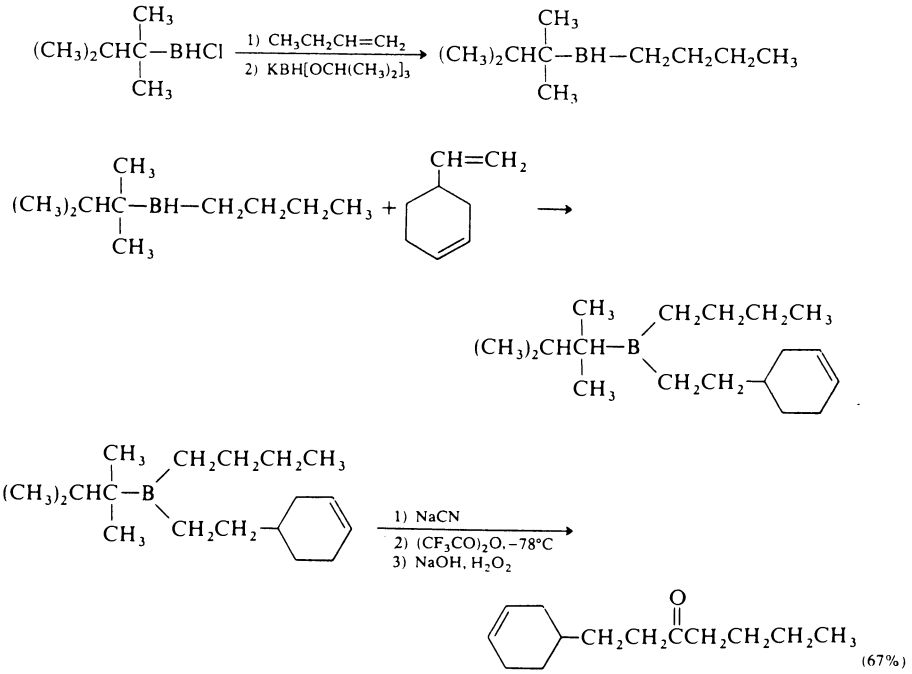
also be reduced with lithium aluminum hydride to give a homologated 9-BBN derivative.[99] The success of the 9-BBN reagent in these procedures depends upon the minimal tendency for the bicyclic ring to participate in the migration process.

96. H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.* **89**, 2738 (1967).
97. M. W. Rathke and H. C. Brown, *J. Am. Chem. Soc.* **89**, 2740 (1967).
98. H. C. Brown, E. F. Knights, and R. A. Coleman, *J. Am. Chem. Soc.* **91**, 2144 (1969).
99. H. C. Brown, T. M. Ford, and J. L. Hubbard, *J. Org. Chem.* **45**, 4067 (1980).

Unsymmetrical ketones can be made using either thexylborane or thexylchloroborane.[100] Thexylborane works well when one of the desired carbonyl substituents is derived from a moderately hindered alkene. Under these circumstances a clean monoalkylation of thexylborane can be accomplished. This can be followed by reaction with the second alkene and carbonylation. Thexylchloroborane



is also a useful reagent for the synthesis of unsymmetrical ketones. It has the advantage of permitting a more general synthesis of dialkylboranes by reaction first with an alkene and then with a reducing agent such as $KBH[OCH(CH_3)_2]_3$.



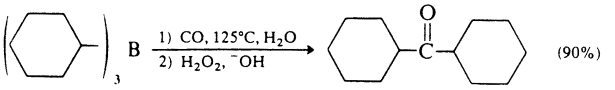
Again the success of this procedure depends upon the thexyl group being noncompetitive with the other two groups in the migration reaction. Scheme 4.8 summarizes some of the different types of transformations which can be carried out *via* carbonylation.

A number of other one-carbon reagents besides carbon monoxide can serve as the migration terminus in a series of reactions that are closely related to the carbonylation just described. Scheme 4.9 gives some examples of the types of

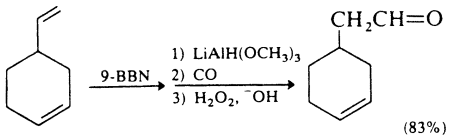
100. H. C. Brown and E. Negishi, *J. Am. Chem. Soc.* **89**, 5285 (1967); S. U. Kulkarni, H. D. Lee, and H. C. Brown, *J. Org. Chem.* **45**, 4542 (1980).

Scheme 4.8. Synthesis via Carbonylation of Organoboranes

1[a] $\left(CH_3CH_2\underset{CH_3}{\underset{|}{C}}H-\right)_3B \xrightarrow[2)\ H_2O_2,\ ^-OH]{1)\ CO,\ 125°C} \left(CH_3CH_2\underset{CH_3}{\underset{|}{C}}H-\right)_3COH$ (87%)

2[b] 

(90%)

3[c] 

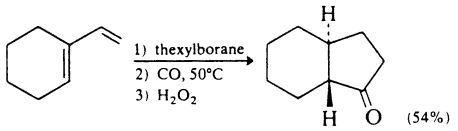
(83%)

4[d] $(CH_3)_2C{=}CH_2 \xrightarrow{\text{thexylborane}} \xrightarrow{CH_2{=}CHCO_2C_2H_5} \xrightarrow[2)\ H_2O_2,\ ^-OAc]{1)\ CO,\ 50°C} (CH_3)_2CHCH_2\overset{\overset{O}{\|}}{C}CH_2CH_2CO_2C_2H_5$ (81%)

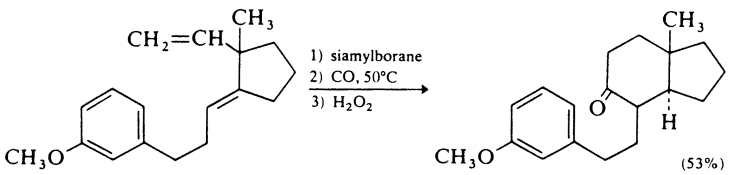
5[e] $CH_3CH{=}CHCH_3 \xrightarrow{B_2H_6} \xrightarrow[2)\ CO]{1)\ LiAlH(OCH_3)_3} \xrightarrow[2)\ H_2O_2,\ OH]{1)\ H_2O,\ H^+} CH_3CH_2\underset{CH_3}{\underset{|}{C}}H\underset{CH_3}{\underset{|}{C}}H\underset{OH}{\underset{|}{C}}HCH_2CH_3$ (82%)

6[f] $CH_3(CH_2)_5CH{=}CH_2 \xrightarrow[2)\ KBH(OR)_3]{1)\ \text{thexylchloroborane}} \xrightarrow{CH_2{=}CH(CH_2)_7CH_3} \xrightarrow[2)\ (CF_3CO)_2O]{1)\ NaCN}$

$CH_3(CH_2)_7\overset{\overset{O}{\|}}{C}(CH_2)_9CH_3$ (74%)

7[g] 

(54%)

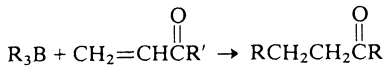
8[h] 

(53%)

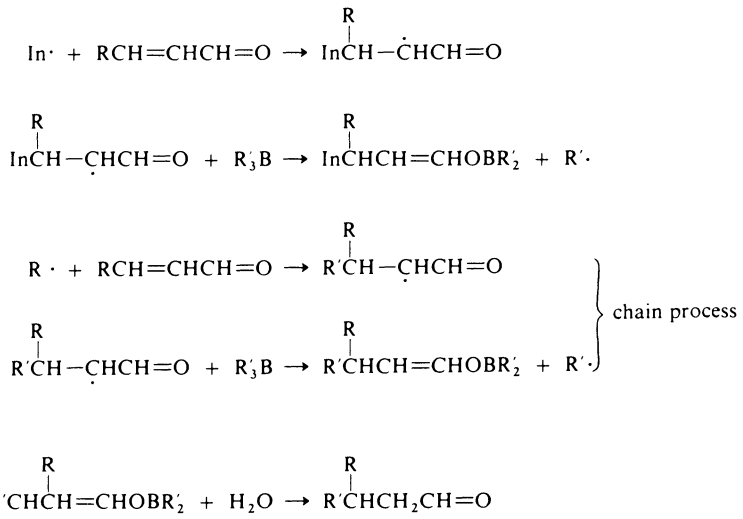
a. H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.* **89**, 2737 (1967).
b. H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.* **89**, 2738 (1967).
c. H. C. Brown, E. F. Knights, and R. A. Coleman, *J. Am. Chem. Soc.* **91**, 2144 (1969).
d. H. C. Brown and E. Negishi, *J. Am. Chem. Soc.* **89**, 5285 (1967).
e. J. L. Hubbard and H. C. Brown, *Synthesis*, 676 (1978).
f. S. U. Kulkarni, H. D. Lee, and H. C. Brown, *J. Org. Chem.* **45**, 4542 (1980).
g. H. C. Brown and E. Negishi, *J. Am. Chem. Soc.* **89**, 5477 (1967).
h. T. A. Bryson and W. E. Pye, *J. Org. Chem.* **42**, 3214 (1977).

reagents which have exhibited this reactivity. Problem 14 deals with the detailed mechanism of these reactions and the reader is encouraged to consider that question to gain mechanistic insight. Perhaps the most generally applicable route developed to date for the preparation of ketones from alkylboranes is the process illustrated by entries 3 and 5 in Scheme 4.9 in which a dialkyl derivative of thexylborane is treated with cyanide ion and then trifluoroacetic anhydride. Although each of the processes illustrated in Scheme 4.9 involves several separate stages, most of them can be carried out by successive additions of reagents to a single reaction vessel.

Organoboranes can also be used to construct carbon–carbon bonds by two other types of reactions in which a migration of an alkyl group from boron to carbon is involved. Certain α,β-unsaturated carbonyl compounds react with trialkylboranes with the net transformation being transfer of one alkyl group from the borane to the β-carbon atom of the unsaturated system. A free-radical mechanism



has been proposed for these reactions.[101] Since only one of the groups in the borane is utilized in this reaction, an effort has been made to develop reaction conditions

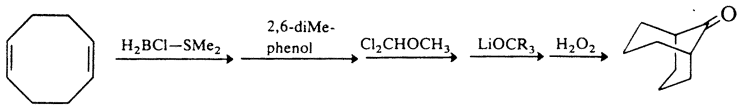


which would utilize the starting alkene more efficiently. Heterocyclic dialkylboranes (borinanes) prepared from 1,4-dienes have proved satisfactory for this purpose.[102] Scheme 4.10 illustrates some examples of reactions of trialkylboranes with α,β-unsaturated carbonyl compounds.

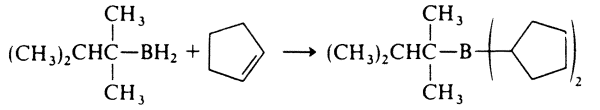
101. G. W. Kabalka, H. C. Brown, A. Suzuki, S. Honma, A. Arase, and M. Itoh, *J. Am. Chem. Soc.* **92**, 710 (1970).
102. E. Negishi and H. C. Brown, *J. Am. Chem. Soc.* **95**, 6757 (1973).

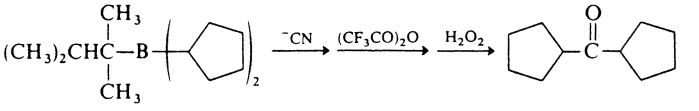
Scheme 4.9. Some One-Carbon Donors in Alcohol and Ketone Synthesis Using Organoboranes

1[a] $(C_4H_9)_3B + HCClF_2 \xrightarrow[65°C,\ 1\ hr]{LiOCR_3} \xrightarrow{H_2O_2} (C_4H_9)_3COH$ (98%)

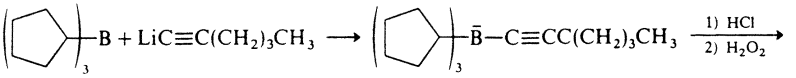
2[b] 

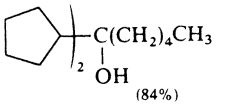
(71%)

3[c] 

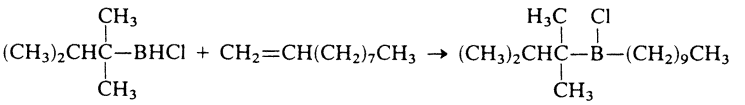


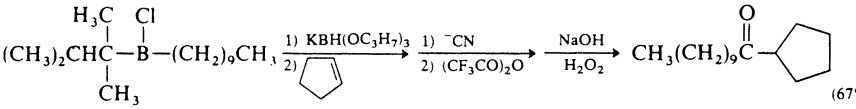
(80%)

4[d] 

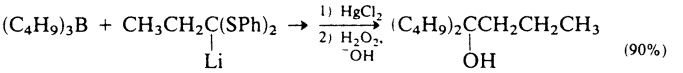


(84%)

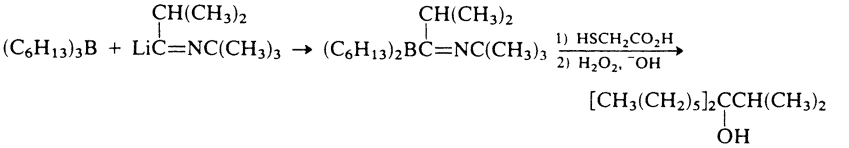
5[e] 



(67%)

6[f] 

(90%)

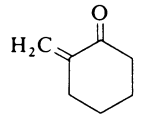
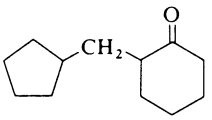
7[g] 

(75%)

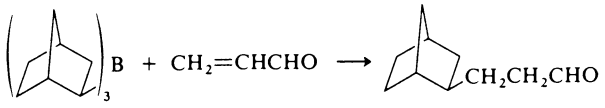
a. H. C. Brown, B. A. Carlson, and R. H. Prager, *J. Am. Chem. Soc.* **93**, 2070 (1971).
b. H. C. Brown and S. U. Kulkarni, *J. Org. Chem.* **44**, 2422 (1979).
c. A. Pelter, K. Smith, M. G. Hutchings, and K. Rowe, *J. Chem. Soc. Perkin Trans 1*, 129 (1975).
d. M. M. Midland and H. C. Brown, *J Org. Chem.* **40**, 2845 (1975).
e. S. U. Kulkarni, H. D. Lee, and H. C. Brown, *J. Org. Chem.* **45**, 4542 (1980).
f. R. J. Hughes, S. Ncube, A. Pelter, K. Smith, E. Negishi, and T. Yoshida, *J. Chem. Soc. Perkin Trans. 1*, 1172 (1977); S. Ncube, A. Pelter, and K. Smith, *Tetrahedron Lett.* 1895 (1979).
g. Y. Yamamoto, K. Kondo and I. Moritani, *J. Org. Chem.* **40**, 3644 (1975).

Scheme 4.10. Alkylation of Organoboranes by α,β-Unsaturated Carbonyl Compounds

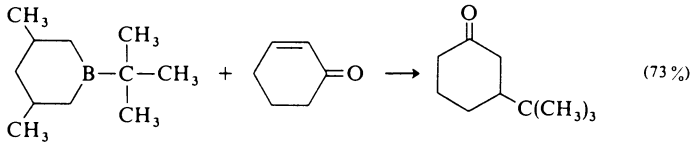
1[a] $(\text{C}_5\text{H}_9)_3\text{B} + \text{CH}_2{=}\text{CHCOCH}_3 \longrightarrow \text{C}_5\text{H}_9\text{CH}_2\text{CH}_2\text{COCH}_3$ (86%)

2[b] $(\text{C}_5\text{H}_9)_3\text{B} +$   (90%)

3[c] $(\text{CH}_3\text{CH}_2\underset{\displaystyle\text{CH}_3}{\underset{|}{\text{CH}}}-)_3\text{B} + \text{CH}_2{=}\text{CHCHO} \rightarrow \text{CH}_3\text{CH}_2\underset{\displaystyle\text{CH}_3}{\underset{|}{\text{CH}}}\text{CH}_2\text{CH}_2\text{CHO}$ (96%)

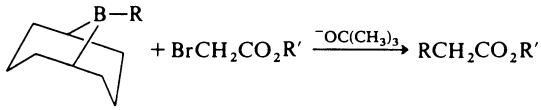
4[c] 

5[d] $(\text{C}_2\text{H}_5)_3\text{B} + \text{CH}_3\text{CH}{=}\text{CHCOCH}_3 \rightarrow \text{CH}_3\text{CH}_2\underset{\displaystyle\text{CH}_3}{\underset{|}{\text{CH}}}\text{CH}_2\text{COCH}_3$ (70%)

6[e] 

a. A. Suzuki, A. Arase, H. Matsumoto, M. Itoh, H. C. Brown, M. M. Rogić, and M. W. Rathke, *J. Am. Chem. Soc.* **89**, 5708 (1967).
b. H. C. Brown, M. W. Rathke, G. W. Kabalka, and M. M. Rogić, *J. Am. Chem. Soc.* **90**, 4166 (1968).
c. H. C. Brown, M. M. Rogić, M. W. Rathke, and G. W. Kabalka, *J. Am. Chem. Soc.* **89**, 5709 (1967).
d. H. C. Brown and G. W. Kabalka, *J. Am. Chem. Soc.* **92**, 714 (1970).
e. E. Negishi and H. C. Brown, *J. Am. Chem. Soc.* **95**, 6757 (1973).

A second means of effecting alkylations of organoboranes involves reactions with certain types of halides, especially α-halocarbonyl compounds.[103] For example, ethyl bromoacetate has been found to alkylate a number of trialkylboranes in

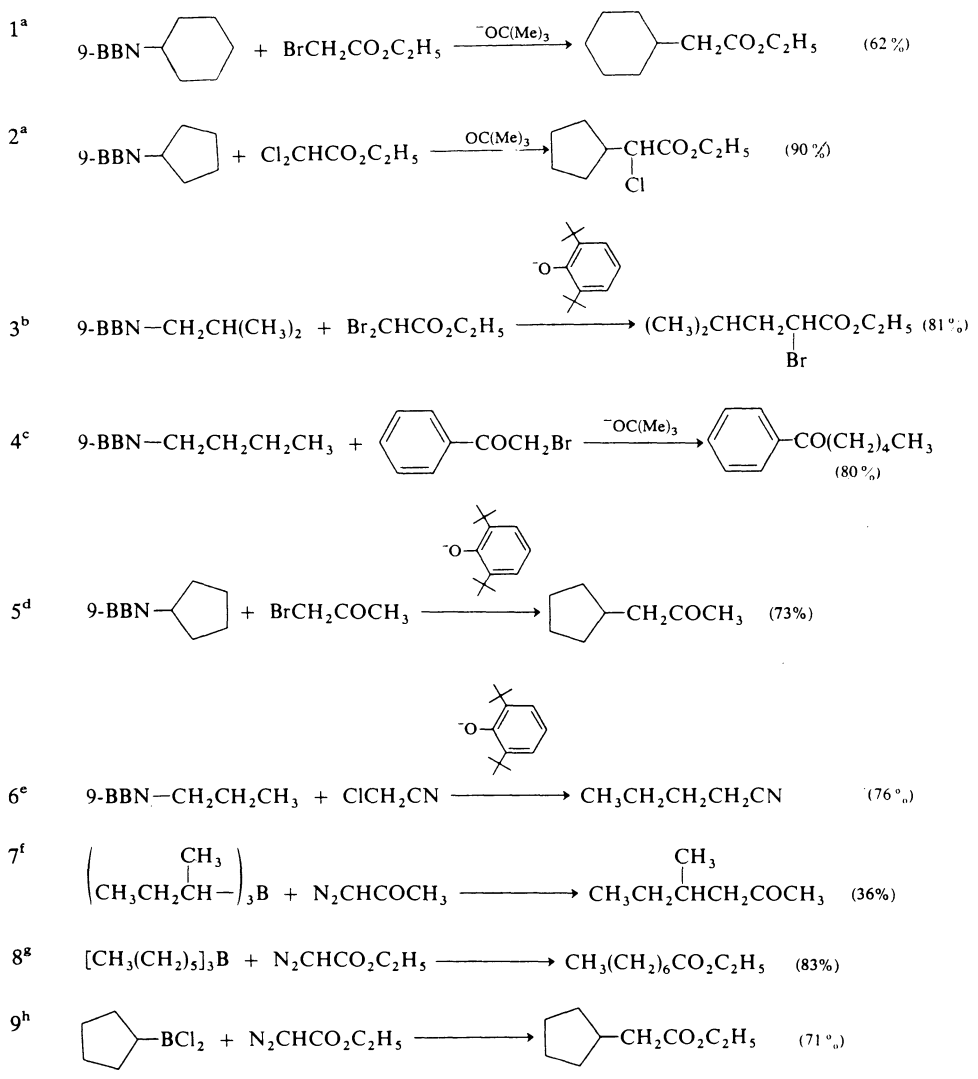


excellent yield. This synthetic transformation is more efficiently carried out using a trialkylborane prepared from the olefin to be alkylated and the dialkylborane 9-BBN.[104] α-Haloketones and α-halonitriles are also capable of alkylating

103. H. C. Brown, M. M. Rogić, M. W. Rathke, and G. W. Kabalka, *J. Am. Chem. Soc.* **90**, 818 (1968).
104. H. C. Brown and M. M. Rogić, *J. Am. Chem. Soc.* **91**, 2146 (1969).

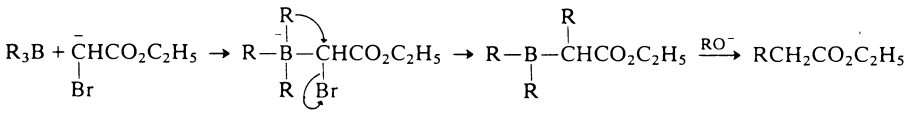
organoboranes. A number of examples of this reaction are summarized in Scheme 4.11.

Scheme 4.11. Alkylation of Trialkylboranes with α-Halocarbonyl and Related Compounds



a. H. C. Brown and M. M. Rogić, *J. Am. Chem. Soc.* **91**, 2146 (1969).
b. H. C. Brown, H. Nambu, and M. M. Rogić, *J. Am. Chem. Soc.* **91**, 6855 (1969).
c. H. C. Brown, M. M. Rogić, H. Nambu, and M. W. Rathke, *J. Am. Chem. Soc.* **91**, 2147 (1968).
d. H. C. Brown, H. Nambu, and M. M. Rogić, *J. Am. Chem. Soc.* **91**, 6853 (1969).
e. H. C. Brown, H. Nambu, and M. M. Rogić, *J. Am. Chem. Soc.* **91**, 6855 (1969).
f. J. Hooz and S. Linke, *J. Am. Chem. Soc.* **90**, 5936 (1968).
g. J. Hooz and S. Linke, *J. Am. Chem. Soc.* **90**, 6891 (1968).
h. J. Hooz, J. N. Bridson, J. G. Caldaza, H. C. Brown, M. M. Midland, and A. B. Levy, *J. Org. Chem.* **38**, 2574 (1973).

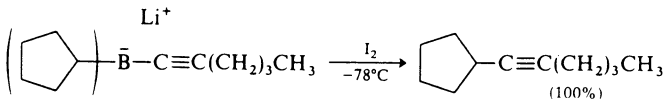
The mechanism by which these alkylations occur is fundamentally similar to the oxidation of organoboranes to alcohols. It is believed that the enolate of the haloester or haloketone reacts with the borane. Subsequently, elimination of halide, followed by migration of one of the boron substituents, occurs. In agreement with this mechanism, retention of configuration of the migrating group is observed.[105]



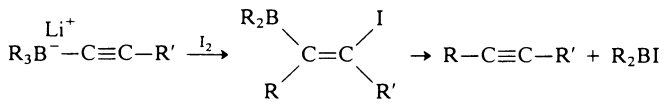
A closely related reaction employs α-diazoesters or α-diazoketones.[106,107] Molecular nitrogen then acts as the leaving group in the migration step. The best results are achieved with dialkylchloroboranes or dichloroboranes.

$$RBCl_2 + N_2CHCO_2CH_3 \rightarrow RCH_2CO_2CH_3$$

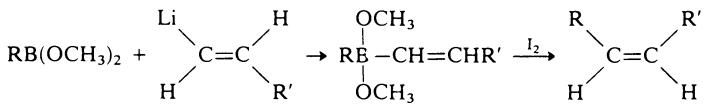
Another route to carbon–carbon bond formation is via iodine-induced rearrangement of adducts of trisubstituted boron compounds and organolithium reagents. The adducts of trialkylboranes with lithium acetylides give an akylated acetylene.[108] The mechanism involves electrophilic attack by iodine on the acetylenic



bond which induces a migration of an alkyl group from boron. This is followed by elimination of dialkylboron iodide.



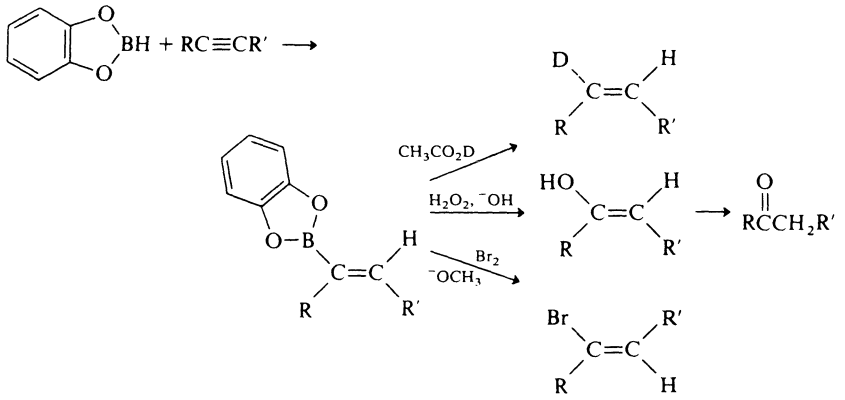
In a similar reaction, vinyllithium reagents add to dimethyl borinates (dimethoxyboranes) to give adducts which decompose to alkenes on treatment with iodine.[109]



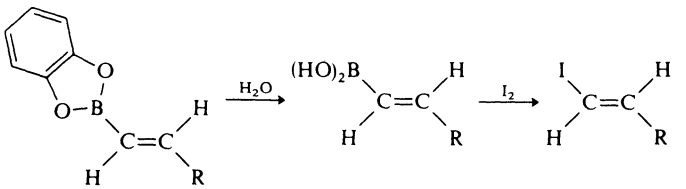
105. H. C. Brown, M. M. Rogić, M. W. Rathke, and G. W. Kabalka, *J. Am. Chem. Soc.* **91**, 2151 (1969).
106. H. C. Brown, M. M. Midland, and A. B. Levy, *J. Am. Chem. Soc.* **94**, 3662 (1972).
107. J. Hooz, J. N. Bridson, J. G. Calzada, H. C. Brown, M. M. Midland, and A. B. Levy, *J. Org. Chem.* **38**, 2574 (1973).
108. A. Suzuki, N. Miyaura, S. Abiko, M. Itoh, H. C. Brown, J. A. Sinclair, and M. M. Midland, *J. Am. Chem. Soc.* **95**, 3080 (1973).
109. D. A. Evans, T. C. Crawford, R. C. Thomas, and J. A. Walker, *J. Org. Chem.* **41**, 3947 (1976).

4.9.4. Hydroboration of Acetylenes

Alkynes are reactive toward hydroboration reagents. The most useful procedures involve addition of a disubstituted borane to the acetylene. Catechol borane (1,3,2-benzodioxaborole), which is prepared from equimolar amounts of catechol (1,2-dihydroxybenzene) and borane, is a particularly useful reagent for hydroboration of acetylenes.[110] Protonolysis of the adduct with acetic acid results in reduction of the original alkyne to the corresponding *cis*-alkene. Oxidative workup with hydrogen peroxide gives ketones via an enol intermediate. Treatment of the vinyl borane with bromine and base leads to the vinyl bromide.[110] The net *anti*-addition has been rationalized on the basis of *anti*-addition of bromine followed by a second *anti*-elimination of bromide and boron but there are exceptions to this generalization.[111]

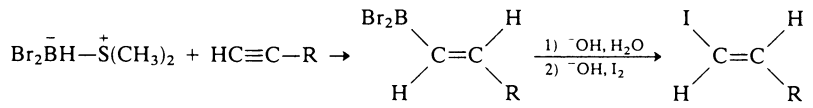


The adducts derived from catechol borane are hydrolyzed by water to vinylboronic acids. These materials, are useful intermediates for preparation of terminal vinyl iodides. Since the hydroboration is *syn* and the iodinolysis occurs with retention of alkene geometry, the iodides which result have the *E* configuration.[112]

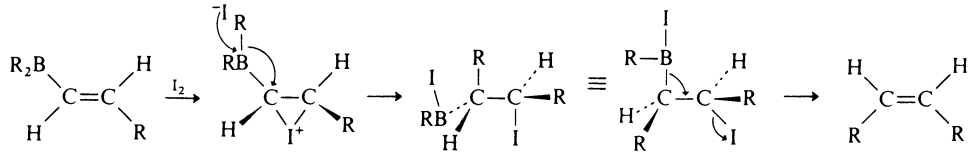


The dimethyl sulfide complex of dibromoborane has also proven to be useful for synthesis of *E*-vinyl iodides from terminal acetylenes.[113]

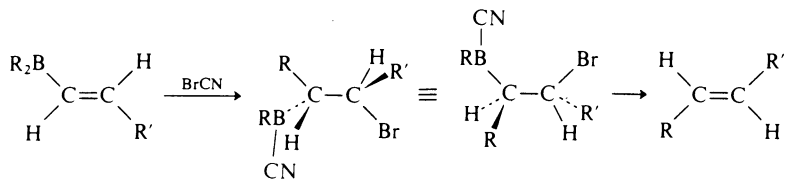
110. H. C. Brown, T. Hamaoka, and N. Ravindran, *J. Am. Chem. Soc.* **95**, 6456 (1973); C. F. Lane and G. W. Kabalka, *Tetrahedron* **32**, 981 (1976).
111. J. R. Wiersig, N. Waespe-Sarcevic, and C. Djerassi, *J. Org. Chem.* **44**, 3374 (1979).
112. H. C. Brown, T. Hamaoka, and N. Ravindran, *J. Am. Chem. Soc.* **95**, 5786 (1973).
113. H. C. Brown and J. B. Campbell, Jr., *J. Org. Chem.* **45**, 389 (1980).



Hydroboration of acetylenes by *dialkylboranes* followed by treatment with iodine results in the formation of the *cis* alkene.[114,115] The mechanism suggested for this process involves alkyl migration initiated by iodination of the double bond, followed by stereospecific elimination of RBI_2:



The corresponding *trans*-alkene can be obtained by using cyanogen bromide in place of iodine.[116] Although the overall mechanism is similar, the cyanogen bromide intermediate eliminates by a *syn* mechanism.



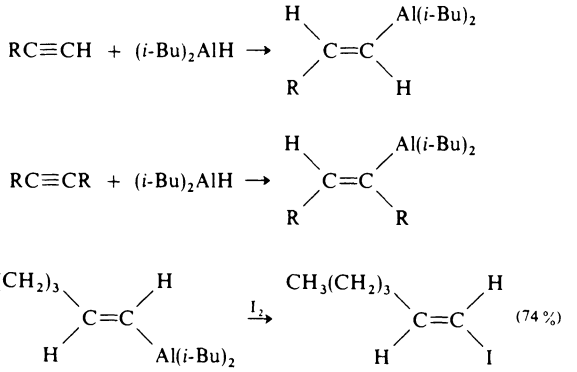
As can be readily judged from the preceding section, organoboranes are versatile intermediates. The hydroboration–oxidation sequence has become an important means of alcohol synthesis, and the carbonylation- and alkylation-type reactions also seem likely to become widely used synthetic procedures. Although diborane is a reducing agent, the reductions are sufficiently slow that ester, cyano, and nitro groups do not interfere with hydroboration. On the other hand, ketone, aldehyde, carboxylic acid, and tertiary amide groups are reduced rapidly with diborane, and such reductions can be competitive with hydroboration.[117] These groups must be converted to protected derivatives before being subjected to hydroborations.

4.10. Hydroalumination

Several dialkylaluminum hydrides, for example, diisobutylaluminum hydride, are commercially available and undergo addition reactions which are analogous to

114. G. Zweifel, H. Arzoumanian, and C. C. Whitney, *J. Am. Chem. Soc.* **89**, 3652 (1967).
115. G. Zweifel, R. P. Fisher, J. T. Snow, and C. C. Whitney, *J. Am. Chem. Soc.* **93**, 6309 (1971).
116. G. Zweifel, R. P. Fisher, J. T. Snow, and C. C. Whitney, *J. Am. Chem. Soc.* **94**, 6560 (1972).
117. H. C. Brown, P. Heim, and N. M. Yoon, *J. Am. Chem. Soc.* **92**, 1637 (1970).

the alkene and acetylene addition reactions of the dialkylboranes.[118] Aluminum is considerably less electronegative than boron and as a result the organoaluminum species share many reactivity characteristics with the magnesium and lithium reagents, which will be discussed in Chapter 6. The addition reaction to alkenes occurs considerably less readily than the corresponding addition of dialkylboranes. Only terminal or strained alkenes react readily at room temperature.[119] With internal and branched alkenes, the addition does not go to completion. The orientation is, however, identical to the case of hydroboration with the aluminum adding to the less substituted sp^2 carbon. The addition to acetylenes occurs more easily and has found more utility for laboratory synthesis. Hydroalumination followed by reaction of the resulting vinylalane with iodine gives rise to vinyl iodides, the reaction proceeding with retention of configuration.[120]



The most useful synthetic reactions of vinylalanes are those in which the alanes intermediates react with organometallic reagents. These reactions will be discussed in Chapter 6.

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Hydrogen Halide Additions

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Solvomercuration

W. Kitching, *Organomet. Chem. Rev.* **3**, 61 (1968).
R. C. Larock, *Angew. Chem. Int. Ed. Engl.* **17**, 27 (1978).

118. T. Mole and E. A. Jeffery, *Organoaluminum Compounds*, Elsevier, Amsterdam (1972), Chaps. 3 and 11.
119. F. Ansinger, B. Fell, and F. Thiessen, *Chem. Ber.* **100**, 937 (1967); R. Schimpf and P. Heimbach, *Chem. Ber.* **103**, 2122 (1970).
120. G. Zweifel and C. C. Whitney, *J. Am. Chem. Soc.* **89**, 2753 (1967).

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A. Hassner, *Acc. Chem. Res.* **4**, 9 (1971).

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W. A. Smit, N. S. Zefirov, I. V. Bodrikov, and M. Z. Krimer, *Acc. Chem. Res.* **12**, 282 (1979).
D. J. Clive, *Tetrahedron* **34**, 1049 (1978).

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T. F. Rutledge, *Acetylenes and Allenes*, Reinhold, New York (1969).
G. Modena and V. Tonellato, *Adv. Phys. Org. Chem.* **9**, 185 (1971).
K. Griesbaum, *Angew. Chem. Int. Ed. Engl.* **5**, 933 (1966).
D. R. Taylor, *Chem. Rev.* **67**, 317 (1967).

Organoboranes as Synthetic Intermediates

H. C. Brown, *Organic Syntheses via Boranes*, John Wiley, New York (1975).
H. C. Brown, *Boranes in Organic Chemistry*, Cornell University Press, Ithaca (1972).
G. Cragg, *Organoboranes in Organic Synthesis*, Marcel Dekker, New York (1973).

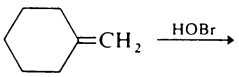
Problems

References to these problems are found on page 623.

1. Predict the direction of addition and structure of the product for each of the following reactions.

(a) $CH_3CH{=}CH_2 + O_2N\text{-}C_6H_3(NO_2)\text{-}SCl \longrightarrow$

(b) $(CH_3)_2C(OH)C{\equiv}COCH_2CH_3 \xrightarrow[2)\ KOH]{1)\ H^+,\ H_2O}$

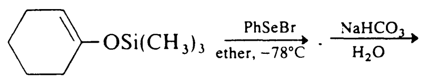
(c)  $\xrightarrow{HOBr}$

(d) $(CH_3)_2C{=}CHCH_3 \xrightarrow[2)\ H_2O_2,\ HO]{1)\ \text{disiamylborane}}$

(e) $CH_3CH_2CH_2CH_2CH{=}CH_2 \xrightarrow{IN_3}$

(f) $(CH_3)_3CCH{=}CHCH_3 \xrightarrow{IN_3}$

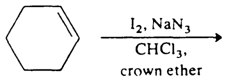
(g) $C_6H_5CH{=}CHCH(OCH_3)_2 \xrightarrow{IN_3}$

(h) 

(i) $HC{\equiv}CCH_2CH_2CO_2H \xrightarrow[CH_2Cl_2]{Hg(OAc)_2} \xrightarrow[10\ min]{H_2O,\ NaHCO_3}$

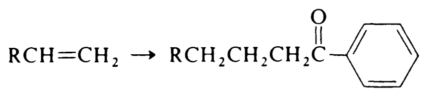
(j) $(CH_3)_3CC{\equiv}CCH_3 \xrightarrow[2)\ H_2C=CHC(=O)CH_3,\ 65^\circ C]{1)\ 9\text{-}BBN,\ 0^\circ C,\ 16\ hr} \xrightarrow[H_2O_2]{NaOH,}$

(k) $H_2C=CHCH_2CH_2CH_2CH_2OH \xrightarrow[2)\ NaBH_4]{1)\ Hg(OAc)_2}$

(l) 

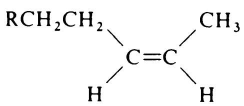
2. Bromination of 4-*t*-butylcyclohexene in methanol gives a 45 : 55 mixture of two compounds, each of composition $C_{11}H_{21}BrO$. Predict the structure and stereochemistry of these two products. How would you confirm your prediction?

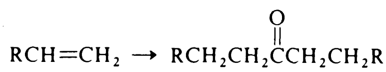
3. Starting with an alkene $RCH=CH_2$, indicate how organoborane intermediates could be used for each of the following synthetic transformations:

(a) 

(b) $RCH=CH_2 \rightarrow RCH_2CH_2CH=O$

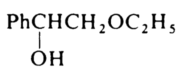
(c) 

(d) $RCH=CH_2 \rightarrow$ 

(e) 

(f) $RCH=CH_2 \rightarrow RCH_2CH_2CH_2CO_2C_2H_5$

4. Hydroboration–oxidation of $PhCH=CHOC_2H_5$ gives **A** as the major product if the hydroboration step is of short duration (7 sec), but **B** is the major product if the hydroboration is allowed to proceed for a longer time (2 hr). Explain.



A

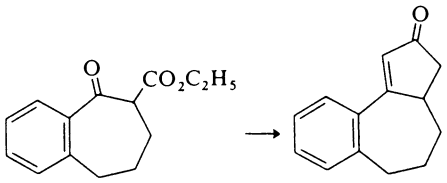
$PhCH_2CH_2OH$

B

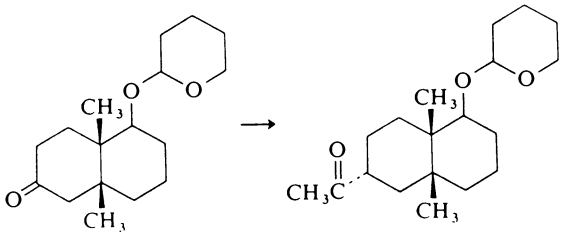
5. Oxymercuration of 4-*t*-butylcyclohexene, followed by $NaBH_4$ reduction, gives *cis*-4-*t*-butylcyclohexanol and *trans*-3-*t*-butylcyclohexanol in approximately equal amounts. 1-Methyl-4-*t*-butylcyclohexene under similar conditions gives only *cis*-4-*t*-butyl-1-methylcyclohexanol. Formulate a mechanism for the oxymercuration–reduction process that is consistent with this stereochemical result.

6. Hydroboration-oxidation of 1,4-di-*t*-butylcyclohexene gave three alcohols: C (77%), D (20%), and E (3%). Oxidation of C gave ketone F, which was readily converted in either acid or base to an isomeric ketone G. Ketone G was the only oxidation product of alcohols D and E. What are the structures of compounds C–G?
7. Suggest synthetic sequences that could accomplish each of the following transformations:

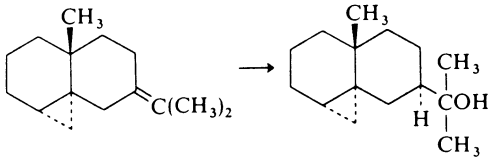
(a)



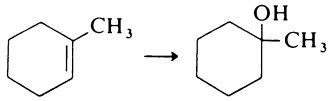
(b)



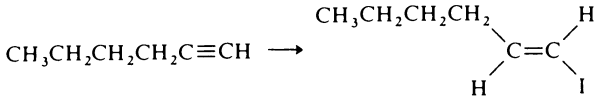
(c)



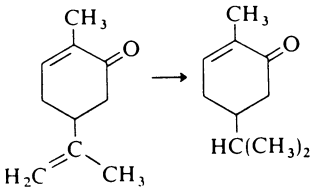
(d)



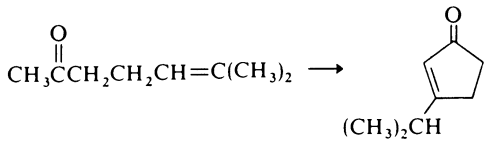
(e)

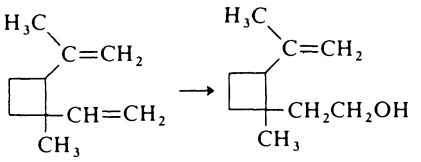


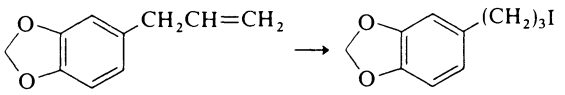
(f)



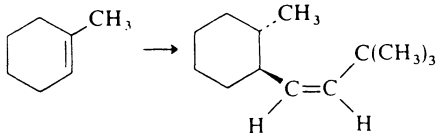
(g)



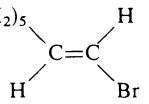
(h) 

(i) 

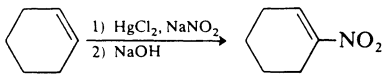
(j) $CH_3CH{=}CHCH_3 \rightarrow CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2CH{=}O$

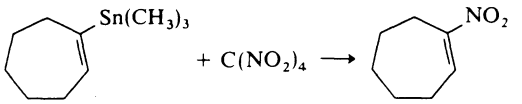
(k) 

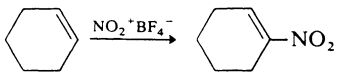
(l) $CH_3CH_2\underset{\displaystyle HC(OCH_3)_2}{\underset{|}{C}}HCH_2CH{=}CH_2 \rightarrow CH_3CH_2\underset{\displaystyle HC(OCH_3)_2}{\underset{|}{C}}HCH_2CH_2CH_2Br$

(m) $CH_3(CH_2)_5C{\equiv}CH \rightarrow$ 

8. Three methods for the preparation of nitroalkenes are outlined as shown. Describe in mechanistic terms how each of these transformations might occur.

(a) 

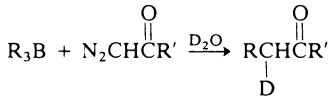
(b) 

(c) 

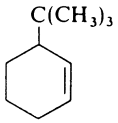
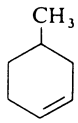
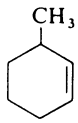
9. The hydration of 5-undecyn-2-one with mercuric sulfate and sulfuric acid in methanol is regioselective, giving 2,5-undecadione in 85% yield. Suggest an explanation for the high selectivity.
10. A procedure for the preparation of allylic alcohols has been devised in which the elements of phenylselenenic acid are added to an alkene, then the reaction mixture is treated with *t*-butyl hydroperoxide. Suggest a mechanistic rationale for this process.

$$CH_3CH_2CH_2CH{=}CHCH_2CH_2CH_3 \xrightarrow[2)\ t\text{-BuOOH}]{1)\ ^{\cdot\cdot}C_6H_5SeOH^{\cdot\cdot}} CH_3CH_2CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH{=}CHCH_2CH_3 \quad (88\%)$$

11. Show, using enolate chemistry and organoselenium reagents, how you could convert 2-phenylcyclohexanone regiospecifically to either 2-phenyl-2-cyclohexen-1-one or 6-phenyl-2-cyclohexen-1-one.
12. When trialkylboranes react with α-diazoketones or α-diazoesters in D_2O, the resulting products are monodeuterated. Formulate the reaction mechanism in sufficient detail to account for this fact.

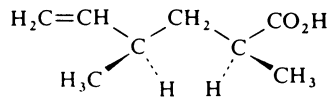


13. On the basis of the mechanistic picture of oxymercuration involving a mercurinium ion, predict the structure and stereochemistry of the major alcohols to be expected by application of the oxymercuration–demercuration sequence to each of the following substituted cyclohexenes.

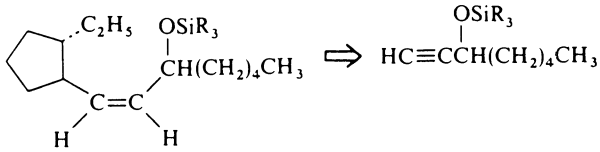
(a)  (b)  (c) 

14. In Scheme 4.9 there are described reactions of organoboranes with cyanide ion, chlorodifluoromethane, dichloromethyl methyl ether, acetylides, α-lithiated diphenylthioacetals and α-lithioimines. Compare the structures of these reagents and the final reaction products from the various reagents. Develop a general mechanistic outline which encompasses all these reactions and discuss the structural features which these reagents have in common with one another and with carbon monoxide.

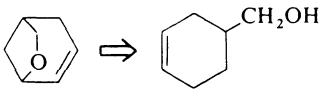
15. Reaction of the unsaturated acid **C** with I_2 in acetonitrile (no base) gives rise in 89% yield to a 20:1 mixture of two stereoisomeric iodolactones. Formulate the complete stereochemistry of both the major and the minor product to be expected under these conditions.

C 

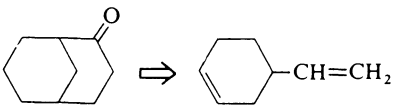
16. Some synthetic transformations are shown in the retrosynthetic format. Propose a short series of reactions (no more than three steps should be necessary) which could effect the synthetic conversion

(a) 

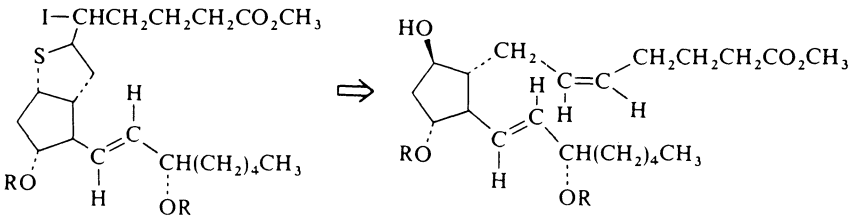
(b)


O
CH2OH

(c)


O
CH=CH2

(d)


I—CHCH2CH2CH2CO2CH3
S
H
C
C
H
RO
CH(CH2)4CH3
OR
HO
CH2
CH2CH2CH2CO2CH3
H
C=C
H
H
C
RO
C
H
CH(CH2)4CH3
OR

5

Reduction of Carbonyl and Other Functional Groups

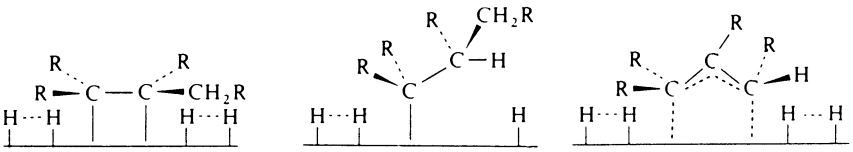
5.1. Addition of Hydrogen

5.1.1. Catalytic Hydrogenation

The most widely used method of adding the elements of hydrogen to a double bond is catalytic hydrogenation. Except for very sterically hindered alkenes, this reaction usually proceeds rapidly and cleanly. The common catalysts are various forms of transition metals, particularly platinum, palladium, rhodium, ruthenium, and nickel. Both the metals, as finely dispersed solids or adsorbed on inert supports such as carbon or alumina, and certain soluble complexes of these metals exhibit catalytic activity. Although carbon–carbon double bonds are the most frequently reduced functional group, many other functionalities are also subject to catalytic hydrogenation under appropriate conditions.

$$RCH{=}CHR + H_2 \xrightarrow{\text{catalyst}} RCH_2CH_2R$$

The mechanistic description of alkene hydrogenation has remained somewhat vague, partly because the heterogeneous catalysts defy study by many of the usual mechanistic techniques. The developing understanding of the chemistry of soluble organometallic species, however, permits some extrapolation to the heterogeneous systems. It is known that hydrogen is adsorbed onto the metal surface, presumably resulting in formation of surface metal hydrides. The alkenes are also adsorbed by the metal surface and at least three types of intermediates have been implicated in processes that occur during hydrogenation. The intermediate initially formed is pictured as attached at both of the carbon atoms of the alkene bond, as shown in **A**. The π electrons of the alkene are used for bonding to the metal surface. Hydrogen



A B C

adsorbed on the surface can be added to the organic residue leading to **B**, in which the reactant is attached to the metal surface by what approximates a σ bond. This intermediate can react with adsorbed hydrogen to give the saturated product. A third species that accounts for the double bond isomerization and exchange of hydrogen that sometimes competes with simple addition of hydrogen is depicted as **C**. The organic molecule in C approximates the allyl radical derived from the alkene by abstraction of a hydrogen atom. The coordination of this intermediate probably involves π rather than σ orbitals. In Chapter 6, the structures of organometallic compounds are discussed. There are examples of each of these three types of bonding of organic molecules to metal atoms in small discrete complexes. This lends some plausibility to the existence of similar entities on metal surfaces.

In most cases, both hydrogen atoms are added to the same side of the substrate (*syn* addition). This can result from nearly simultaneous addition of both hydrogen atoms. If hydrogenation occurs in two steps, the intermediate must remain bonded to the metal surface in such a way that single-bond rotations do not change the original stereochemical configuration. Adsorption to the catalyst surface normally involves the less sterically hindered side of the molecule. Scheme 5.1 illustrates some hydrogenations in which the *syn* addition from the less hindered side is observed. There are sufficient examples of alternate modes of addition, as is noted in Scheme 5.1, that independent corroboration of the stereochemistry is normally desirable.

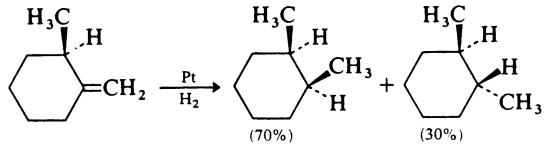
The stereochemistry of hydrogenation is affected by the presence of polar functional groups that can govern the mode of adsorption of the molecule to the catalyst surface. For instance, there are a number of examples where the presence of a hydroxyl group results in hydrogen being introduced from the side of the molecule carrying the polar group. This implies that the molecule is adsorbed preferentially in such a way that the hydroxyl group can interact strongly with the catalyst surface. This behavior can be illustrated with the alcohol (**1**) and ester (**2**). Although the overall shape and the size of the two functional groups are similar, the alcohol gives primarily the product with a *cis* ring junction (**3**), while the ester gives the product with a *trans* ring junction (**4**).[1] The stereoselectivity of hydroxyl-directed hydrogenation is a function of solvent and catalyst. The ratio **3**:**4** when

1. H. W. Thompson, *J. Org. Chem.* **36**, 2577 (1971); H. W. Thompson, E. McPherson and B. L. Lences, *J. Org. Chem.* **41**, 2903 (1976).

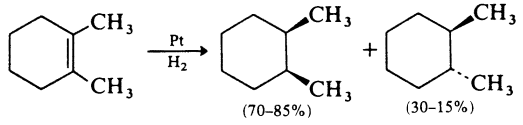
Scheme 5.1. Stereochemistry of Hydrogenation of Some Olefins

A. Examples of Preferential *syn* Addition from Less Hindered Side

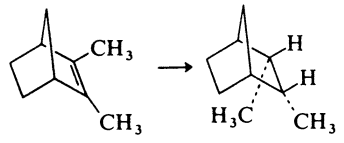
1[a]



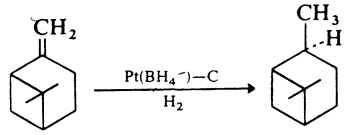
2[b]



3[c]

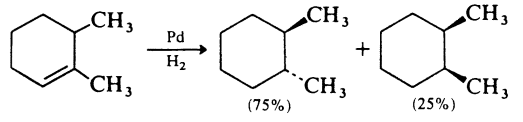


4[b]

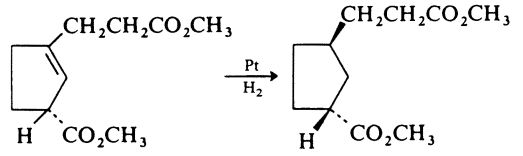


B. Exceptions

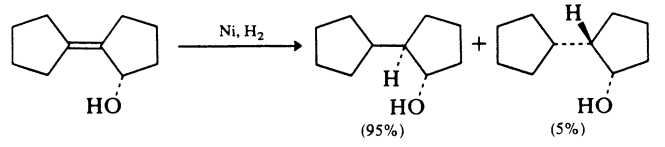
5[a]



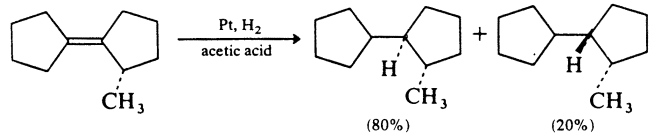
6[d]



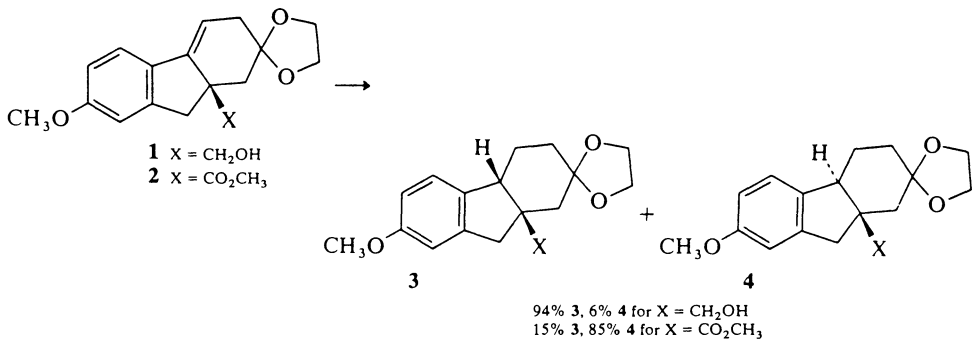
7[e]



8[f]



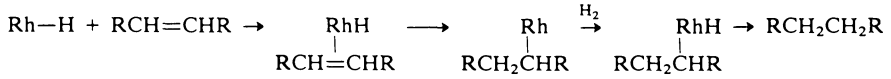
a. S. Siegel and G. V. Smith, *J. Am. Chem. Soc.* **82**, 6082, 6087 (1960).
b. C. A. Brown, *J. Am. Chem. Soc.* **91**, 5901 (1969).
c. K. Alder and W. Roth, *Chem. Ber.* **87**, 161 (1954).
d. J. P. Ferris and N. C. Miller, *J. Am. Chem. Soc.* **88**, 3522 (1966).
e. S. Mitsui, Y. Senda and H. Saito, *Bull. Chem. Soc. Japan* **39**, 694 (1966).
f. S. Siegel and J. R. Cozort, *J. Org. Chem.* **40**, 3594 (1975).



$X = CH_2OH$ can be changed to favor **4** by using hexane as a solvent, for example.

Catalytic hydrogenations are usually extremely clean reactions without by-product formation, unless reduction of other groups is competitive. Careful study, however, sometimes reveals that double-bond migration may take place in competition with reduction. For example, hydrogenation of 1-pentene over Raney nickel is accompanied by isomerization to *cis*- and *trans*-2-pentene.[2] The isomerized products are converted to pentane, but at a slower rate than 1-pentene. Exchange of hydrogen atoms from the substrate for hydrogen from the catalyst surface has often been detected by using deuterium-labeled substrates or by carrying out the catalytic reduction in a deuterium atmosphere. Allylic positions undergo such exchange particularly rapidly.[3] Both of these observations can be explained by the intervention of the π-allyl intermediate **C**. It can be desorbed from the catalyst surface with a double-bond shift, since hydrogen can be added to either end of the allyl system. Hydrogen exchange at the allyl position can occur if the allyl intermediate is reversibly converted to the intermediate **A**.

In addition to heterogeneous transition metals, certain soluble mononuclear transition metal complexes are active hydrogenation catalysts.[4] The best-studied example of a homogeneous catalyst for hydrogenation of alkenes is tris(triphenylphosphine)chlororhodium, known as *Wilkinson's catalyst*.[5] This and related homogeneous catalysts usually minimize exchange and isomerization processes. Mechanistically, it is believed that the hydrogenation takes place by transfer of hydrogen to alkene by way of a metal hydride intermediate. The metal center



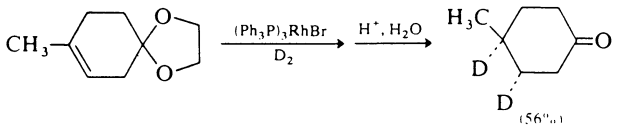
is coordinated by phosphine ligands during the hydrogenation process. When

2. H. C. Brown and C. A. Brown, *J. Am. Chem. Soc.* **85**, 1005 (1963).
3. G. V. Smith and J. R. Swoap, *J. Org. Chem.* **31**, 3904 (1966).
4. A. J. Birch and D. H. Williamson, *Org. Reactions*, **24**, 1 (1976); B. R. Jones, *Homogeneous Hydrogenation*, John Wiley and Sons, New York (1973).
5. J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).

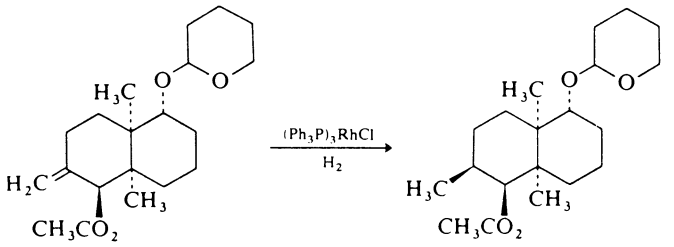
optically active phosphines are used the catalyst is chiral and, as a result, certain olefins can be reduced to optically active products. More is said about this in Section 11.3. Scheme 5.2 gives some examples of hydrogenation carried out with

Scheme 5.2. Homogeneous Catalytic Hydrogenation

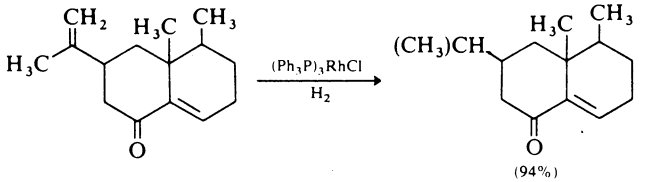
1[a]



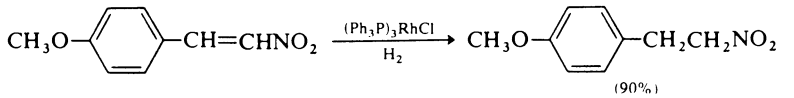
2[b]



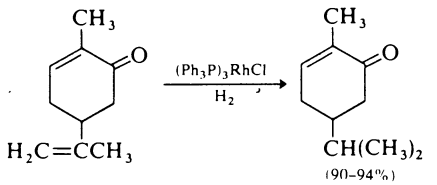
3[c]



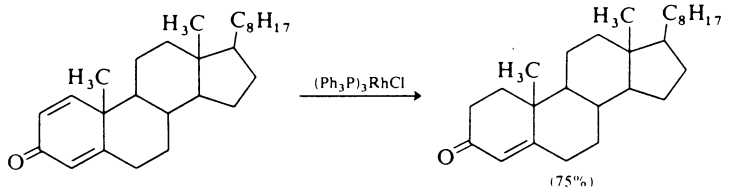
4[d]



5[e]



6[f]



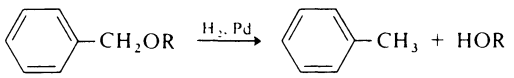
a. W. C. Agosta and W. L. Schreiber, *J. Am. Chem. Soc.* **93**, 3947 (1971).
b. E. Piers, W. de Waal, and R. W. Britton, *J. Am. Chem. Soc.* **93**, 5113 (1971).
c. M. Brown and L. W. Piszkiewicz, *J. Org. Chem.* **32**, 2013 (1967).
d. R. E. Harmon, J. L. Parsons, D. W. Cooke, S. K. Gupta, and J. Schoolenberg, *J. Org. Chem.* **34**, 3684 (1969).
e. R. E. Ireland and P. Bey, *Org. Synth.* **53**, 63 (1973).
f. C. Djerassi and J. Gutzwiller, *J. Am. Chem. Soc.* **88**, 4536 (1966).

homogeneous catalysts. One potential advantage of homogeneous catalysts is the ability to achieve a high degree of selectivity among different potentially reducible functional groups. Entries 3, 4, 5, and 6 are examples of such selectivity.

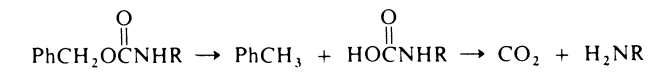
The partial reduction of alkynes to *cis*-alkenes is another important synthetic application of hydrogenation catalysts. This transformation can be carried out under heterogeneous or homogeneous conditions but the catalyst selected must be one which permits the desired partial reduction. Among heterogeneous catalysts the one which is found most successful is *Lindlar's catalyst*, which is a lead-modified palladium–$CaCO_3$ catalyst.[6] A nickel–boride catalyst prepared by reduction of nickel salts with sodium borohydride is also useful.[7] A homogeneous rhodium catalyst derived from the norbornadiene complex of Rh(I)Cl and phosphine ligands has shown good selectivity in acetylene reductions.[8]

Many other functional groups are also reactive under conditions of catalytic hydrogenation. The reduction of nitro compounds to amines, for example, usually proceeds very rapidly. Ketones, aldehydes, and esters can all be reduced to alcohols but in most applications the hydride transfer agents to be discussed in Section 5.2 have supplanted catalytic reduction for preparative purposes. Amides and nitriles can be reduced to amines. The former reaction requires very vigorous conditions and is seldom used now, but the hydrogenation of nitriles remains a valuable reaction. Scheme 5.3 gives some indication of the approximate conditions for reduction of these functional groups.

Certain types of functionality can be removed and replaced by hydrogen under catalytic hydrogenation conditions. This is called *hydrogenolysis*. For example, aromatic halogen substituents are usually removed by reduction over metal catalysts. Aliphatic halides are less reactive but hydrogenolysis is promoted by base.[9] Carbon oxygen bonds at benzyl and allyl positions are cleaved by catalytic hydrogenation.[10]



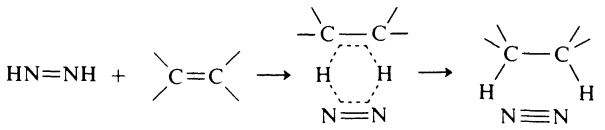
This facile cleavage of the benzyl oxygen bond has made the benzyl group a useful "protecting group" during multistep syntheses. A particularly important example is the use of the carbobenzyloxy group in peptide synthesis. The protecting group is removed by hydrogenolysis to liberate a nucleophilic amino group. The substituted carbamic acid generated by benzyl hydrogenolysis decarboxylates spontaneously:



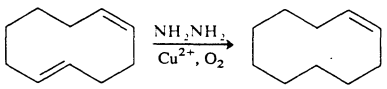
6. H. Lindlar and R. Dubuis, *Org. Synth.* **V**, 880 (1973).
7. H. C. Brown and C. A. Brown, *J. Am. Chem. Soc.* **85**, 1005 (1963); E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **91**, 4318 (1969).
8. R. R. Schrock and J. A. Osborn, *J. Am. Chem. Soc.* **98**, 2143 (1976).
9. A. R. Pinder, *Synthesis*, 425 (1980).
10. W. H. Hartung and R. Simonoff, *Org. React.* **7**, 263 (1953).

5.1.2. Other Hydrogen-Transfer Reagents

Catalytic hydrogenation transfers the elements of molecular hydrogen to various unsaturated functional groups without intervention of a discrete polar intermediate. One other species which has a similar capacity finds some specialized use in reduction of carbon–carbon bonds. This is diimide HN=NH, an unstable molecule which is generated *in situ*. Several methods for generation of diimide have been developed and some examples are summarized in Scheme 5.4. Simple olefins are reduced efficiently by the reagent, but most of the other easily reduced functional groups, particularly nitro and carbonyl groups, are unaffected by diimide. This permits reduction of carbon–carbon double bonds in the presence of these groups. The mechanism of the reaction has been pictured as a transfer of hydrogen to the multiple bond via a nonpolar transition state with loss of nitrogen:



In agreement with this mechanism is the fact that the addition has been demonstrated to be *syn* for several typical alkenes.[11] The rate of diimide reductions has been shown to be affected by torsional and angle strain in the alkene.[12] More strained double bonds react at accelerated rates. For example, the more strained *trans* double bond is selectively reduced in *cis*, *trans*-1,5-cyclodecadiene.[13] Diimide



reduction exhibits selectivity for terminal over internal double bonds in polyunsaturated systems.[14]

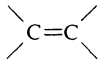
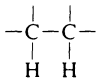
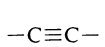
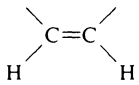
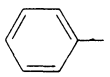
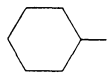
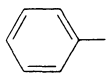
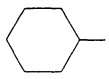
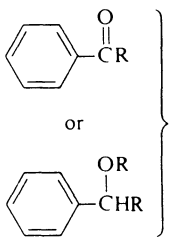
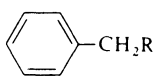
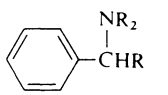
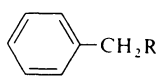
5.2. Group III Hydride-Transfer Reagents

5.2.1. Reduction of Carbonyl Compounds

Most reductions of carbonyl and other functional groups are now done with reagents that transfer a hydride ion from boron or aluminum. The numerous

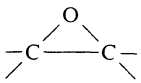
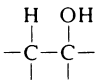
11. E. J. Corey, D. J. Pasto, and W. L. Mock, *J. Am. Chem. Soc.* **83**, 2957 (1961).
12. E. W. Garbisch, Jr., S. M. Schildcrout, D. B. Patterson, and C. M. Sprecher, *J. Am. Chem. Soc.* **87**, 2932 (1965).
13. J. G. Traynham, G. R. Franzen, G. A. Kresel, and D. J. Northington, Jr., *J. Org. Chem.* **32**, 3285 (1967).
14. E. J. Corey, H. Yamamoto, D. K. Herron, and K. Achiwa, *J. Am. Chem. Soc.* **92**, 6635 (1970); E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.* **92**, 6636, 6637 (1970).

Scheme 5.3. Conditions for Catalytic

Functional group	Reduction product	Common catalysts	Typical reaction conditions
		Pd, Pt, Ni, Ru, Rh	Rapid at R.T. and 1 atm except for highly substituted or hindered cases
		Pd	R.T. and low pressure, quinoline or lead added to deactivate catalyst
		Rh, Pt	Moderate pressure (5–10 atm), 50–100°C
		Ni, Pd	High pressure (100–200 atm), 100–200°C
		Pt, Ru	Moderate rate at R.T. and 1–4 atm, acid-catalyzed
		Cu–Cr, Ni	High pressure, 50–100°C
		Pd	R.T., 1–4 atm, acid-catalyzed
		Pd, Ni	50–100°C, 1–4 atm

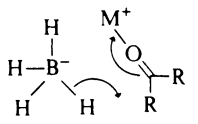
reagents of this type that have become available provide a considerable degree of selectivity and stereochemical control. Sodium borohydride and lithium aluminum hydride are not only the most familiar examples, but also indicate the range in selectivity possible with hydride reducing agents. Sodium borohydride is a mild reducing agent, reducing only aldehydes and ketones rapidly. Lithium aluminum hydride is one of the most powerful hydride-transfer agents; it will reduce ketones, esters, acids, nitriles, and amides quite rapidly. The reactivity of these reagents, along with that of several other related reducing agents, is summarized in Table 5.1.

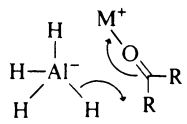
Reduction of Various Functional Groups[a]

Functional group	Reduction product	Common catalysts	Typical reaction conditions
$RCCl$ (O)	RCH (O)	Pd	R.T., 1 atm, quinoline or other catalyst moderator used
$RCOH$ (O)	RCH_2OH	Pd, Ni, Ru	Very strenuous conditions required
$RCOR$ (O)	RCH_2OH	Cu–Cr, Ni	200°C, high pressure
$RC{\equiv}N$	RCH_2NH_2	Ni, Rh	50–100°C, usually high pressure, NH_3 added to increase yield of primary amine
$RCNH_2$ (O)	RCH_2NH_2	Cu–Cr	Very strenuous conditions required
RNO_2	RNH_2	Pd, Ni, Pt	R.T., 1–4 atm
RCR (NR)	R_2CHNHR	Pd, Pt	R.T., 4–100 atm
R–Cl R–Br R–I	R–H	Pd	Order of reactivity: I > Br > Cl > F, bases promote reaction for R = alkyl
		Pt, Pd	Proceeds slowly at R.T., 1–4 atm, acid-catalyzed

a. General references: M. Freifelder, *Catalytic Hydrogenation in Organic Synthesis: Procedures and Commentary*, Wiley-Interscience, New York (1978); P. N. Rylander, *Catalytic Hydrogenation in Organic Syntheses*, Academic Press, New York (1979); R. L. Augustine, *Catalytic Hydrogenation*, Marcel Dekker, New York (1965).

The mechanism by which all the group III complex hydrides effect reduction is believed to be quite similar. It involves nucleophilic transfer of hydride to the carbonyl group. Activation of the carbonyl group by coordination with a metal cation is probably involved under most conditions. Since all of the hydrides are

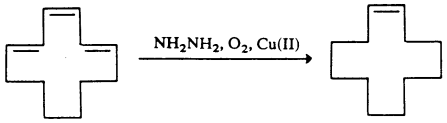


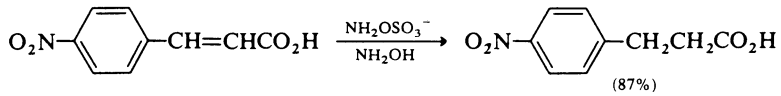


Scheme 5.4. Reductions with Diimide

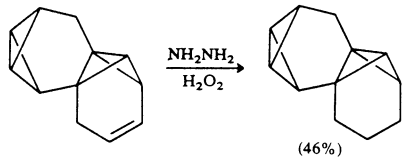
1[a] $CH_2{=}CHCH_2OH \xrightarrow[RCO_2H,\ 25°]{Na^+{}^-O_2C{-}N{=}N{-}CO_2{}^-Na^+} CH_3CH_2CH_2OH$ (78%)

2[b] $(CH_2{=}CHCH_2)_2S \xrightarrow{C_7H_7SO_2NHNH_2,\ heat} (CH_3CH_2CH_2)_2S$ (93–100%)

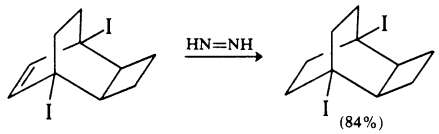
3[c] 

4[d] 

(87%)

5[e] 

(46%)

6[f] 

(84%)

a. E. E. van Tamelen, R. S. Dewey, and R. J. Timmons, *J. Am. Chem. Soc.* **83**, 3725 (1961).
b. E. E. van Tamelen, R. S. Dewey, M. F. Lease, and W. H. Pirkle, *J. Am. Chem. Soc.* **83**, 4302 (1961).
c. M. Ohno and M. Okamoto, *Org. Synth.* **49**, 30 (1969).
d. W. Durckheimer, *Justus Liebigs Ann. Chem.* **721**, 240 (1969).
e. L. A. Paquette, A. R. Browne, E. Chamot, and J. F. Blount, *J. Am. Chem. Soc.* **102**, 643 (1980).
f. J. R. Wiseman and J. J. Vanderbilt, *J. Am. Chem. Soc.* **100**, 7730 (1978).

eventually transferred, there are actually several distinct reducing agents functioning during the reduction. This somewhat complicates the interpretation of rates and stereochemistry, but has not detracted from the synthetic usefulness of the reagents.[15]

$$BH_4^- + R_2CO \rightarrow R_2CHO\bar{B}H_3$$

$$R_2CHO\bar{B}H_3 + R_2CO \rightarrow [R_2CHO]_2\bar{B}H_2$$

$$[R_2CHO]_2\bar{B}H_2 + R_2CO \rightarrow [R_2CHO]_3\bar{B}H$$

$$[R_2CHO]_3\bar{B}H + R_2CO \rightarrow [R_2CHO]_4\bar{B}$$

Reduction with $NaBH_4$ is usually done in aqueous or alcoholic solution, in which case the intermediate alkoxyboranes are solvolyzed to liberate the product alcohol.

The mechanism for reduction with $LiAlH_4$ is quite similar. However, since lithium aluminum hydride reacts very rapidly with protic solvents to release hydrogen, reductions must be carried out in aprotic solvents, usually ether or tetrahydrofuran. The product alcohol is then liberated by hydrolysis of the resulting aluminum alkoxides.

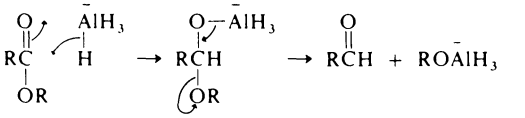
15. B. Rickborn and M. T. Wuesthoff, *J. Am. Chem. Soc.* **92**, 6894 (1970).

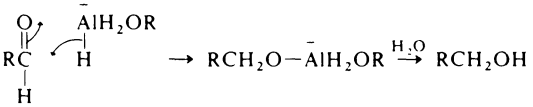
Table 5.1. Relative Reactivity of Hydride-Donor Reducing Agents

Hydride donors	Reduction products[a]						
	Iminium ion	Acyl halide	Aldehyde	Ketone	Ester	Amide	Carboxylate salt
$LiAlH_4$[b]	Amine	Alcohol	Alcohol	Alcohol	Alcohol	Amine	Alcohol
$LiAlH_2(OCH_2CH_2OCH_3)_2$[c]		Alcohol	Alcohol	Alcohol	Alcohol	Amine	Alcohol
$LiAlH[OC(CH_3)_3]_3$[d]		Aldehyde[e]	Alcohol	Alcohol	Alcohol[f]	Aldehyde[f]	NR
$NaBH_4$[b]	Amine		Alcohol	Alcohol	Alcohol[f]	NR	NR
$NaBH_3CN$[g]	Amine		Alcohol[f]	NR	NR	NR	NR
B_2H_6[h]			Alcohol	Alcohol	NR	Amine	Alcohol[i]
AlH_3[i]		Alcohol	Alcohol	Alcohol	Alcohol	Amine	Alcohol
$[(CH_3)_2CHCH(CH_3)-]_2BH$[k]			Alcohol	Alcohol	NR	Aldehyde[e]	NR
$[(CH_3)_2CHCH_2-]_2AlH$[l]			Alcohol	Alcohol	Aldehyde[e]	Aldehyde[e]	Alcohol

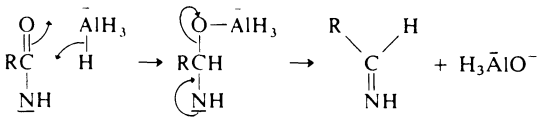
a. Products shown are the usual products of synthetic operations. Where no entry is given the combination has not been studied or is not of major synthetic utility.
b. See the general references at the end of the chapter.
c. J. Malek and M. Cerny, *Synthesis*, 217 (1972); E. R. H. Walker, *Q. Rev. Chem. Soc.* **5**, 23 (1976).
d. H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.* **78**, 252 (1956); **80**, 5372 (1958); H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.* **80**, 5377 (1958); H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.* **86**, 1089 (1964).
e. Reaction must be controlled by use of a stoichiometric amount of reagent and low temperature.
f. Reaction occurs only slowly.
g. C. F. Lane, *Synthesis*, 135 (1975).
h. H. C. Brown, P. Heim, and N. M. Yoon, *J. Am. Chem. Soc.* **92**, 1637 (1970); N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.* **38**, 2786 (1973); H. C. Brown and P. Heim, *J. Org. Chem.* **38**, 912 (1973).
i. Reaction occurs via the triacyl borate.
j. H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc.* **88**, 1464 (1966).
k. H. C. Brown, D. B. Bigley, S. K. Arora, and N. M. Yoon, *J. Am. Chem. Soc.* **92**, 7161 (1970); H. C. Brown and V. Varma, *J. Org. Chem.* **39**, 1631 (1974).
l. E. Winterfeldt, *Synthesis*, 617 (1975); H. Reinheckel, K. Haage, and D. Jahnke, *Organomet. Chem. Rev.* **4**, 47 (1969).

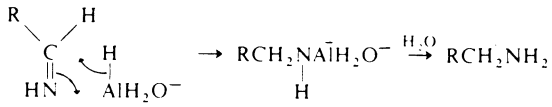
Hydride reduction of carboxylic acid derivatives, such as the conversion of esters to alcohols, involves elimination steps in addition to hydride transfer.



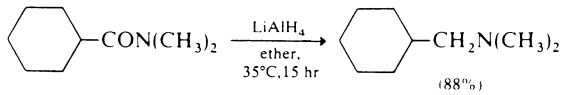


Amides are reduced to amines because the nitrogen group is a poorer leaving group than oxygen at the intermediate stage of the reduction. Primary and secondary amides are rapidly deprotonated by the strongly basic $LiAlH_4$.

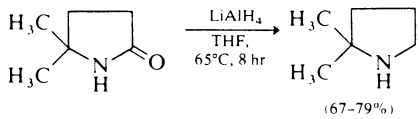




Reductions of amides constitute an important method of synthesis of amines:



Ref. 16a



Ref. 16b

Several factors affect the reactivity of the boron and aluminum hydrides. These include the nature of the metal cation present and the ligands, in addition to hydride, in the complex hydride. Some of these effects can be illustrated by considering the reactivity of ketones and aldehydes toward various hydride-transfer reagents. Comparison of the reactivity of $LiAlH_4$ with $NaAlH_4$ showed the former compound to be the more reactive.[17] This can be attributed to the greater Lewis acid strength of the smaller lithium cation. Substances, such as the crown ethers, which can complex the metal cation of complex hydrides, cause reduced rates of reaction,[18] because of the reduced intensity of metal ion coordination at the carbonyl. An extensive series of aluminum hydrides in which one or more of the hydrides is replaced by an alkoxide ligand have been prepared. These are prepared by addition of the calculated amount of the appropriate alcohol. These reagents generally show

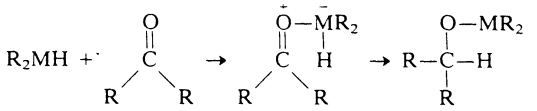
$$LiAlH_4 + 2ROH \rightarrow LiAlH_2(OR)_2 + 2H_2$$
$$LiAlH_4 + 3ROH \rightarrow LiAlH(OR)_3 + 3H_2$$

increased solubility, particularly at low temperatures, in organic solvents and are useful in certain selective reductions.[19] Lithium tri-*t*-butoxyaluminum hydride and sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al)[20] are examples of these types of reagents which have come into wide synthetic use. Their reactivity toward typical functional groups is included in Table 5.1. Sodium cyanoborohydride[21] is a useful derivative of sodium borohydride. The electron-attracting cyano substituent

16a. A. C. Cope and E. Ciganek, *Org. Synth.* **IV**, 339 (1963).
16b. R. B. Moffett, *Org. Synth.* **IV**, 354 (1963).
17. E. C. Ashby and J. R. Boone, *J. Am. Chem. Soc.* **98**, 5524 (1976).
18. H. Handel and J.-L. Pierre, *Tetrahedron Lett.*, 741 (1976); K. E. Wiegers and S. G. Smith, *J. Org. Chem.* **43**, 1126 (1978).
19. J. Malek and M. Cerny, *Synthesis*, 217 (1972).
20. Trademark of Aldrich Chemical Company.
21. C. F. Lane, *Synthesis*, 135 (1975).

reduces reactivity and only iminium functions with positively charged nitrogen atoms are rapidly reduced by this reagent.

Closely related to but distinct from the anionic boron and aluminum hydrides are the neutral derivatives of borane (BH_3) and alane (AlH_3). These species also contain hydrogens which can be transferred as hydride. The boranes and alanes differ from the complex hydrides in being electrophilic species by virtue of the vacant *p* orbital. The reduction processes are normally pictured as intramolecular hydride transfers in the complex between the substrate and reductant. Borane itself



and several of its alkyl derivatives and alane and its derivatives, especially diisobutylaluminum hydride (DIBAL), are the best known examples of this class of reductants. Their reactivity towards typical functionalities is included in Table 5.1.

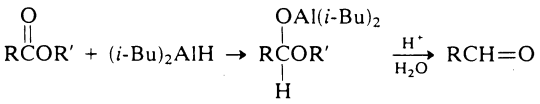
In synthesis the principal factors which must be controlled in functional group reductions are selectivity and stereochemistry. Both issues are usually addressed by choice of a particular reducing agent. Let us consider first the matter of selectivity. Selectivity can involve two issues. First it may be desirable to effect a *partial reduction*. In that case a reagent which will effect only partial reduction of the functional group in question is required. The second way in which selectivity can arise is the need to achieve *reduction of one group in the presence of another*. In this case the reagent must have differing reactivity toward the two functionalities in question. The reagents in Table 5.1 are arranged in approximate order of decreasing reactivity as nucleophilic hydride donors. The reducible groups are arranged in order of decreasing reactivity toward nucleophilic reducing agents. By considering the issue of selectivity with certain specific reagents, the utilization of the relative reactivity relationships embodied in Table 5.1 can be illustrated.

One of the more difficult partial reductions to accomplish is the conversion of a carboxylic acid derivative to an aldehyde without overreduction to the alcohol. Several approaches have been used to achieve this selectivity. One is to replace some of the hydrogens in group III hydrides by more bulky groups, thus modifying reactivity by steric factors. Lithium tri-*t*-butoxyaluminum hydride[22] is an example of this approach. As noted in Table 5.1, lithium tri-*t*-butoxyaluminum hydride can be used to reduce acid chlorides to the aldehyde stage without extensive overreduction to the alcohol. The excellent solubility properties of sodium bis(2-methoxyethoxy)aluminum hydride make it a useful reagent for selective reductions.[19] The reagent is soluble in toluene even at −70°C. It is possible to reduce esters to aldehydes with this reagent. Lactones are reduced to lactols by this reagent.

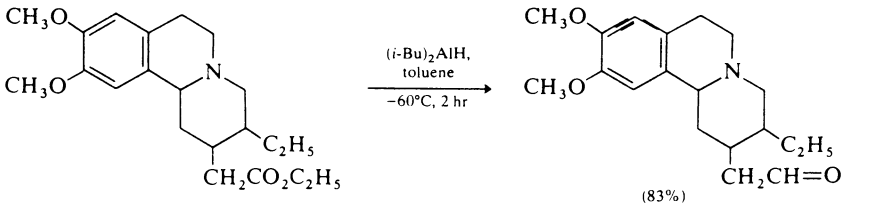
Probably the most widely used reagent for the partial reduction of esters and lactones at the present time is diisobutylaluminum hydride.[23] By use of a controlled

22. H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.* **80**, 5377 (1958).
23. E. Winterfeldt, *Synthesis*, 617 (1975).

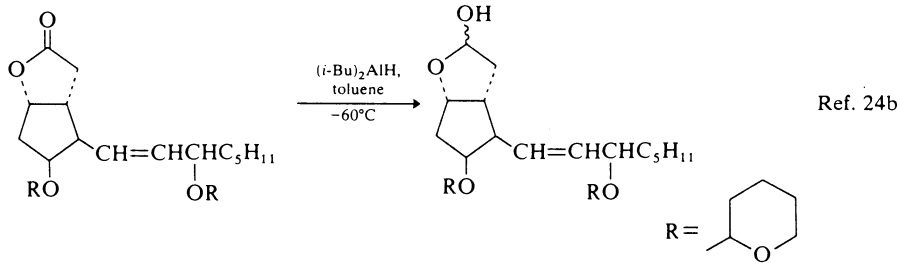
amount of the reagent and low temperature, partial reduction can be reliably achieved. The partial reduction results from the relative stability of the intermediate that is formed. The aldehyde is not liberated until the hydrolytic workup and



therefore is not reduced. At higher temperatures, diisobutylaluminum hydride reduces esters to primary alcohols.

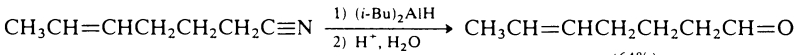


Ref. 24a



Ref. 24b

Another useful approach to aldehydes is by partial reduction of nitriles to imines. The imines are then hydrolyzed to the aldehyde. Diisobutylaluminum hydride is probably the best reagent for this purpose,[25,26] but triethoxyaluminum hydride has also been used.[27]



Ref. 25

The second general context in which selectivity arises is the need to reduce one group in the presence of another. If the group to be reduced is more reactive than the one to be left unchanged, it is simply a matter of selecting a reagent which will react only with the more reactive group. Sodium borohydride, for example, is very useful in this respect since it will reduce ketones and aldehydes faster than it reduces esters. Sodium cyanoborohydride[28] is a close relative of sodium borohy-

24a. C. Szantay, L. Toke, and P. Kolonits, *J. Org. Chem.* **31**, 1447 (1966).
24b. E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.* **91**, 5675 (1969).
25. N. A. LeBel, M. E. Post, and J. J. Wang, *J. Am. Chem. Soc.* **86**, 3759 (1964).
26. R. V. Stevens and J. T. Lai, *J. Org. Chem.* **37**, 2138 (1972); S. Trofimenko, *J. Org. Chem.* **29**, 3046 (1964).
27. H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.* **86**, 1085 (1964).
28. C. F. Lane, *Synthesis*, 135 (1975).

dride, but is considerably less reactive toward carbonyl groups at neutral pH. The reagent is useful for reducing C=N systems to amines. This reaction occurs rapidly at pH values where the C=N system is protonated. At pH 6–7, $NaBH_3CN$ is essentially unreactive toward carbonyl compounds, but readily reduces the protonated imines. This permits preparation of amines from carbonyl compounds without isolation of the intermediate imines. The carbonyl compound and ammonia or an alkylamine are in equilibrium with the imine. Since the imine is selectively reduced as it is formed *in situ*, the reaction leads in good yield to the substituted amine.[29]

$$R_2C{=}O + R'NH_2 + H^+ \rightleftarrows R_2C{=}\overset{\overset{H}{|}}{\overset{+}{N}}R'$$

$$R_2C{=}\overset{\overset{H}{|}}{\overset{+}{N}}R' + BH_3CN^- \rightarrow R_2CHNHR'$$

Diborane is another useful selective reducing agent. Perhaps most unique is its ability to selectively reduce carboxylic acid groups to primary alcohols under mild conditions.[30] Diborane is much less reactive toward some of the other functional groups that would be attacked by the ionic hydride reducing agents or by catalytic hydrogenation under the conditions necessary to reduce the carboxyl group. For example, ester, nitro, and cyano groups are much more slowly reduced by diborane than is the carboxyl group. The rapid reaction between carboxylic acids and diborane is related to the electrophilicity of diborane. A triacyloxyborane is the initial intermediate. The carbonyl group in this molecule, which is essentially

$$3RCO_2H + BH_3 \rightarrow (RCO_2)_3B + H_2$$

a mixed anhydride, is activated by the electron-accepting nature of the trivalent boron atom.

$$\overset{\overset{O}{\|}}{RC}{-}O{-}B(O_2CR)_2 \rightarrow \overset{\overset{O}{\|}}{RC}{-}\overset{+}{O}{=}\overset{-}{B}(O_2CR)_2$$

Diborane is also a useful reagent for reducing amides. Tertiary and secondary amides are quite easily reduced, but primary amides react only slowly.[31] Amides require vigorous conditions for complete reduction by $LiAlH_4$. Selective reduction of amides in the presence of such functional groups as ester and nitro are therefore best done with diborane.

Another approach to reduction of a relatively unreactive group such as an amide in the presence of more easily reduced groups is to convert the amide to a more reactive species. One such method is conversion of the amide to an *O*-alkyl derivative having a positive charge on nitrogen.[32] This method has proven successful

29. R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.* **93**, 2897 (1971).
30. M. N. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.* **38**, 2786 (1973).
31. H. C. Brown and P. Heim, *J. Org. Chem.* **38**, 912 (1973).
32. R. F. Borch, *Tetrahedron Lett.*, 61 (1968).

$$\mathrm{RC(=O)NR_2 + Et_3O^+ \rightarrow RC(OEt)=NR_2^+}$$

$$\mathrm{RC(OEt)=NR_2^+ + NaBH_4 \rightarrow RCH_2NR_2}$$

for tertiary and secondary, but not primary amides. Other substances which are easily derived from amides and more reactive toward hydride reducing agents are α-thioalkylimmonium ions[33] and α-chloroimmonium ions.[34]

$$\mathrm{RC(=O)NR_2 \xrightarrow{P_2S_5} RC(=S)NR_2 \xrightarrow[(CH_3)_3O^+]{CH_3I\ or} RC(SCH_3)=NR_2^+ \xrightarrow{NaBH_4} RCH_2NR_2}$$

$$\mathrm{RC(=O)NR_2 \xrightarrow{POCl_3} R{-}C(Cl)=NR_2^+ \xrightarrow{NaBH_4} RCH_2NR_2}$$

An important case involving selectivity toward two reducible groups arises in the reduction of unsaturated carbonyl compounds. The hydride reduction of α,β-unsaturated carbonyl compounds can take either of two courses. Initial reaction at the carbonyl group gives allylic alcohols. Usually, no further reduction takes place, since the unconjugated carbon–carbon double bond is inert to nucleophilic species. If initial attack is at the double bond, an enolate is produced. In protic solvents, this can lead to the carbonyl compound, which can, in turn, be reduced, resulting ultimately in the saturated alcohol. For this reason, it is fairly common to find both saturated and unsaturated alcohols as products of $NaBH_4$ or $LiAlH_4$ reduction of conjugated unsaturated ketones.[35] The extent of reduction to the saturated alcohol is usually greater with $NaBH_4$ than with $LiAlH_4$. Reagents have now been developed

1,2-reduction

$$\mathrm{R_2C{=}CHC(=O)R' + [H^-] \rightarrow R_2C{=}CHCH(O^-)R' \xrightarrow{H^+} R_2C{=}CHCH(OH)R'}$$

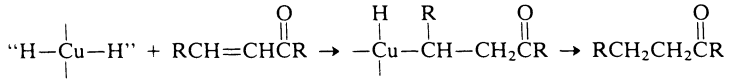
1,4-reduction leading to saturated alcohol

$$\mathrm{R_2C{=}CHC(=O)R' + [H^-] \rightarrow R_2CH{-}CH{=}C(O^-)R' \xrightarrow{H^+} R_2CHCH_2C(=O)R'}$$

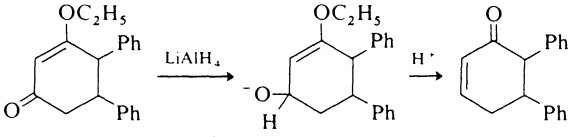
$$\mathrm{R_2CHCH_2C(=O)R' + [H^-] \rightarrow R_2CHCH_2CH(O^-)R' \xrightarrow{H^+} R_2CHCH_2CH(OH)R'}$$

33. S. Raucher and P. Klein, *Tetrahedron Lett.*, 4061 (1980); R. J. Sundberg, C. P. Walters, and J. D. Bloom, *J. Org. Chem.* **46**, 3730 (1981).
34. M. E. Kuehne and P. J. Shannon, *J. Org. Chem.* **42**, 2082 (1977).
35. M. R. Johnson and B. Rickborn, *J. Org. Chem.* **35**, 1041 (1970); W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965).

which can reduce either the carbonyl group or the carbon–carbon double bond selectively. Diisobutylaluminum hydride[36] and the dialkylborane 9-BBN[37] (see Section 4.9.1 for the synthesis of this reagent) give exclusive carbonyl reduction for a variety of α,β-unsaturated carbonyl compounds. Selective reduction of the carbon–carbon double bond can usually be achieved by catalytic hydrogenation. Alternatively, a series of reagents prepared from a hydride reducing agent and copper salts also give primarily the saturated ketones.[38,39] Similar reagents have been shown to reduce α,β-unsaturated esters[39] and nitriles[40] to the corresponding saturated compounds. The mechanistic details of these conjugate reductions have not been studied thoroughly. A good possibility is the formation of an alkylcopper hydride which then eliminates the reduced compound.



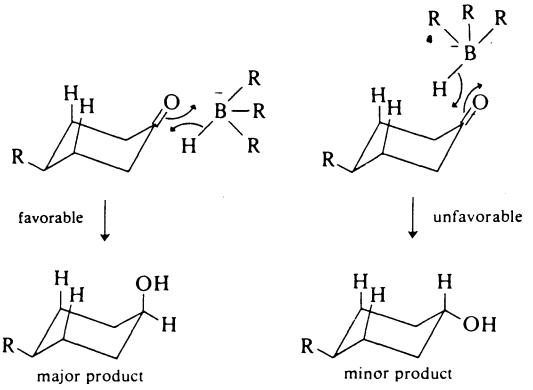
The enol ethers of β-dicarbonyl compounds are reduced to α,β-unsaturated ketones by $LiAlH_4$ followed by hydrolysis.[41] Reduction proceeds only to the allylic alcohol, but subsequent treatment with acid effects hydrolysis of the enol ether and dehydration.



This reaction has found use as a method for synthesis of substituted cyclohexenones.

Another important aspect of the reactivity of hydride reducing agents is their stereoselectivity. The stereochemistry of hydride reduction has been studied most thoroughly with cyclohexanone derivatives. Some reagents give predominantly axial alcohols from substituted cyclohexanones, while others give primarily equatorial alcohols. It has been observed that axial alcohols are most likely to be formed with sterically demanding hydride transfer agents. There has been general agreement that this occurs because the equatorial direction of attack is more open and therefore preferred by bulky reagents. The phrase "steric approach control" was coined to describe this behavior.[42]

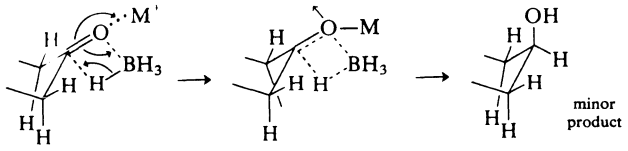
36. K. E. Wilson, R. T. Seidner, and S. Masamune, *Chem. Commun.*, 213 (1970).
37. S. Krishnamurthy and H. C. Brown, *J. Org. Chem.* **42**, 1197 (1977).
38. CuH, BuLi: S. Masamune, G. S. Bates, and P. E. Georghiou, *J. Am. Chem. Soc.* **96**, 3686 (1974); CuI, $LiAlH_4$: E. C. Ashby, J. J. Lin and R. Kovar, *J. Org. Chem.* **41**, 1939 (1976); E. C. Ashby, J.-J. Lin, and A. B. Goel, *J. Org. Chem.* **43**, 183 (1978).
39. M. F. Semmelhack, R. D. Stauffer, and A. Yamashita, *J. Org. Chem.* **42**, 3180 (1977).
40. M. E. Osborn, J. F. Pegues, and L. A. Paquette, *J. Org. Chem.* **45**, 167 (1980).
41. H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.* **84**, 4527 (1962); W. F. Gannon and H. O. House, *Org. Synth.* **40**, 14 (1960).
42. W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.* **78**, 2579 (1956).



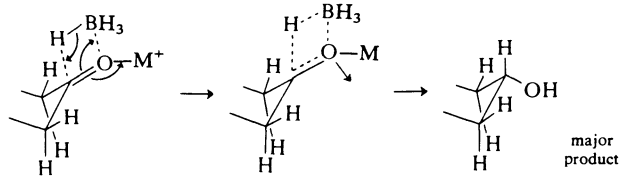
Steric Approach Control

With less hindered hydride donors, particularly sodium borohydride and lithium aluminum hydride, cyclohexanones give predominantly the equatorial alcohol. There has been less agreement about the factors that lead to this result. The equatorial alcohols are, of course, the more stable of the two isomers. The stereochemistry of hydride reduction is determined by kinetic control, but it was argued that the relative stability of the equatorial alcohol might be reflected in the transition state and be the dominant factor when no major steric problems intervened. A number of objections were raised to this idea. The common hydride reductions are exothermic reactions with low activation energies. The transition state should resemble starting ketone and reflect little of the structural features that are present in the product, so that it is difficult to see why product stability should determine the product composition.

A more acceptable explanation of the preference for equatorial alcohols in the absence of overriding steric factors involves an analysis of the torsional strain that develops in the two transition states.[43] The preference for equatorial alcohol



Torsional strain as oxygen passes through an eclipsed conformation

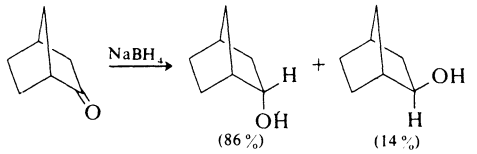


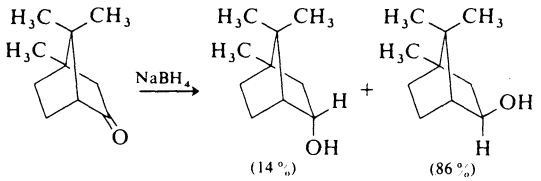
Oxygen moves away from equatorial hydrogens: no torsional strain

43. M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199 (1968); M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968); M. Cherest and H. Felkin, *Tetrahedron Lett.*, 383 (1971).

is then explained on the basis of the torsional strain that develops in the transition state leading to axial alcohols. Alternatively, it has been suggested that the carbonyl group π-antibonding orbital which will act as the acceptor orbital has its greatest density on the axial side because of interaction with the C2–C3 and C5–C6 σ bonds.[44] (See Section 3.10 of Part A for additional discussion).

When the ketones are relatively hindered—as, for example, in the bicyclo[2.2.1]heptan-2-one system—steric effects govern the stereochemistry of reduction even for small hydride reagents such as sodium borohydride and lithium aluminum hydride.





A large number of data have been accumulated[45] on the stereoselective reduction of cyclic ketones and it is now a relatively straightforward matter to predict and control such reactions. Table 5.2 compares the course of reduction of several ketones with hydrides of increasing steric bulk. The trends in the table illustrate the increasing importance of steric approach control as both the hydride reagent and the ketone become more highly substituted. Highly hindered hydride reducing agents are therefore chosen if an axial cyclohexanol is desired.

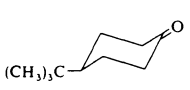
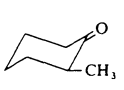
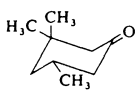
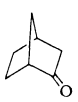
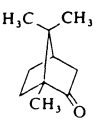
Among the most stereoselective of the hydride reducing agents are those containing several large alkyl substituents. These reagents can be prepared from organoboranes or aluminum alkyls. A good example of these substances is the trisiamylborohydride ion which is prepared from trisiamylborane and *t*-butyllithium.

$$[(CH_3)_2\overset{CH_3}{\overset{|}{C}}H]_3B + (CH_3)_3CLi \rightarrow [(CH_3)_2\overset{CH_3}{\overset{|}{C}}H]_3\bar{B}H\ Li^+$$

This material and the related tris(*sec*-butyl)borohydrides are sold commercially under the name Selectrides.[46]

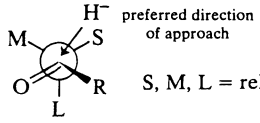
44. J. Klein, *Tetrahedron Lett.*, 4307 (1973).
45. D. C. Wigfield, *Tetrahedron* **35**, 449 (1979); D. C. Wigfield and D. J. Phelps, *J. Org. Chem.* **41**, 2396 (1976).
46. A. trademark of the Aldrich Chemical Company.

Table 5.2. Stereoselectivity of Hydride Reducing Agents

	Percentage alcohol favored by steric approach control				
					
Reducing agent	% axial	% axial	% axial	% *endo*	% *exo*
$NaBH_4$	20[b]	25[c]	58[c]	86[d]	86[d]
$LiAlH_4$	8	24	83	89	92
$LiAl(OMe)_3H$	9	69		98	99
$LiAl(t\text{-}BuO)_3H$	9[e]	36[f]	95	94[f]	94[f]
$(CH_3CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}H-)_3\bar{B}H\ Li^+$	93[g]	98[g]	99.8[g]	99.6[g]	99.6[g]
$\left[(CH_3)_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH\right]_3\bar{B}H\ Li^+$	>99[h]	>99[h]		>99[h]	NR[h]

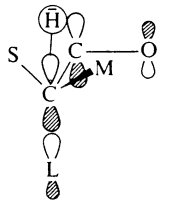
a. Except where otherwise noted, data are those given by H. C. Brown and W. C. Dickason, *J. Am. Chem. Soc.* **92**, 709 (1970). Data for many other cyclic ketones and reducing agents are given by A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron* **18**, 705 (1962) and W. T. Wipke and P. Gund, *J. Am. Chem. Soc.* **98**, 8107 (1976).
b. P. T. Lansbury and R. E. MacLeay, *J. Org. Chem.* **28**, 1940 (1963).
c. B. Rickborn and W. T. Wuesthoff, *J. Am. Chem. Soc.* **92**, 6894 (1970).
d. H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.* **88**, 2811 (1966).
e. J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Lett.*, 6127 (1968).
f. E. C. Ashby, J. P. Sevenair, and F. R. Dobbs, *J. Org. Chem.* **36**, 197 (1971).
g. H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.* **94**, 7159 (1972).
h. S. Krishnamurthy and H. C. Brown, *J. Am. Chem. Soc.* **98**, 3383 (1976).

The stereochemistry of reduction of acyclic aldehydes and ketones is a function of the substitution on the adjacent carbon atom and can be predicted on the basis of a conformational model of the transition state as shown.[43]

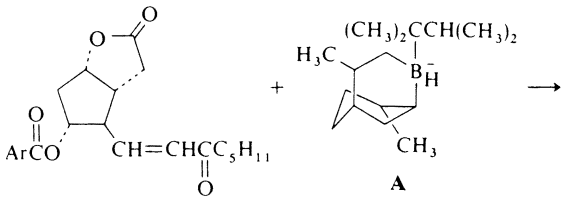


This model, which originally evolved from empirical observation, is rationalized by a combination of steric and stereoelectronic effects. From a purely steric standpoint, an approach involving less steric interaction with L and M by approaching from the direction of the smallest substituent is favorable. The stereoelectronic effect involves the interaction between the hydride ion and the LUMO of the carbonyl group. This orbital, which must accept the electrons of the incoming nucleophile, is stabilized when the bond to group L is perpendicular to the plane of the carbonyl group.[47] This conformation permits a favorable interaction with the vacant antibonding σ^* orbital, associated with the C—L bond.

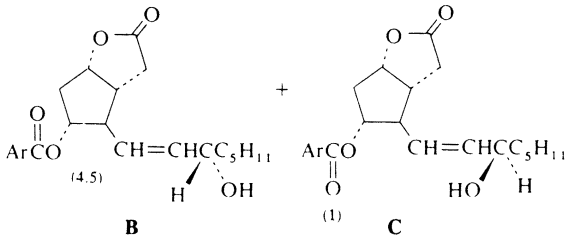
47. N. T. Anh, *Top. Current Chem.* **88**, 145 (1980).



Steric factors arising from groups more remote from the center undergoing reduction can also influence the stereochemical course of reduction. These steric factors are magnified by using bulky reducing agents. For example, a 4.5 : 1 preference for **B** over **C** is achieved by using the very bulky trialkylborohydride **A** in reduction of the side chain of a prostaglandin intermediate.[48]



A



B **C**

5.2.2. Reduction of Other Functional Groups

Although reductions of the common carbonyl and carboxylic acid derivatives are the most prevalent cases for application of metal-hydride reductions, there are certain other systems that have been of sufficient synthetic utility to discuss at this point. Scheme 5.5 summarizes some of these systems. Hydride donor reagents can effect replacement of halogen or sulfonate groups by hydrogen. All of the anionic aluminum and boron hydrides exhibit this reactivity. The reaction is particularly rapid and efficient in polar aprotic solvents such as dimethyl sulfoxide, dimethylformamide, and hexamethylphosphoric triamide. Table 5.3 gives some indication of relative reactivity. For substrates subject to nucleophilic attack it seems likely that this reaction proceeds by an S_N2 mechanism. However, the range of halides which can be reduced includes aryl halides and bridgehead halides which cannot react by

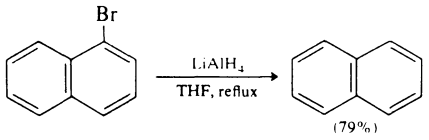
48. E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Am. Chem. Soc.* **93**, 1491 (1971).

Scheme 5.5. Reduction of Other

Halides

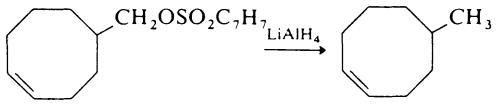
1[a] $CH_3(CH_2)_5CHCH_3 \xrightarrow[DMSO]{NaBH_4} CH_3(CH_2)_6CH_3$ (67%)
Cl

2[b] $CH_3(CH_2)_8CH_2I \xrightarrow[HMPA]{NaBH_3CN} CH_3(CH_2)_8CH_3$ (88–90%)

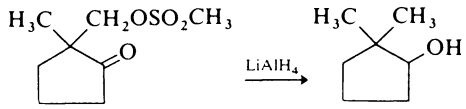
3[c] 

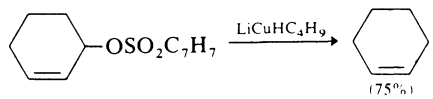
(79%)

Sulfonates

4[d] 

(33%)

5[e] 

6[f] 

(75%)

the S_N2 mechanism.[49] With vinyl halides there can be loss of stereochemical integrity, a result which would be consistent with involvement of a radical intermediate.[50] Formation and subsequent decomposition of a radical anion by one-electron transfer is the most likely mechanism for reductive dehalogenation of halides which cannot react by an S_N2 mechanism. One experimental test for the involvement of

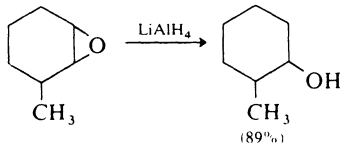
$$R{-}X + e^- \rightarrow R{-}X^{\cdot -}$$
$$R{-}X^{\cdot -} \rightarrow R^{\cdot} + X^-$$
$$R^{\cdot} + H^- \rightarrow R{-}H + e^-$$

radical intermediates is to study 5-hexenyl systems and look for the characteristic cyclization to cyclopentanes (see Section 12.5, Part A). When applied to 5-hexenyl bromide and iodide, no cyclization occurred with $LiAlH_4$. However, 2,2-dimethyl-5-hexenyl bromide and iodide gave mainly cyclic product.[51] This result clearly

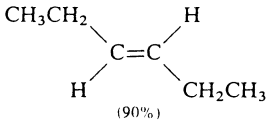
49. C. W. Jefford, D. Kirkpatrick, and F. Delay, *J. Am. Chem. Soc.* **94**, 8905 (1972).
50. S. K. Chung, *J. Org. Chem.* **45**, 3513 (1980).
51. E. C. Ashby, R. N. DePriest, and A. B. Goel, *Tetrahedron Lett.*, 1763 (1981).

Epoxides

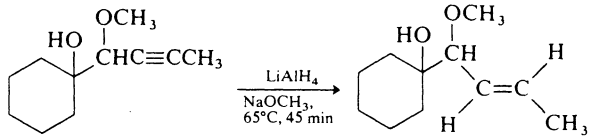
7[g]



Acetylenes

8[h] $CH_3CH_2C{\equiv}CCH_2CH_3 \xrightarrow[120\text{–}150°C,\ 4.5\ hr]{LiAlH_4}$  (90%)

9[i]



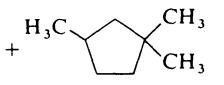
a. R. O. Hutchins, D. Hoke, J. Keogh, and D. Koharski, *Tetrahedron Lett.*, 3495 (1969); H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.* **34**, 3923 (1969).
b. R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *Org. Synth.* **53**, 107 (1973).
c. H. C. Brown and S. Krishnamurthy, *J. Org. Chem.* **34**, 3918 (1969).
d. A. C. Cope and G. L. Woo, *J. Am. Chem. Soc.* **85**, 3601 (1963).
e. A. Eschenmoser and A. Frey, *Helv. Chim. Acta* **35**, 1660 (1952).
f. S. Masamune, G. S. Bates, and P. E. Geoghiou, *J. Am. Chem. Soc.* **96**, 3686 (1974).
g. B. Rickborn and W. E. Lamke, II, *J. Org. Chem.* **32**, 537 (1967).
h. E. F. Magoon and L. H. Slaugh, *Tetrahedron* **23**, 4509 (1967).
f. D. A. Evans and J. V. Nelson, *J. Am. Chem. Soc.* **102**, 774 (1980).

indicates the involvement of radical intermediates, at least in the branched chain system.

$$CH_2{=}CH(CH_2)_3CH_2I + LiAlH_4 \xrightarrow[1\ hr]{24°C} CH_2{=}CH(CH_2)_3CH_3$$

$$CH_2{=}CH(CH_2)_2\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}CH_2I + LiAlH_4 \xrightarrow[24\ hr]{24°C} CH_2{=}CH(CH_2)_2\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}CH_3 \quad (94\%)$$

(3%)



(81%)

The presence of transition metal ions has a catalytic effect on reduction of halides and tosylates by $LiAlH_4$.[52] Various "copper hydrides," in particular, are effective for removal of halide and tosylate groups.[53]

52. E. C. Ashby and J. J. Lin, *J. Org. Chem.* **43**, 1263 (1978).
53. S. Masamune, G. S. Bates, and P. E. Georghiou, *J. Am. Chem. Soc.* **96**, 3686 (1974), E. C. Ashby, J. J. Lin, and A. B. Goel, *J. Org. Chem.* **43**, 183 (1978).

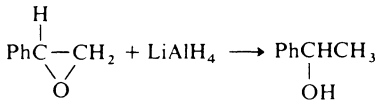
Table 5.3. Reaction Conditions for Reductive Replacement of Halogen and Tosylate by Hydride Donors

	Approximate conditions for complete reduction	
	Halides	Tosylates
$NaBH_3CN$[a]	1-Iodododecane, HMPA, 25°C, 4 hr	1-Dodecyl tosylate, HMPA, 70°C, 8 hr
$NaBH_4$[b]	1-Bromododecane, DMSO, 85°C, 1.5 hr	1-Dodecyl tosylate, DMSO, 85°C, 2 hr
$LiAlH_4$[c,d]	1-Bromooctane, THF, 25°C, 1 hr	1-Octyl tosylate, DME, 25°C, 6 hr
$LiB(C_2H_5)_3H$[c]	1-Bromooctane, THF, 25°C, 3 hr	

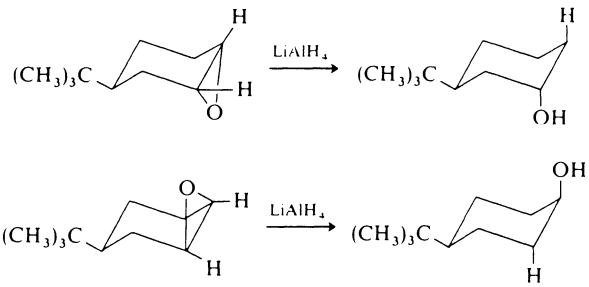
a. R. O. Hutchins, D. Kandasamy, C. A. Maryanoff, D. Masilamani, and B. E. Maryanoff, *J. Org. Chem.* **42**, 82 (1977).
b. R. O. Hutchins, D. Kandasamy, F. Dux, III, C. A. Maryanoff, D. Rotstein, B. Goldsmith, W. Burgoyne, F. Cistone, J. Dalessandro, and J. Puglis, *J. Org. Chem.* **43**, 2259 (1978).
c. S. Krishnamurthy and H. C. Brown, *J. Org. Chem.* **45**, 849 (1980).
d. S. Krishnamurthy, *J. Org. Chem.* **45**, 2550 (1980).

The primary synthetic value of these reductions is the removal of hydroxyl functionality by conversion first to a halide or tosylate followed by reduction. Scheme 5.5 gives some examples where the reaction has been used for synthesis.

Epoxides are converted to alcohols by $LiAlH_4$. The reaction occurs by nucleophilic attack, which takes place preferentially at the less hindered carbon of the epoxide. Cyclohexene epoxides are preferentially reduced through transition

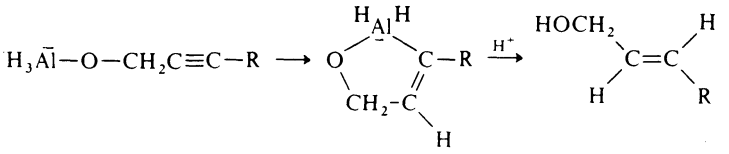


states involving diaxial opening.[54] Lithium triethylborohydride is a superior reagent for reduction of epoxides that are relatively unreactive or prone to rearrangement.[55]



54. B. Rickborn and J. Quartucci, *J. Org. Chem.* **29**, 3185 (1964); B. Rickborn and W. E. Lamke, II. *J. Org. Chem.* **32**, 537 (1967); D. K. Murphy, R. L. Alumbaugh, and B. Rickborn, *J. Am. Chem. Soc.* **91**, 2649 (1969).
55. H. C. Brown, S. C. Kim, and S. Krishnamurthy, *J. Org. Chem.* **45**, 1 (1980).

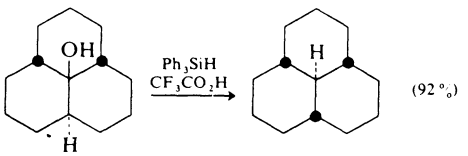
Alkynes are reduced to *trans*-alkenes by lithium aluminum hydride.[56] This method then is complementary to the catalytic reduction, which gives *cis*-alkenes. The reduction of acetylenes in synthesis frequently involves acetylenic alcohols and special reaction conditions are advantageous with these compounds. The hydroxyl group plays a specific role in the reaction, probably involving a cyclic intermediate.



The efficiency and stereospecificity of the reduction is improved by using a 1:2 mixture of $LiAlH_4$–$NaOCH_3$ as the reducing agent.[57] The mechanistic basis of this effect has not been studied in detail. The considerable difference in reactivity in the presence of a hydroxyl function is illustrated by entries 8 and 9, Scheme 5.5. The acetylenic alcohol is reduced in 45 minutes at 65°C, while the hydrocarbon requires several hours at 120°C for complete conversion.

5.3. Group IV Hydride Donors

Though not nearly so widely useful as the boron and aluminum hydrides, silicon and carbon can both act as hydride donors under certain circumstances.[58] The silicon–hydrogen bond is reactive toward carbonium ions, resulting in reduction of the carbonium ion to the hydrocarbon. This reaction is preparatively useful for reduction of alcohols that can be converted to carbonium ions in trifluoroacetic



(92%) Ref. 59

acid. Under similar conditions silanes act to reduce aromatic aldehydes and ketones to alkylaromatics.[60] Two hydride abstraction steps are involved.

56. E. F. Magoon and L. H. Slaugh, *Tetrahedron*, **23**, 4509 (1967).
57. E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Am. Chem. Soc.* **89**, 4245 (1967); B. B. Molloy and K. L. Hauser, *J. Chem. Soc. Chem. Commun.*, 1017 (1968).
58. D. N. Kursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, 633 (1974).
59. F. A. Carey and H. S. Tremper, *J. Org. Chem.* **36**, 758 (1971).
60. C. T. West, S. J. Donnelly, D. A. Kooistra, and M. P. Doyle, *J. Org. Chem.* **38**, 2675 (1973); M. P. Doyle, D. J. DeBruyn, and D. A. Kooistra, *J. Am. Chem. Soc.* **94**, 3659 (1972); M. P. Doyle and C. T. West, *J. Org. Chem.* **40**, 3821 (1975).

$$\mathrm{ArCR} \underset{\mathrm{O}}{\overset{\|}{} } + \mathrm{H^+} \rightleftarrows \mathrm{Ar\overset{+}{C}R} \underset{\mathrm{OH}}{\overset{|}{}}$$

$$\mathrm{Ar\overset{+}{C}R} \underset{\mathrm{OH}}{\overset{|}{}} + \mathrm{R_3SiH} \rightarrow \mathrm{ArCHR} \underset{\mathrm{OH}}{\overset{|}{}}$$

$$\mathrm{ArCHR} \underset{\mathrm{OH}}{\overset{|}{}} + \mathrm{H^+} \rightleftarrows \mathrm{Ar\overset{+}{C}HR} + \mathrm{H_2O}$$

$$\mathrm{Ar\overset{+}{C}HR} + \mathrm{R_3SiH} \rightarrow \mathrm{ArCH_2R}$$

When the reaction is carried out in alcoholic solvents with controlled amounts of acid, ethers are formed as a result of partial reduction of the hemiacetal. This reaction is applicable to aliphatic as well as aromatic compounds since the remaining alkoxy group provides the requisite stabilization for the carbonium ion intermediate.

$$\mathrm{R_2C{=}O + R'OH} \xrightarrow[\mathrm{R_3SiH}]{\mathrm{H^+}} \mathrm{R_2CHOR'}$$

Aliphatic ketones can be reduced to hydrocarbons by using triethylsilane and gaseous BF_3.[61] The BF_3 is a sufficiently strong Lewis acid to promote formation of a carbonium ion from the intermediate alcohol. In acidic aqueous media, alcohols are formed from aliphatic ketones but for preparative purposes this is not as convenient as sodium borohydride reduction.

Aromatic carboxylic acids and esters are reduced to methyl groups in a process in which trichlorosilane, Cl_3SiH, is the reductant.[62]

$$\mathrm{ArCO_2H \text{ or } ArCO_2CH_3} \xrightarrow[\substack{2)\ \mathrm{Cl_3SiH},\\ \mathrm{R_3N}}]{1)\ \mathrm{(CH_3)_3SiI}} \mathrm{ArCH_2SiCl_3} \xrightarrow{\mathrm{^-OH}} \mathrm{ArCH_3}$$

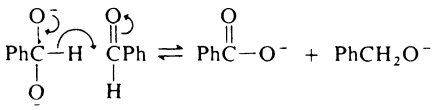
The mechanism of this reaction has not been delineated in detail.

There is also a group of reactions in which hydride is transferred from carbon. The carbon–hydrogen bond has little intrinsic tendency to break in the way required for hydride transfer. These reactions usually proceed via cyclic transition states in which new C–H bonds are formed simultaneously with the cleavage. Hydride transfer is facilitated by high charge density on the donor carbon atom. The Cannizzaro reaction, the base-catalyzed disproportionation of aldehydes, is one example of a hydride-transfer reaction.[63] A general mechanism is outlined below:

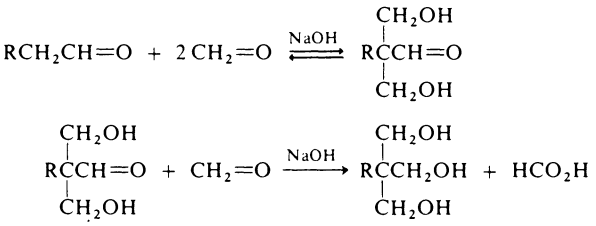
$$\mathrm{PhCH{=}O + \bar{O}H \rightleftarrows PhC(H)(O^-)(OH)}$$

$$\mathrm{PhC(H)(O^-)(OH) + \bar{O}H \rightleftarrows PhC(H)(O^-)(O^-) + H_2O}$$

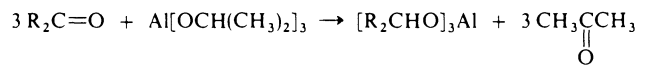
61. J. L. Frey, M. Orfanopoulos, M. G. Adlington, W. R. Dittman, Jr., and S. B. Silverman, *J. Org. Chem.* **43**, 374 (1978).
62. R. A. Benkeser, E. C. Mozdzen, and C. L. Muth, *J. Org. Chem.* **44**, 2185 (1979).
63. C. G. Swain, A. L. Powell, W. A. Sheppard, and C. R. Morgan, *J. Am. Chem. Soc.* **101**, 3576 (1979).



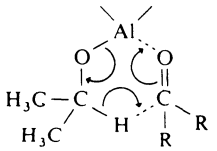
The hydride transfer is believed to occur from a species bearing two negative charges, and presumably this high charge density is responsible for the ease of hydride transfer. The reaction is not adaptable to aldehydes with enolizable hydrogen because the aldol condensation and subsequent transformations intervene. The Cannizzaro reaction has limited modern synthetic utility. The role of reducing agent and substrate can be assumed by two different aldehydes. If this is desired, formaldehyde is usually used as the reducing agent. The synthesis of polyhydroxymethyl compounds makes use of formaldehyde both for aldol condensation and reduction:



Aluminum alkoxides catalyze transfer of hydride from alcohols to ketones. This reaction can be driven to completion if one of the ketones is removed from the reaction system, by distillation, for example. This reaction, usually carried out with aluminum isopropoxide, is known as the Meerwein–Pondorff–Verley reaction.[64] The reaction proceeds via a cyclic transition state involving coordination of

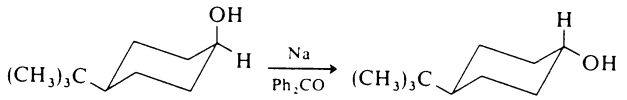


the aluminum atom with the carbonyl group. Hydride donation usually takes place from the less hindered side of the carbonyl group, so that in reductions of cyclohexanones, for example, the axial alcohol is the major product.[65]

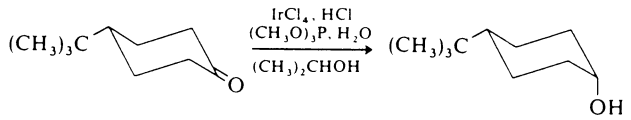


Similar hydride transfers occur with sodium alkoxides on heating. Since this process effects equilibration of stereoisomeric alcohols, it results in the preferential formation of the more stable of two epimeric alcohols. The normal procedure is to add a small amount of a carbonyl compound, frequently benzophenone, to act as the initial hydride acceptor and catalyze the reaction.

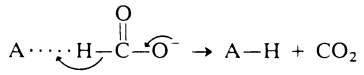
64. A. L. Wilds, *Org. React.* **2**, 178 (1944).
65. F. Nerdel, D. Frank, and G. Barth, *Chem. Ber.* **102**, 395 (1969).



A novel reduction process, catalyzed by iridium chloride, characterized by very high axial-to-equatorial product ratios, apparently involves hydride transfer from the isopropanol used in the reaction, although the detailed mechanism of the reaction is not established.[66]



Formic acid also can act as a donor of hydrogen. The driving force for the hydride transfer is formation of carbon dioxide.



The Clark–Eschweiler reductive alkylation of amines is a useful example of this reaction. Heating a primary or secondary amine with formaldehyde and formic acid results in complete methylation to the tertiary amine.[67]

$$RNH_2 + CH_2{=}O + HCO_2H \rightarrow RN(CH_3)_2$$

The hydride acceptor is the iminium ion from condensation of the amine with formaldehyde.

5.4. Hydrogen Atom Donors

Reduction by hydrogen atom donors necessarily involves intermediates with unpaired electrons. Tri-*n*-butyltin hydride is the most important example of this type of reducing agent. It is able to reductively replace halogen by hydrogen in many types of halogen compounds. Mechanistic studies have indicated a free-radical chain mechanism.[68] The order of reactivity for the halides is RI > RBr > RCl > RF,[69] which reflects the relative ease of the halogen atom abstraction.

66. E. L. Eliel, T. W. Doyle, R. O. Hutchins, and E. C. Gilbert, *Org. Synth.* **50**, 13 (1970).
67. M. L. Moore, *Org. React.* **5**, 301 (1949); S. H. Pine and B. L. Sanchez, *J. Org. Chem.* **36**, 829 (1971).
68. L. W. Menapace and H. G. Kuivila, *J. Am. Chem. Soc.* **86**, 3047 (1964).
69. H. G. Kuivila and L. W. Menapace, *J. Org. Chem.* **28**, 2165 (1963).

$$\text{In}\cdot + \text{Bu}_3\text{SnH} \rightarrow \text{In}-\text{H} + \text{Bu}_3\text{Sn}\cdot$$
$$\text{Bu}_3\text{Sn}\cdot + \text{R}-\text{X} \rightarrow \text{R}\cdot + \text{Bu}_3\text{SnX}$$
$$\text{R}\cdot + \text{Bu}_3\text{SnH} \rightarrow \text{RH} + \text{Bu}_3\text{Sn}\cdot$$

Tri-*n*-butyltin hydride shows substantial selectivity toward polyhalogenated compounds, permitting partial dehalogenation. The reason for the greater reactivity of more highly halogenated carbons toward reduction lies in the stabilizing effect that the remaining halogen has on the radical intermediate. This selectivity has been used, for example, to reduce dihalocyclopropanes to monohalocyclopropanes (entries 3 and 4, Scheme 5.6).

A procedure which is catalytic in Bu_3SnH and uses $NaBH_4$ as the stoichiometric reagent has been developed.[70] This procedure has advantages in the isolation and purification of product.

The reductive dehalogenation can also be applied to the conversion of acid chlorides to aldehydes.[71]

$$\text{RCOCl} \xrightarrow{\text{Bu}_3\text{SnH}} \text{RCHO}$$

A competing reaction leading to conversion of some of the aldehyde to an ester occurs under some conditions.

$$\text{RC(=O)Cl} + \text{Bu}_3\text{Sn}\cdot \rightarrow \text{RC(=O)}\cdot + \text{Bu}_3\text{SnCl}$$
$$\text{RC(=O)}\cdot + \text{RCH=O} \rightarrow \text{RC(=O)}-\text{O}-\dot{\text{C}}\text{HR}$$
$$\text{RC(=O)}-\text{O}-\dot{\text{C}}\text{HR} + \text{Bu}_3\text{SnH} \rightarrow \text{RC(=O)CH}_2\text{R} + \text{Bu}_3\text{Sn}\cdot$$

Tri-*n*-butyltin hydride also serves as a hydrogen atom donor in a procedure for deoxygenation of alcohols.[72] The alcohol is converted to a thiobenzoate or dithiocarbonate. These thioesters undergo a radical reaction with tri-*n*-butyltin hydride. This

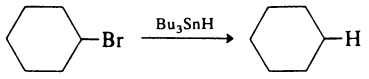
$$\text{R}-\text{OC(=S)Ph} + \text{Bu}_3\text{SnH} \rightarrow \text{ROC(S}-\text{SnBu}_3\text{)Ph} \rightarrow \text{R}\cdot + \text{PhC(=O)S}-\text{SnBu}_3$$
$$\text{R}\cdot + \text{Bu}_3\text{SnH} \rightarrow \text{R}-\text{H} + \text{Bu}_3\text{Sn}\cdot$$

procedure gives good yields with secondary alcohols. Because of the poorer stability of primary radicals the fragmentation step takes a different course with thioesters of primary alcohols.

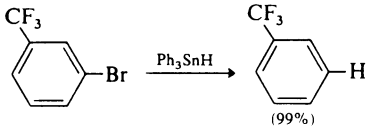
70. E. J. Corey and J. W. Suggs, *J. Org. Chem.* **40**, 2554 (1975).
71. H. G. Kuivila and E. J. Walsh, Jr., *J. Am. Chem. Soc.* **88**, 571 (1966); E. J. Walsh, Jr., and H. G. Kuivila, *J. Am. Chem. Soc.* **88**, 576 (1966).
72. D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin I*, 1574 (1975).

Scheme 5.6. Dehalogenations with Stannanes

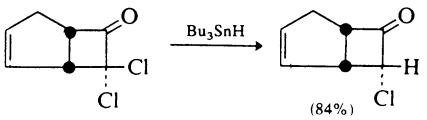
1[a]



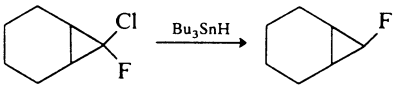
2[b]



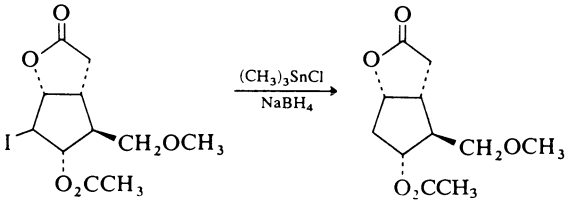
3[c]



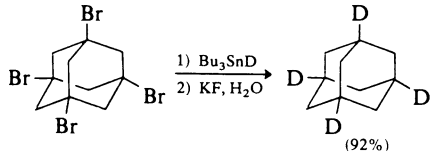
4[d]



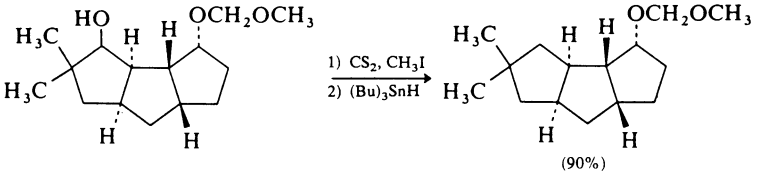
5[e]



6[f]



a. H. G. Kuivila, L. W. Menapace, and C. R. Warner, *J. Am. Chem. Soc.* **84**, 3584 (1962).
b. D. H. Lorenz, P. Shapiro, A. Stern, and E. I. Becker, *J. Org. Chem.* **28**, 2332 (1963).
c. W. T. Brady and E. F. Hoff, Jr. *J. Org. Chem.* **35**, 3733 (1970).
d. T. Ando, F. Namigata, H. Yamanaka, and W. Funasaka, *J. Am. Chem. Soc.* **89**, 5719 (1967).
e. E. J. Corey and J. W. Suggs, *J. Org. Chem.* **40**, 2554 (1975).
f. J. E. Leibner and J. Jacobus, *J. Org. Chem.* **44**, 449 (1979).



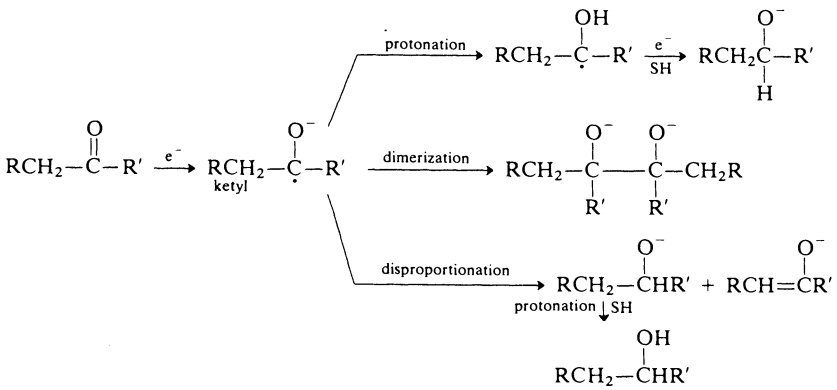
Ref. 73

73. K. Tatsuta, K. Akimoto, and M. Kinoshita, *J. Am. Chem. Soc.* **101**, 6116 (1979).

Another group of synthetically useful reductions employs a metal as the reducing agent. The organic substrate under these conditions accepts one or more electrons from the metal. The subsequent course of the reaction depends on the substrate and reaction conditions. Three broad classes of reactions can be recognized and these will be discussed separately. These include reactions in which the overall change involves (a) net addition of hydrogen, (b) reductive removal of a functional group, and (c) reactions in which carbon–carbon bonds are formed.

5.5.1. Addition of Hydrogen

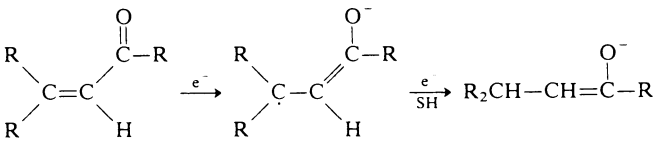
Although the method has been supplanted for synthetic purposes by hydride donors, the reduction of ketones to alcohols in ammonia or alcohols provides some mechanistic insight into this group of reactions. The overall course of the reaction of ketones with metal reductants is determined by the fate of the initial ketyl formed by a single-electron transfer. The intermediate, depending on its structure and the medium, may be protonated, may disproportionate or may dimerize.[74] In hydroxylic



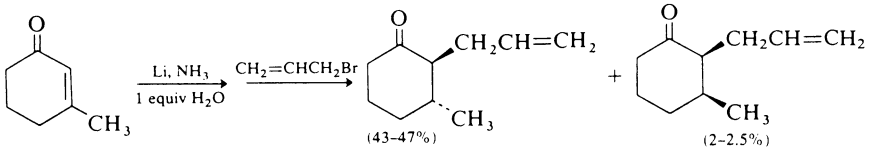
solvents such as liquid ammonia or in the presence of alcohols, the two possible protonation processes dominate over dimerization. As will be discussed in Section 5.5.3, dimerization may become the dominant process under other conditions.

α,β-Unsaturated carbonyl compounds are cleanly reduced to the enolate of the corresponding saturated ketone on reduction with lithium in ammonia.[75] Usually

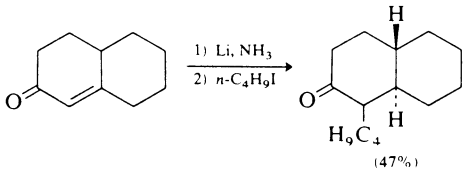
74. V. Rautenstrauch and M. Geoffroy, *J. Am. Chem. Soc.* **99**, 6280 (1977); J. W. Huffman and W. W. McWhorter, *J. Org. Chem.* **44**, 594 (1979).
75. D. Cain, *Org. Reactions*, **23**, 1 (1976).



an alcohol is added to the reduction solution to serve as the proton source. As mentioned in Chapter 1, this is one of the best methods for generating a specific enolate of a ketone. The enolates generated by conjugate reduction can undergo the characteristic reactions which were discussed in Chapters 1 and 2. When this is the objective of the reduction, it is important to use only one equivalent of the proton donor. Ammonia, being a weaker acid than an aliphatic ketone, does not act as a proton donor toward an enolate. If the saturated ketone is the desired product the enolate is protonated either by use of excess proton donor during the reduction or on workup.

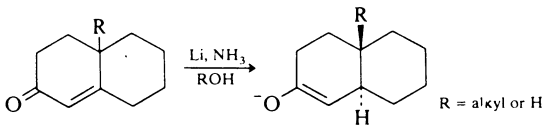


Ref. 76a



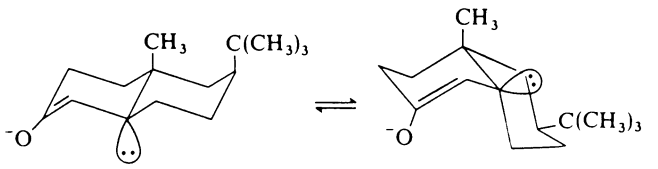
Ref. 76b

The stereochemistry of conjugate reduction is established by the proton transfer to the β-carbon. In the well-studied case of $\Delta^{1,9}$-2-octalones the ring junction is usually *trans*.[77] Exceptions to the preference for formation of the *trans*-ring fusion



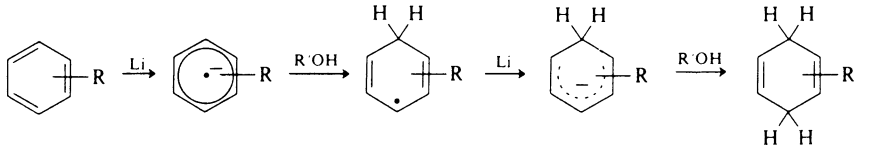
by axial protonation can usually be traced to unfavorable steric interactions in the chair–chair conformation of the dianion intermediate.[75] For example, 6-β-*t*-butyl-$\Delta^{1,9}$-2-octalone gives predominantly the *cis*-ring junction because a chair–chair conformation is precluded by the bulky *t*-butyl substituent. Stereochemical

76a. D. Caine, S. T. Chao, and H. A. Smith, *Org. Synth.* **56**, 52 (1977).
76b. G. Stork, P. Rosen and N. L. Goldman, *J. Am. Chem. Soc.* **83**, 2965 (1961).
77. G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.* **87**, 275 (1965); M. J. T. Robinson, *Tetrahedron* **21**, 2475 (1965).

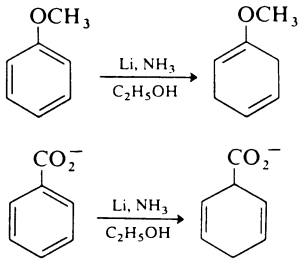


results in other series usually reflect two basic requirements. There is a preference for protonation perpendicular to the enolate system and, given that this requirement is met, the stereochemistry will normally correspond to the most stable conformation of the dianion intermediate.

Dissolving-metal systems constitute the most general method for partial reduction of aromatic rings.[78] The usual reducing medium is lithium or sodium in an alcohol or liquid ammonia. The reaction is initiated by electron transfer, and the radical anion is then protonated by the solvent. The isolated double bonds in the



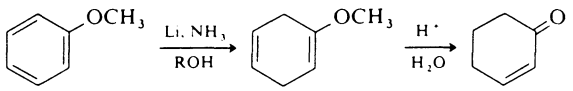
dihydro system are much less easily reduced than the conjugated ring system, so the reduction stops at the dihydro stage. The rate of reduction is affected in a predictable way by substituent groups. Electron-releasing groups retard the electron transfer, whereas electron-withdrawing groups facilitate reduction. Alkyl and alkoxy aromatics, phenols, and benzoate salts are among the most useful substrates for Birch reduction, since many other functional groups, e.g., ketones, nitro, are reduced in preference to the ring. The substituents also govern the position of protonation. Alkyl and alkoxy aromatics normally give the 2,5-dihydro derivative after complete protonation. Benzoate salts give 1,4-dihydro derivatives.



The structure of the products is determined by the site of protonation of the intermediate radical anion. In general, electron-releasing substituents favor protonation at the *ortho* and *meta* positions, leading to 2,5-dihydro products, whereas electron-attracting groups favor the *ipso* and *para* position.[79] The reduction of

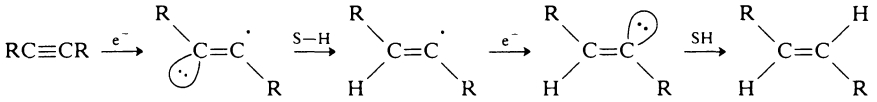
78. A. J. Birch and G. Subba Rao, *Adv. Org. Chem.* **8**, 1 (1972); R. G. Harvey, *Synthesis*, 161 (1970).
79. A. J. Birch, A. L. Hinde, and L. Radom, *J. Am. Chem. Soc.* **102**, 3370 (1980).

methoxybenzenes is of importance in the synthesis of cyclohexenones via hydrolysis of the intermediate enol ethers:



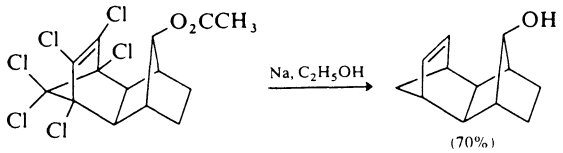
Scheme 5.7 lists some examples of the use of the Birch Reduction.

Reduction of acetylenes with sodium in ammonia,[80] lithium in low molecular weight amines[81] or sodium in hexamethylphosphoric triamide containing *t*-butanol as a proton source[82] all lead to predominantly the *trans*-alkene. This method supplements $LiAlH_4$ reduction as a means of converting acetylenes to *trans*-alkenes. The reaction is assumed to involve successive electron transfer and proton transfer steps.



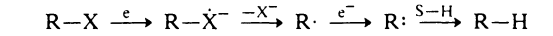
5.5.2. Reductive Removal of Functional Groups

The reductive removal of halogen can be accomplished with lithium or sodium. Tetrahydrofuran-*t*-butanol is a useful solvent medium. Good results also have been achieved with polyhalogenated compounds using sodium in ethanol. An important



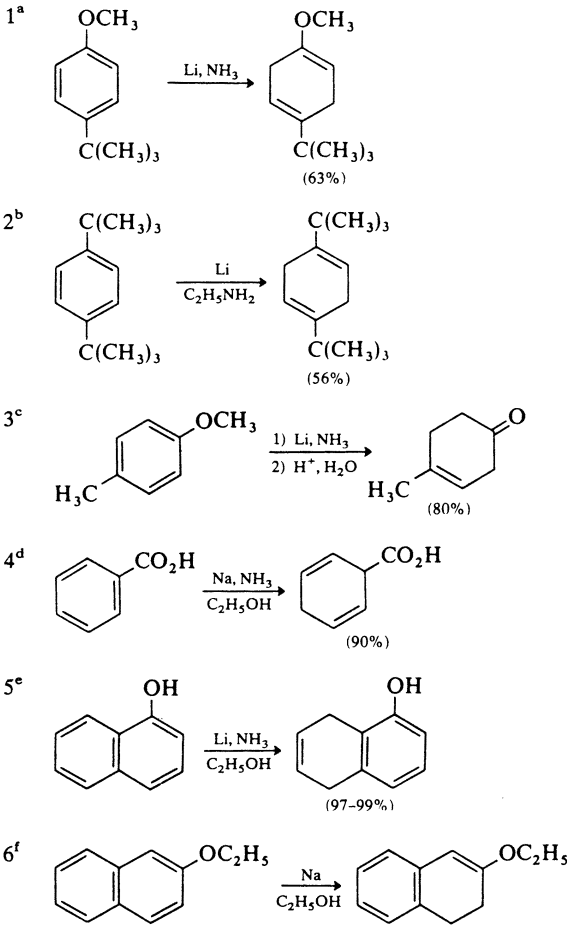
Ref. 83

synthetic application of this reaction is in the conversion of dichloro- and dibromocyclopropanes to cyclopropanes. This is a useful reaction because the dihalocyclopropanes are easily accessible *via* carbene reactions (see Section 9.1.3). This method can also be used to introduce deuterium at a specific site. Some examples of these types of reactions are given in Scheme 5.8. The mechanism of these reductive dehalogenations presumably involves formation of the radical anion of the halogen compound which then fragments and is reduced to a carbanion.



80. K. N. Campbell and T. L. Eby, *J. Am. Chem. Soc.* **63**, 216, 2683 (1941); A. L. Henne and K. W. Greenlee, *J. Am. Chem. Soc.* **65**, 2020 (1943).
81. R. A. Benkeser, G. Schroll, and D. M. Sauve, *J. Am. Chem. Soc.* **77**, 3378 (1955).
82. H. O. House and E. F. Kinloch, *J. Org. Chem.* **39**, 747 (1974).
83. B. V. Lap and M. N. Paddon-Row, *J. Org. Chem.* **44**, 4979 (1979).

Scheme 5.7. Birch Reduction of Aromatic Rings

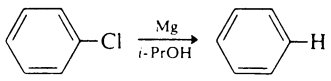


a. D. A. Bolon, *J. Org. Chem.* **35**, 715 (1970).
b. H. Kwart and R. A. Conley, *J. Org. Chem.* **38**, 2011 (1973).
c. E. A. Braude, A. A. Webb and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3328 (1958); W. C. Agosta and W. L. Schreiber, *J. Am. Chem. Soc.* **93**, 3947 (1971).
d. M. E. Kuehne and B. F. Lambert, *Org. Synth.* **V**, 400 (1973).
e. C. D. Gutsche and H. H. Peter, *Org. Synth.* **IV**, 887 (1963).
f. M. D. Soffer, M. P. Bellis, H. E. Gellerson, and R. A. Stewart, *Org. Synth.* **IV**, 903 (1963).

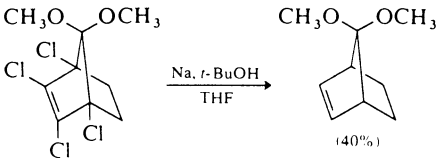
Scheme 5.8. Reductive Dehalogenation and Deoxygenation

A. Dehalogenation

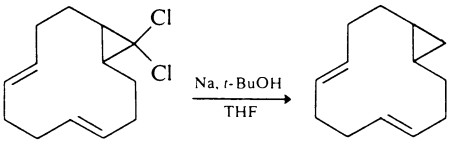
1[a]



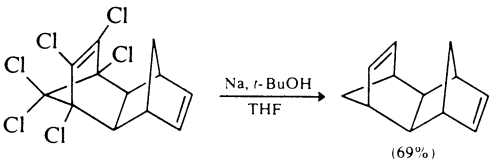
2[b]



3[c]

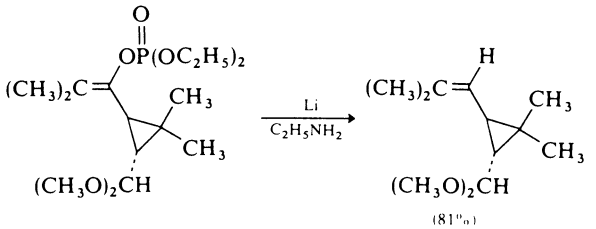


4[d]

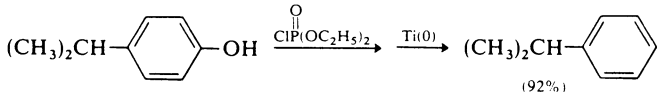


B. Deoxygenation

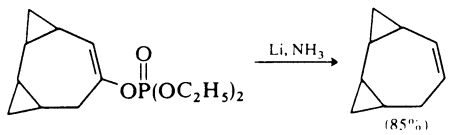
5[e]



6[f]



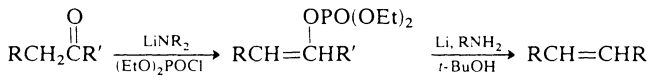
7[g]



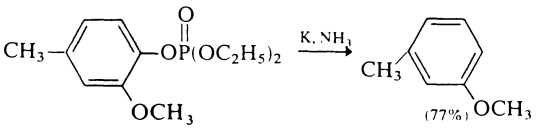
a. D. Bryce-Smith and B. J. Wakefield, *Org. Synth.* **47**, 103 (1967).
b. P. G. Gassman and J. L. Marshall, *Org. Synth.* **48**, 68 (1968).
c. P. G. Gassman, J. Seter, and F. J. Williams, *J. Am. Chem. Soc.* **93**, 1673 (1971).
d. B. V. Lap and M. N. Paddon-Row, *J. Org. Chem.* **44**, 4979 (1979).
e. S. C. Welch and T. A. Valdes, *J. Org. Chem.* **42**, 2108 (1977).
f. S. C. Welch and M. E. Walter, *J. Org. Chem.* **43**, 4797 (1978).
g. M. R. Detty and L. A. Paquette, *J. Am. Chem. Soc.* **99**, 821 (1977).

Whether the fragmentation and reduction are separate steps or a concerted process is not certain.

Reductive removal of vinyl phosphate groups is one of the better methods for conversion of a carbonyl compound to an alkene.[84] The required vinyl phosphates are obtained easily from the enolate. The enolate can be phosphorylated either

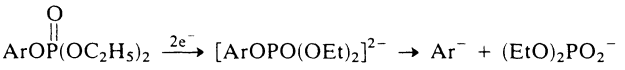


with diethyl phosphorochloridate or *N,N,N',N'*-tetramethyldiamidophosphorochloridate.[85] Reductive removal of oxygen from aromatic rings can also be achieved by reductive cleavage of diethyl aryl phosphate esters. There are also examples of



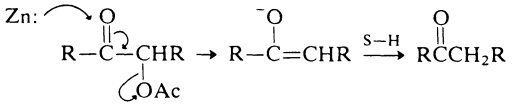
Ref. 86

the application of the method to saturated alcohols.[87] Mechanistic studies of the cleavage of aryl dialkyl phosphates have indicated that the crucial C–O bond cleavage occurs after transfer of two electrons.[83] For preparative purposes, titanium



metal can be used in place of sodium or lithium in liquid ammonia for both the vinyl phosphate[89] and aryl phosphate[90] cleavages. The titanium metal is generated *in situ* from $TiCl_3$ by reduction with potassium metal in tetrahydrofuran.

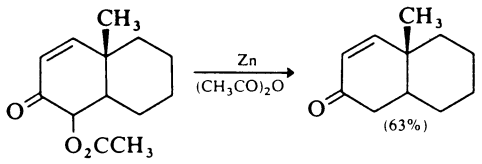
Both metallic zinc and aluminum amalgam are useful reducing agents which are milder than the alkali metals. These reductants effect the selective removal of oxygen and sulfur functionality α to carbonyl groups or other good electron acceptors. The mechanistic picture which seems most generally applicable to these reactions is a net two-electron reduction with expulsion of the oxygen or sulfur functionality as an anion. The reaction evidently is a concerted process since the isolated functional groups are not reduced under these conditions. Some examples of this type of reaction are given in Scheme 5.9.



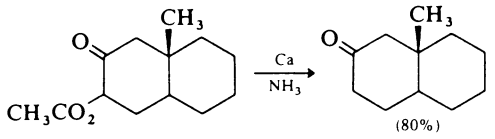
84. R. E. Ireland and G. Pfister, *Tetrahedron Lett.* 2145 (1969).
85. R. E. Ireland, D. C. Muchmore, and U. Hengartner, *J. Am. Chem. Soc.* **94**, 5098 (1972).
86. R. A. Rossi and J. F. Bunnett, *J. Org. Chem.* **38**, 2314 (1973).
87. R. R. Muccino and C. Djerassi, *J. Am. Chem. Soc.* **96**, 556 (1974).
88. S. J. Shafer, W. D. Closson, J. M. F. vanDijk, O. Piepers, and H. M. Buck, *J. Am. Chem. Soc.* **99**, 5118 (1977).
89. S. C. Welch and M. E. Walters, *J. Org. Chem.* **43**, 2715 (1978).
90. S. C. Welch and M. E. Walters, *J. Org. Chem.* **43**, 4797 (1978).

Scheme 5.9. Reductive Removal of Functional Groups

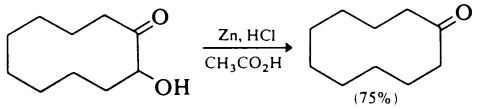
1[a]



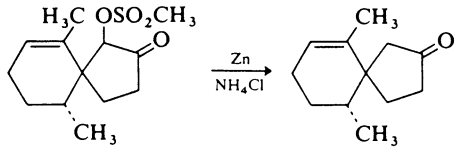
2[b]



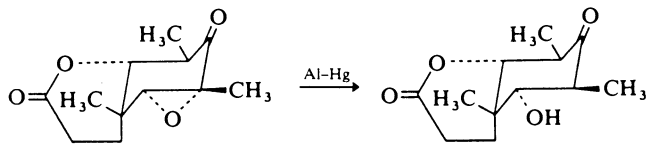
3[c]



4[d]



5[e]



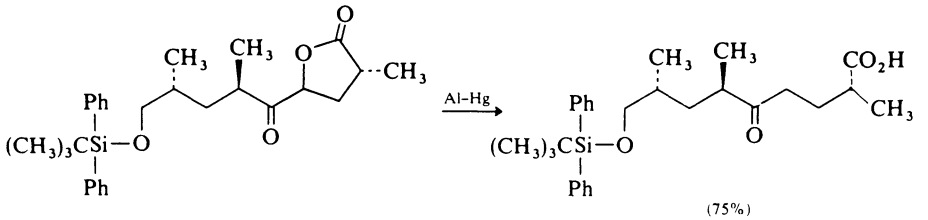
Vinylogous oxygen functions are also subject to reductive eliminations by zinc or aluminum amalgam (entry 8, Scheme 5.9).[91]

5.5.3. Reductive Carbon–Carbon Bond Formation

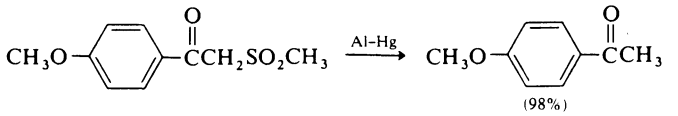
Since reductions by metal atoms often occur as one-electron processes, intermediate radicals are frequently involved in dissolving-metal reductions. When the reaction conditions are adjusted so that coupling of these intermediates competes favorably with other processes, the formation of carbon–carbon bonds will occur. A useful example which has been known for a long time is the reductive coupling of acetone to 2,3-dimethylbutane-2,3-diol (pinacol). Considerable effort has been

91. L. E. Overman and C. Fukaya, *J. Am. Chem. Soc.* **102**, 1454 (1980).

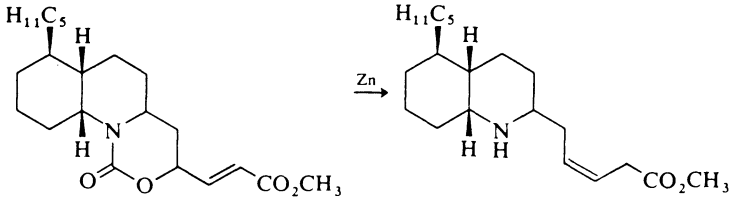
6[f]



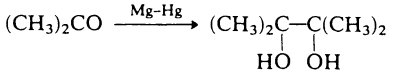
7[g]



8[h]

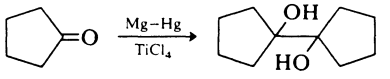


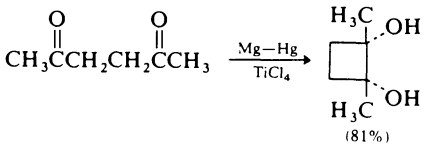
a. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.* **74**, 4223 (1952).
b. J. A. Marshall and H. Roebke, *J. Org. Chem.* **34**, 4188 (1969).
c. A. C. Cope, J. W. Barthel, and R. D. Smith, *Org. Synth.* **IV**, 218 (1963).
d. T. Ibuka, K. Hayashi, H. Minakata, and Y. Inubushi, *Tetrahedron Lett.*, 159 (1979).
e. E. J. Corey, E. J. Trybulski, L. S. Melvin, Jr., K. C. Nicolaou, J. A. Secrist, R. Lett, P. W. Sheldrake, J. R. Falck, D. J. Brunelle, M. F. Haslanger, S. Kim, and S. Yoo, *J. Am. Chem. Soc.* **100**, 4618 (1978).
f. P. A. Grieco, E. Williams, H. Tanaka, and S. Gilman, *J. Org. Chem.* **45**, 3537 (1980).
g. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **86**, 1639 (1964).
h. L. E. Overman and C. Fukaya, *J. Am. Chem. Soc.* **102**, 1454 (1980).



Ref. 92

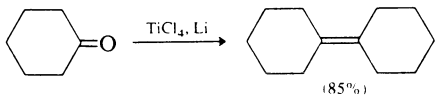
devoted recently to developing conditions for this reaction which would be widely applicable. These studies have led to several titanium reagents which are effective, particularly Ti metal generated by reduction of $TiCl_4$ with magnesium.[93]





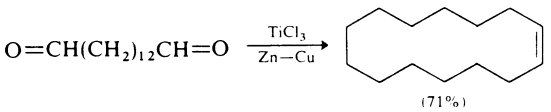
92. R. Adams and E. W. Adams, *Org. Synth.* **1**, 448 (1932).
93. E. J. Corey, R. L. Danheiser, and S. Chandrashekaran, *J. Org. Chem.* **41**, 260 (1976).

Titanium metal generated by reduction with stronger reducing agents such as $LiAlH_4$, Li, or K results in the coupling and reduction proceeding to an alkene.[94]



Both unsymmetrical diols and alkenes can be prepared by using these methods with two different carbonyl compounds. An excess of the less valuable component is used to achieve high yields of unsymmetrical product from the more valuable substrate.

A version of the titanium-mediated reductive coupling in which $TiCl_3$–Zn–Cu serves as the reductant is efficient in closing large-membered rings. The mechanism

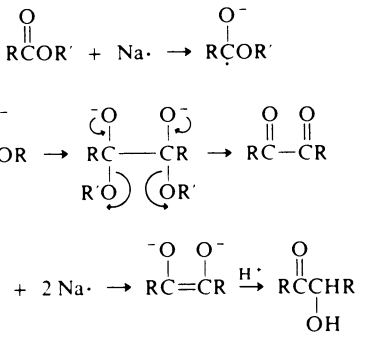


Ref. 94

of the reductive coupling to alkenes is thought to involve a heterogeneous process taking place at a metal surface. This can, of course, help to explain its efficiency at ring formation.

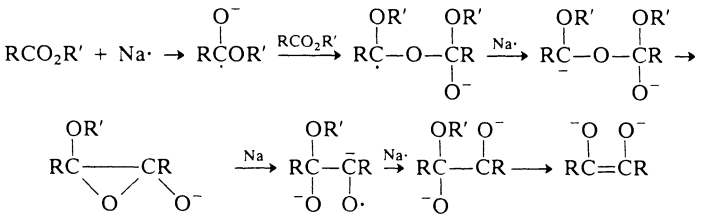
A second important reductive coupling procedure involves the reduction of esters to α-hydroxy ketones (acyloins).[95] This reaction is usually carried out with sodium metal in an inert solvent. Diesters undergo intramolecular reactions and this is also an important method for preparation of medium and large carbocyclic rings. There has been considerable discussion of the mechanism of the acyloin condensation but the picture may be complicated by the possibility that the reaction is a heterogeneous one, taking place on the surface of the reacting metal.

A simple formulation of the reaction mechanism envisages coupling of radicals generated by one-electron transfer.



94. J. E. McMurry and M. P. Fleming, *J. Org. Chem.* **41**, 896 (1976); J. E. McMurry and L. R. Krepski, *J. Org. Chem.* **41**, 3929 (1976); J. E. McMurry, M. P. Fleming, K. L. Kees, and L. R. Krepski, *J. Org. Chem.* **43**, 3255 (1978).
95. J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. Reactions* **23**, 259 (1976).

An alternative mechanism has been suggested. It bypasses the α-dicarbonyl intermediate, since this is a species with questionable involvement in the reaction.[96]



Regardless of the mechanism, the product prior to neutralization is the dianion of the α-hydroxy ketone, an enediolate. It has been found that overall yields are greatly improved if trimethylsilyl chloride is present during the reaction to trap these dianions as stable trimethylsilyl ethers.[97] In contrast to the strongly basic enediolates, which tend to promote condensation and other competing reactions, the silyl ethers are neutral and entirely stable to the reaction conditions. Simple hydrolysis converts the silyl ethers to acyloins. This modified version of the reaction has been applied to intramolecular cyclizations leading to small, medium, and large rings, as well as to intermolecular couplings.

A few examples of these types of reductive couplings which have been employed in synthetic work are given in Scheme 5.10.

5.6. Reductive Deoxygenation of Carbonyl Groups

Several methods have been used to reductively remove carbonyl groups from organic molecules. Methods that achieve complete reduction to a methylene group and others which give rise to alkenes are known. Some examples are given in Scheme 5.11.

Zinc and hydrochloric acid is able to reduce certain carbonyl groups to methylene. The oxygen is believed to be eliminated as water from a partially reduced intermediate bound to zinc. This reaction is known as the Clemmensen reduction.[98] The corresponding alcohols are not reduced to hydrocarbons under the conditions of the reactions, so they obviously cannot be intermediates in the overall process. The mechanism of the reaction is not known in detail. Formation of carbon–zinc bonds at the metal surface may be involved.

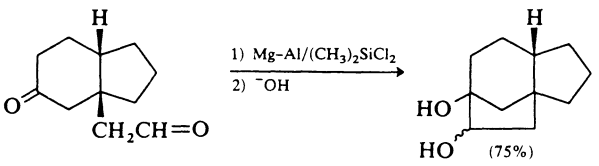
The reaction is commonly carried out in hot concentrated hydrochloric acid with ethanol as a cosolvent. These conditions preclude the presence of acid-sensitive or hydrolyzable functional groups. This methodology is usually quite efficient for

96. J. J. Bloomfield, D. C. Owsley, C. Ainsworth, and R. E. Robertson, *J. Org. Chem.* **40**, 393 (1975).
97. K. Ruhlmann, *Synthesis*, 236 (1971).
98. E. Vedejs, *Org. React.* **22**, 401 (1975).

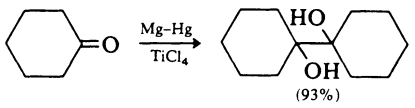
Scheme 5.10. Reductive Carbon–Carbon Bond Formation

A. Pinacol Formation

1[a]

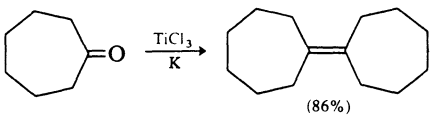


2[b]

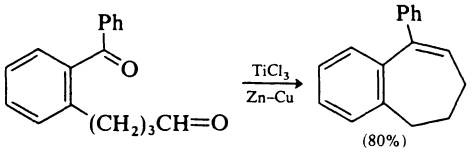


B. Alkene Formation

3[c]

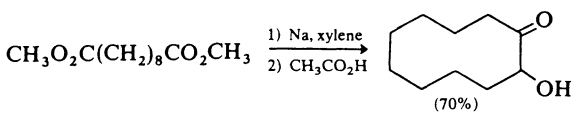


4[c]

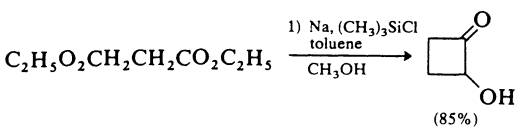


C. Acyloin Formation

5[d]



6[e]



a. E. J. Corey and R. L. Carney, *J. Am. Chem. Soc.* **93**, 7318 (1971).
b. E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *J. Org. Chem.* **41**, 260 (1976).
c. J. E. McMurry, M. P. Fleming, K. L. Kees, and L. R. Krepski, *J. Org. Chem.* **43**, 3255 (1978).
d. N. L. Allinger, *Org. Synth.* **IV**, 840 (1963).
e. J. J. Bloomfield and J. M. Nelke, *Org. Synth.* **57**, 1 (1977).

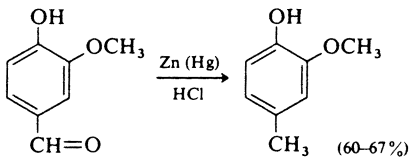
aryl ketones but less reliable with unconjugated ketones. A modification in which ether saturated with dry hydrogen chloride is the solvent gave good results in the reduction of steroidal ketones.[99]

99. M. Toda, M. Hayashi, Y. Hirata, and S. Yamamura, *Bull. Chem. Soc. Japan* **45**, 264 (1972).

Scheme 5.11. Carbonyl-to-Methylene Reductions

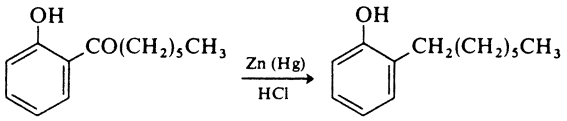
Clemmensen

1[a]



(60–67%)

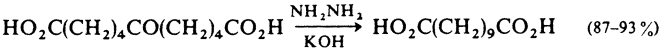
2[b]



(81–86%)

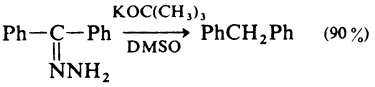
Wolff–Kishner

3[c]



(87–93%)

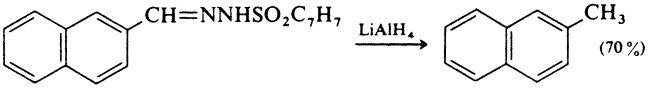
4[d]



(90%)

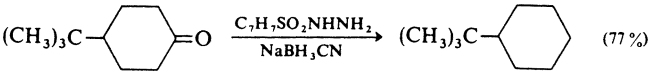
Tosylhydrazone Reduction

5[e]



(70%)

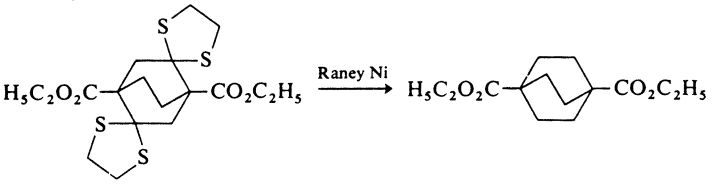
6[f]



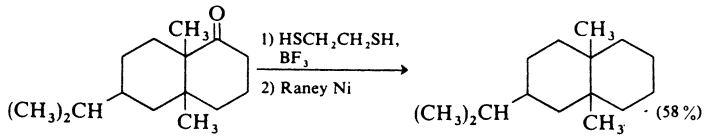
(77%)

Thioketal Desulfurization

7[g]



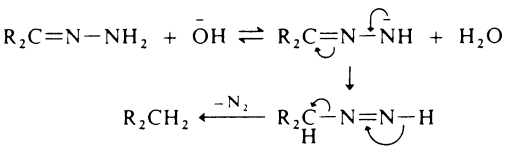
8[h]



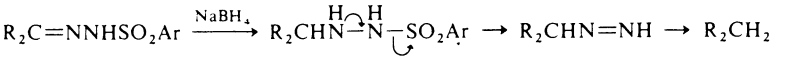
(58%)

a. R. Schwarz and H. Hering, *Org. Synth.* **IV**, 203 (1963).
b. R. R. Read and J. Wood, Jr., *Org. Synth.* **III**, 444 (1955).
c. L. J. Durham, D. J. McLeod, and J. Cason, *Org. Synth.* **IV**, 510 (1963).
d. D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Am. Chem. Soc.* **84**, 1734 (1962).
e. L. Caglioti and M. Magi, *Tetrahedron* **19**, 1127 (1963).
f. R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *J. Am. Chem. Soc.* **93**, 1793 (1971).
g. J. D. Roberts and W. T. Moreland, Jr., *J. Am. Chem. Soc.* **75**, 2167 (1953).
h. P. N. Rao, *J. Org. Chem.* **36**, 2426 (1971).

The Wolff–Kishner reaction involves the base-catalyzed decomposition of hydrazones.[100] Alkyldiimides are believed to be formed and then to collapse with loss of nitrogen:

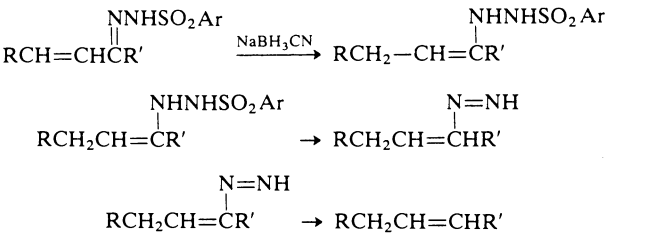


The reduction of tosylhydrazones by $LiAlH_4$ or $NaBH_4$ also converts carbonyl groups to methylene.[101] It is believed that a diimide intermediate is involved, as in the Wolff–Kishner reaction. Excellent yields have also been reported using the



milder reducing agent sodium cyanoborohydride.[102] This reagent is added to a mixture of the carbonyl compound to be reduced and *p*-toluenesulfonylhydrazide. Hydrazone formation is faster than reduction of the carbonyl group by cyanoborohydride. As the hydrazone is formed, it is reduced to the hydrocarbon by $NaBH_3CN$.

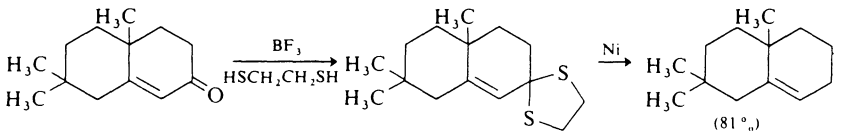
Reduction of tosylhydrazones of α,β-unsaturated ketones gives alkenes with the double bond being located between the former carbonyl and α-carbon atoms.[103] This reaction is believed to proceed via an initial conjugate reduction followed by decomposition of the resulting vinylhydrazine to a vinyl diimide.



Catecholborane or sodium borohydride in acetic acid can also be used as reducing agents in this reaction.[104]

Carbonyl groups can also be reduced to methylene via thioketal intermediates. The preparation of the cyclic thioketals derived from ethanedithiol is common. Reaction of the thioketal with excess Raney nickel causes hydrogenolysis of the C–S bonds.

100. D. Todd, *Org. React.* **4**, 378 (1948); Huang-Minlon, *J. Am. Chem. Soc.* **68**, 2487 (1946).
101. L. Caglioti, *Tetrahedron* **22**, 487 (1966).
102. R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.* **95**, 3662 (1973).
103. R. O. Hutchins, M. Kacher, and L. Rua, *J. Org. Chem.* **40**, 923 (1975).
104. G. W. Kabalka, D. T. C. Yang, and J. D. Baker, Jr., *J. Org. Chem.* **41**, 574 (1976); R. O. Hutchins and N. R. Natale, *J. Org. Chem.* **43**, 2299 (1978).

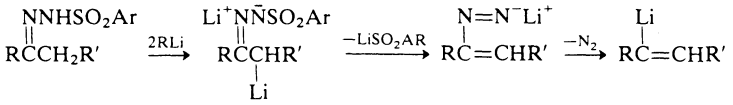


Ref. 105

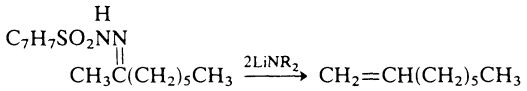
Tri-*n*-butyltin hydride is an alternative reagent for desulfurization.[106]

The use of silane reagents to reduce ketones to methylene groups is another method which has already been discussed (Section 5.3).

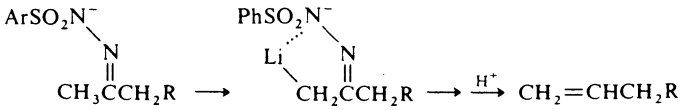
The conversion of ketones to alkenes via tosylhydrazones is known as the *Shapiro reaction*. This reaction occurs when the tosylhydrazone is treated with two equivalents of an alkyllithium or a lithium dialkylamide.[107,108] The reaction proceeds through the anion of a vinyldiimide which decomposes to a vinyllithium reagent. Contact of this intermediate with a proton source gives the alkene. Scheme 5.12



includes some examples of this very useful reaction. The Shapiro reaction has been particularly useful for cyclic ketones, but the scope of the reaction has also been extended to include acyclic systems. In the case of unsymmetrical acyclic ketones questions of both regiochemistry and stereochemistry arise. For 2-octanone tosylhydrazone, the exclusive product is 1-octene.[108] This regiospecificity has been shown



to depend on the stereochemistry of the C=N double bond in the starting hydrazone. There is evidently a strong preference for abstracting the proton *syn* to the arenesulfonyl group, probably because this permits chelation with the lithium atom. The Shapiro reaction converts α,β-unsaturated ketones to dienes (entries

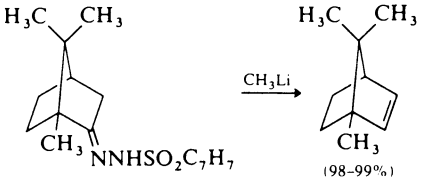


3–5, Scheme 5.12). When isomeric dienes are possible, the product, at least under some conditions, also depends upon the stereochemistry of the tosylhydrazone.[109]

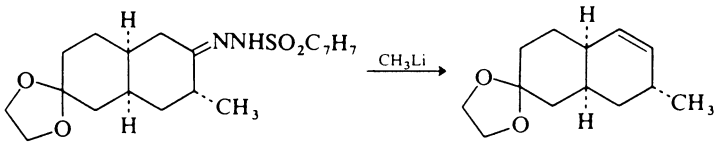
105. F. Sondheimer and S. Wolfe, *Can. J. Chem.* **37**, 1870 (1959).
106. C. G. Gutierrez, R. A. Stringham, T. Nitasaka, and K. G. Glasscock, *J. Org. Chem.* **45**, 3393 (1980).
107. R. H. Shapiro, *Org. React.* **23**, 405 (1976); R. H. Shapiro and M. J. Heath, *J. Am. Chem. Soc.* **89**, 5734 (1967).
108. K. J. Kolonko and R. H. Shapiro, *J. Org. Chem.* **43**, 1404 (1978).
109. W. G. Dauben, G. T. Rivers, and W. T. Zimmerman, *J. Am. Chem. Soc.* **99**, 3414 (1977).

Scheme 5.12. Conversion of Ketones to Olefins via Sulfonylhydrazones

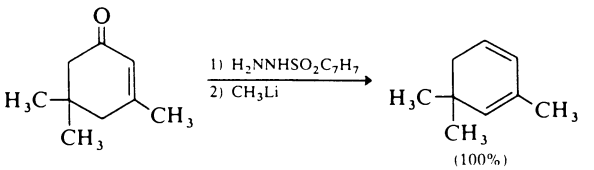
1[a]



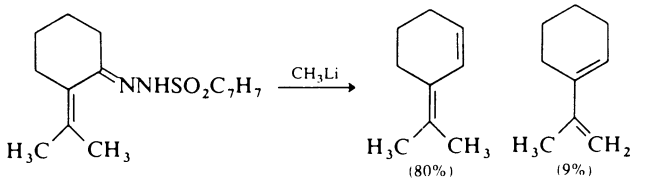
2[b]



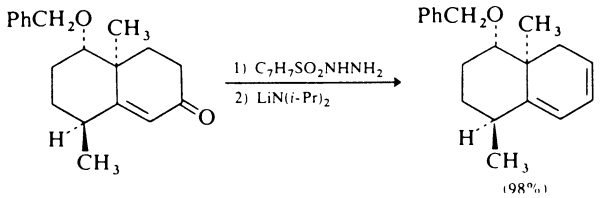
3[c]



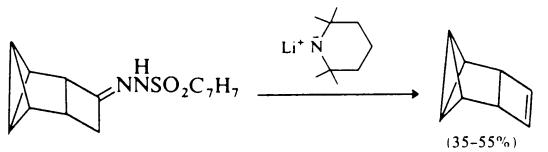
4[d]



5[e]



6[f]



a. R. H. Shapiro and J. H. Duncan, *Org. Synth.* **51**, 66 (1971).
b. W. L. Scott and D. A. Evans, *J. Am. Chem. Soc.* **94**, 4779 (1972).
c. W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, and K. Tomer, *J. Am. Chem. Soc.* **90**, 4762 (1968).
d. W. G. Dauben, G. T. Rivers, and W. T. Zimmerman, *J. Am. Chem. Soc.* **99**, 3414 (1977).
e. P. A. Grieco, T. Oguri, C.-L. J. Wang, and E. Williams, *J. Org. Chem.* **42**, 4113 (1977).
f. L. R. Smith, G. E. Gream, and J. Meinwald, *J. Org. Chem.* **42**, 927 (1977).

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R. L. Augustine (ed.), *Reduction Techniques and Applications in Organic Synthesis*, Marcel Dekker, New York (1968).

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P. N. Rylander, *Catalytic Hydrogenation in Organic Syntheses*, Academic Press, New York (1979).
M. Freifelder, *Catalytic Hydrogenation in Organic Synthesis. Procedures and Commentary*, John Wiley and Sons, New York (1978).
B. R. James, *Homogeneous Hydrogenation*, John Wiley and Sons, New York (1973).

Metal Hydrides

A. Hajos, *Complex Hydrides and Related Reducing Agents in Organic Synthesis*, Elsevier Scientific, New York (1979).
H. C. Brown, *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, New York (1972).

Dissolving-Metal Reduction

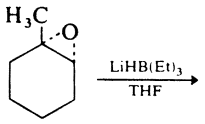
A. A. Akhrem, I. G. Rshetova and Y. A. Titov, *Birch Reduction of Aromatic Compounds*, IFI/Plenum, New York (1972).

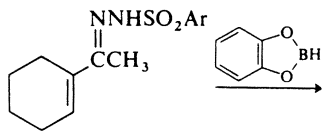
Problems

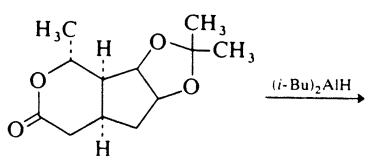
References for these problems will be found on page 624.

1. Give the product(s) to be expected from the following reactions. Be sure to specify all facets of stereochemistry.

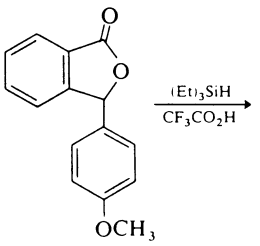
(a) $(CH_3)_2CHCH{=}CHCH{=}CHCO_2CH_3 \xrightarrow{(i\text{-}Bu)_2AlH}$

(b) 

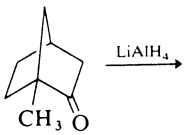
(c) 

(d) 

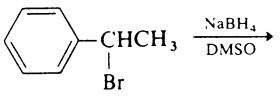
(e)



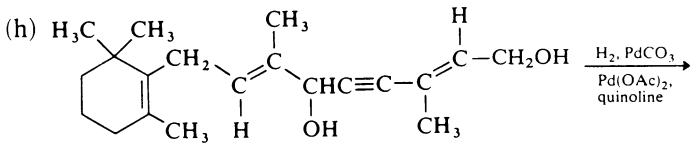
(f)



(g)

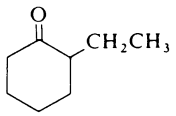


(h)

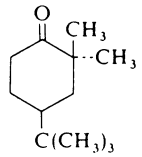


2. Indicate the stereochemistry of the major alcohol that would be formed by sodium borohydride reduction of each of the cyclohexanone derivatives shown:

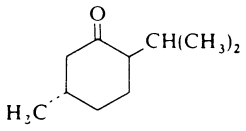
(a)



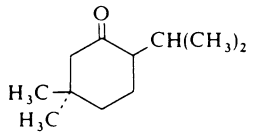
(c)



(b)

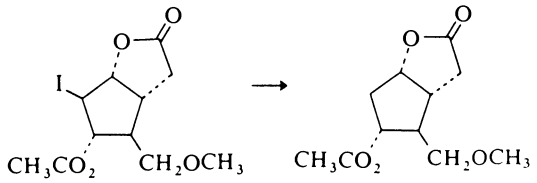


(d)

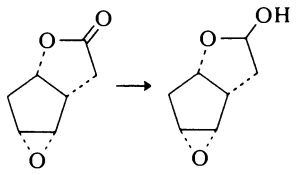


3. Indicate reaction conditions that would accomplish each of the following transformations in one step:

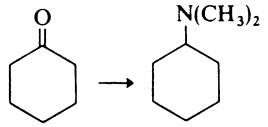
(a)



(b)



(c)



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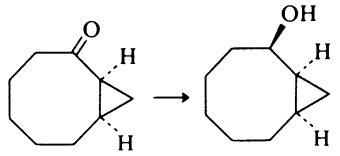

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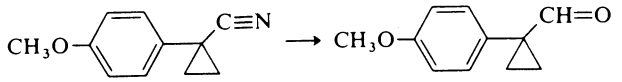

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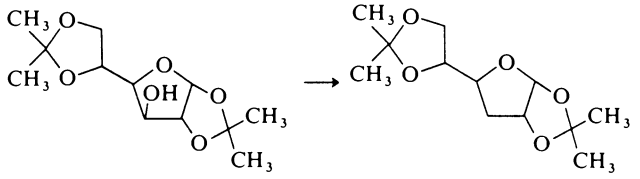

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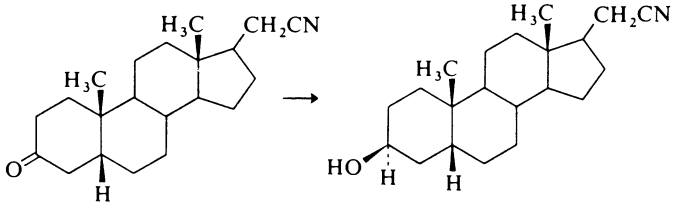

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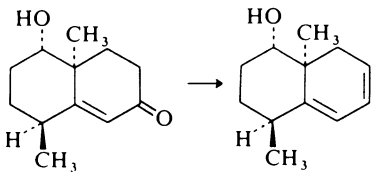

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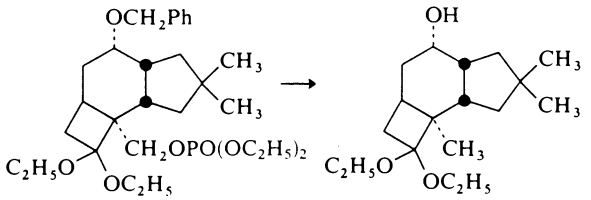

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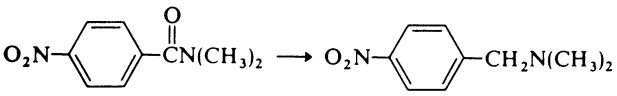

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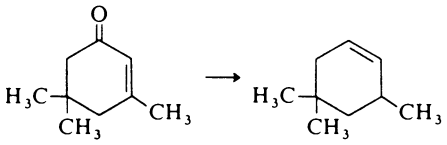
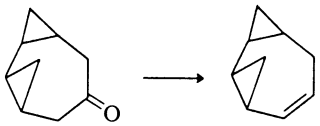
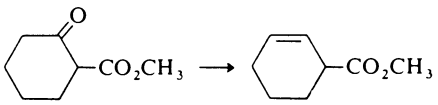


(l)

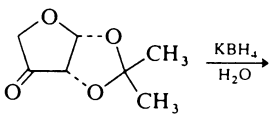


(m)

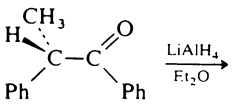


4. Predict the stereochemistry of the products from the following reactions and justify your prediction:

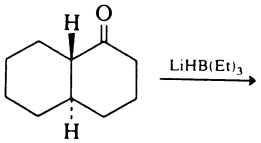
(a)



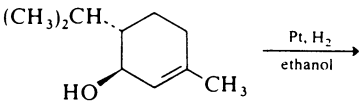
(b)



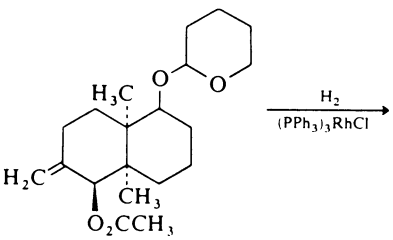
(c)

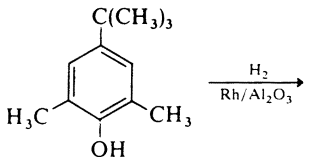


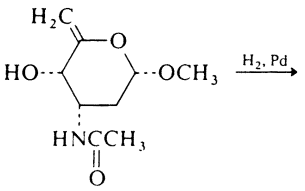
(d)



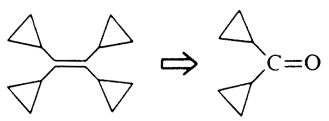
(e)

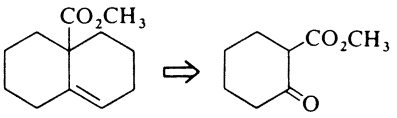


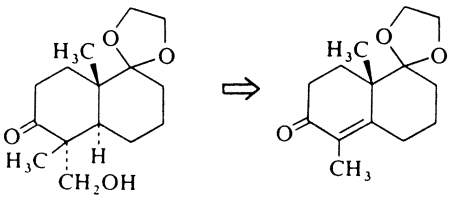
(f) 

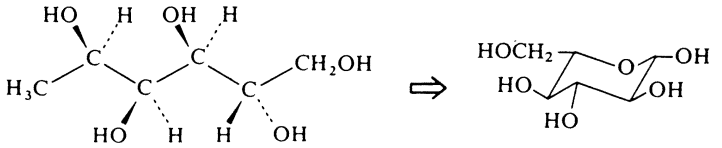
(g) 

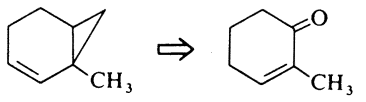
5. Suggest a convenient method for carrying out the following syntheses. The compound on the left is to be synthesized from the one on the right (retrosynthetic notation). No more than three steps should be necessary.

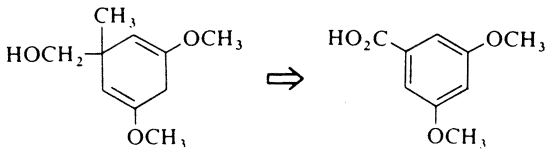
(a) 

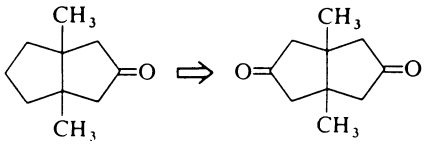
(b) 

(c) 

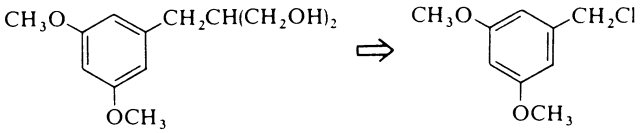
(d) 

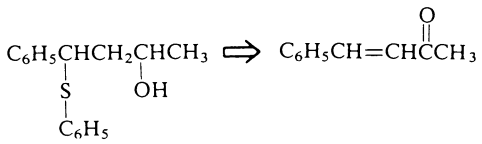
(e) 

(f) 

(g) 

(h) *meso*-$(CH_3)_2CHCHCHCH(CH_3)_2$ ⇨ $(CH_3)_2CHCO_2CH_3$
HO OH

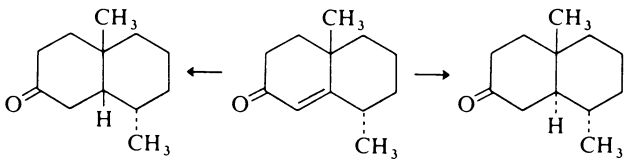
(i) 

(j) 

6. Offer an explanation to account for the observed differences in rate which are described.
   (a) $LiAlH_4$ reduces the ketone camphor about 30 times faster than does $NaAlH_4$.
   (b) The rate of reduction of camphor by $LiAlH_4$ is decreased by a factor of about 4 when a crown ether is added to the reaction mixture.
   (c) For reduction of cyclohexanones by lithium tri-*t*-butoxyaluminum hydride, the addition of one methyl group at C-3 has little effect on the rate but a second group has a large effect. The addition of a third methyl group at C-5 has no effect. The effect of a fourth group is also rather small.

	Rate:
cyclohexanone	439
3-methylcyclohexanone	280
3,3-dimethylcyclohexanone	17.5
3,3,5-trimethylcyclohexanone	17.4
3,3,5,5-tetramethylcyclohexanone	8.9

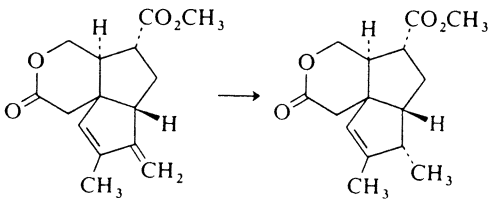
7. Suggest reaction conditions appropriate for stereoselectively converting the octalone shown to each of the diastereomeric decalones.



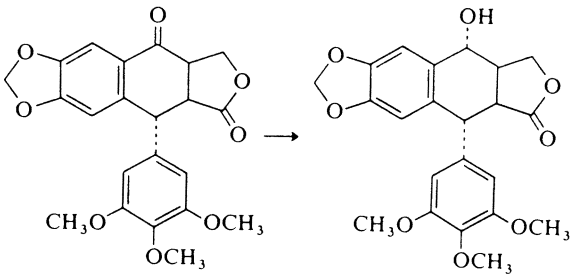
8. The fruit of a shrub which grows in Sierra Leone is very toxic and has been used as a rat poison. The toxic principle has been identified as *Z*-18-fluoro-9-octadecenoic acid. Suggest a synthesis for this material from 8-fluorooctanol, 1-chloro-7-iodoheptane, acetylene, and any other necessary organic or inorganic reagents.

9. Each of the following molecules contains more than one potentially reducible group. Indicate a reducing agent which would be suitable for effecting the desired selective reduction. Explain the basis for the expected selectivity.

(a)



(b)



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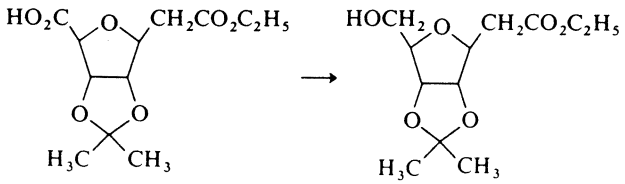
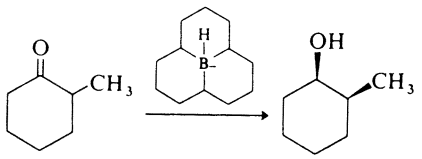
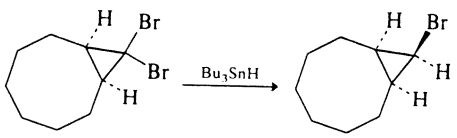


10. Explain the basis of the observed stereoselectivity for the following reductions:

(a)



(b)



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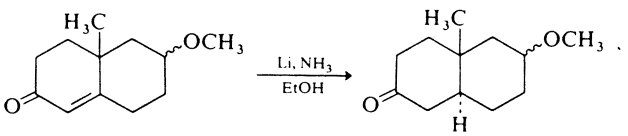
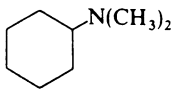
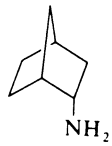
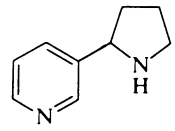


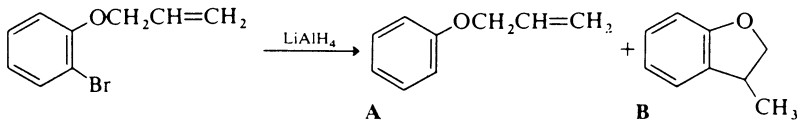
11. A valuable application of sodium cyanoborohydride is in the synthesis of amines by reductive amination. What combination of carbonyl and amine components would you choose to prepare the following amines by this route? Explain your choices.

(a) 

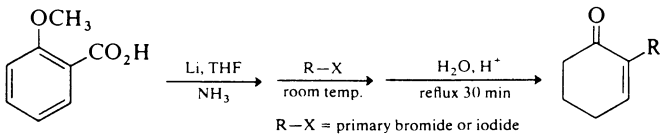
(b) 

(c) 

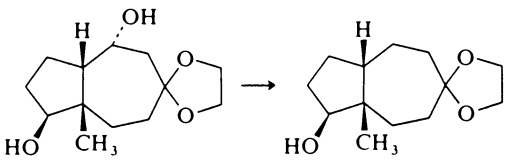
12. The reduction of *o*-bromophenyl allyl ether by $LiAlH_4$ has been studied in several solvents. In ether two products are formed. The ratio A:B increases with increasing $LiAlH_4$ concentration. When $LiAlD_4$ is used as the reductant, about half of the product **B** is a monodeuterated derivative. Provide a mechanistic rationale for these results. What is the most likely location of the deuterium atom in the deuterated product? Why is the product not completely deuterated?



13. A simple synthesis of 2-substituted cyclohexanones has been developed. Although the yields are only 25–30%, it is carried out as a "one-pot" process using the sequence of reactions shown below. Explain the mechanistic basis of this synthesis and identify the intermediate present after each stage of the reaction.



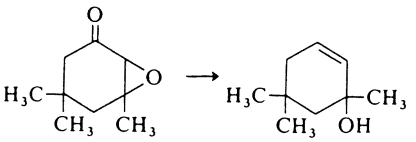
14. Birch reduction of 3,4,5-trimethoxybenzoic acid gives in 94% yield a dihydrobenzoic acid which bears only *two* methoxy substituents. Suggest a plausible structure for this product based on the mechanism of the Birch reduction.
15. In a multistep synthetic sequence it was necessary to remove selectively one of two secondary hydroxyl groups.

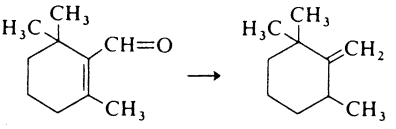


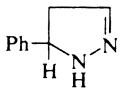
Consider several (at least three) methods by which this transformation might be accomplished. Discuss the relative merits of the various possibilities and recommend one as the most likely to succeed or most convenient.

16. Wolff–Kishner reduction of ketones that bear other functional groups sometimes give products other than the corresponding methylene compound. Some examples are given. Indicate a mechanism for each of the reactions.

(a) $(CH_3)_3CC(=O)CH_2OPh \longrightarrow (CH_3)_3CCH{=}CH_2$

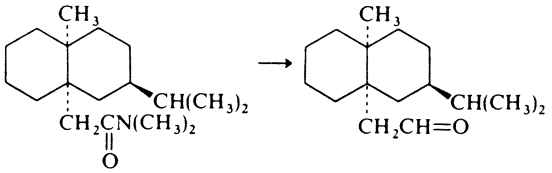
(b) 

(c) 

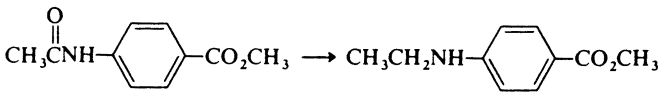
(d) $PhCH{=}CHCH{=}O \rightarrow$ 

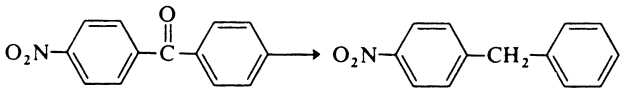
17. Suggest reagents and reaction conditions that would be suitable for each of the following selective or partial reductions:

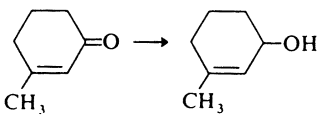
(a) $HO_2C(CH_2)_4CO_2C_2H_5 \rightarrow HOCH_2(CH_2)_4CO_2C_2H_5$

(b) 

(c) $CH_3C(=O)(CH_2)_2CO_2C_8H_{17} \rightarrow CH_3(CH_2)_3CO_2C_8H_{17}$

(d) 

(e) 

(f) 

6

Organometallic Reagents

The use of organometallic reagents in organic synthesis had its beginning around 1900 with the work of Victor Grignard, who discovered that alkyl and aryl halides reacted with magnesium metal to give homogeneous solutions. These "Grignard reagents" proved to be reactive carbon nucleophiles and have remained very useful synthetic reagents since that time. Organolithium reagents came into synthetic use somewhat later. In the last 20 years the number of useful synthetic reactions involving metal ions and organometallic compounds has expanded enormously. Certain of the transition metals, such as copper, palladium, and nickel, have gained important places in synthetic methodology. In addition to providing reagents for organic synthesis, the systematic study of the reaction of organic compounds with metal ions has created a large number of organometallic compounds, many with unique structures and reactivity. We shall consider here first the reagents such as the Grignard reagents and organolithium compounds. The role of transition metals in organic synthesis will then be given attention. The final section of the chapter illustrates briefly a few typical organometallic compounds.

6.1. Organic Derivatives of Group I and II Metals

6.1.1. Preparation and Properties

The organic derivatives of lithium and magnesium are the most important of the group I and II organometallics. The metals in these two groups are the most electropositive of the elements. The polarity of the metal–carbon bond is such as to place high electron density on carbon. This electronic distribution is responsible for the strong nucleophilicity and basicity that characterize these compounds. As

will be discussed in detail below, both Grignard reagents and organolithium compounds react rapidly with most carbonyl groups to give addition products.

$$R{-}M + R'_2C{=}O \rightarrow R{-}\underset{\displaystyle R'}{\overset{\displaystyle O^-M^+}{\underset{|}{\overset{|}{C}}}}{-}R'$$

The discovery by Grignard that organic halides react with metallic magnesium to give nucleophilic organomagnesium compounds was a landmark in organic synthesis. The reaction of a halide with metallic magnesium in diethyl ether remains the principal method of synthesis. The order of reactivity is RI > RBr > RCl.

$$RX + Mg \rightarrow RMgX$$

Solutions of some Grignard reagents such as methylmagnesium bromide, ethylmagnesium bromide, and phenylmagnesium bromide are available commercially. Some Grignard reagents are formed in tetrahydrofuran more rapidly than in ether. This is true of vinyl Grignard reagents, for example.[1] The preference for ether solvents is a result of the excellent solubility of Grignard reagents in ethers. This solubility is the result of strong Lewis acid–base complex formation between the ether molecules and the magnesium atom. The ether molecules are held quite

$$R{-}\underset{\displaystyle OR'_2}{\overset{\displaystyle Br}{\underset{|}{\overset{|}{Mg}}}}{\leftarrow}OR'_2$$

tightly in the magnesium coordination sphere. For example, phenylmagnesium bromide has been shown by X-ray methods to retain the coordinated ether molecules in the crystalline state.[2]

Halides that are unreactive toward the usual magnesium shavings can be induced to react by using an extremely reactive form of magnesium which is obtained by reducing magnesium salts with sodium or potassium metal.[3] Even fluorides, which are normally unreactive, form Grignard reagents under these conditions.

The mechanism of the Grignard reaction has not been specified precisely. The reaction takes place at the metal surface. One likely mechanism commences with a one-electron transfer,[4] followed by rapid recombination of the organic group with a magnesium ion. The carbon–bromine bond must break prior to or during the reaction with magnesium.

$$R{-}Br + Mg \rightarrow R{-}Br^{\cdot -} + Mg(I)$$

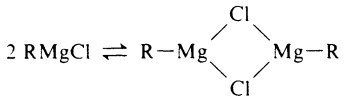
$$R{-}Br^{\cdot -} + Mg(I) \rightarrow RMgBr$$

1. D. Seyferth and F. G. A. Stone, *J. Am. Chem. Soc.* **79**, 515 (1957); H. Normant, *Adv. Org. Chem.* **2**, 1 (1960).
2. G. D. Stucky and R. E. Rundle, *J. Am. Chem. Soc.* **85**, 1002 (1963).
3. R. D. Rieke and S. E. Bales, *J. Am. Chem. Soc.* **96**, 1775 (1974); R. D. Rieke, *Acc. Chem. Res.* **10**, 301 (1977).
4. H. R. Rogers, C. L. Hill, Y. Fujuwara, R. J. Rogers, H. L. Mitchell, and G. M. Whitesides, *J. Am. Chem. Soc.* **102**, 217 (1980).

The familiar designation RMgX is basically a correct structural representation for most Grignard reagents in ether solution, but an equilibrium exists with magnesium bromide and the dialkylmagnesium. The position of the equilibrium depends upon the solvent and the identity of the specific organic group, but lies far to the left in ether solvents for simple aryl-, alkyl-, and alkenylmagnesium halides.

$$2RMgX \rightleftharpoons R_2Mg + MgX_2$$

Solutions of organomagnesium compounds in diethyl ether contain aggregated species.[5] Dimers predominate in ether solutions of alkylmagnesium chlorides. The



corresponding bromides and iodides show concentration-dependent behavior; in very dilute solutions, they exist as monomers. In tetrahydrofuran, there is less tendency to aggregate, and several alkyl and aryl Grignard reagents have been found to be monomeric in this solvent.

Most simple organolithium reagents can also be prepared by reaction of the appropriate halide with lithium metal. The simple alkyllithium reagents exist mainly as hexamers in hydrocarbon solvents.[6] In ethers the evidence indicates that tetramers are dominant.[7] The tetramers, in turn, are solvated with ether molecules.[8] Certain highly hindered alkyllithiums have been observed to be more reactive than simpler alkyl systems. This has been attributed to steric hindrance, which prevents the formation of the tetramer. Higher reactivity is generally associated with the less-aggregated species.[9]

$$R{-}X + 2Li \rightarrow RLi + LiX$$

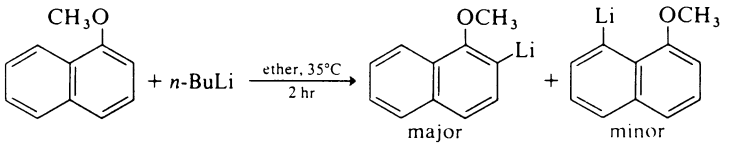
There are three other methods that are especially useful for preparing organolithium reagents. The first of these is hydrogen–metal exchange or metalation. This reaction is the usual method preparing alkynylmagnesium and alkynyllithium reagents. The reaction depends on the relative acidity of a hydrogen bound to *sp* carbon.

$$H{-}C{\equiv}C{-}R + R'MgBr \rightarrow BrMgC{\equiv}C{-}R + R'{-}H$$
$$H{-}C{\equiv}C{-}R + R'Li \rightarrow LiC{\equiv}C{-}R + R'{-}H$$

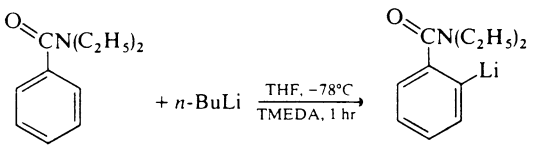
5. E. C. Ashby and M. B. Smith, *J. Am. Chem. Soc.* **86**, 4363 (1964); F. W. Walker and E. C. Ashby, *J. Am. Chem. Soc.* **91**, 3845 (1969).
6. G. Fraenkel, W. E. Beckenbaugh, and P. P. Yang, *J. Am. Chem. Soc.* **98**, 6878 (1976); G. Fraenkel, M. Henrichs, J. M. Hewitt, B. M. Su, and M. J. Geckle, *J. Am. Chem. Soc.* **102**, 3345 (1980).
7. H. L. Lewis and T. L. Brown, *J. Am. Chem. Soc.* **92**, 4664 (1970); P. West and R. Waack, *J. Am. Chem. Soc.* **89**, 4395 (1967); T. L. Brown, *Adv. Organometal. Chem.* **3**, 365 (1965).
8. P. D. Bartlett, C. V. Goebel, and W. P. Weber, *J. Am. Chem. Soc.* **91**, 7425 (1969).
9. W. H. Glaze and C. H. Freeman, *J. Am. Chem. Soc.* **91**, 7198 (1969).

Scheme 6.1. Organolithium

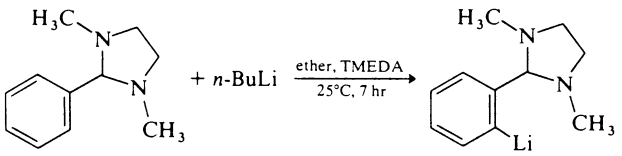
1[a]



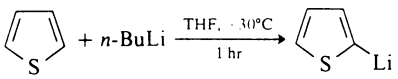
2[b]



3[c]



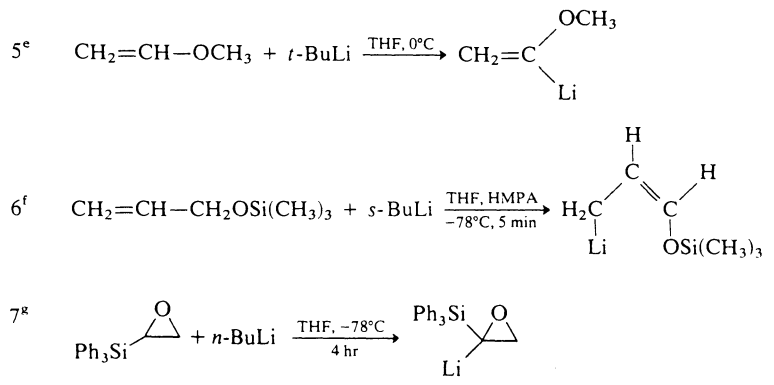
4[d]



Although of limited utility for other Grignard reagents, metalation is an important means of preparing a variety of lithium compounds. The position of metalation is determined by the relative acidity of the available hydrogens and the directing effect of substituent groups. Benzyl and allyl hydrogens are relatively reactive toward lithiation because of resonance stabilization of the resulting anion. Substituents which can complex the metal atom, such as sulfonyl, alkoxy, and amido have a powerful effect on the position of lithiation in aromatic compounds.[10] In heterocyclic compounds the preferred site for lithiation is usually adjacent to the heteroatom. Scheme 6.1 gives some examples of the preparation of organolithium compounds by this method.

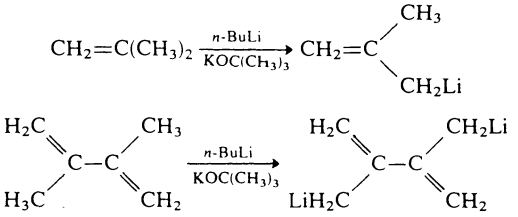
Reaction conditions can be modified to accelerate the rate of lithiations when necessary. Addition of tertiary amines, especially tetramethylethylenediamine (TMEDA), accelerates lithiation, probably by chelating the lithium metal and promoting the formation of monomeric reagent.[11] Hydrocarbons lacking directing substituents are not usually very reactive toward metalation but it has been found that a mixture of *n*-butyllithium and potassium *t*-butoxide[12] is sufficiently reactive

10. D. W. Slocum and C. A. Jennings, *J. Org. Chem.* **41**, 3653 (1976); H. W. Gschwend and H. R. Rodriguez, *Org. React.* **26**, 1 (1979).
11. G. G. Eberhardt and W. A. Butte, *J. Org. Chem.* **29**, 2928 (1964); R. West and P. C. Jones, *J. Am. Chem. Soc.* **90**, 2656 (1968); S. Akiyama and J. Hooz, *Tetrahedron Lett.* 4115 (1973).
12. L. Lochmann, J. Pospisil, and D. Lim, *Tetrahedron Lett.*, 257 (1966).



a. B. M. Graybill and D. A. Shirley, *J. Org. Chem.* **31**, 1221 (1966).
b. P. A. Beak and R. A. Brown, *J. Org. Chem.* **42**, 1823 (1977); **44**, 4463 (1979).
c. T. D. Harris and G. P. Roth, *J. Org. Chem.* **44**, 2004 (1979).
d. E. Jones and I. M. Moodie, *Org. Synth.* **50**, 104 (1970).
e. J. E. Baldwin, G. A. Höfle, and O. W. Lever, Jr., *J. Am. Chem. Soc.* **96**, 7125 (1974).
f. W. C. Still and T. L. Macdonald, *J. Org. Chem.* **41**, 3620 (1976).
g. J. J. Eisch and J. E. Galle, *J. Am. Chem. Soc.* **98**, 4646 (1976).

to give allyl anions from alkenes such as isobutene and 2,3-dimethyl-1,3-butadiene.[13]

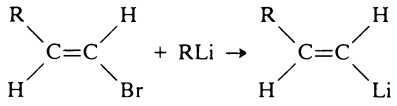


Metal–halogen exchange is a second important method for preparation of organolithium reagents. This reaction proceeds in the direction of forming the more

$$RX + R'Li \rightarrow RLi + R'X$$

stable organolithium reagent. Thus, by use of *n*-butyllithium or *t*-butyllithium, organolithium compounds with adjacent stabilizing substituents are readily prepared. This route is particularly useful for converting alkenyl halides to the corresponding lithium reagents, since the halides react only sluggishly with lithium metal. The reaction proceeds to give an alkenyllithium reagent because of the higher electronegativity of sp^2 carbon, compared to sp^3 carbon.

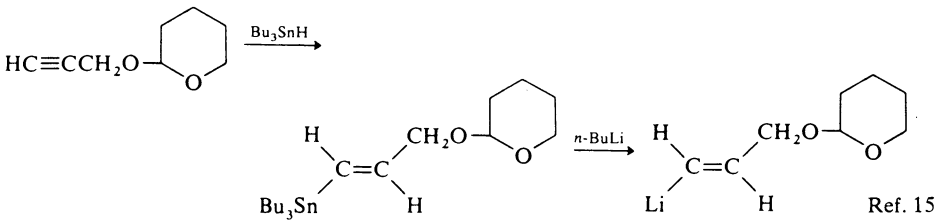
13. M. Schlosser and J. Hartmann, *Angew. Chem. Int. Ed.* **12**, 508 (1973); J. J. Bahl, R. B. Bates, and B. Gordon III, *J. Org. Chem.* **44**, 2290 (1979); M. Schlosser and G. Rauchschwalbe, *J. Am. Chem. Soc.* **100**, 3258 (1978).



Metal–halogen exchange is a rapid reaction and can usually be carried out at −60 to −120°C. This makes it possible to prepare aryllithium compounds containing functional groups such as cyano and nitro which would be reactive with the organolithium reagent at higher temperatures. Entries 6 and 7 in Scheme 6.2 are examples.

A third useful method of preparing organolithium reagents involves metal–metal exchange. The reaction between two organometallic reagents will proceed in the direction of placing the more electropositive metal on the more electronegative carbon position. Vinyltin reagents are particularly significant from a synthetic point of view, since they can be readily prepared from acetylenes. Organotin

$$Ph_3SnCH_2CH{=}CH_2 + PhLi \rightarrow CH_2{=}CHCH_2Li + Ph_4Sn \qquad \text{Ref. 14}$$



Ref. 15

$$\underset{\underset{SnBu_3}{|}}{RCHOR'} + nBuLi \xrightarrow{-78°C} \underset{\underset{Li}{|}}{RCHOR'} \qquad \text{Ref. 16}$$

$$R_2NCH_2SnBu_3 + nBuLi \xrightarrow{0°C} R_2NCH_2Li \qquad \text{Ref. 17}$$

reagents have also been useful in preparation of α-lithioethers and α-lithioamines. The precursor stannanes are available from easily accessible starting materials.

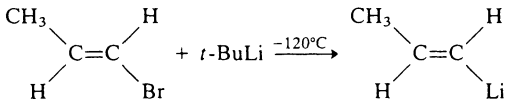
$$RCH{=}O + Bu_3SnLi \rightarrow \underset{\underset{SnBu_3}{|}}{RCH{-}O^-} \xrightarrow{R'X} \underset{\underset{SnBu_3}{|}}{RCHOR'}$$

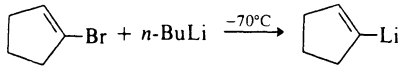
$$R_2NCH_2SPh + Bu_3SnLi \rightarrow R_2NCH_2SnBu_3$$

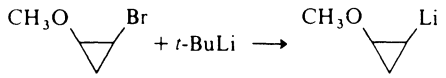
The preparation of alkyllithiums and alkylmagnesium bromides[18] from the alkyl halides by reaction with the metals occurs with loss of stereochemical integrity at the site of the reaction. Stereoisomeric halides give rise to organometallics of identical composition. Cyclopropyl halides and vinyl halides are converted to

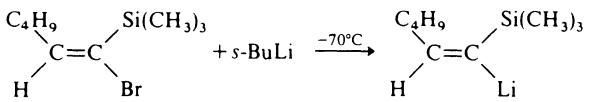
14. D. Seyferth and M. A. Weiner, *Org. Synth.* **V**, 452 (1973).
15. E. J. Corey and R. H. Wollenberg, *J. Org. Chem.* **40**, 2265 (1975).
16. W. C. Still, *J. Am. Chem. Soc.* **100**, 1481 (1978).
17. D. J. Peterson, *J. Am. Chem. Soc.* **93**, 4027 (1971).
18. W. H. Glaze and C. M. Selman, *J. Org. Chem.* **33**, 1987 (1968); W. H. Glaze and C. M. Selman, *J. Organometal. Chem.* **11**, p. 3 (1968).

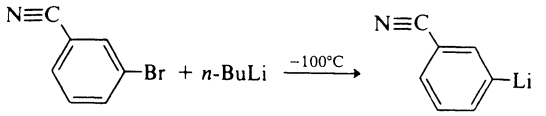
Scheme 6.2. Organolithium Reagents by Halogen–Metal Exchange

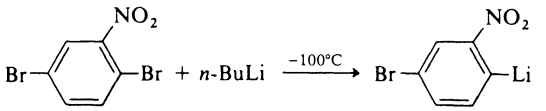
1[a] 

2[b] 

3[c] 

4[d] 

5[e] 

6[f] 

a. H. Neuman and D. Seebach, *Tetrahedron Lett.*, 4839 (1976).
b. J. Millon, R. Lorne and G. Linstrumelle, *Synthesis*, 434 (1975).
c. E. J. Corey and P. Ulrich, *Tetrahedron Lett.*, 3685 (1975).
d. R. B. Miller and G. McGarvey, *J. Org. Chem.* **44**, 4623 (1979).
e. W. E. Parham and L. D. Jones, *J. Org. Chem.* **41**, 1187 (1976).
f. W. E. Parham and R. M. Piccirilli, *J. Org. Chem.* **42**, 257 (1977).

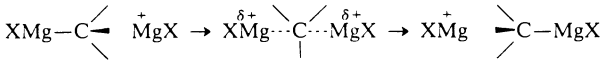
Grignard reagents with partial retention of configuration, and the reagents, once formed, are configurationally stable.[19]

Significant retention of configuration occurs when certain organolithium compounds are prepared by metal–halogen exchange. Net retention is low in the preparation of alkyllithium compounds by these methods[20] but high for cyclopropyl and vinyl systems.[21] With alkyl systems, the extent of racemization is increased in the presence of ethers. Hydrocarbons are the preferred solvents if racemization is to be avoided.

Once formed, secondary organomagnesium compounds undergo stereochemical inversion only slowly. *Endo-* and *exo*-norbornylmagnesium bromide

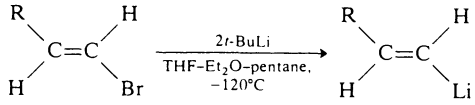
19. T. Yoshino and Y. Manabe, *J. Am. Chem. Soc.* **85**, 2860 (1963); H. M. Walborsky and A. E. Young, *J. Am. Chem. Soc.* **86**, 3288 (1964).
20. R. L. Letsinger, *J. Am. Chem. Soc.* **72**, 4842 (1950); D. Y. Curtin and W. J. Koehl, Jr., *J. Am. Chem. Soc.* **84**, 1967 (1962).
21. H. M. Walborsky, F. J. Impastato, and A. E. Young, *J. Am. Chem. Soc.* **86**, 3283 (1964); D. Seyferth and L. G. Vaughan, *J. Am. Chem. Soc.* **86**, 883 (1964); M. J. S. Dewar and J. M. Harris, *J. Am. Chem. Soc.* **91**, 3652 (1969).

require one day at room temperature to equilibrate.[22] NMR studies have also demonstrated that inversion of configuration at the carbon–magnesium bond is slow on the NMR time scale even up to 170°C.[23] In contrast, the inversion of configuration in primary alkylmagnesium halides is fast.[24] The half-life for inversion of 2-methylbutylmagnesium bromide, for example, is less than a second at 25°C in ether. This difference in the primary and secondary systems may be the result of a mechanism in which inversion accompanies exchange of alkyl groups between magnesium atoms:

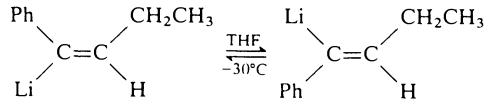


If such a bridged intermediate is required, the larger steric bulk of the secondary systems could greatly retard the reaction. Primary alkyllithium reagents also undergo rapid inversion of configuration at carbon.[25]

The preparation of vinyllithium compounds by halogen–metal exchange at low temperature occurs with retention of configuration.[26] The reaction must be carried



out at low temperature, but once formed the vinyllithium reagents are configurationally stable even at room temperature.[26] The preparation of vinyllithiums from vinyl halides and lithium metal also appears to occur with retention of configuration, at least to an extent of about 95%.[27] Because of the conjugation with the phenyl group, 1-lithio-1-phenyl-1-butene undergoes configurational equilibration more easily, especially in THF.[28]



From the point of view of synthetic planning it is important to recognize that stereochemical configuration at sp^3 carbon will not usually be preserved during

22. F. R. Jensen and K. L. Nakamaye, *J. Am. Chem. Soc.* **88**, 3437 (1966); N. G. Krieghoff and D. O. Cowan, *J. Am. Chem. Soc.* **88**, 1322 (1966).
23. E. Pechhold, D. G. Adams, and G. Fraenkel, *J. Org. Chem.* **36**, 1368 (1971).
24. G. M. Whitesides, M. Witanowski, and J. D. Roberts, *J. Am. Chem. Soc.* **87**, 2854 (1965); G. M. Whitesides and J. D. Roberts, *J. Am. Chem. Soc.* **87**, 4878 (1965); G. Fraenkel and D. T. Dix, *J. Am. Chem. Soc.* **88**, 979 (1966).
25. G. Fraenkel, W. E. Beckenbaugh, and P. P. Yang, *J. Am. Chem. Soc.* **98**, 6878 (1976).
26. N. Neumann and D. Seebach *Tetrahedron Lett.*, 4839 (1976); R. B. Miller and G. McGarvey, *J. Org. Chem.* **44**, 4623 (1979).
27. J. Millon, R. Lorne, and G. Linstrumelle, *Synthesis*, 434 (1975).
28. E. J. Panek, B. L. Neff, H. Chu, and M. G. Panek, *J. Am. Chem. Soc.* **97**, 3996 (1975).

formation of an alkyllithium or alkylmagnesium reagent. Alkenyllithium reagents, on the other hand, can be prepared stereospecifically at low temperatures and in many cases subsequent reactions with electrophiles will also be stereospecific.

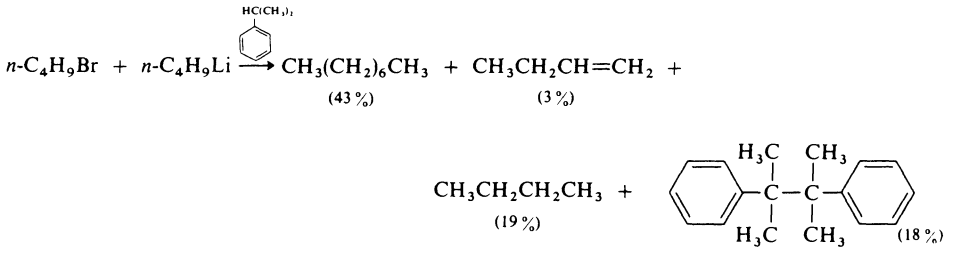
6.1.2. Reactions

The organometallic compounds of the group I and II metals are strongly basic and nucleophilic. Although the alkylation of organometallics by alkyl halides might seem to offer a general synthetic method for unsymmetrical hydrocarbons, the utility of this reaction is limited in saturated systems. A very old reaction of this type is the *Wurtz coupling* of halides by sodium metal, in which an organosodium compound has been supposed to be an intermediate. Recent studies have indicated that these couplings involve radicals generated by redox processes, rather than S_N2

$$RX + Na \rightarrow R^{\cdot} + Na^{+} + X^{-}$$

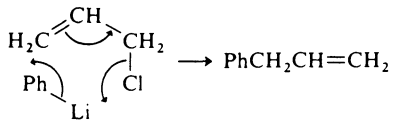
$$2R^{\cdot} \rightarrow R{-}R$$

substitutions.[29] More extensive studies have been carried out on the organolithium–alkyl halide reaction. Several results from simple alkyllithium–alkyl halide coupling reactions lead to the conclusion that radicals are involved. Intermediate radicals have been detected spectroscopically by ESR and CIDNP techniques.[30] The simple alkylation product is accompanied by products formed by disproportionation and symmetrical coupling of the postulated radical intermediates.[31]

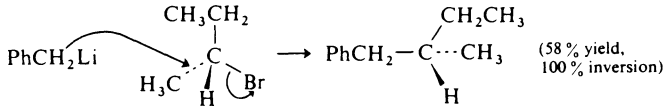


With allyl halides, a cyclic concerted mechanism has been proposed.[32] Support for this mechanism includes an isotope labeling study which showed that when allyl chloride-1-^{14}C reacts with phenyllithium, about three fourths of the product has the labeled carbon at the terminal methylene group.

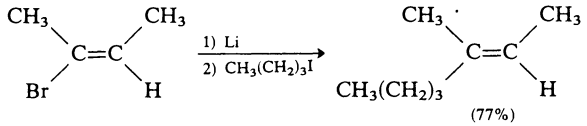
29. J. F. Garst and R. H. Cox, *J. Am. Chem. Soc.* **92**, 6389 (1970).
30. G. A. Russell and D. W. Lamson, *J. Am. Chem. Soc.* **91**, 3967 (1969); H. R. Ward and R. G. Lawler, *J. Am. Chem. Soc.* **89**, 5518 (1967); A. R. Lepley and R. L. Landau, *J. Am. Chem. Soc.* **91**, 748 (1969); H. R. Ward, R. G. Lawler, and R. A. Cooper, *J. Am. Chem. Soc.* **91**, 746 (1969).
31. D. Bryce-Smith, *J. Chem. Soc.*, 1603 (1956).
32. R. M. Magid and J. G. Welch, *J. Am. Chem. Soc.* **90**, 5211 (1968); R. M. Magid, E. C. Nieh, and R. D. Gandour, *J. Org. Chem.* **36**, 2099 (1971); R. M. Magid and E. C. Nieh, *J. Org. Chem.* **36**, 2105 (1971).



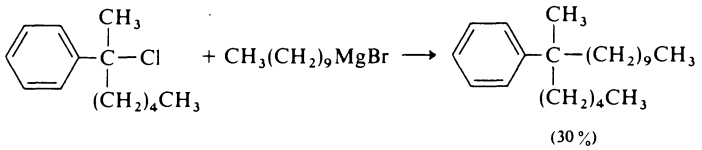
Organolithium reagents in which the carbanion is a relatively delocalized one also appear to constitute an exception to the radical-coupling mechanism. Allyllithium and benzyllithium both react with secondary alkyl bromides in fair yield,



with a high degree of inversion of configuration at the site of bromide displacement.[33] Vinyllithium reagents can be alkylated in good yields by alkyl iodides and bromides.[34]

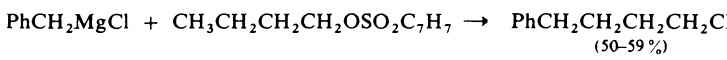


The alkylation of Grignard reagents is of some synthetic value when methyl, allyl, or benzyl halides are involved:

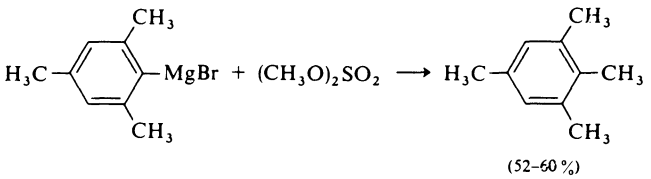


Ref. 35

Synthetically useful alkylations of Grignard reagents also occur with alkyl sulfates and sulfonates:



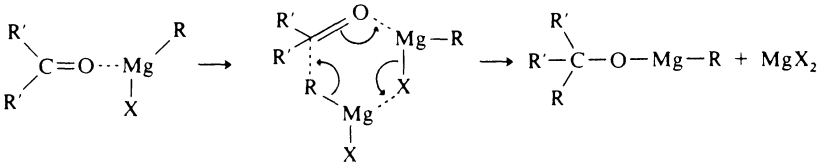
Ref. 36



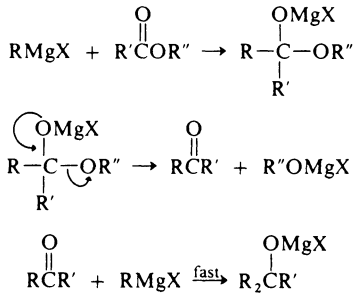
Ref. 37

33. L. H. Sommer and W. D. Korte, *J. Org. Chem.* **35**, 22 (1970).
34. J. Millon, R. Lorne, and G. Linstrumelle, *Synthesis*, 434 (1975).
35. C. F. Hobbs and W. C. Hammann, *J. Org. Chem.* **35**, 4188 (1970); R. G. Gough and J. A. Dixon, *J. Org. Chem.* **33**, 2148 (1968).
36. H. Gilman and J. Robinson, *Org. Synth.* **II**, 47 (1943).
37. L. I. Smith, *Org. Synth.* **II**, 360 (1943).

The most important type of reaction of Grignard reagents is the family of reactions involving addition to carbonyl groups. The transition state for addition of Grignard reagents is often represented as a cyclic array containing the carbonyl and two molecules of Grignard reagent. There is in fact considerable evidence for a termolecular transition state arising by attack of a Grignard reagent on a carbonyl–Grignard complex.[38]

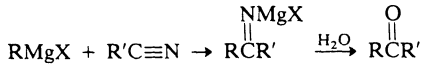


When the initial Grignard–carbonyl adduct contains a potential leaving group, this adduct breaks down and a second Grignard reagent can add. It is difficult to



control Grignard additions to esters in such a way as to provide ketones, because the ketone products are more reactive than the esters. The addition of Grignard reagents to ketones, aldehydes, and esters forms the basis for synthetic methods that can provide alcohols having a variety of structures, as summarized in Scheme 6.3.

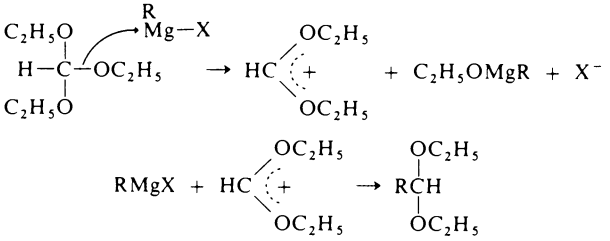
In addition, Grignard reagents are used for the synthesis of ketones via reactions with nitriles. Hydrocarbon solvents are favored for this reaction.[39] The preparation



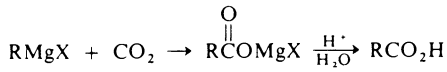
of ketones from acid chlorides can be carried out at low temperature if an excess of the acid chloride is used.[40] Tetrahydrofuran is the preferred solvent. Careful control of the reaction conditions is required to prevent formation of tertiary alcohols as competing products. 2-Pyridinethiolate esters, which are easily prepared

38. E. C. Ashby, R. B. Duke, and H. M. Neuman, *J. Am. Chem. Soc.* **89**, 1964 (1967); E. C. Ashby, *Pure Appl. Chem.* **52**, 545 (1980).
39. P. Canonne, G. B. Foscolos, and G. Lemay, *Tetrahedron Lett.*, 155 (1980).
40. F. Sato, M. Inoue, K. Oguro, and M. Sato, *Tetrahedron Lett.*, 4303 (1979).

from acid chlorides, also react with Grignard reagents to give ketones.[41] Aldehydes can be obtained by reaction with triethyl orthoformate. The addition in this case must be preceded by elimination of one of the alkoxy groups. The elimination is presumably catalyzed by magnesium acting as a Lewis acid.[42] The acetals formed

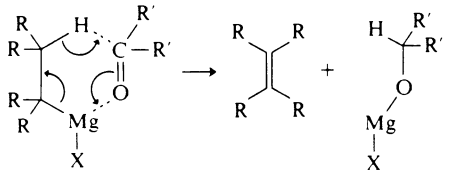


by addition are stable to the reaction conditions, but are hydrolyzed to aldehydes by aqueous acid. Carboxylic acids are obtained easily from Grignard reagents by reaction with carbon dioxide. Scheme 6.3 includes some specific examples of procedures described in *Organic Syntheses.*



Grignard reagents, it must be remembered, are quite restricted in the functional groups that can be present in either the organometallic or carbonyl compound. Alkene, ether, and acetal groups ordinarily cause no difficulty, but unprotected —OH, NH, or SH groups and carbonyl groups cannot be present.

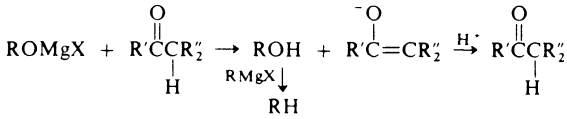
Grignard additions are sensitive to steric effects, and with hindered ketones, a competing process involving reduction of the carbonyl group is observed. A cyclic transition state similar to that proposed for Meerwein–Pondorff–Verley reduction can account for this transformation. The extent of this reaction increases with



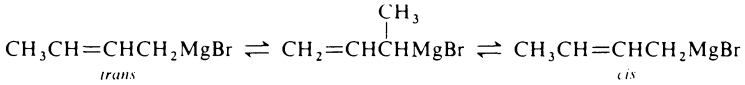
increasing steric bulk in both the ketone and the Grignard reagent. For example, no addition occurs between diisopropyl ketone and isopropylmagnesium bromide, and the reduction product diisopropylcarbinol is formed in 70% yield.[43] Reduction can be minimized in troublesome cases by using benzene or toluene as a reaction solvent.[44]

41. T. Mukaiyama, M. Araki, and H. Takei, *J. Am. Chem. Soc.* **95**, 4763 (1973); M. Araki, S. Sakata, H. Takai, and T. Mukaiyama, *Bull. Chem. Soc. Japan* **47**, 1777 (1974).
42. E. L. Eliel and F. W. Nader, *J. Am. Chem. Soc.* **92**, 584 (1970).
43. D. O. Cowan and H. S. Mosher, *J. Org. Chem.* **27**, 1 (1962).
44. P. Canonne, G. B. Foscolos, and G. Lemay, *Tetrahedron Lett.*, 4383 (1979).

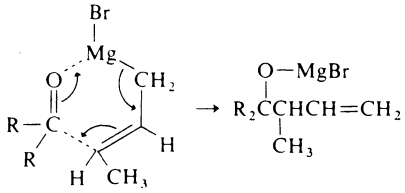
Enolization of the ketone is also occasionally a competing reaction. Since the enolate is unreactive toward Grignard addition, the ketone is recovered after hydrolysis. Enolization has been shown to be especially important when a considerable portion of the Grignard reagent is present as an alkoxide.[45] Alkoxides are formed as the addition reaction proceeds. They are also formed by oxidation processes if oxygen is not excluded. As with reduction, enolization is most seriously competitive in cases where addition is retarded by steric factors.



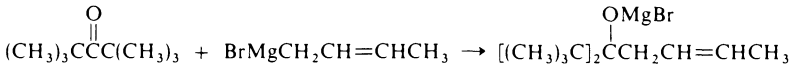
Structural rearrangements are not encountered with saturated Grignard reagents. Allyl and homoallyl systems can give products resulting from structural isomerization. 2-Butenylmagnesium bromide and 1-methylpropenylmagnesium bromide are in equilibrium in solution. Addition products are derived from the latter compound, although it is the minor component at equilibrium.[46] Addition is



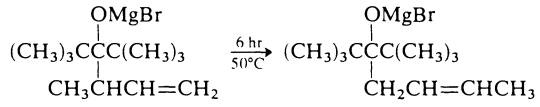
believed to occur through a cyclic transition state that leads to allylic rearrangement.



This mode of addition is supplanted by reaction at the primary carbon when highly hindered ketones are involved. This is undoubtedly the result of a steric effect.

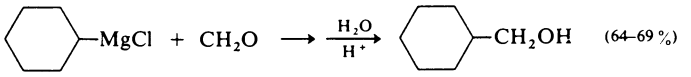


The adducts of allyl Grignard reagents to ketones can undergo isomerization to less hindered isomers by reversal of the addition step.[47]



45. H. O. House and D. D. Traficante, *J. Org. Chem.* **28**, 355 (1963).
46. R. A. Benkeser, W. G. Young, W. E. Broxterman, D. A. Jones, Jr., and S. J. Piaseczynski, *J. Am. Chem. Soc.* **91**, 132 (1969).
47. R. A. Benkeser, M. P. Siklosi, and E. C. Mozdzen, *J. Am. Chem. Soc.* **100**, 2134 (1978).

A. Primary Alcohols from Formaldehyde

1[a] 

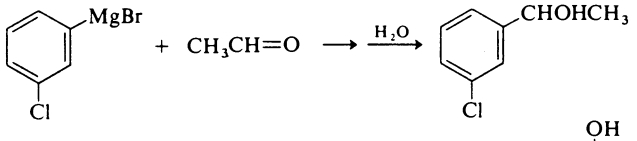
(64–69 %)

B. Primary Alcohols from Ethylene Oxide

2[b] $CH_3(CH_2)_3MgBr + H_2C\!-\!CH_2 \;(\text{O}) \longrightarrow CH_3(CH_2)_5OH$ (60–62 %)

C. Secondary Alcohols from Aldehydes

3[c] $PhCH{=}CHCH{=}O + HC{\equiv}CMgBr \xrightarrow[H^+]{H_2O} HC{\equiv}CCH(OH)CH{=}CHPh$ (58–69 %)

4[d] 

(82–85 %)

5[e] $CH_3CH{=}CHCH{=}O + CH_3MgCl \xrightarrow{H_2O} CH_3CH{=}CHCH(OH)CH_3$ (81–86 %)

6[f] $(CH_3)_2CHMgBr + CH_3CH{=}O \rightarrow (CH_3)_2CHCH(OH)CH_3$ (53–54 %)

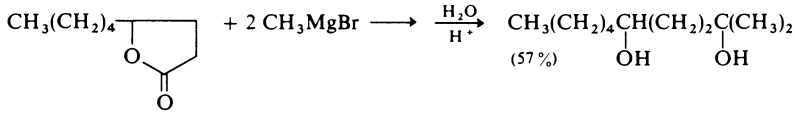
D. Secondary Alcohols from Formate Esters

7[g] $2\,CH_3(CH_2)_3MgBr + HCO_2C_2H_5 \xrightarrow[H^+]{H_2O} (CH_3CH_2CH_2CH_2)_2CHOH$ (83–85 %)

E. Tertiary Alcohols from Esters and Lactones

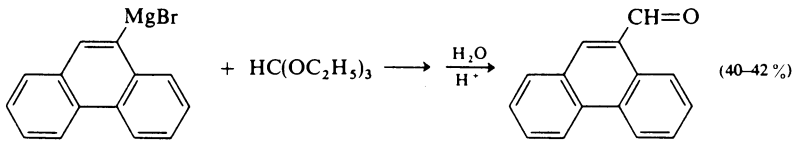
8[h] $3\,C_2H_5MgBr + (C_2H_5O)_2CO \xrightarrow[NH_4Cl]{H_2O} (C_2H_5)_3COH$ (82–88 %)

9[i] $2\,PhMgBr + PhCO_2C_2H_5 \xrightarrow{H_2O} Ph_3COH$ (89–93 %)

10[j] 

(57 %)

F. Aldehydes from Ethyl Orthoformate

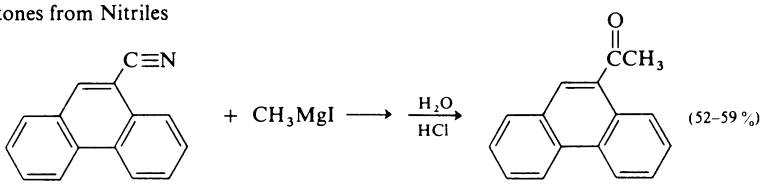
11[k] 

(40–42 %)

12[l] $CH_3(CH_2)_4MgBr + HC(OC_2H_5)_3 \xrightarrow[H^+]{H_2O} CH_3(CH_2)_4CH{=}O$ (45–50 %)

G. Ketones from Nitriles

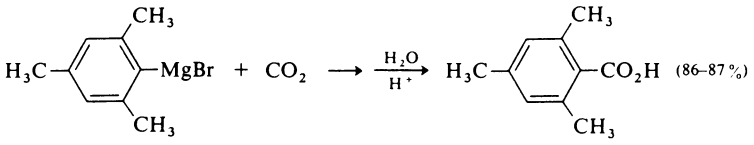
13[m]



14[n] $CH_3OCH_2C{\equiv}N + PhMgBr \xrightarrow[HCl]{H_2O} PhC(=O)CH_2OCH_3$ (71–78 %)

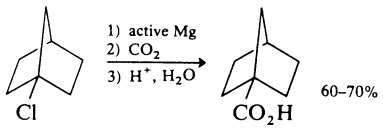
H. Carboxylic Acids by Carbonation

15[o]



16[p] $CH_3CH_2CH(MgBr)CH_3 + CO_2 \xrightarrow[H^+]{H_2O} CH_3CH_2CH(CO_2H)CH_3$ (76–86 %)

17[q]



I. Amines from Imines

18[r] $PhCH{=}NCH_3 + PhCH_2MgCl \xrightarrow{H_2O} PhCH(NHCH_3)CH_2Ph$ (96 %)

J. Olefins after Dehydration of Intermediate Alcohols

19[s] $PhCH{=}CHCH{=}O + CH_3MgBr \xrightarrow{H_2SO_4} PhCH{=}CHCH{=}CH_2$ (75 %)

20[t] $2\,PhMgBr + CH_3CO_2C_2H_5 \xrightarrow[H_2O]{H^+} Ph_2C{=}CH_2$ (67–70 %)

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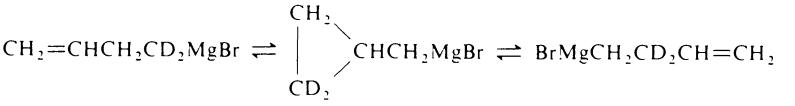
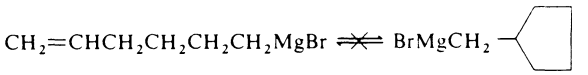
a. H. Gilman and W. E. Catlin, *Org. Synth.* **I**, 182 (1932).
b. E. E. Dreger, *Org. Synth.* **I**, 299 (1932).
c. L. Skattebøl, E. R. H. Jones, and M. C. Whiting, *Org. Synth.* **IV**, 792 (1963).
d. C. G. Overberger, J. H. Saunders, R. E. Allen, and R. Gander, *Org. Synth.* **III**, 200 (1955).
e. E. R. Coburn, *Org. Synth.* **III**, 696 (1955).
f. N. L. Drake and G. B. Cooke, *Org. Synth.* **II**, 406 (1943).
g. G. H. Coleman and D. Craig, *Org. Synth.* **II**, 179 (1943).
h. W. W. Moyer and C. S. Marvel, *Org. Synth.* **II**, 602 (1943).
i. W. E. Bachman and H. P. Hetzner, *Org. Synth.* **III**, 839 (1955).
j. J. Colonge and R. Marey, *Org. Synth.* **IV**, 601 (1963).
k. C. A. Dornfeld and G. H. Coleman, *Org. Synth.* **III**, 701 (1955).
l. G. B. Bachman, *Org. Synth.* **II**, 323 (1943).
m. J. E. Callen, C. A. Dornfeld, and G. H. Coleman, *Org. Synth.* **III**, 26 (1955).
n. R. B. Moffett and R. L. Shriner, *Org. Synth.* **III**, 562 (1955).
o. D. M. Bowen, *Org. Synth.* **III**, 553 (1955).
p. H. Gilman and R. H. Kirby, *Org. Synth.* **I**, 353 (1932).
q. R. D. Rieke, S. E. Bales, P. M. Hudnall, and G. S. Poindexter, *Org. Synth.* **59**, 85 (1977).
r. R. B. Moffett, *Org. Synth.* **IV**, 605 (1963).
s. O. Grummitt and E. I. Becker, *Org. Synth.* **IV**, 771 (1963).
t. C. F. H. Allen and S. Converse, *Org. Synth.* **I**, 221 (1932).

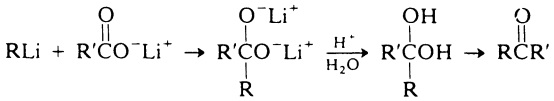
3-Butenylmagnesium bromide is in mobile equilibrium with a small amount of cyclopropylmethylmagnesium bromide. The existence of the equilibrium has been established by deuterium-labeling techniques.[48] Cyclopropylmethylmagnesium bromide[49] and cyclopropylmethyllithium[50] have been prepared by working at low temperatures. At room temperature, the ring-opened 3-butenyl reagents



are formed. When the olefinic bond is further removed, as in 5-hexenylmagnesium bromide, there is no evidence that equilibration with a cyclic form occurs.[51]



The reactivity of the alkyl- and aryllithium compounds is generally similar to that of the Grignard reagents. The alkyllithiums show higher reactivity toward addition to carbonyl groups and are less likely to undergo the competing reduction reaction. This is illustrated by the comparative reactivity of ethyllithium and ethylmagnesium bromide toward adamantanone; an 83% yield of the desired tertiary alcohol is obtained with ethyllithium, whereas the Grignard reagent gives mainly the reduction product 2-adamantanol. Even *t*-butyllithium adds smoothly to adamantanone, giving an 80% yield of the highly crowded 2-*t*-butyl-2-adamantanol.[52] Enolization (deprotonation) of ketones and aldehydes can lead to some reduction in yields.[53] Reactions involving organolithium reagents are subject to similar limitations on the types of functional groups that can be present in the reacting molecules. One reaction that is quite efficient for alkyllithium reagents but poor for Grignard reagents is the synthesis of ketones from carboxylic acids.[54] The success of this reaction depends upon the stability of the dilithio adduct that is formed. This intermediate does not break down until hydrolysis, at which time the ketone is liberated. Some examples of this reaction are shown in Section B, Scheme 6.4. A study aimed at optimizing yields in these reactions found that

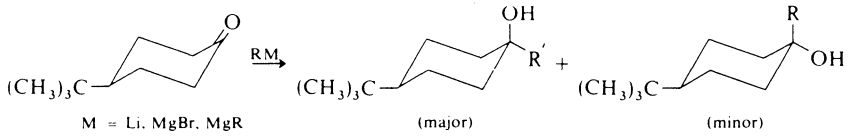


48. M. E. H. Howden, A. Maercker, J. Burdon, and J. D. Roberts, *J. Am. Chem. Soc.* **88**, 1732 (1966).
49. D. J. Patel, C. L. Hamilton, and J. D. Roberts, *J. Am. Chem. Soc.* **87**, 5144 (1965).
50. P. T. Lansbury, V. A. Pattison, W. A. Clement, and J. D. Sidler, *J. Am. Chem. Soc.* **86**, 2247 (1964).
51. R. C. Lamb, P. W. Ayers, M. K. Toney, and J. F. Garst, *J. Am. Chem. Soc.* **88**, 4261 (1966).
52. J. L. Fry, E. M. Engler, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **94**, 4628 (1972).
53. J. D. Buhler, *J. Org. Chem.* **38**, 904 (1973).
54. M. J. Jorgenson, *Org. React.* **18**, 1 (1971).

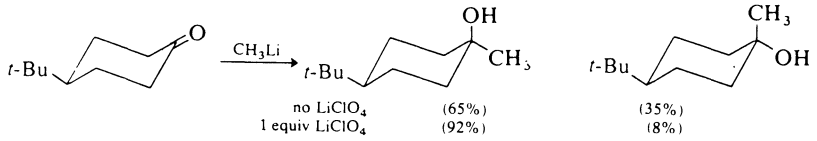
carbinol formation was a major competing process if the reaction was not carried out in such a way that all of the lithium reagent was consumed prior to hydrolytic workup.[55] This results from very fast conversion of the hydrated ketone to the ketone which evidently then captures unreacted lithium reagent.

Scheme 6.4 summarizes some examples of the important synthetic reactions in which organolithium reagents act as nucleophiles. In addition to this type of reactivity, the lithium reagents have enormous importance in synthesis as bases or lithiating reagents. In this context, the commercially available methyl, butyl, and *t*-butyl reagents are used most frequently.

The stereochemistry of the addition of methylmagnesium bromide, dimethylmagnesium, and methyllithium to various cyclohexanone derivatives has been studied.[56] Although the stereoselectivity is usually not high, there is generally a preference for attack from the equatorial direction to give the axial alcohol; this preference for equatorial attack increases as the size of the alkyl group increases. Generalization from these results suggests that steric factors govern the direction of addition of organometallic compounds to carbonyl groups. Bicyclic ketones also



react with organolithium and organomagnesium reagents to give the products of addition from the less hindered side of the carbonyl group. With alkyllithium reagents added salts can improve the stereoselectivity. For example, one equivalent of lithium perchlorate changes the ratio in favor of addition from the equatorial direction when methyllithium is added to 4-*t*-butylcyclohexanone.[57]



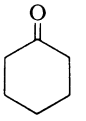
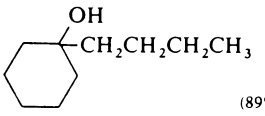
The stereochemistry of addition of organometallic reagents to acyclic carbonyl compounds parallels to a considerable extent the behavior of the hydride reducing agents as discussed in Section 5.2. Thus early studies established the behavior which is summarized by the statement which has come to be known as "Cram's rule." This statement, put forward as an empirical generalization, predicts the preferential addition of organometallic reagents from the less hindered side of a conformation which places the carbonyl oxygen and the largest α-substituent *anti*.[58] Subsequent

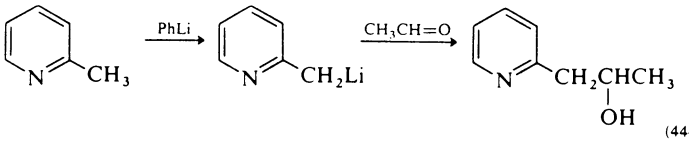
55. R. Levine, M. J. Karten, and W. M. Kadunce, *J. Org. Chem.* **40**, 1770 (1975).
56. E. C. Ashby and J. T. Laemmle, *Chem. Rev.* **75**, 521 (1975).
57. E. C. Ashby and S. A. Noding, *J. Org. Chem.* **44**, 4371 (1979).
58. D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.* **74**, 5828 (1952).

Scheme 6.4. Synthetic Procedures

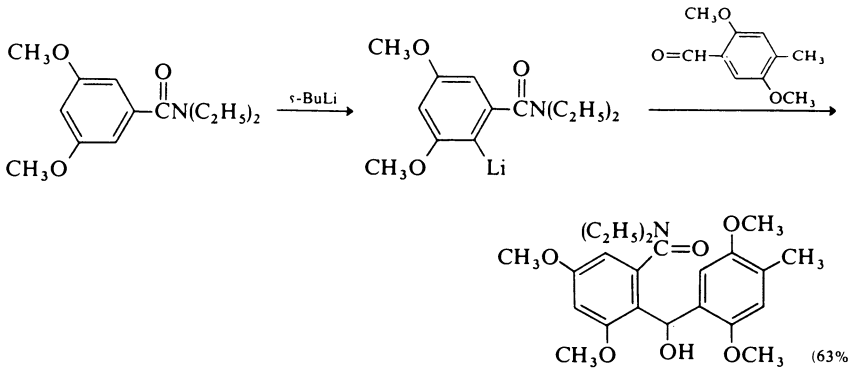
A. Reactions with Aldehydes and Ketones to give Alcohols

1[a] $CH_2{=}CHCH_2Li + CH_3\overset{O}{\overset{\|}{C}}CH_2CH(CH_3)_2 \rightarrow CH_2{=}CHCH_2\overset{OH}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}CH_2CH(CH_3)_2$ (70–72%)

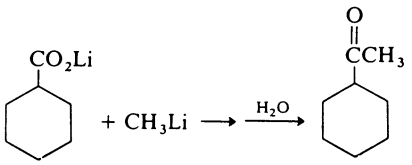
2[b] $C_4H_9Li +$   (89%)

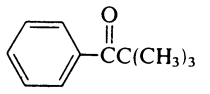
3[c]  (44–50%)

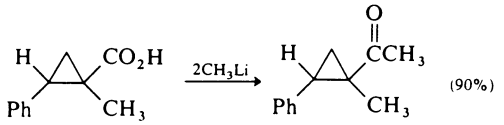
4[d] $CH_3CH{=}CHBr \xrightarrow[-120°C]{2\ t\text{-BuLi}} CH_3CH{=}CHLi \xrightarrow{PhCH=O} CH_3CH{=}CHCHPh$ (72%)
|
OH

5[e] 

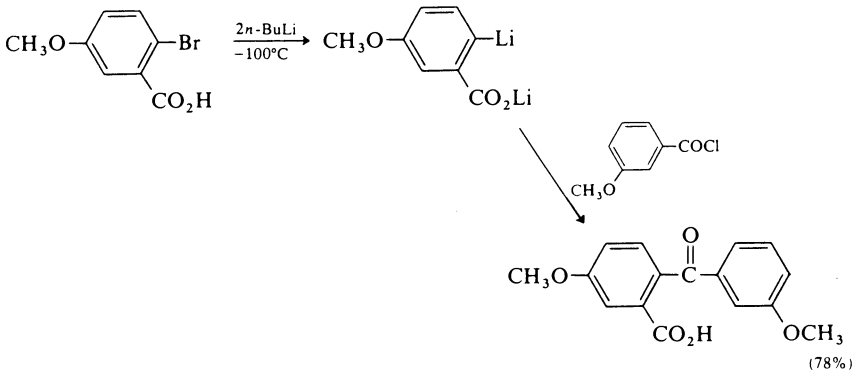
B. Reactions with Carboxylate Salts, Acid Chlorides, and Acid Anhydrides to give Ketones

6[f]  (91%)

7[g] $(CH_3)_3CCO_2H + 2PhLi \xrightarrow{H_2O}$  (65%)

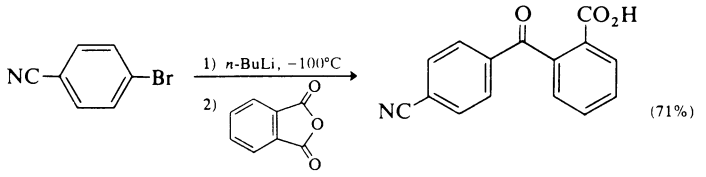
8[h]  (90%)

9[i]



(78%)

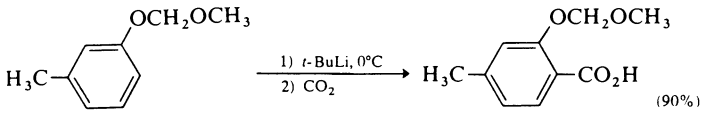
10[j]



(71%)

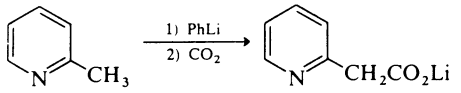
C. Reactions with Carbon Dioxide to give Carboxylic Acids

11[k]



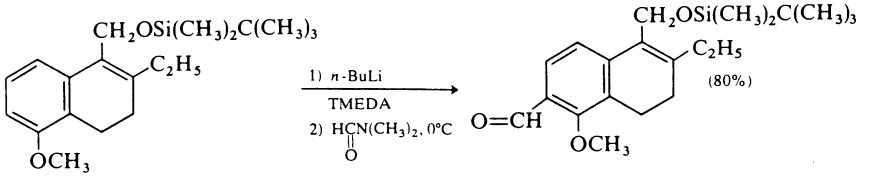
(90%)

12[l]



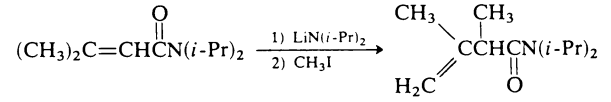
D. Other Reactions

13[m]



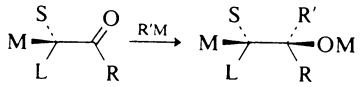
(80%)

14[n]



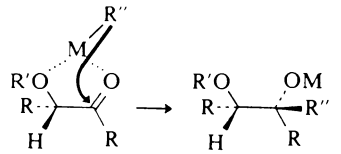
(98%)

a. D. Seyferth and M. A. Weiner, *Org. Synth.* **V**, 452 (1973).
b. J. D. Buhler, *J. Org. Chem.* **38**, 904 (1973).
c. L. A. Walter, *Org. Synth.* **III**, 757 (1955).
d. H. Neumann and D. Seebach, *Tetrahedron Lett.*, 4839 (1976).
e. S. O. deSilva, M. Watanabe, and V. Snieckus, *J. Org. Chem.* **44**, 4802 (1979).
f. T. M. Bare and H. O. House, *Org. Synth.* **49**, 81 (1969).
g. R. Levine and M. J. Karten, *J. Org. Chem.* **41**, 1176 (1976).
h. C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *J. Am. Chem. Soc.* **88**, 3347 (1966).
i. W. E. Parham, C. K. Bradsher, and K. J. Edgar, *J. Org. Chem.* **46**, 1057 (1981).
j. W. E. Parham and R. M. Piccirilli, *J. Org. Chem.* **41**, 1268 (1976).
k. R. C. Ronald, *Tetrahedron Lett.*, 3973 (1975).
l. R. B. Woodward and E. C. Kornfeld, *Org. Synth.* **III**, 413 (1955).
m. A. S. Kende and J. R. Rizzi, *J. Am. Chem. Soc.* **103**, 4247 (1981).
n. M. Majewski, G. B. Mpango, M. T. Thomas, A. Wu, and V. Snieckus, *J. Org. Chem.* **46**, 2029 (1981).

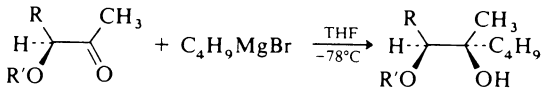


interpretation of the basis for this stereoselectivity in terms of steric, torsional, and stereoelectronic effects parallels the interpretation of hydride stereoselectivity as discussed in Section 5.2.[59]

For ketones and aldehydes where adjacent substituents permit the possibility of chelation in the transition state, the stereochemistry can often be interpreted in terms of the steric requirements of the chelated transition state. In the case of additions to α-alkoxyketones, an assumption that the α-alkoxyketone will form a chelate with the incoming metal ion and that the addition will then occur from the least hindered side of this chelate allows prediction of the stereochemistry of addition. A study based on this hypothesis revealed that Grignard reagents in THF



gave optimal stereoselectivity, the predicted product being obtained with a specificity of 100:1 for several Grignard reagents.[60]



$R = C_7H_{15}$ $\quad R' = CH_2OCH_3$, $CH_2OCH_2CH_2OCH_3$, CH_2Ph, CH_2OCH_2Ph

A similar study with β-alkoxyaldehydes revealed that neither Grignard reagents nor organolithium compounds gave high stereoselectivity in addition reactions.[61]

6.2. Organic Derivatives of Group IIb Metals

In this section, we will discuss organometallics in which the metal is cadmium,[62] mercury,[63] or zinc. Grignard reagents and organolithium compounds can be con-

59. For summaries, see P. A. Bartlett, *Tetrahedron* **36**, 2 (1980), especially pp. 15–18, and J. D. Morrison and H. S. Mosher, *Asymmetric Organic Reactions*, Prentice-Hall, Englewood Cliffs, New Jersey (1976), Chap 3.
60. W. C. Still and J. H. McDonald, III, *Tetrahedron Lett.*, 1031 (1980).
61. W. C. Still and J. A. Schneider, *Tetrahedron Lett.*, 1035 (1980).
62. P. R. Jones and P. J. Desio, *Chem. Rev.* **78**, 491 (1978).
63. R. C. Larock, *Angew. Chem. Internat. Ed. Engl.* **17**, 27 (1978).

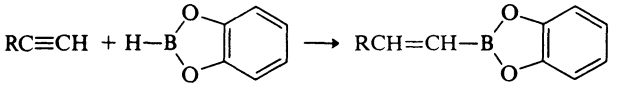
verted to these heavy-metal derivatives by reaction with salts of these metals. The reaction is driven forward by the tendency for formation of the ionic salt of the more electropositive metal. Organomercury compounds can also be prepared from

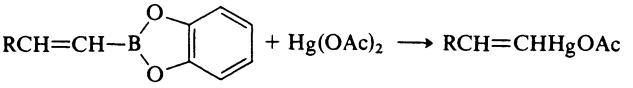
$$2RMgX + HgX_2 \rightarrow R_2Hg + 2MgX_2$$

$$2RMgX + CdX_2 \rightarrow R_2Cd + 2MgX_2$$

$$R_3B + 3Hg(O_2CCH_3)_2 \rightarrow 3RHgO_2CCH_3$$

trialkylboranes.[64] This method is also applicable to vinylmercury compounds, with acetylenes being the ultimate starting materials.[65]

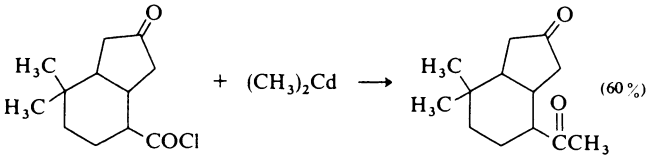




Organomercury and organocadmium compounds are much less reactive than the corresponding lithium or magnesium derivatives, and are therefore useful for certain reactions where selectivity is important. One useful synthetic application of this strategy is the preparation of ketones from acid chlorides and cadmium reagents. Cadmium reagents are useful because they are too unreactive to add to the product ketone, and the reaction therefore stops at the ketone.

$$[(CH_3)_2CHCH_2CH_2]_2Cd + ClCCH_2CH_2CO_2CH_3 \rightarrow (CH_3)_2CHCH_2CH_2COCH_2CH_2COCH_3 \quad (73\text{–}75\,\%)$$

Ref. 66a



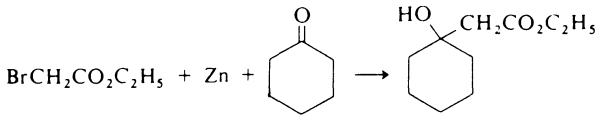
Ref. 66b

Organomercury compounds have had limited use in synthesis. One promising procedure, based on the availability of the mercury compounds from alkenes via organoboranes, is the synthesis of primary halides from alkenes. This procedure has the opposite regioselectivity to the direct ionic addition of hydrogen bromide to terminal alkenes.[67]

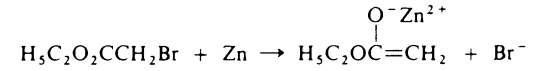
$$CH_3(CH_2)_6CH{=}CH_2 \xrightarrow[3)\ Br_2]{1)\ B_2H_6 \quad 2)\ Hg(O_2CCH_3)_2} CH_3(CH_2)_8Br \quad (69\,\%)$$

64. R. C. Larock and H. C. Brown, *J. Am. Chem. Soc.* **92**, 2467 (1970).
65. R. C. Larock, S. K. Gupta, and H. C. Brown, *J. Am. Chem. Soc.* **94**, 4371 (1972).
66a. J. Cason and F. S. Prout, *Org. Synth.* **III**, 601 (1955).
b. M. Miyano and C. R. Dorn, *J. Org. Chem.* **37**, 268 (1972).
67. J. J. Tufariello and M. M. Hovey, *J. Am. Chem. Soc.* **92**, 3221 (1970).

The most frequently used reaction involving zinc is the Reformatsky reaction, which uses zinc, ethyl bromoacetate, and carbonyl compounds to give β-hydroxyesters.[68] The reaction by which the organozinc intermediate is formed is presumably similar to that in Grignard reagent formation. The adjacent carbonyl



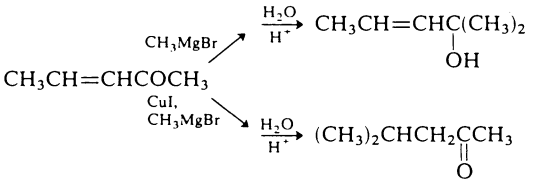
group can delocalize the negative charge on the carbon, however, so that the nucleophile is best described as a zinc enolate.[69] The enolate can then carry out a



nucleophilic attack on the carbonyl group, in the same way as an enolate formed by a deprotonation process. Substituted α-bromoesters and α-bromoketones also undergo addition to carbonyl groups in the presence of metallic zinc. Scheme 6.5 gives some examples of the Reformatsky reaction.

6.3. Organocopper Intermediates

Development of the chemistry of organocopper intermediates over the past decade has put many important new reactions at the disposal of synthetic chemists. These advances received initial impetus from the study of the catalytic effect of copper salts on reactions of Grignard reagents with α,β-unsaturated ketones.[70] It was known that while Grignard reagents normally added to the carbonyl group, the presence of a catalytic amount of Cu(I) led to conjugate addition being the dominant reaction. Mechanistic studies pointed to a very rapid reaction by an



organocopper intermediate. Further studies led to the characterization of organocopper reagents prepared by reactions of alkyllithiums with copper salts.[71]

68. R. L. Shriner, *Org. React.* **1**, 1 (1942); M. W. Rathke, *Org. React.* **22**, 423 (1975).
69. W. R. Vaughan and H. P. Knoess, *J. Org. Chem.* **35**, 2394 (1970).
70. H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.* **31**, 3128 (1966).
71. E. C. Ashby and J. J. Lin, *J. Org. Chem.* **42**, 2805 (1977); E. C. Ashby and J. J. Watkins, *J. Am. Chem. Soc.* **99**, 5312 (1977).

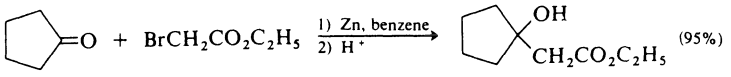
Scheme 6.5. Condensation of α-Halocarbonyl Compounds Using Zinc—The Reformatsky Reaction

1[a] $CH_3(CH_2)_3\underset{\displaystyle C_2H_5}{\underset{|}{C}}HCH{=}O + Br\underset{\displaystyle CH_3}{\underset{|}{C}}HCO_2C_2H_5 \xrightarrow[2)\ H^+]{1)\ Zn} CH_3(CH_2)_3\underset{\displaystyle C_2H_5}{\underset{|}{C}}H\overset{\displaystyle OH}{\overset{|}{C}}H\underset{\displaystyle CH_3}{\underset{|}{C}}HCO_2C_2H_5$ (87%)

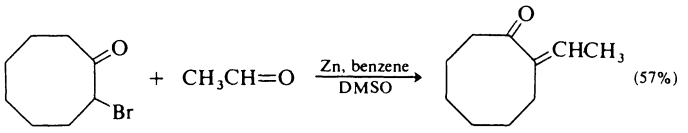
2[b] $PhCH{=}O + BrCH_2CO_2C_2H_5 \xrightarrow[2)\ H^+]{1)\ Zn} Ph\overset{\displaystyle OH}{\overset{|}{C}}HCH_2CO_2C_2H_5$ (61–64%)

3[c] $CH_3(CH_2)_4CH{=}O + BrCH_2CO_2C_2H_5 \xrightarrow[2)\ H^+]{1)\ Zn} CH_3(CH_3)_4\overset{\displaystyle OH}{\overset{|}{C}}HCH_2CO_2C_2H_5$ (50–80%)

4[d] $PhCH_2CH{=}O + BrCH_2CO_2C_2H_5 \xrightarrow[THF]{Zn,\ (MeO)_3B} PhCH_2\overset{\displaystyle OH}{\overset{|}{C}}HCH_2CO_2C_2H_5$ (90%)

5[e] 

(95%)

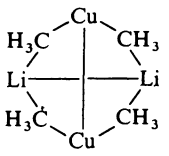
6[f] 

(57%)

a. K. L. Rinehart, Jr., and E. G. Perkins, *Org. Synth.* **IV**, 444 (1963).
b. C. R. Hauser and D. S. Breslow, *Org. Synth.* **III**, 408 (1955).
c. J. W. Frankenfeld and J. J. Werner, *J. Org. Chem.* **34**, 3689 (1969).
d. M. W. Rathke and A. Lindert, *J. Org. Chem.* **35**, 3966 (1970).
e. J. F. Ruppert and J. D. White, *J. Org. Chem.* **39**, 269 (1974).
f. T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Am. Chem. Soc.* **89**, 5727 (1967).

$$RLi + Cu(I) \rightarrow RCu + Li^+$$
$$2RLi + Cu(I) \rightarrow R_2CuLi + Li^+$$
$$3RLi + 2Cu(I) \rightarrow R_3CuLi_2 + Li^+$$

The species from the 2:1 mole ratio are known as cuprates and have been the most useful synthetic reagents. In solution lithium dimethylcuprate exists as a dimer $[LiCu(CH_3)_2]_2$,[72] but the precise structure of the reagent is not known. It is often represented as four methyl groups attached to a tetrahedron of metal atoms.

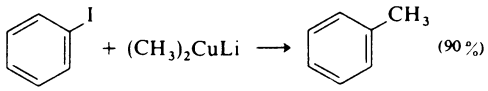


72. R. G. Pearson and C. D. Gregory, *J. Am. Chem. Soc.* **98**, 4098 (1976).

Cuprates in which two different groups are attached as copper substituents have been developed. These have important advantages in cases where one of the groups is a valuable synthetic intermediate. Scheme 6.6 presents some of these mixed cuprate reagents. In each instance the alkyl group is the most reactive ligand and undergoes the same type of reaction as do the alkyl groups in dialkylcuprates.

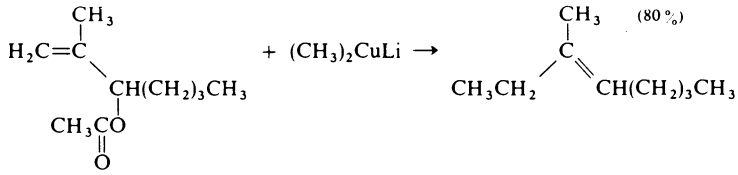
There has been much study on the effect of solvents and temperature on the preparation and reactivity of organocuprate reagents. Such studies have found, for example, that $(CH_3)_2SCuBr$, a readily prepared and purified complex of cuprous bromide, is an especially useful source of the Cu(I).[73] The temperature of preparation and solvent can also have noticeable effects on reactivity.[74] The most general description of the organocuprate reagents is that they are extremely reactive nucleophiles at soft carbon centers. The most characteristic reactions are displacement of halides and sulfonates at both sp^3 and sp^2 carbon, allylic displacements, epoxide ring opening, conjugate addition to α,β-unsaturated carbonyl compounds, and additions to acetylenes.[75] Scheme 6.7 gives some examples of each type of reaction and these are discussed separately in the paragraphs which follow.

Corey and Posner discovered that lithium dimethylcuprate could replace iodine or bromine by methyl in a variety of compounds, including aryl and vinyl halides. This method of replacement of halide by alkyl is much more satisfactory and general than displacement by Grignard or lithium reagents.[76] Allylic halides usually give



$$PhCH{=}CHBr + (CH_3)_2CuLi \rightarrow PhCH{=}CHCH_3 \quad (81\%)$$

both S_N2 and S_N2' products although $RCuBF_3$ is reported to give nearly completely the S_N2' product.[77] Allyl acetates undergo displacement with allylic shift.[78] Propargylic acetates, halides, and sulfonates react to give substantial amounts of allenes



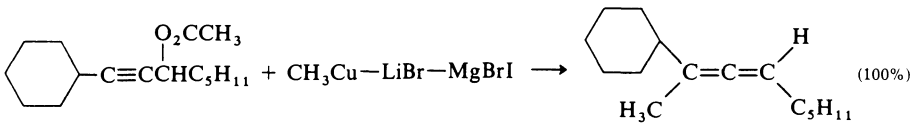
73. H. O. House, C.-Y. Chu, J. M. Wilkins, and M. J. Umen, *J. Org. Chem.* **40**, 1460 (1975).
74. R. H. Schwartz and J. San Filippo, Jr., *J. Org. Chem.* **44**, 2705 (1979).
75. G. H. Posner, *Org. React.* **19**, 1 (1972); **22**, 253 (1975); G. H. Posner, *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, New York (1980).
76. E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.* **89**, 3911 (1967).
77. K. Maruyama and Y. Yamamoto, *J. Am. Chem. Soc.* **99**, 8068 (1977).
78. R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Am. Chem. Soc.* **92**, 735 (1970); E. E. van Tamelen and J. P. McCormick, *J. Am. Chem. Soc.* **92**, 737 (1970).

Scheme 6.6. Mixed Cuprate Reagents

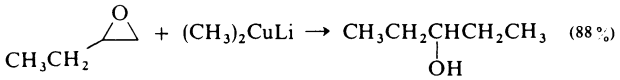
	Mixed cuprate	Reactivity
1[a]	$[RC{\equiv}C{-}Cu{-}R]Li$	Conjugate addition to α,β-unsaturated ketones and certain esters.
2[b,c]	$[ArS{-}Cu{-}R]Li$	Nucleophilic substitution and conjugate addition to unsaturated ketones. Ketones from acid chlorides.
3[b]	$[(CH_3)_3CO{-}Cu{-}R]Li$	Nucleophilic substitution and conjugate addition to unsaturated ketones.
4[d]	$[N{\equiv}C{-}Cu{-}R]Li$	Opens epoxides.
5[e]	$R{-}Cu{-}BF_3$	Conjugate addition including successful reaction with acrylate esters and acrylonitriles. S_N2' displacement of allyl halides.

a. H. O. House and M. J. Umen, *J. Org. Chem.* **38**, 3893 (1973); E. J. Corey, D. Floyd, and B. H. Lipshutz, *J. Org. Chem.* **43**, 3418 (1978).
b. G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Am. Chem. Soc.* **95**, 7788 (1973).
c. G. H. Posner and C. E. Whitten, *Org. Synth.* **55**, 123 (1975).
d. R. D. Acker, *Tetrahedron Lett.*, 3407 (1977).
e. K. Maruyama and Y. Yamamoto, *J. Am. Chem. Soc.* **99**, 8068 (1977); Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.* **100**, 3240 (1978).

resulting from attack at the acetylenic bond with shift of an electron pair.[79] The extent of allene formation versus direct substitution depends upon the particular copper reagent which is used. The highest ratio of allenic product is with CH_3Cu–LiBr–MgBrI, which is prepared by addition of methylmagnesium bromide to a 1 : 1 LiBr–CuI mixture.[80]



Saturated epoxides are opened in good yield by lithium dimethylcuprate.[81] The methyl group is introduced at the less hindered carbon of the epoxide:



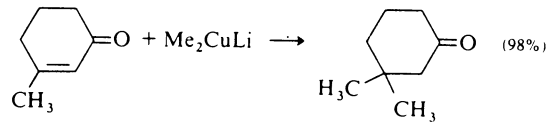
Epoxides having vinyl substituents undergo attack by the reagent at the double bond, with a concomitant shift of the double bond and ring opening.[82]

79. P. Rona and P. Crabbé, *J. Am. Chem. Soc.* **90**, 4733 (1968); R. A. Amos and J. A. Katzenellenbogen, *J. Org. Chem.* **43**, 555 (1978); D. J. Pasto, S.-K. Chou, E. Fritzen, R. H. Shults, A. Waterhouse, and G. F. Hennion, *J. Org. Chem.* **43**, 1389 (1978).
80. T. L. Macdonald, D. R. Reagan, and R. S. Brinkmeyer, *J. Org. Chem.* **45**, 4740 (1980).
81. C. R. Johnson, R. W. Herr, and D. M. Wieland, *J. Org. Chem.* **38**, 4263 (1973).
82. R. J. Anderson, *J. Am. Chem. Soc.* **92**, 4978 (1970); R. W. Herr and C. R. Johnson, *J. Am. Chem. Soc.* **92**, 4979 (1970).

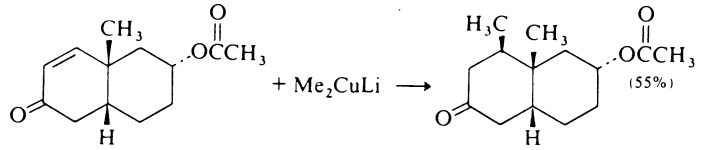
Scheme 6.7. Reactions of

A. Conjugate Addition Reactions

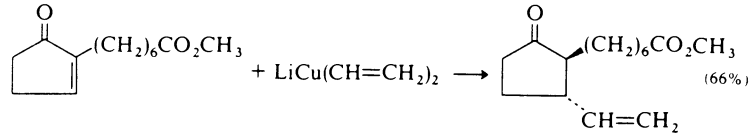
1[a]



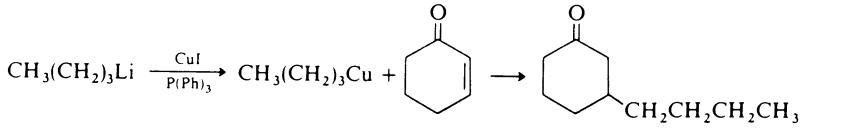
2[b]



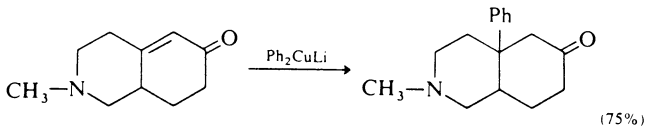
3[c]



4[d]

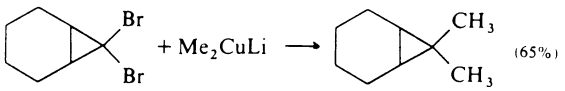


5[e]

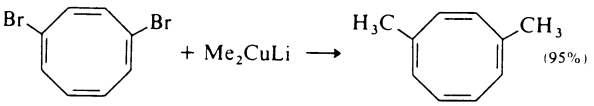


B. Halide Substitution

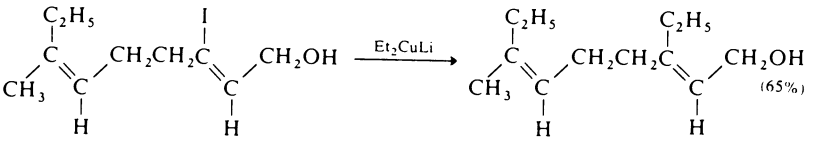
6[f]



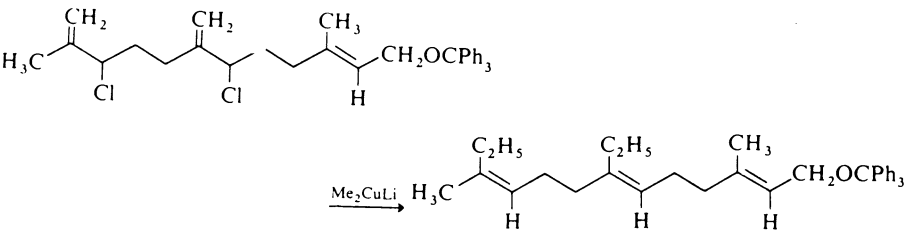
7[g]



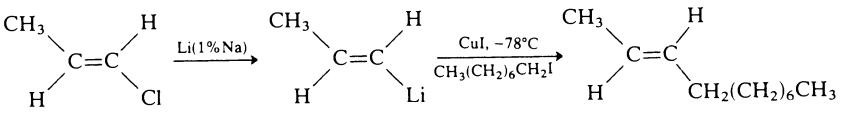
8[h]



9[i]



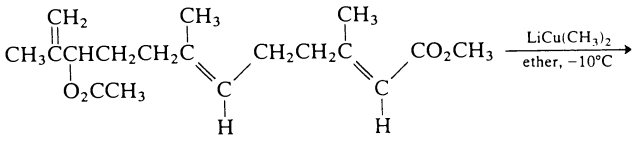
10[j]

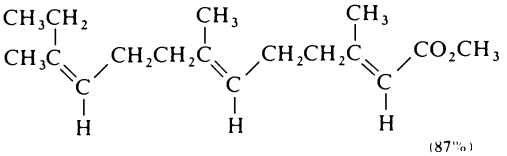


(90–93%)

C. Displacement of Allylic Acetates

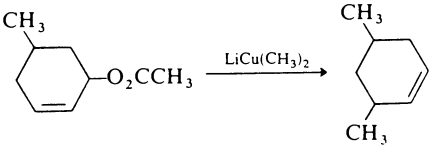
11[k]





(87%)

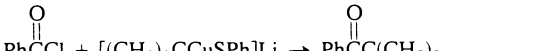
12[l]



(90–95%)

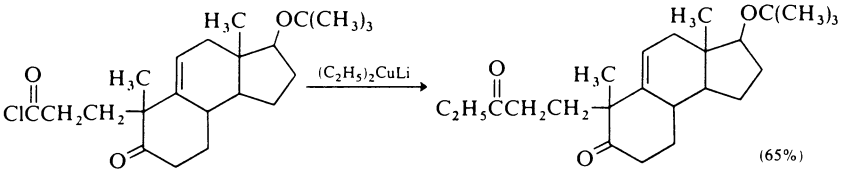
D. Ketones from Acid Chlorides

13[m]



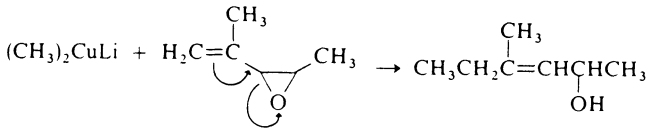
(84–87%)

14[n]

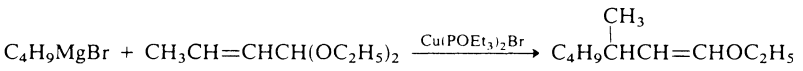


(65%)

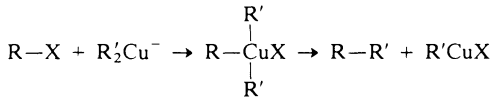
a. H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.* **31**, 3128 (1966).
b. J. A. Marshall and G. M. Cohen, *J. Org. Chem.* **36**, 877 (1971).
c. F. S. Alvarez, D. Wren, and A. Prince, *J. Am. Chem. Soc.* **94**, 7823 (1972).
d. M. Suzuki, T. Suzuki, T. Kawagishi, and R. Noyori, *Tetrahedron Lett.*, 1247 (1980).
e. N. Finch, L. Blanchard, R. T. Puckett, and L. H. Werner, *J. Org. Chem.* **39**, 1118 (1974).
f. E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.* **89**, 3911 (1967).
g. W. E. Konz, W. Hechtl and R. Huisgen, *J. Am. Chem. Soc.* **92**, 4104 (1970).
h. E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Am. Chem. Soc.* **90**, 5618 (1968).
i. E. E. van Tamelen and J. P. McCormick, *J. Am. Chem. Soc.* **92**, 737 (1970).
j. G. Linstrumelle, J. K. Krieger, and G. M. Whitesides, *Org. Synth* **55**, 103 (1976).
k. R. J. Anderson, C. A. Henrick, J. B. Siddall, and R. Zurfluh, *J. Am. Chem. Soc.* **94**, 5379 (1972).
l. H. L. Goering and V. D. Singleton, Jr., *J. Am. Chem. Soc.* **98**, 7854 (1976).
m. G. Posner and C. E. Whitten, *Org. Synth.* **55**, 122 (1976).
n. W. G. Dauben, G. Ahlgren, T. J. Leitereg, W. C. Schwarzel, and M. Yoshioko, *J. Am. Chem. Soc.* **94**, 8593 (1972).



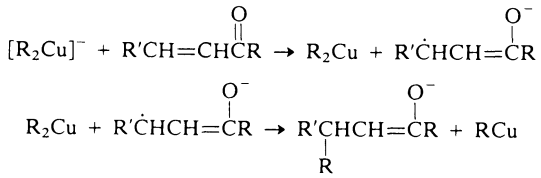
Cuprates from Grignard reagents react with allylic acetals to give vinyl ethers.[83]



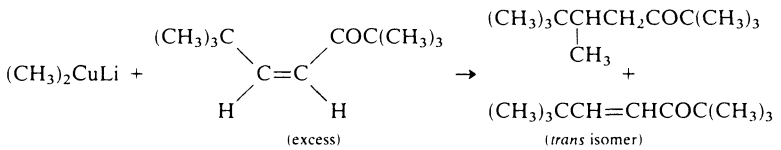
All of these reactions are illustrative of the very powerful nucleophilicity that organocuprates exhibit toward carbon. The reactions are generally considered to proceed by direct displacement on the substrate. Secondary tosylates react with inversion of stereochemistry, as is the case for classical S_N2 reactions.[84] The overall mechanism probably consists of two steps. First an oxidative addition to the metal in which the copper acts as a nucleophile. This is followed by migration of one of the alkyl groups from copper. This kind of process is well documented by mechanistic studies with other types of organometallic compounds.



The conjugate addition reactions probably occur by an electron transfer mechanism.[85] The products of the electron transfer step must combine faster than

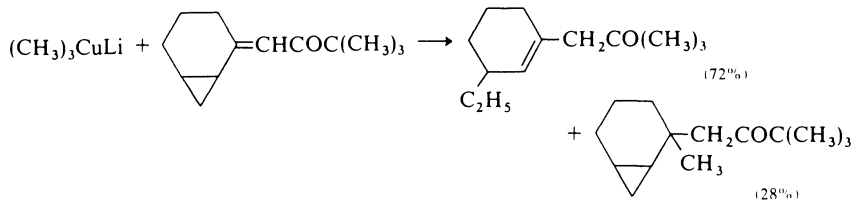


they diffuse apart so no *free* radicals are generated. The intermediacy of a radical anion species can be detected in special cases by double-bond isomerization or rearrangement.



Ref. 85a

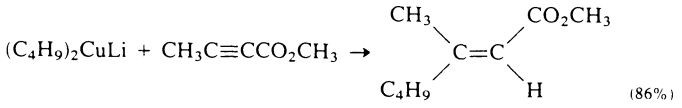
83. J. F. Normant, A. Commercon, M. Bourgain, and J. Villieras, *Tetrahedron Lett.*, 3833 (1975).
84. C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.* **95**, 7783 (1973).
85a. H. O. House, *Acc. Chem. Res.* **9**, 59 (1976).
b. H. O. House and P. D. Weeks, *J. Am. Chem. Soc.* **97**, 2770, 2778 (1975).
c. H. O. House and K. A. J. Snoble, *J. Org. Chem.* **41**, 3076 (1976).



Both the double-bond isomerization and cyclopropane ring opening can be accounted for by a radical anion intermediate. The geometric isomerization of the hindered α,β-unsaturated ketone in the first example gives evidence that an intermediate with single-bond character lives long enough to permit bond rotation. The cyclopropane ring opening can be accounted for by an intermediate with radical character at the β-carbon atom.

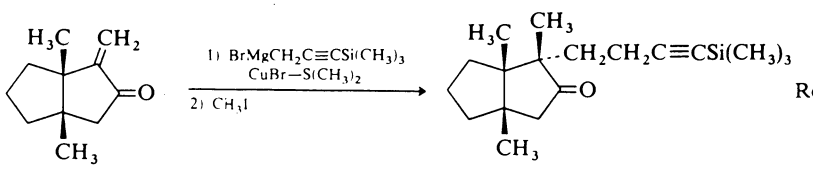
There is also a correlation between the reduction potential of the carbonyl compound and the ease of reaction with cuprate reagents. The more easily reduced, the more reactive is the compound toward organocuprate reagents. Compounds such as α,β-unsaturated esters and nitriles which are not as easily reduced as α,β-unsaturated ketones do not react readily with simple alkyl cuprates even though they are good acceptors in conjugate addition reactions involving other types of nucleophiles (Michael reactions).

All of the mixed organocopper reagents shown in Scheme 6.6 react with α,β-unsaturated ketones. The efficiency of the reaction can be promoted by the addition of trialkylphosphines.[86] α,β-Unsaturated esters are borderline in terms of reactivity toward simple cuprates. Unsubstituted and monosubstituted acrylates generally are reactive but more extensively substituted acrylates are not. The R–Cu–BF_3 reagents are more reactive than simple cuprates toward α,β-unsaturated esters and also react with α,β-unsaturated nitriles.[87] Boron trifluoride has been found to catalyze addition of dimethylcuprate to very hindered α,β-unsaturated ketones.[88] Conjugated acetylenic esters react readily with cuprate reagents, with *syn* addition being the kinetically preferred mode of addition.[89]

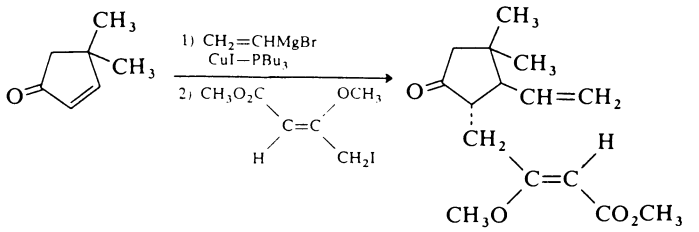


Prior to protonolysis, the products of conjugate addition to unsaturated carbonyl compounds are enolates and, therefore, potential nucleophiles. A useful elaboration of the conjugate addition is to combine it with an alkylation which can add a second organic group by taking advantage of the nucleophilicity of the enolate intermediate.

86. M. Suzuki, T. Suzuki, T. Kawagishi, and R. Noyori, *Tetrahedron Lett.*, 1247 (1980).
87. Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.* **100**, 3240 (1978).
88. A. B. Smith, III and P. J. Jerris, *J. Am. Chem. Soc.* **103**, 194 (1981).
89. R. J. Anderson, V. L. Corbin, G. Cotterrell, G. R. Cox, C. A. Henrick, F. Schaub, and J. B. Siddall, *J. Am. Chem. Soc.* **97**, 1197 (1975).



Ref. 90a



Ref. 90b

The cuprate reagents which have been discussed in the preceding section are normally prepared by reaction of an organolithium reagent with a copper(I) salt, using a 2 : 1 ratio of lithium reagent to copper(I). There are also valuable synthetic procedures which involve organocopper intermediates which are not formed in stoichiometric amount, but are generated in the reacting system via a catalytic amount of added copper(I) species. The copper-catalyzed addition of Grignard reagents to α,β-unsaturated esters is often an efficient procedure. Some examples of this reaction are shown in Scheme 6.8. The presence of a copper catalyst also permits opening of epoxide rings by Grignard reagents in good yield.[91]

$$C_4H_9MgBr + H_2C\overset{O}{\diagup\!\diagdown}CH_2 \xrightarrow{CuBr} C_4H_9CH_2CH_2OH \quad (88\%)$$

In both cases the active organometallic species is presumed to be an organocopper compound.

Vinylcopper reagents and vinylcuprates can be prepared from vinyllithium reagents in the same manner as for alkyl and aryl reagents. In addition, vinylcopper

$$RCH{=}CHLi + Cu(I) \rightarrow RCH{=}CHCu$$
$$2RCH{=}CHLi + Cu(I) \rightarrow (RCH{=}CH)_2Cu^- + Li^+$$

reagents can be made by addition of copper reagents to acetylenes. These vinylcopper reagents can be alkylated and undergo conjugate addition reactions in the usual way. This method is very useful for carbon chain extension with incorporation of a double bond. The addition to acetylenes is stereospecifically *syn* and the resulting vinylcopper reagents are configurationally stable at low temperature so that the stereochemistry can be predicted. Some examples of formation and transformation of vinylcopper reagents are given in Scheme 6.9.

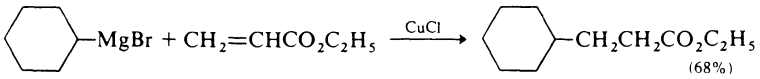
90a. L. A. Paquette and Y.-K. Han, *J. Am. Chem. Soc.* **103**, 1831 (1981).
b. S. Danishefsky, K. Vaughan, R. Gadwood, and K. Tsuzuki, *J. Am. Chem. Soc.* **103**, 4136 (1981).
91. G. Huynh, F. Derguini-Boumechal, and G. Linstrumelle, *Tetrahedron Lett.*, 1503 (1979).

Scheme 6.8. Copper-Catalyzed Additions to Unsaturated Esters

1[a] $(CH_3)_2C{=}C(CO_2CH_3)_2 + CH_3MgBr \xrightarrow{CuCl} \xrightarrow{H_2O} (CH_3)_3CCH(CO_2CH_3)_2$ (84–94%)

2[b] $CH_3CH{=}CHCO_2\underset{CH_3}{\underset{|}{C}}HCH_2CH_3 \quad CH_3(CH_2)_3MgBr \xrightarrow{CuCl} CH_3(CH_2)_3\underset{CH_3}{\underset{|}{C}}HCH_2CO_2\underset{CH_3}{\underset{|}{C}}HCH_2CH_3$ (51%)

3[c] $H_5C_2O_2CCH{=}CHCO_2C_2H_5 + (CH_3)_2CHMgBr \xrightarrow{CuCl} H_5C_2O_2C\underset{(CH_3)_2CH}{\underset{|}{C}}HCH_2CO_2C_2H_5$ (81%)

4[d] 

a. E. L. Eliel, R. O. Hutchins, and M. Knoeber, *Org. Synth.* **50**, 38 (1970).
b. T. Kindt-Larsen, V. Bitsch, I. G. K. Andersen, A. Jart, and J. Munch-Petersen, *Acta Chem. Scand.* **17**, 1426 (1963).
c. V. K. Andersen and J. Munch-Petersen, *Acta Chem. Scand.* **16**, 947 (1962).
d. S.-H. Liu, *J. Org. Chem.* **42**, 3209 (1977).

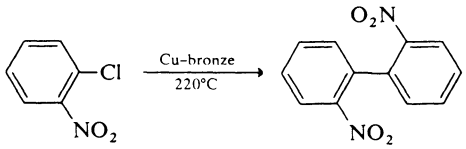
$$C_2H_5MgBr + CuBr \rightarrow C_2H_5CuMgBr_2$$

$$C_2H_5CuMgBr_2 + CH_3C{\equiv}CH \rightarrow \begin{matrix} C_2H_5 & & CuMgBr_2 \\ & C{=}C & \\ CH_3 & & H \end{matrix}$$

Ref. 92

$$\begin{matrix} C_2H_5 & & CuMgBr \\ & C{=}C & \\ CH_3 & & H \end{matrix} \xrightarrow{H_2O} \begin{matrix} C_2H_5 & & H \\ & C{=}C & \\ CH_3 & & H \end{matrix}$$

Organocopper intermediates are involved in another broad class of reactions which accomplish the coupling of two organic substrates. The classical example of this type of reaction is the *Ullman coupling* of aryl halides, which is usually done with a copper–bronze alloy. Good yields in this reaction are limited to halides with electron-attracting substituents.[93] Mechanistic and synthetic work has revealed the

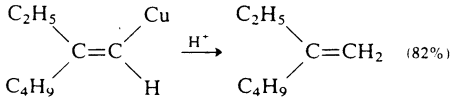


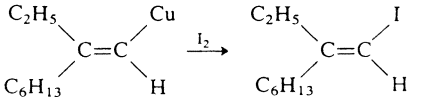
Ref. 94

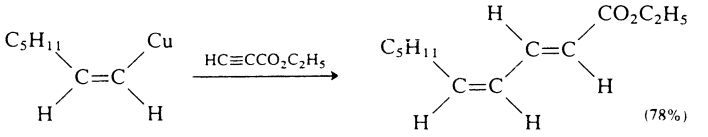
involvement of arylcopper intermediates and permitted improved yields. Soluble Cu(I) salts, particularly the trifluoromethanesulfonate, effect the reaction at lower

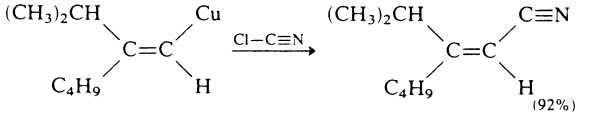
92. H. Westmijze, H. Kleijn, and P. Vermeer, *Tetrahedron Lett.*, 2023 (1977); H. Westmijze, J. Meijer, H. J. T. Bos, and P. Vermeer, *Rec. Trav. Chim. Pays-Bas.* **95**, 299, 304 (1976).
93. P. E. Fanta, *Chem. Rev.* **64**, 613 (1964); *Synthesis*, 9 (1974).
94. R. C. Fuson and E. A. Cleveland, *Org. Synth.* **III**, 339 (1955).

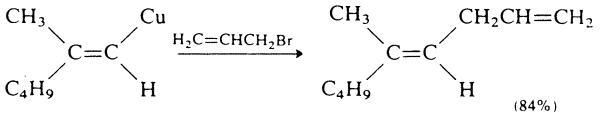
Scheme 6.9. Generation and Reactions of Vinylcopper Reagents by Additions to Acetylenes

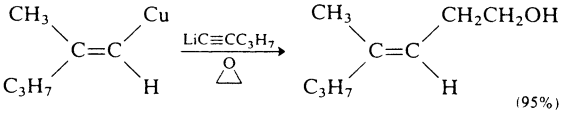
1[a] $C_2H_5MgBr + CuBr + C_4H_9C{\equiv}CH \rightarrow$  (82%)

2[b] $C_2H_5Cu(SMe_2)MgBr_2 + C_6H_{13}C{\equiv}CH \rightarrow$  (63%)

3[c] $(C_5H_{11})_2CuLi + HC{\equiv}CH \rightarrow$  (78%)

4[d] $(CH_3)_2CHCuMgBr_2 + C_4H_9C{\equiv}CH \rightarrow$  (92%)

5[e] $CH_3Cu(SMe_2)MgBr_2 + C_4H_9C{\equiv}CH \rightarrow$  (84%)

6[f] $C_3H_7Cu(SMe_2)MgBr_2 + CH_3C{\equiv}CH \rightarrow$  (95%)

a. J.-F. Normant, G. Cahiez, M. Bourgain, C. Chuit, and J. Villieras, *Bull. Chim. Soc. France*, 1656 (1974).
b. N. J. LaLima, Jr. and A. B. Levy, *J. Org. Chem.* **43**, 1279 (1978).
c. A. Alexakis, J. Normant, and J. Villieras, *Tetrahedron Lett.*, 3461 (1976).
d. H. Westmijze and P. Vermeer, *Synthesis*, 784 (1977).
e. A. Marfat, P. R. McGuirk, and P. Helquist, *J. Org. Chem.* **44**, 3888 (1979).
f. P. R. McGuirk, A. Marfat, and P. Helquist, *Tetrahedron Lett.*, 2465 (1978).

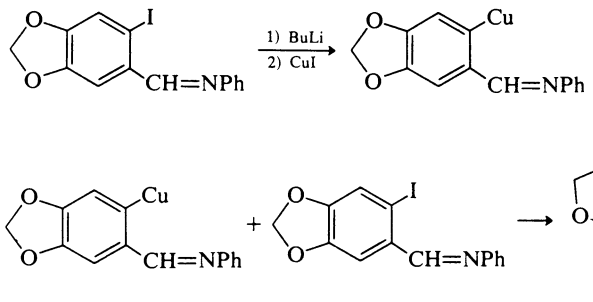
temperatures and under homogeneous conditions and this has permitted kinetic studies. An oxidative addition is believed to be involved.[95] It is likely that Cu(I) species are also involved in the heterogeneous Ullman reaction.

$$Ar{-}X + Cu(I) \rightarrow [Ar{-}Cu{-}X]^+$$

$$[Ar{-}Cu{-}X]^+ + Ar{-}X \rightarrow Ar{-}Ar + [CuX_2]^+$$

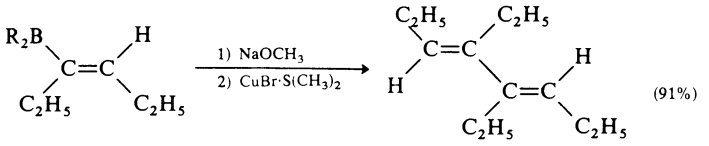
Arylcopper intermediates can be generated from organolithium intermediates.[96] These materials then react with a second aryl halide to effect formation of a biaryl. This procedure is suitable for the synthesis of unsymmetrical biaryls. In essence, it is just a variant of the reaction of cuprate reagents with halides.

95. T. Cohen and I. Cristea, *J. Am. Chem. Soc.* **98**, 748 (1976).
96. F. E. Ziegler, I. Chliwner, K. W. Fowler, S. J. Kanfer, S. J. Kuo, and N. D. Sinha, *J. Am. Chem. Soc.* **102**, 790 (1980).



Ref. 96

Vinylboranes prepared from acetylenes by hydroboration are dimerized to conjugated dienes on reaction with sodium methoxide and $Cu(I)Br{\cdot}S(CH_3)_2$.[97]



(91%)

Related reactions occur with other vinylboron compounds.[98] Vinylcoppers prepared by metal–metal exchange from the corresponding lithium compounds undergo thermal decomposition resulting in coupling to a diene and deposition of the metal at or near room temperature.[99]

$$CH_3CH{=}CHLi + [CuI(PBu_3)]_4 \rightarrow [CH_3CH{=}CHCu(PBu_3)]_n \xrightarrow{\Delta} CH_3CH{=}CHCH{=}CHCH_3$$

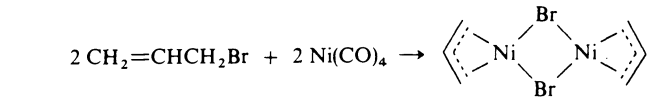
The mechanism of the coupling reactions is not known in detail. They formally involve one-electron oxidation of the alkyl moiety to the equivalent of a radical, followed by combination of two such groups. Both the oxidation and coupling probably take place while the alkyl group remains in the metal coordination sphere, so that free-radical intermediates are not necessarily involved.

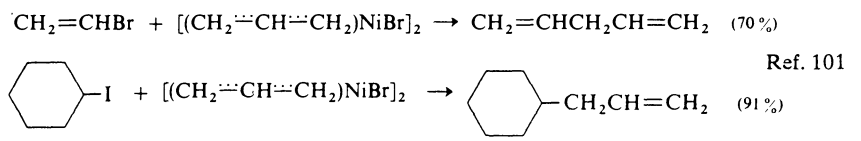
6.4. Synthetic Applications of Other Transition Metals

6.4.1. Reactions Involving Organonickel Compounds

The most useful synthetic processes which have been developed around the chemistry of nickel involve the coupling of halides. Allyl halides react with nickel carbonyl, $Ni(CO)_4$, to give π-allyl complexes. These compounds can react with a variety of halides to replace the halogen with an allyl group.[100] These reactions

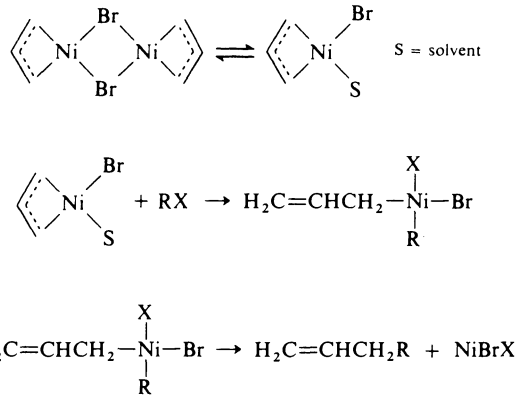
97. J. B. Campbell, Jr. and H. C. Brown, *J. Org. Chem.* **45**, 549 (1980).
98. H. C. Brown and J. B. Campbell, Jr., *J. Org. Chem.* **45**, 389 (1980). Y. Yamamoto, H. Yatagai, K. Maruyama, A. Sonoda, and S.-I. Murahashi, *J. Am. Chem. Soc.* **99**, 5652 (1977).
99. G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Am. Chem. Soc.* **93**, 1379 (1971).
100. M. F. Semmelhack, *Org. React.* **19**, 115 (1972).



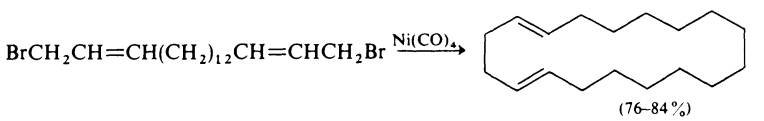


Ref. 101

are believed to proceed by oxidative addition of the halide to the nickel, followed by combination of the two organic groups with elimination of Ni(II). Oxidative addition can be viewed as a process in which the metal donates two electrons to the organic substrate, forming a carbon–metal bond, displacing the halide ion, and giving the organometallic species. When, subsequently, a second organic group becomes bound to the nickel atom, the intermediate decomposes with formation of the new carbon–carbon bond and elimination of nickel.

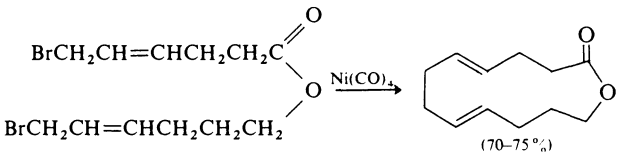


Nickel carbonyl causes the coupling of allyl halides when the reaction is carried out in very polar solvents such as dimethylformamide or dimethyl sulfoxide. This coupling reaction has been used intramolecularly to bring about the cyclization of bis-allylic halides, and has been found useful in the preparation of rings of up to 18 atoms.



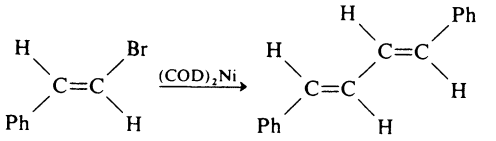
Ref. 102

101. E. J. Corey and M. F. Semmelhack, *J. Am. Chem. Soc.* **89**, 2755 (1967).
102. E. J. Corey and E. K. W. Wat, *J. Am. Chem. Soc.* **89**, 2757 (1967).

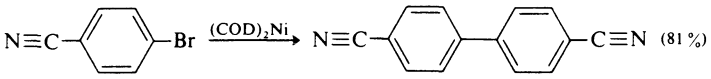


Ref. 103

Another nickel complex, bis-(1,5-cyclooctadiene)nickel(0), $(COD)_2Ni$, has been found to bring about coupling of other halides, in addition to the allylic types that are reactive toward nickel carbonyl:

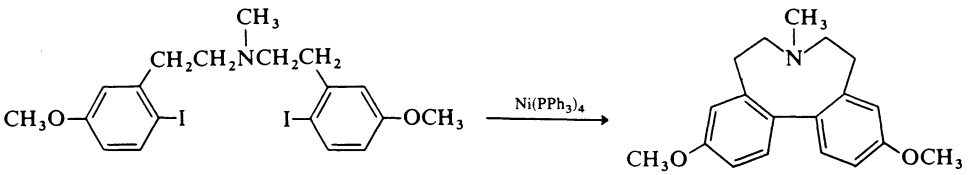


Ref. 104



Ref. 105

A complex of nickel and triphenylphosphine, $Ni(Ph_3P)_4$ is also effective at coupling aryl halides,[106] and, again large rings can be formed. This material is made by reducing $Ni(PPh_3)_2Cl_2$ with zinc in the presence of additional Ph_3P.



Ref. 107

This reaction can be made catalytic in nickel by use of zinc as an *in situ* reductant to regenerate the active nickel(0) species.[108]

Mechanistic study of the aryl couplings have revealed the importance of changes in redox state which accompany reaction of transition metal species with organic halides.[109] Ni(I), Ni(II) and Ni(III) species are believed to be involved. Phosphine ligands are present but have been omitted from the equations for simplicity. The

103. E. J. Corey and H. A. Kirst, *J. Am. Chem. Soc.* **94**, 667 (1972).
104. M. F. Semmelhack, P. M. Helquist, and J. D. Gorzynski, *J. Am. Chem. Soc.* **94**, 9234 (1972).
105. M. F. Semmelhack, P. M. Helquist, and L. D. Jones, *J. Am. Chem. Soc.* **93**, 5908 (1971).
106. A. S. Kende, L. S. Liebeskind, and D. M. Braitsch, *Tetrahedron Lett.*, 3375 (1975).
107. S. Brandt, A. Marfat, and P. Helquist, *Tetrahedron Lett.*, 2193 (1979).
108. M. Zembayashi, K. Tamao, J. Yoshida, and M. Kumada, *Tetrahedron Lett.*, 4089 (1977).
109. T. T. Tsou and J. K. Kochi, *J. Am. Chem. Soc.* **101**, 7547 (1979).

initiation by electron transfer: $ArNi(II)X + ArX \rightarrow ArNi(III)X^+ + Ar\cdot + X^-$

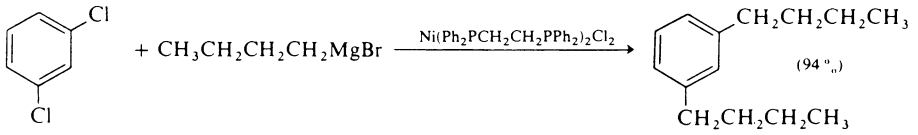
propagation: $ArNi(III)X^+ + ArNi(II)X \rightarrow Ar_2Ni(III)X + Ni^{2+} + X^-$

$Ar_2Ni(III)X \rightarrow Ar{-}Ar + Ni(I)X$

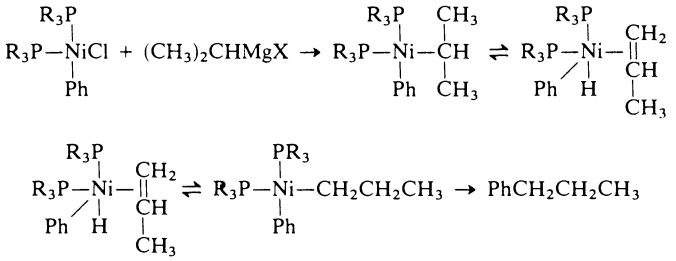
$Ni(I)X + ArX \rightarrow ArNi(III)X^+ + X^-$

detailed kinetics are inconsistent with a simpler mechanism involving formation and decomposition of a biarylnickel(II) intermediate.

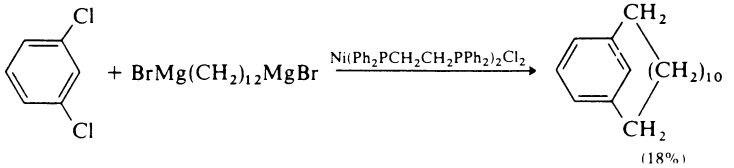
Nickel(II) salts are able to catalyze the reaction of Grignard reagents with vinyl and aryl halides. A soluble phosphine complex, $Ni(Ph_2PCH_2CH_2PPh_2)_2Cl_2$, has been shown to be an effective catalyst.[110] With secondary Grignard reagents under some conditions, the final product contains the corresponding primary alkyl



substituent.[111] The most likely mechanism for this rearrangement involves an organonickel intermediate, which is converted to a nickel–alkene complex. Recombination of the alkene with nickel can then occur in the opposite direction from elimination:



This reaction, when applied to dihaloarenes and Grignard reagents from dihalides, gives products of the cyclophane type.[112]

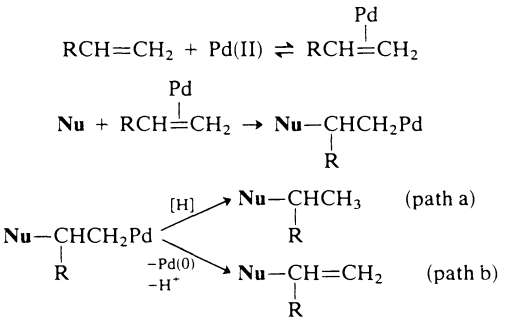


The relative efficiency of the various nickel catalysts in forming large rings probably is the result of the groups being bound to a single nickel atom prior to the elimination and coupling.

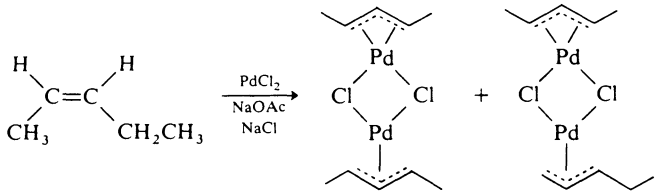
110. K. Tamao, K. Sumitani, and M. Kumada, *J. Am. Chem. Soc.* **94**, 4374 (1972).
111. K. Tamao, Y. Kiso, K. Sumitani, and M. Kumada, *J. Am. Chem. Soc.* **94**, 9268 (1972).
112. K. Tamao, S. Kodama, T. Nakatsuka, Y. Kiso, and M. Kumada, *J. Am. Chem. Soc.* **97**, 4405 (1975).

6.4.2. Reactions Involving Palladium

For the most part, organic reactions involving palladium do not involve the preparation of organopalladium compounds followed by addition of a second reagent. Instead, organopalladium species are usually generated *in situ* in the course of the reactions. Indeed, in some of the most useful processes only a *catalytic amount* of palladium is used. Three types of organopalladium intermediates are of primary importance in the reactions which have had synthetic application. Alkenes react with Pd(II) to give π complexes which are subject to nucleophilic attack. These reactions are closely related to the solvomercuration reactions discussed in Chapter 4. The products that are derived from the resulting intermediates depend upon specific reaction conditions. The palladium can be replaced by hydrogen under reductive conditions. In the absence of a reducing agent, an elimination of Pd(0) and a proton occurs (path b). The final product under these conditions is the result of substitution of a vinyl hydrogen by a nucleophile. We will return to specific examples of these reactions shortly.



The second type of palladium intermediate is a π-allyl complex of Pd(II). The π-allyl complexes can be obtained from Pd(II) salts and allylic acetates, allyl ethers, and other allylic compounds having potential leaving groups.[113] The same π-allyl complexes can be prepared from alkenes by reaction with palladium chloride or palladium trifluoroacetate.[114] For unsymmetrical alkenes with more than one reactive allylic position, the latter method gives rise to mixtures of π-allyl complexes.

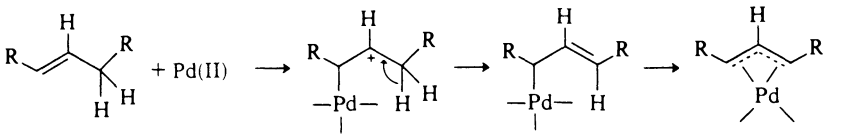


113. R. Huttel, *Synthesis*, 225 (1970); B. M. Trost, *Tetrahedron* **33**, 2615 (1977).

114a. B. M. Trost and P. J. Metzner, *J. Am. Chem. Soc.* **102**, 3572 (1980).

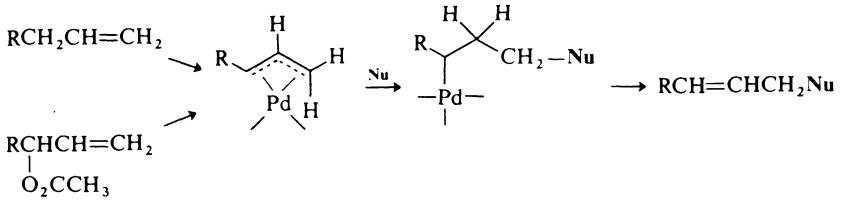
b. B. M. Trost, P. E. Strege, L. Weber, T. J. Fullerton, and T. J. Dietsche, *J. Am. Chem. Soc.* **100**, 3407 (1978).

The overall reaction is formulated as an electrophilic bond formation, followed by loss of a proton. The proton loss probably proceeds via an unstable species in which hydrogen is bound to palladium. Dimerization or addition of other ligands to



palladium is required to fully coordinate the palladium ion. The π-allyl complexes can be isolated as halide-bridged dimers.

These π-allyl complexes are electrophilic in character and undergo reaction with a variety of nucleophiles.



After the nucleophilic addition occurs, the resulting palladium intermediate usually breaks down by elimination of Pd(0) and H^+.

The third general type of reactivity involves the reaction of Pd(0) species with halides by oxidative addition, generating reactive σ-bonded intermediates. This reaction is most useful for aryl and vinyl halides but the products from saturated halides usually decompose by elimination. The σ-bonded Pd(II) species formed by

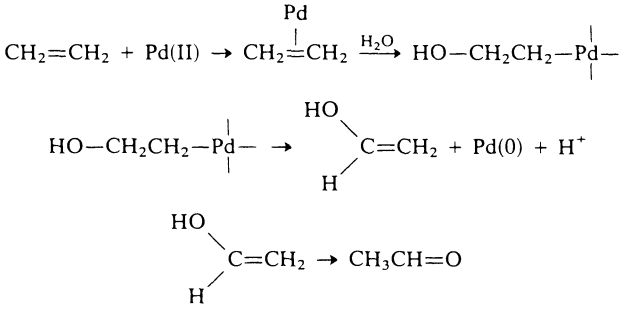
$$RCH{=}CHX + Pd(0) \rightarrow RCH{=}CH{-}\underset{|}{Pd}{-}X$$

$$ArX + Pd(0) \rightarrow Ar{-}\underset{|}{Pd}{-}X$$

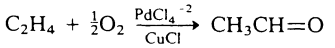
oxidative addition can then react with a wide variety of unsaturated compound with the formation of new carbon–carbon bonds.

In considering the mechanisms involved in the organopalladium chemistry to be discussed below, several general points should be kept in mind. Frequently, reactions involving organopalladium intermediates are done in the presence of phosphine ligands. These ligands coordinate at palladium and can play a key role in the course of the reaction. A second general point to recognize is the relative weakness of the Pd—C bond and, especially, the instability of carbon–palladium bonds in the presence of a β-hydrogen atom. The final stage of many palladium-mediated reactions is the elimination of Pd(0) and H^+ (or "Pd—H"). This tendency toward elimination distinguishes organopalladium species from the organometallics we have discussed to this point. Finally, organopalladium species with two organic substituents show the same tendency to decomposition with recombination of the organic groups that was exhibited by nickel reagents. The paragraphs which follow concentrate on some of the more valuable synthetic reactions which involve organopalladium intermediates.

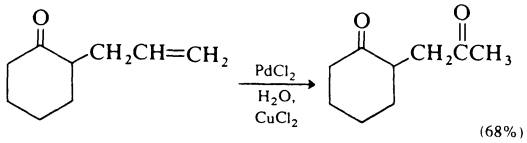
A very important industrial process involving Pd–alkene complexes is the *Wacker reaction*, a catalytic process for conversion of ethylene to acetaldehyde. The first step is an addition of water mediated by electrophilic Pd(II). The addition intermediate then undergoes the characteristic elimination of Pd(0) and H^+ to generate the enol of acetaldehyde. The reaction is run with only a catalytic amount



of Pd. The coreagents $CuCl_2$ and O_2 serve to reoxidize the Pd(0) to Pd(II). Under these conditions the overall transformation is

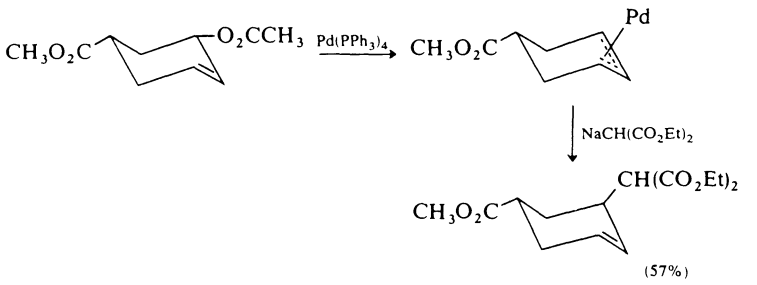


When applied to other terminal alkenes, these conditions lead to methyl ketones.



Ref. 115

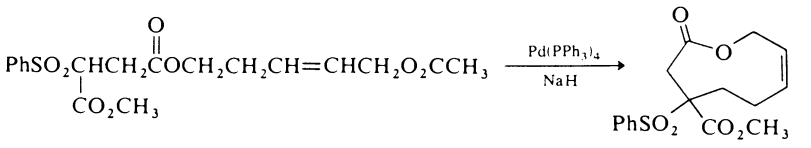
One of the most synthetically useful reactions involving organopalladium intermediates is that between π-allyl complexes and relatively stable carbanions such as those derived from malonate esters and β-ketoesters. The π-allyl complexes can be synthesized separately and used in stoichiometric amount[116] or they can be generated *in situ* by reaction of allylic acetates with a catalytic amount of *tetrakis* (triphenylphosphine)palladium.[117] In the catalytic version of the reaction, the π-allyl complex is formed by reaction of the allylic acetate and the Pd(0) species which is regenerated in the elimination step.



Ref. 118

115. J. Tsuji, I. Shimizu, and K. Yamamoto, *Tetrahedron Lett.*, 2975 (1976).
116. B. M. Trost, W. P. Conway, P. E. Strege, and T. J. Dietsche, *J. Am. Chem. Soc.* **96**, 7165 (1974), B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton, and T. J. Dietsche, *J. Am. Chem. Soc.* **100**, 3416 (1978); B. M. Trost, *Acc. Chem. Res.* **13**, 385 (1980).
117. B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.* **102**, 4730 (1980).
118. B. M. Trost and P. E. Strege, *J. Am. Chem. Soc.* **99**, 1649 (1977).

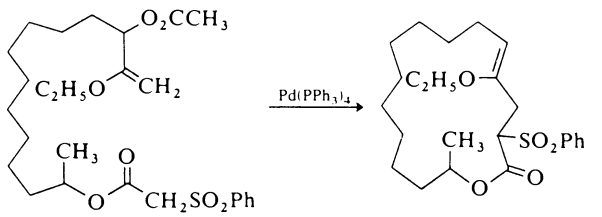
The reaction has also been used intramolecularly to close rings. β-Sulfonylesters have proven particularly useful in this application. These reactions have been found to be effective for formation of both medium and large rings. In some cases, medium-sized rings are formed in preference to six- and seven-membered rings.[119]



Ref. 119a

(54%)

+5% of *trans*-isomer

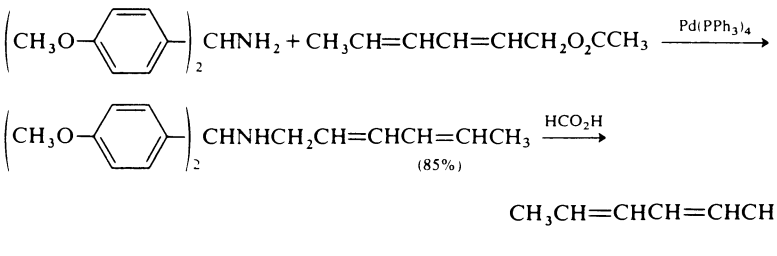


Ref. 119b

(60%)

The sulfonyl substituent can be removed by reduction after the ring closure (see section 5.5.2).

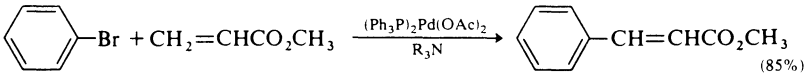
Amines are also reactive as nucleophiles toward π-allyl complexes and a process for synthesis of allylic amines is based on this reaction. 4,4′-Dimethoxydiphenylmethylamine proved to be a convenient nucleophile from which the substituent group could be removed by subsequent hydrolysis.[120]



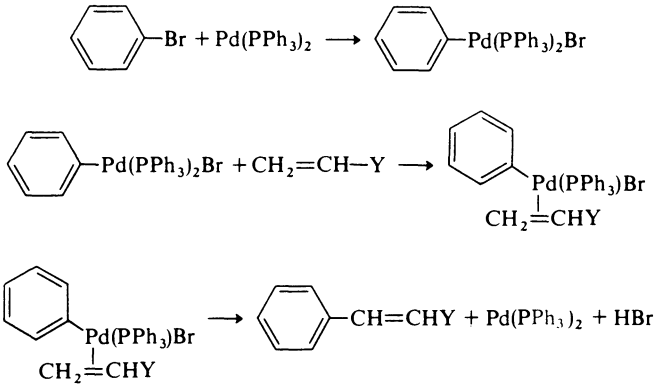
The third important type of reactivity of palladium, namely, oxidative addition to Pd(0), is the foundation for several methods of forming carbon–carbon bonds. Aryl[121a] and vinyl[121b] halides react with alkenes in the presence of catalytic amounts

119a. B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.* **102**, 4743 (1980).
b. B. M. Trost and S. J. Brickner, *J. Am. Chem. Soc.* **105**, 568 (1983).
120. B. M. Trost and E. Keinan, *J. Org. Chem.* **44**, 3451 (1979).
121a. H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.* **96**, 1133 (1974); R. F. Heck, *Acc. Chem. Res.* **12**, 146 (1979).
b. B. A. Patel and R. F. Heck, *J. Org. Chem.* **43**, 3898 (1978); B. A. Patel, J. I. Kim, D. D. Bender, L. C. Kao, and R. F. Heck, *J. Org. Chem.* **46**, 1061 (1981); J. I. Kim, B. A. Patel, and R. F. Heck, *J. Org. Chem.* **46**, 1067 (1981).

of Pd(II) salts and undergo net substitution of the halides by the alkenyl group. The reaction has been observed for simple alkenes, aryl-substituted alkenes, *N*-vinylamides, and electron-deficient olefins such as acrylate esters and acrylonitrile.[122] These reactions are carried out in the presence of a phosphine-type

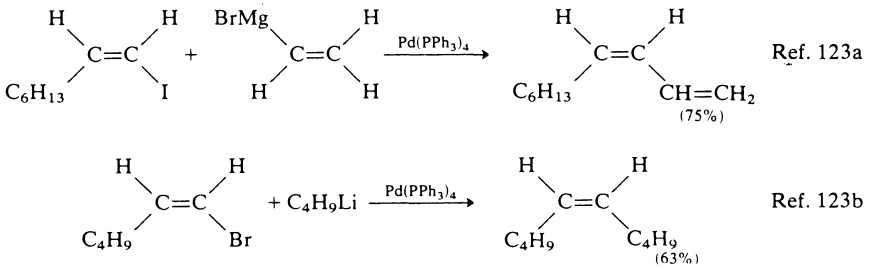


ligand, tri-*o*-tolylphosphine being the preferred phosphine for many cases. The reaction is believed to be initiated by oxidative addition of the halide to palladium(0) which is generated *in situ* from the palladium catalyst. The arylated palladium



intermediate then reacts as an electrophile toward the alkene, generating a palladium species with two carbon ligands. This intermediate decomposes with carbon–carbon bond formation. Only a catalytic amount of a palladium salt is needed since the active catalyst is regenerated in this step.

Tetrakis(triphenylphosphine)palladium couples vinyl halides with Grignard reagents.

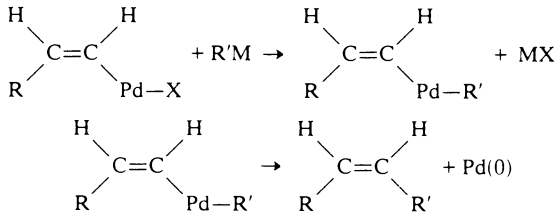


122. C. B. Ziegler, Jr. and R. F. Heck, *J. Org. Chem.* **43**, 2941 (1978); W. C. Frank, Y. C. Kim, and R. F. Heck, *J. Org. Chem.* **43**, 2947 (1978); C. B. Ziegler, Jr. and R. F. Heck, *J. Org. Chem.* **43**, 2949 (1978); H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.* **96**, 1133 (1974).

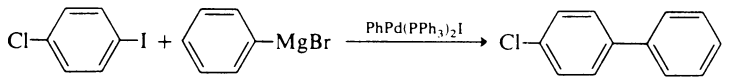
123a. M. P. Dang and G. Linstrumelle, *Tetrahedron Lett.*, 191 (1978).

b. M. Yamamura, I. Moritani, and S. Murahashi, *J. Organometal. Chem.* **91**, C39 (1975).

These processes are probably similar to the halide–alkene couplings except that the reactive disubstituted Pd(II) intermediate is now generated from the nucleophilic organometallic reagent.

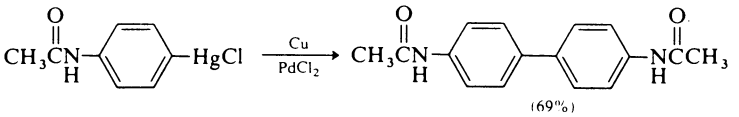


Unsymmetrical biaryls can be prepared by reaction of aryl Grignard reagents or aryllithiums with aryl halides in the presence of an arylpalladium intermediate which serves as a catalyst. The arylpalladium catalyst is generated from the halide by oxidative addition.

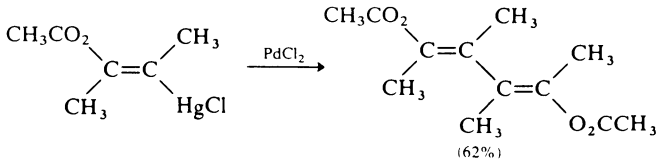


Ref. 124

Synthesis of symmetrical biaryls and symmetrical coupling of vinyl groups has been achieved using organomercury intermediates. These reactions probably also proceed by formation of a disubstituted palladium complex which decomposes with the formation of Pd(0). There are also palladium-based procedures for coupling

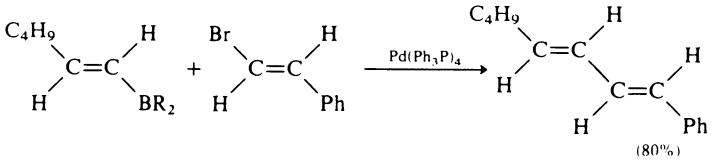


Ref. 125



Ref. 126

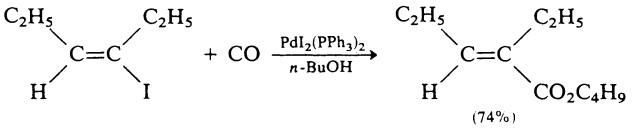
of vinyl halides and vinylboranes. This method provides a route to unsymmetrical conjugated dienes.



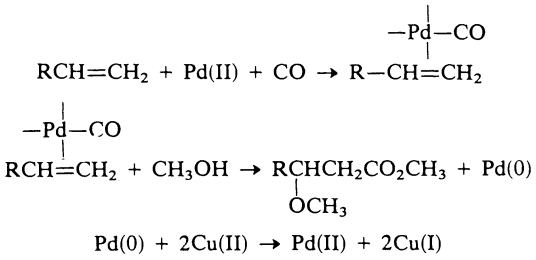
Ref. 127

124. A. Sekiya and N. Ishikawa, *J. Organometal. Chem.* **118**, 349 (1976).
125. R. A. Kretchmer and R. Glowinski, *J. Org. Chem.* **41**, 2661 (1976).
126. R. C. Larock, *J. Org. Chem.* **41**, 2241 (1976).
127. M. Miyaura, K. Yamada, and A. Suzuki, *Tetrahedron Lett.*, 3437 (1979).

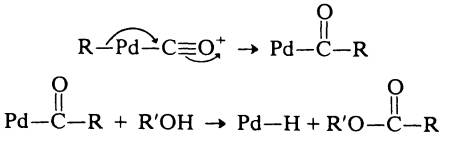
Organopalladium species generated from halides by oxidative addition react with carbon monoxide in the presence of alcohols to give esters.[128]



Complexes of alkenes are also reactive toward carbon monoxide. A catalytic process which includes copper(II) results in concomitant addition of nucleophilic solvent. The copper(II) functions to reoxidize Pd to the +2 oxidation state.[129] A crucial

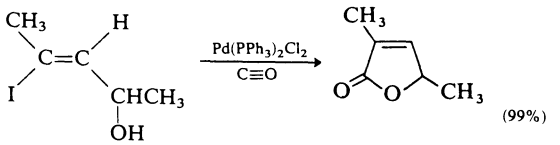


step in both of these reactions is the carbonyl-insertion step. This is a common reaction with palladium and certain other metals and takes place by migration of the alkyl group from metal to carbon. The detailed mechanisms of such reactions



can be shown to involve addition and elimination of the phosphine ligands to the complex and, as a result, the efficiency of individual reactions can often be improved by careful study of the effect of the added ligands.

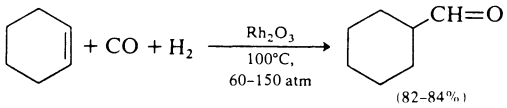
Application of the carbonylation reaction to halides with appropriately placed hydroxyl groups leads to lactone formation. In this case the intermediate acylpalladium intermediate is trapped intramolecularly.[130]



128. A. Schoenberg, I. Bartoletti, and R. F. Heck, *J. Org. Chem.* **39**, 3318 (1974).
129. D. E. James and J. K. Stille, *J. Am. Chem. Soc.* **98**, 1810 (1976).
130. A. Cowell and J. K. Stille, *J. Am. Chem. Soc.* **120**, 4193 (1980).

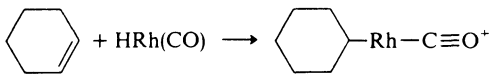
6.4.3. Reactions Involving Rhodium, Iron, and Cobalt

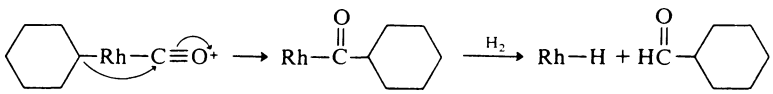
Each of these metals has several specialized reactions which are of value in organic synthesis. Rhodium and cobalt are active catalysts for the reaction of alkenes with hydrogen and carbon monoxide. This reaction can be controlled to yield aldehydes (hydroformylation).[131]



Ref. 132

A key step in this reaction is the migration of the alkyl group from the metal atom to give complexed carbonyl group.





A related version of great economic interest is the *Fischer–Tropsch* process for reductive conversion of carbon monoxide to hydrocarbons.[133] This reaction is catalyzed by a number of metals but cobalt and iron have been most closely studied. The key reaction steps are reduction of metal-complexed carbon monoxide and carbonyl insertion reactions. The hydrocarbon chain is built up by a series of successive carbonyl insertion and reduction steps.

$$M + CO \rightarrow M{-}CO$$

$$M{-}CO + H_2 \rightarrow M{-}CH_3$$

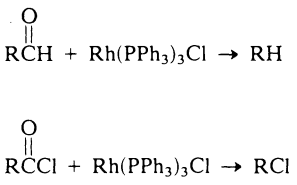
$$M{-}CH_3 + CO \rightarrow OC{-}M{-}CH_3$$

$$OC{-}M{-}CH_3 \rightarrow M{-}\overset{\overset{O}{\|}}{C}{-}CH_3$$

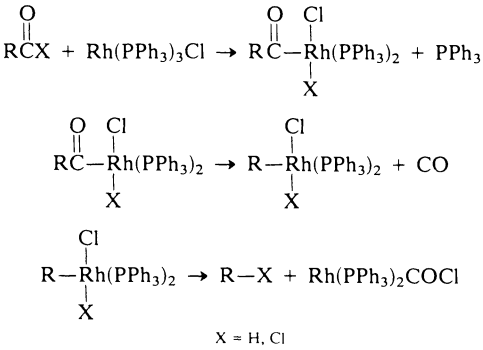
$$M{-}\overset{\overset{O}{\|}}{C}{-}CH_3 + H_2 \rightarrow M{-}CH_2CH_3 \quad \text{etc.}$$

The key carbonyl insertion reaction which is involved in both hydroformylation and the Fischer–Tropsch reaction can be reversible. This reaction is of occasional preparative use for the decarbonylation of aldehydes[134] and acyl halides.[135] In both

131. R. L. Pruett, *Adv. Organometal. Chem.* **17**, 1 (1979).
132. P. Pino and C. Botteghi, *Org. Synth.* **57**, 11 (1977).
133. C. Masters, *Adv. Organometal. Chem.* **17**, 61 (1979).
134. J. A. Kampmeier, S. H. Harris, and D. K. Wedgaertner, *J. Org. Chem.* **45**, 315 (1980).
135. J. K. Stille and M. T. Regan, *J. Am. Chem. Soc.* **96**, 1508 (1974). J. K. Stille and R. W. Fries, *J. Am. Chem. Soc.* **96**, 1514 (1974).

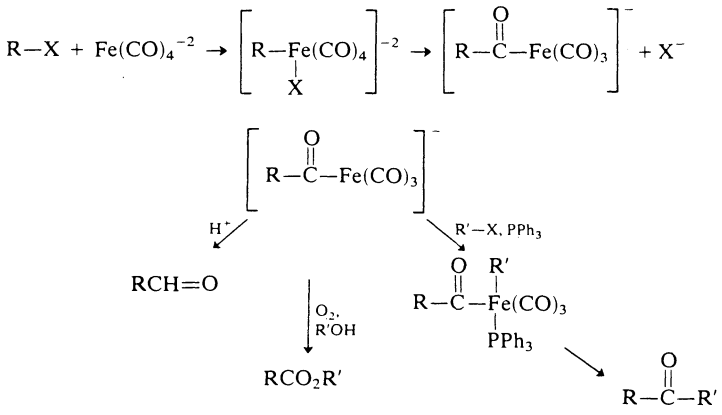


cases the reaction is considered to proceed via an acylrhodium complex. The expulsion of the hydrocarbon or halide is a reductive elimination, that is, the



opposite of the oxidative addition process noted in organonickel and organopalladium chemistry.

The iron chemistry which is related to these reversible carbonylations is most usefully revealed by an ionic compound, sodium tetracarbonylferrate.[136] The highly carbonylated Fe(−2) anion can effect the conversion of alkyl halides and tosylates into aldehydes, ketones, and carboxylic acid derivatives. The reactions begin by oxidative addition of the halide to the very nucleophilic iron atom, followed by carbonyl insertion. This particular reagent illustrates several of the crucial reactions



136. J. P. Collman, *Acc. Chem. Res.* **8**, 342 (1975); R. G. Finke and T. N. Sorrell, *Org. Synth.* **59**, 102 (1979).

which have made the transition metals useful in organic synthesis. The first step in each path is the oxidative addition. Reaction with carbon monoxide results in migration of the alkyl group and formation of the acyliron complex. This reaction is promoted by addition of the phosphines, presumably as a result of the phosphine inducing the migration as it is bound to iron. The acyliron intermediates are reactive toward protons (giving aldehydes), toward O_2 and other oxidants (giving carboxylic acids and esters), and toward alkyl halides (giving ketones as the result of decomposition of an acyl alkyl iron intermediate).

The adducts of halides with tetracarbonylferrate also react with activated alkenes such as acrylonitrile, acrylate esters, and α,β-unsaturated ketones.[137]

$$[RFe(CO)_4]^- + CH_2{=}CH{-}Z \rightarrow R{-}\overset{\overset{O}{\|}}{C}{-}CH_2CH_2Z$$

The overall process is the equivalent of conjugate addition of an acyl anion. Good yields are reported.

$$C_4H_9I + CH_2{=}\overset{\overset{CH_3}{|}}{C}CN + Na_2Fe(CO)_4 \rightarrow \underset{(80\%)}{C_4H_9\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{CH_3}{|}}{C}HCN}$$

6.5. Organometallic Compounds with π-Bonding

The organometallics in the previous sections have in most cases involved carbon–metal bonds in which a single carbon atom could be recognized as being the atom to which the metal was attached. The organic ligands which are discussed in this section are bound to metals by electrons in π-molecular orbitals that are delocalized over more than one carbon atom. Among the classes of organic molecules that have been observed to form this type of bond are the simple alkenes, allyl groups, dienes, the cyclopentadiene anion, and aromatic compounds. There are well-characterized compounds in which delocalized π-bonding with the metal involves an even larger number of carbon atoms. This group of compounds has grown exceedingly rapidly and only some representative examples can be discussed here.

π-Complexes of alkenes were first observed with platinum; subsequently, complexes with many other transition metals have been isolated. The bonding in such complexes is the result of two major contributions. The ligand acts as an electron donor toward the metal by transferring electron density from its filled π orbital to an unfilled metal orbital. There is also a contribution called "back-bonding" which involves interaction of a filled metal orbital with the empty π-antibonding orbital of the olefin. These two types of bonding are represented in Figure 6.1. This general concept of the

137. M. P. Cooke, Jr. and R. M. Parlman, *J. Am. Chem. Soc.* **99**, 5222 (1977).

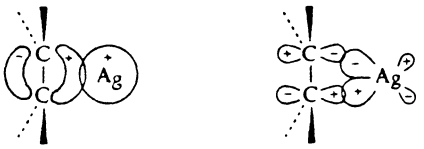
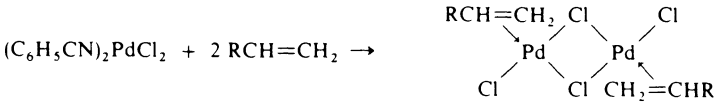
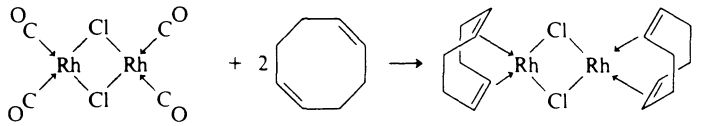


Figure 6.1. Representation of π bonding in olefin–transition-metal complexes.

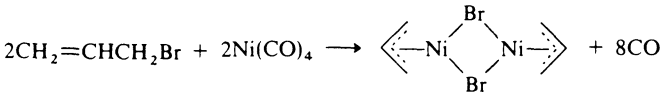
bonding will pertain to most complexes discussed in this section, although details vary as the nature of the organic π ligand and the identity of the transition metal change. Alkene complexes have most often been prepared by displacement of some other ligand by the alkene. Both thermal and photochemical reactions have been utilized. For example, alkenes react with platinum and palladium salts by displacing solvent or

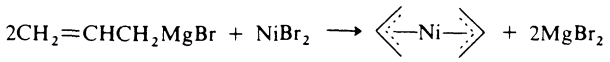


halide ions from the coordination sphere of the metal.[138] Displacement of carbon monoxide from metal carbonyls is also a common preparative method.[139] The dimeric



π-allylnickel(I) bromides which are prepared readily from allyl bromides and nickel carbonyl are examples of compounds with π-allyl ligands.[140] Bis(allylnickel) can be prepared by reaction of allyl magnesium bromide and nickel bromide.[141]

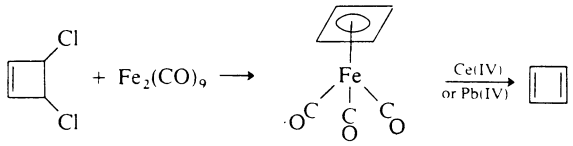




Organometallics involving organic ligands having a cyclic array of four carbon atoms have been of particular interest because the ligand in this case is a cyclobutadiene derivative. Derivatives containing this ligand were first prepared in the

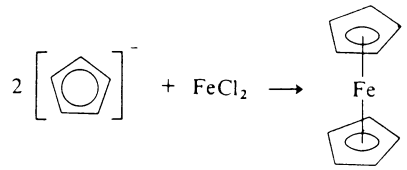
138. M. S. Kharasch, R. C. Seyler, and F. R. Mayo, *J. Am. Chem. Soc.* **60**, 882 (1938).
139. J. Chatt and L. M. Venanzi, *J. Chem. Soc.*, (1957).
140. E. J. Corey and M. F. Semmelhack, *J. Am. Chem. Soc.* **89**, 2755 (1967).
141. D. Walter and G. Wilke, *Angew. Chem. Int. Ed.* **5**, 897 (1966).

late 1950s, and a complex of the parent cyclobutadiene was reported in 1965.[142] Subsequent studies have provided strong evidence that oxidative decomposition of such complexes releases cyclobutadiene and its derivatives. All the evidence available indicates that cyclobutadienes have very short lifetimes, but the products

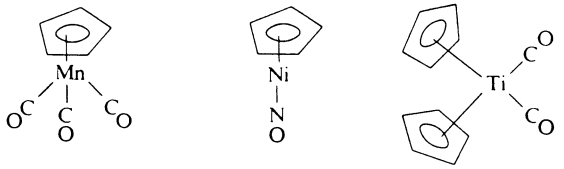


derived by "trapping" experiments are best explained as being reaction products of cyclobutadiene.[143] Scheme 6.10 presents some examples of reactions in which cyclobutadiene is generated by oxidation of its iron tricarbonyl complex and then undergoes addition reactions with other reagents in solution. The carbocyclic ring in the cyclobutadiene-iron tricarbonyl molecule behaves chemically as a reactive aromatic ring and a number of electrophilic substitutions can be carried out on the complex.[144]

One of the best known of the π-organometallic compounds is ferrocene. This compound is a neutral molecule that is derived from two cyclopentadienide anions and iron(II). Two convenient methods of preparation have been described.[145]

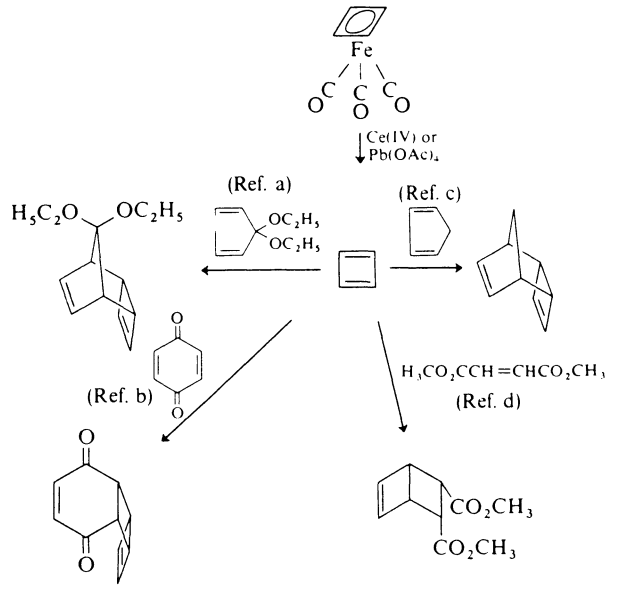


Related compounds in which other metals are present have been prepared. Many of these have ligands in addition to cyclopentadienide attached to the metal.[146] The total number of electrons contributed by the ligands plus the valence electrons of the metal atom (or ion) usually is 18, to satisfy the "effective atomic number rule."[147]



142. G. F. Emerson, L. Watts, and R. Pettit, *J. Am. Chem. Soc.* **87**, 131 (1965); R. Pettit and J. Henery, *Org. Synth.* **50**, 21 (1970).
143. R. H. Grubbs and R. A. Grey, *J. Am. Chem. Soc.* **95**, 5765 (1973).
144. J. D. Fitzpatrick, L. Watts, G. F. Emerson, and R. Pettit, *J. Am. Chem. Soc.* **87**, 3254 (1965).
145. G. Wilkinson, *Org. Synth.* **IV**, 473, 476 (1963).
146. M. L. H. Green, *Organometallic Compounds*, Vol. II, Methuen and Co., London (1968), pp. 90–139.
147. M. Tsutsui, M. N. Levy, A. Nakamura, M. Ichikawa, and K. Mori, *Introduction to Metal π-Complex Chemistry*, Plenum Press, New York (1970), pp. 44 and 45.

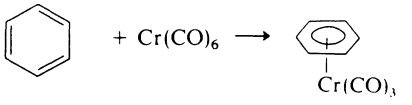
Scheme 6.10. Reactions of Cyclobutadiene



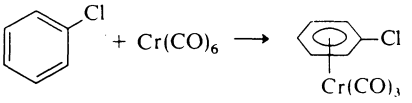
a. J. C. Barborak and R. Pettit, *J. Am. Chem. Soc.* **89**, 3080 (1967).
b. J. C. Barborak, L. Watts, and R. Pettit, *J. Am. Chem. Soc.* **88**, 1328 (1966).
c. L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Am. Chem. Soc.* **88**, 623 (1966).
d. P. Reeves, J. Henery, and R. Pettit, *J. Am. Chem. Soc.* **91**, 5889 (1969).

Numerous chemical reactions have been carried out on ferrocene and its derivatives. The molecule behaves as an electron-rich aromatic system, and many of the typical aromatic substitutions occur readily. Reagents such as the halogens that are relatively strong oxidizing agents, however, react by oxidation–reduction, with a change in the oxidation state and coordination sphere of the iron atom.

The most useful π complexes of aromatic compounds from the synthetic point of view are the complexes obtained by heating benzene and substituted derivatives with $Cr(CO)_6$. The aromatic rings in these complexes are subject to *nucleophilic*



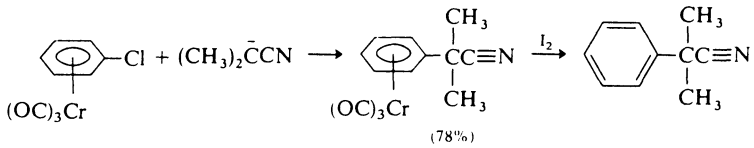
Ref. 148



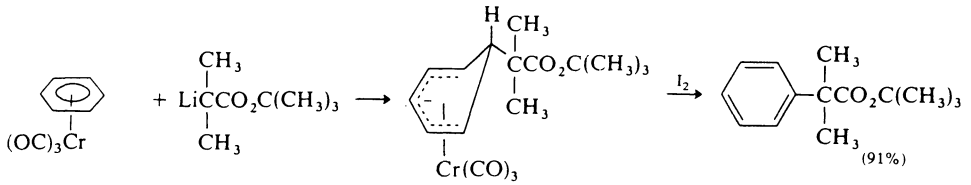
Ref. 149

attack. Reaction with certain carbanions, results in arylation of the carbanion, a reaction which is synthetically useful.[150] Complexes not containing a halogen leaving

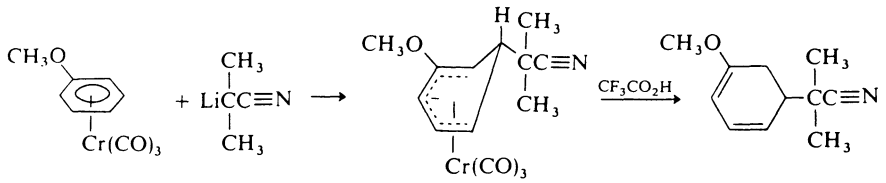
148. W. Strohmeier, *Chem. Ber.* **94**, 2490 (1961).
149. J. F. Bunnett and H. Hermann, *J. Org. Chem.* **36**, 4081 (1971).
150. M. F. Semmelhack and H. T. Hall, *J. Am. Chem. Soc.* **96**, 7091 (1974).



group can also act as arylating agents. The intermediate addition product is oxidized by I_2.[151] Existing substituent groups such as CH_3, OCH_3, and $^{+}N(CH_3)_3$ exert a



directive effect, often resulting in a major amount of the *meta* substitution product.[152] The intermediate adducts can be converted to cyclohexadiene derivatives if the complex is destroyed by protonolysis.[153] Not all carbon nucleophiles will add



to arenechromiumtricarbonyl complexes. For example, alkyllithium reagents,[154] Grignard reagents, and simple ketone enolates do not react in this manner.

Organometallic chemistry remains a very active field of research. New types of compounds, new reactions, and useful catalytic reactivity are being discovered at a rapid rate. The examples given in this section are some of the best known and most useful reactions but a wide variety of others are known which have not been included for lack of space.

General References

Organomagnesium and Organolithium Reagents

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151. M. F. Semmelhack, H. T. Hall, M. Yoshifuji, and G. Clark, *J. Am. Chem. Soc.* **97**, 1247 (1975); M. F. Semmelhack, H. T. Hall, Jr., R. Farina, M. Yoshifuji, G. Clark, T. Bargar, K. Hirotsu, and J. Clardy, *J. Am. Chem. Soc.* **101**, 3535 (1979).
152. M. F. Semmelhack, G. R. Clark, R. Farina, and M. Saeman, *J. Am. Chem. Soc.* **101**, 217 (1979).
153. M. F. Semmelhack, J. J. Harrison, and Y. Thebtaranonth, *J. Org. Chem. Soc.* **44**, 3275 (1979).
154. R. J. Card and W. S. Trahanovsky, *J. Org. Chem.* **45**, 2555, 2560 (1980).

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Other Organometallic Intermediates and Compounds

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M. Tsutsui, M. N. Levy, A. Nakamura, M. Ichikawa, and K. Mori, *Introduction to Metal π-Complex Chemistry*, Plenum Press, New York (1970).
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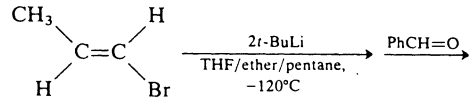
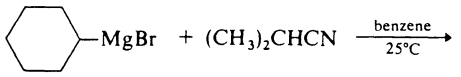
H. Alper, Ed., *Transition Metal Organometallics in Organic Synthesis*, Vols. I and II, Academic Press, New York (1978).

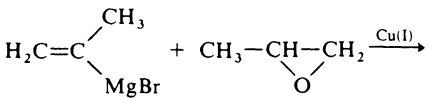
Problems

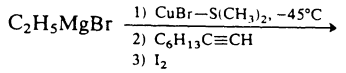
References for these problems will be found on page 625.

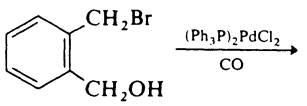
1. Predict the product of the following reactions. Be sure to specify all elements of stereochemistry.

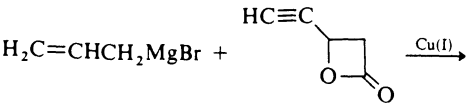
(a) 

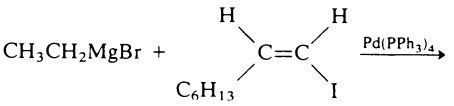
(b) 

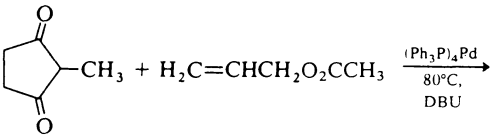
(c) 

(d) 

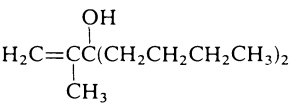
(e) 

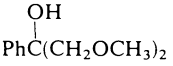
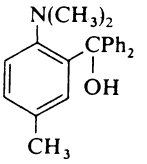
(f) 

(g) 

(h) 

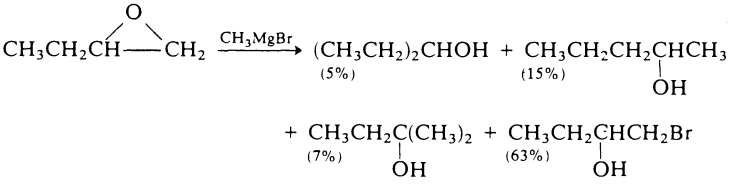
2. Suggest a synthesis of each of the following compounds from readily available materials using organometallic reagents:

(a) $H_2C{=}CHCH_2CH_2CH_2OH$ (b) 

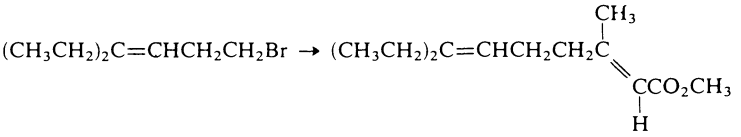
(c)  (d) 

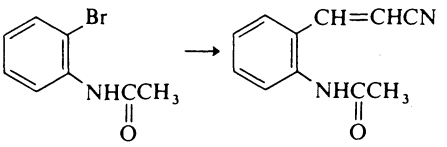
(e) $(CH_3)_3CCH(CO_2C_2H_5)_2$ (f) $H_2C{=}CHCH{=}CHCH{=}CH_2$

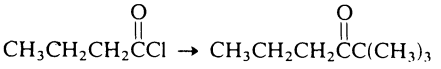
3. Reaction of the epoxide of 1-butene with methyllithium gives 3-pentanol in 90% yield. In contrast, methylmagnesium bromide under similar conditions gives the array of products shown below. Explain the difference in the reactivity of the two organometallic compounds toward this epoxide.



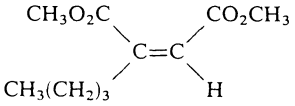
4. Indicate appropriate conditions and reagents for effecting the following transformations. "One-pot" processes are possible in all cases.

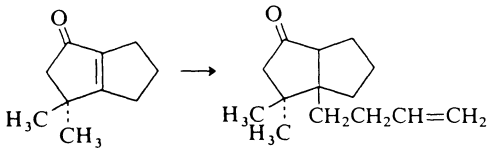
(a) 

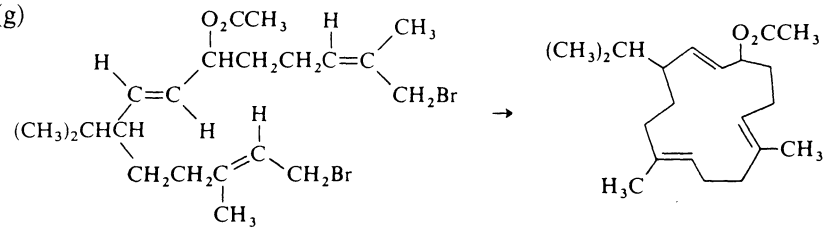
(b) 

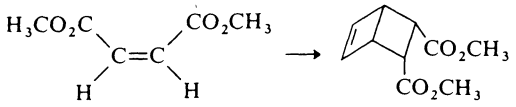
(c) 

(d) $C_6H_{13}MgBr \rightarrow C_6H_{13}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CHCH_2CH{=}CH_2$

(e) $CH_3CH_2CH_2CH_2Br + CH_3O_2CC{\equiv}CCO_2CH_3 \rightarrow$ 

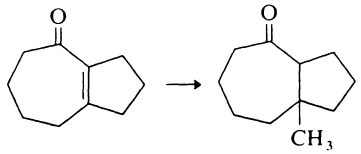
(f) 

(g) 

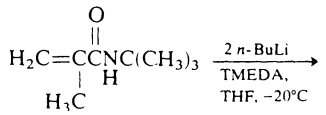
(h) 

(i) $(CH_3)_2C{=}\overset{\displaystyle Br}{\overset{|}{C}}CCH_3 \rightarrow (CH_3)_2C{=}\overset{\displaystyle CH_3}{\overset{|}{C}}CH{=}CHCO_2H$

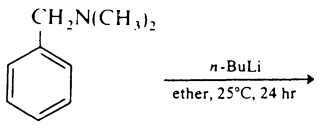
(j) $ClC(=O)(CH_2)_6CO_2C_2H_5 \rightarrow (CH_3)_2CH(CH_2)_2C(=O)(CH_2)_6CO_2C_2H_5$

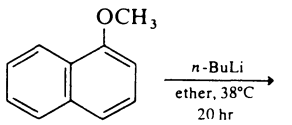
(k) 

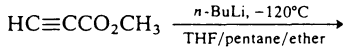
5. Each of the following compounds gives products in which one or more lithium atoms have been introduced under the conditions specified. Predict the structures of the lithiated product on the basis of structural features known to promote lithiation and/or stabilization of lithiated species. The number of lithium atoms introduced is equal to the number of moles of lithium reagent used in each case.

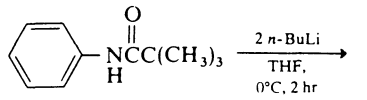
(a) 

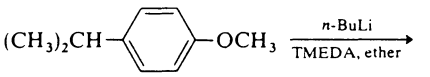
(b) $(CH_3)_2C{=}CH_2 \xrightarrow[\text{TMEDA, hexane}]{n\text{-BuLi}}$

(c) 

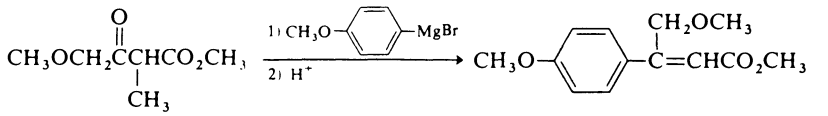
(d) 

(e) 

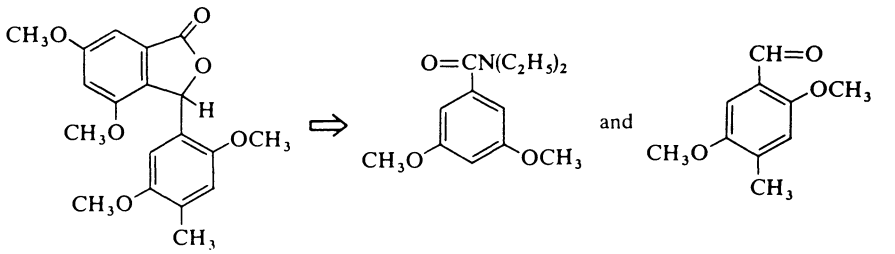
(f) 

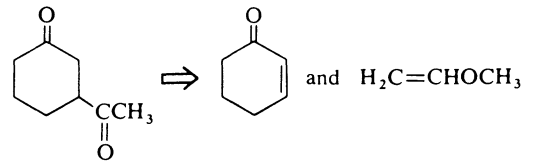
(g) 

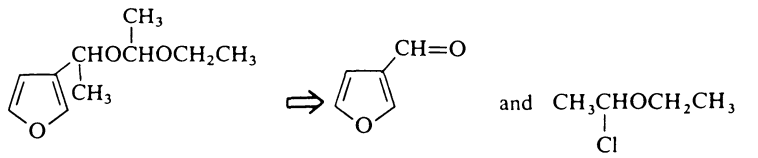
6. It has been suggested that the conversion shown below, if carried out by a Grignard addition and subsequent dehydration would be a poor process. Can you offer an explanation as to why such a proposed transformation would be unlikely to be satisfactory?

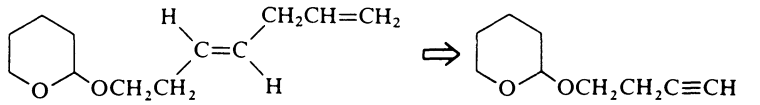


7. Short synthetic sequences involving no more than three steps can be used to prepare the compound shown on the left from the potential starting material on the right. Suggest an appropriate series of reactions for each transformation.

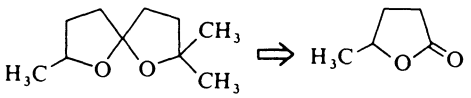
(a) 

(b) 

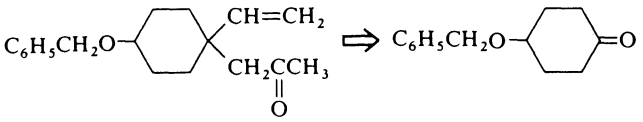
(c) 

(d) 

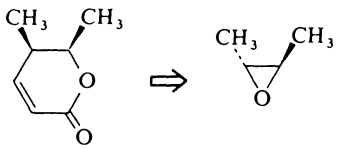
(e)



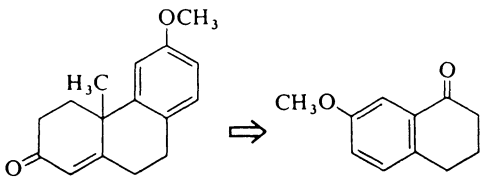
(f)



(g)

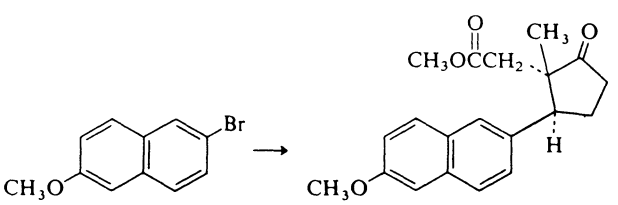


(h)

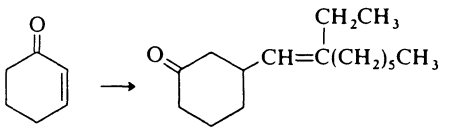


8. The conversions shown were carried out in a multistep, but "one-pot," synthetic process in which none of the intermediates needs to be isolated. Show how you could perform the transformation by suggesting a sequence of organic and inorganic reagents to be employed and the approximate reaction conditions.

(a)

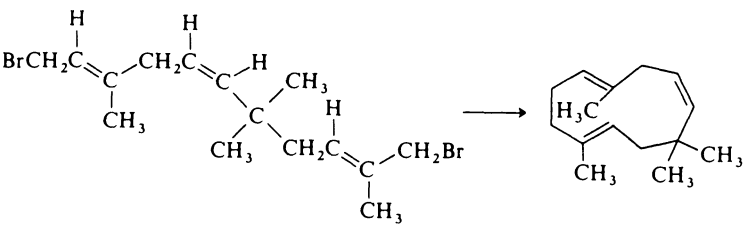


(b)

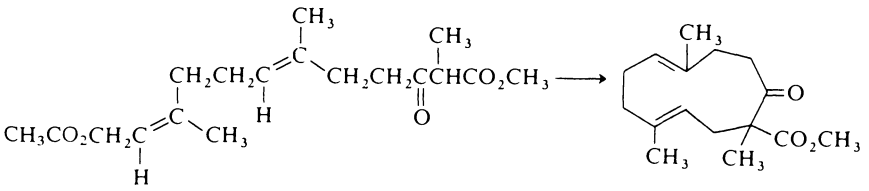


9. A number of macrocyclic syntheses which are effected by transition metal reagents have been described. Suggest an organometallic reagent or metal complex which could bring about the following conversions:

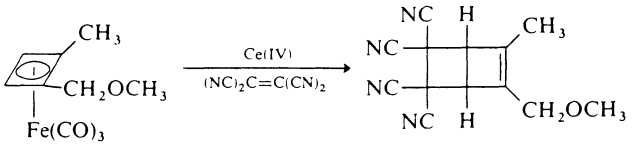
(a)



(b)

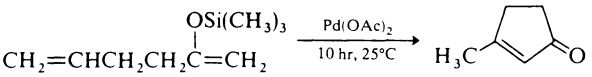


10. The cyclobutadiene complex **1** can be prepared in optically active form. When the complex is reacted with an oxidizing agent and a compound capable of trapping cyclobutadienes, the products are racemic. When the reaction is carried only to partial completion, the recovered complex remains optically active. Discuss the relevance of these results to the following question. "In oxidative decomposition of cyclobutadiene complexes, is the cyclobutadiene liberated from the complex before or after it has reacted with the trapping reagent?"



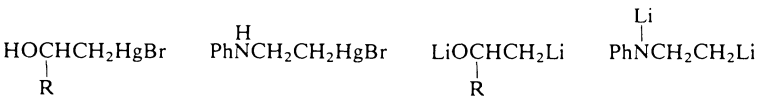
1

11. Certain unsaturated enol silyl ethers are cyclized by treatment with $Pd(OAc)_2$. For example,



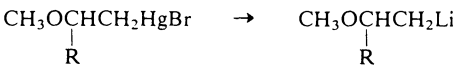
The reaction leads to the formation of metallic palladium. Suggest a mechanism for this process.

12. The solvomercuration reaction (Section 4.3) provides a convenient source of such organomercury compounds as **1** and **2**. How could these be converted to functionalized lithium reagents such as **3** and **4**?

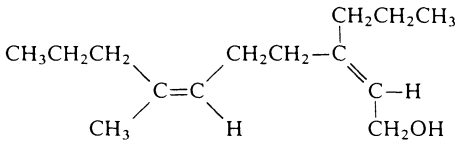


1 **2** **3** **4**

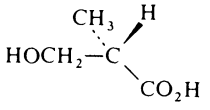
Would the procedure you have suggested also work for the following transformation? Explain your reasoning.



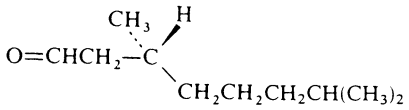
13. The compound shown below is a constituent of the pheromone of the codling moth. It has been synthesized using *n*-propyl bromide, propyne, 1-pentyne, ethylene oxide, and CO_2 as the source of the carbon atoms. Devise a route for such a synthesis. Hint: Extensive use of the chemistry of organocopper reagents is the basis for the existing synthesis.



14. *S*-3-Hydroxy-2-methylpropanoic acid, **1**, can be obtained enantiomerically pure from isobutyric acid by a microbiological oxidation. The aldehyde **2** is available from a natural product, pulegone, also in enantiomerically pure form.

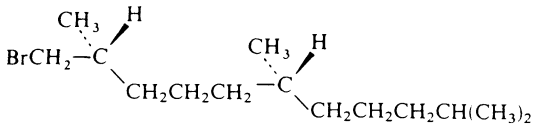


1



2

Devise a synthesis of **3**, a compound of interest as a starting material for the synthesis of α-tocopherol (vitamin E).



3

7

Cycloadditions and Unimolecular Rearrangements and Eliminations

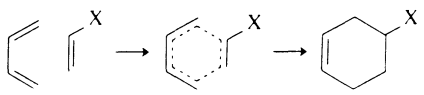
Other than a few free-radical processes, most of the reactions described to this point have involved polar or easily polarizable reactants. Carbanion reactions, reactions of alkenes with electrophiles, nucleophilic additions to carbonyl groups, metal-promoted and organometallic reactions fall into this category. The reactions to be examined in the present chapter, on the other hand, occur by a reorganization of valence electrons through activated complexes which are not appreciably more polar than the reactants. These reactions, as will be seen, usually proceed through cyclic transition states which contain four, five, or six atoms. Energy sufficient to achieve the transition state is provided by thermal or photochemical excitation of the reacting molecules. Other polar or radical-generating reagents having high chemical potential energy are not usually involved.

Many of the reactions to be discussed are concerted and may be treated mechanistically in light of the concepts of orbital-symmetry control introduced in Part A, Chapter 10. Some others may appear similar, but on mechanistic scrutiny have been found to proceed through discrete, short-lived intermediates.

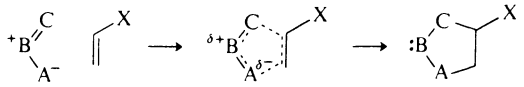
7.1. Cycloaddition Reactions

The reactions to be discussed in this section result in the formation of a new ring from two reacting molecules. A concerted mechanism requires that a single

transition state, and therefore no intermediate, lie on the reaction path between reactants and adduct. Two typical cycloadditions that are believed to occur by concerted mechanisms are the *Diels–Alder reaction*,



and *1,3-dipolar cycloaddition reactions*:

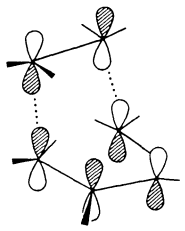


A firm understanding of concerted cycloadditions had to await the formulation of the reaction mechanism within the framework of molecular orbital theory. Consideration of the molecular orbitals of reactants and products revealed that in some cases a smooth transformation of orbitals of the reactant to those of the product is possible. In other cases, reactions that appear feasible, if no consideration is given to the symmetry and spatial orientation of the orbitals, are found to require high-energy transition states when the orbital properties are considered in detail. Those considerations have permitted description of many types of cycloadditions as "allowed" or "forbidden." As has been discussed (Part A, Chapter 10), the application of orbital-symmetry relationships permits a conclusion as to whether a given concerted reaction is or is not energetically feasible. In this chapter, the synthetic application of these reactions will be emphasized. The same orbital-symmetry relationships that are informative as to the feasibility of a given reaction often are predictive of features of the regiochemistry and stereochemistry of cycloaddition products. This predictability is an attractive feature for synthetic purposes. Further, cycloaddition reactions can enhance the efficiency of a synthetic sequence since *two* new bonds are formed in a single procedure, often with high regioselectivity, stereoselectivity, and stereospecificity.

7.1.1. The Diels–Alder Reaction: General Features

The addition of alkenes to dienes is a very useful method for the formation of six-membered carboxyclic rings. The reaction is known as the *Diels–Alder reaction*.[1] The concerted nature of the mechanism was generally agreed on and the stereospecificity of the reaction was firmly established even before the importance of orbital symmetry was recognized. In the terminology of orbital-symmetry

1. L. W. Butz and A. W. Rytina, *Org. React.* **5**, 136 (1949); M. C. Kloetzel, *Org. React.* **4**, 1 (1948); H. L. Holmes, *Org. React.* **4**, 60 (1948); A. Wasserman, *Diels–Alder Reactions*, Elsevier, New York, (1965); R. Huisgen, R. Grashey, and J. Sauer, in *Chemistry of Alkenes*, S. Patai (ed.), Interscience, New York (1964), pp. 878–928.



LUMO of dienophile

HOMO of diene

Figure 7.1. Cycloaddition of an alkene and a diene showing interaction of LUMO of alkene with HOMO of diene.

classification, the Diels–Alder reaction is a $[{}_{\pi}4_s + {}_{\pi}2_s]$ cycloaddition, an allowed process. The stereochemistry of both the diene and the alkene (the alkene is often called the dienophile) is retained in the cyclization process. The transition state for addition requires the diene to adopt the *s-cis* conformation. The diene and alkene approach each other in parallel planes. The orbital-symmetry properties of the system permit stabilization of the transition state through bonding interactions between C-1 and C-4 of the diene and the carbon atoms of the dienophilic double bond in a six-center arrangement as illustrated in Figure 7.1.

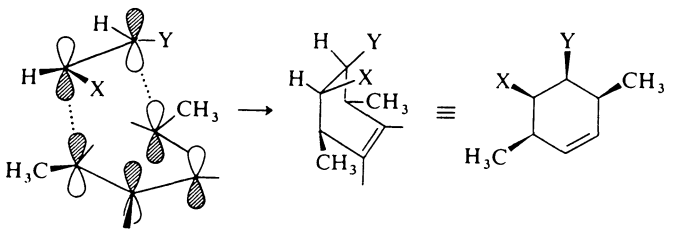
There is a further stereochemical variable in the transition state which can lead to mixtures of products in some cases. This involves the relative orientation of the diene and dienophile in the transition state. The two possible orientations, which are referred to as *endo* and *exo* addition, are illustrated in Figure 7.2.

Whether the products of *endo* and *exo* addition will be distinguishable depends, of course, on the extent of substitution present in the reactant molecules. For example, additions involving either butadiene or a *trans*-symmetrically disubstituted alkene as one of the reactants will give the same adduct by either mode of addition. Usually, the *endo* mode of addition is preferred, especially when X or Y is an unsaturated group such as a carbonyl. The empirical rule which describes the preference for *endo* addition of α,β-unsaturated dienophiles is called the *Alder rule*. The preference for this mode of addition, which is often sterically more congested, is the result of a combination of dipolar and van der Waals attractions, as well as orbital interactions involving X or Y and the diene system. The relative importance of each of these factors in determining the *exo* : *endo* ratio probably varies from system to system.[2]

There is a well-established electronic substituent effect in the Diels–Alder addition. The most favorable alkenes for reaction with most dienes are those bearing electron-attracting groups. Thus, among the most reactive dienophiles are quinones, maleic anhydride, and nitroalkenes. α,β-Unsaturated esters, ketones, and nitriles are also effective dienophiles. It is significant that if a relatively electron-deficient

2. Y. Kobuke, T. Sugimoto, J. Furukawa, and T. Funco, *J. Am. Chem. Soc.* **94**, 3633 (1972); K. L. Williamson and Y.-F. L. Hsu, *J. Am. Chem. Soc.* **92**, 7385 (1970).

(a) *Endo* Addition



(b) *Exo* Addition

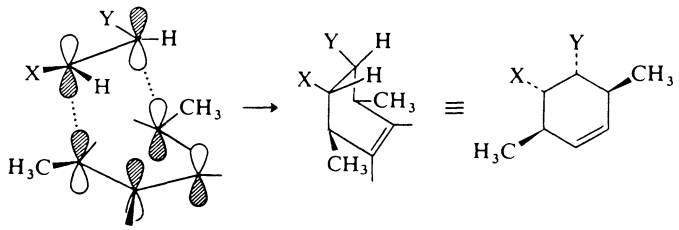
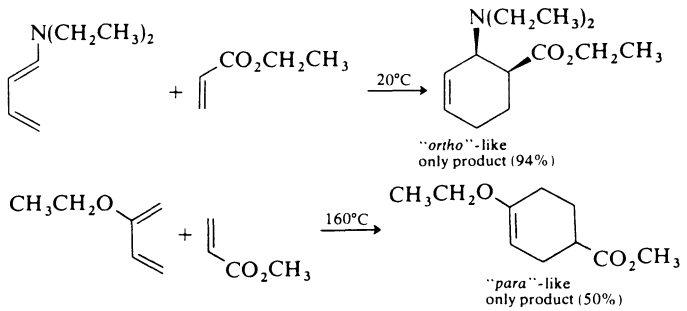


Figure 7.2. *Endo* and *exo* addition in a Diels–Alder reaction.

diene is utilized, the polarity of the transition state is apparently reversed, and electron-rich dienophiles are then preferred. For example, in the reaction of hexachlorocyclopentadiene with styrenes, the reaction is facilitated by styrenes with electron-releasing groups.[3]

A question of regioselectivity arises when both the diene and the alkene are unsymmetrically substituted. Generally, there is a preference for the "*ortho*" and "*para*" orientations, respectively, as in the examples shown.[4]

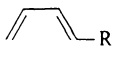


This preference can be rationalized by qualitative molecular orbital considerations that assume that the favored transition state will be that in which there is the strongest interaction between the HOMO of the diene and the LUMO of the

3. J. Sauer and H. Wiest, *Angew. Chem. Int. Ed. Engl.* **1**, 269 (1962).
4. J. Sauer, *Angew. Chem. Int. Ed. Engl.* **6**, 16 (1967).

dienophile.[5] In the most common cases, the dienophile bears an electron-withdrawing substituent and the diene an electron-releasing one. Here the interaction is between the LUMO of the dienophile and the HOMO of the diene. The strongest interactions occur between the carbon atoms with the largest coefficients, as the diagram in Figure 7.3 depicts, and lead to the regioselective preferences observed.

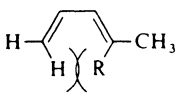
Diels–Alder cycloadditions are sensitive to steric effects of two major types. Bulky substituents on the dienophile or on the termini of the diene can hinder approach of the two components to each other and decrease the rate of reaction. This can be seen in the relative reactivity of 1-substituted butadienes toward maleic anhydride[6]:



R	k_{rel} (25°C)
$-H$	1
$-CH_3$	4.2
$-C(CH_3)_3$	<0.05

Substitution of hydrogen by methyl results in a slight rate *increase*, probably as a result of an electronic effect, while a 1-*tert*-butyl substituent produces a significant rate *decrease*. Apparently, any steric retardation to approach of the dienophile by a methyl substituent is insignificant compared to its electronic effect. With the larger *tert*-butyl group, the steric effect is dominant.

The other steric effect has to do with intramolecular van der Waals repulsions between substituents in the diene. Adoption of the *s-cis* conformation of the diene in the transition state may be accompanied by an unfavorable repulsion between substituents that do not interact strongly in the ground state. Toward tetracyanoethylene (a very reactive dienophile), *trans*-1,3-pentadiene is 10^3 times more reactive than 4-methyl-1,3-pentadiene because of the unfavorable interaction between the additional methyl substituent and the hydrogen at C-1 in the *s-cis* conformation.[7] Relatively small substituents at C-2 and C-3 of the diene exert little



R	k_{rel}
$-H$	1
$-CH_3$	10^{-3}

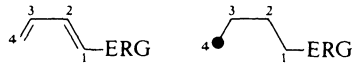
steric influence on the rate of Diels–Alder addition. 2,3-Dimethylbutadiene reacts with maleic anhydride about ten times faster than butadiene does and, again, an

5. a. K. N. Houk, *J. Am. Chem. Soc.* **95**, 4092 (1973).
   b. K. N. Houk, *Acc. Chem. Res.* **8**, 361 (1975).
   c. I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley-Interscience, New York (1976).
   d. O. Eisenstein, J. M. LeFour, N. T. Anh, and R. F. Hudson, *Tetrahedron* **33**, 523 (1977).
6. D. Craig, J. J. Shipman, and R. B. Fowler, *J. Am. Chem. Soc.* **83**, 2885 (1961).
7. C. A. Stewart, Jr., *J. Org. Chem.* **28**, 3320 (1963).

(a) Coefficient of C-2 is higher than coefficient of C-1 in LUMO of dienophile bearing an electron-withdrawing substituent.

EWG is a π acceptor as $-C(O)R$, $-NO_2$, $-CN$

(b) Coefficient of C-4 is higher than coefficient of C-1 in HOMO of diene bearing an electron-releasing substituent at C-1.



ERG is a π donor such as $-OR$, $-SR$, $-OSiMe_3$

(c) Coefficient of C-1 is higher than coefficient of C-4 in HOMO of diene bearing an electron-releasing substituent at C-2.

(d) Regioselectivity of Diels–Alder addition corresponds to that given by matching carbon atoms having the largest coefficients in the frontier orbitals.

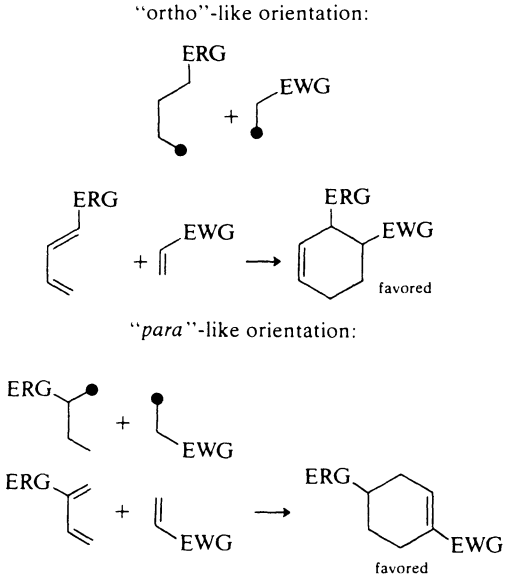
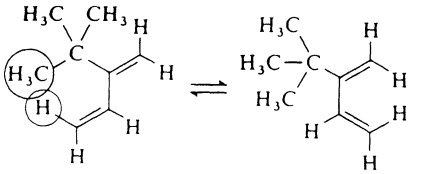


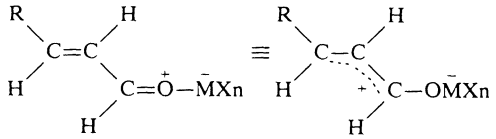
Figure 7.3. HOMO–LUMO interactions can serve to rationalize regioselectivity of Diels–Alder cycloaddition reactions.

electronic effect is probably largely responsible. 2-*Tert*-butyl-1,3-butadiene is 27 times more reactive than butadiene because of preferential stabilization of the *s-cis* conformation relative to the *s-trans* conformation. The reaction of 2-*tert*-butyl-1,3-butadiene with maleic anhydride has an activation energy of only 6.3 kcal/mol,

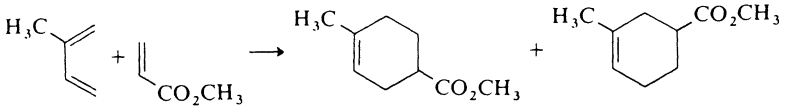


and the conformational equilibrium in the ground state is reflected directly in the rate of reaction. The presence of *tert*-butyl substituents at both C-2 and C-3, however, prevents attainment of the *s-cis* conformation, and Diels–Alder reactions of 2,3-di(*tert*-butyl-1,3-butadiene) have not been observed.[8]

Lewis acids, particularly aluminum chloride, have been noted to catalyze Diels–Alder cycloadditions.[9–11] The catalytic effect is attributed to coordination of the Lewis acid with the dienophile. The complexed dienophile is then more electro-



philic and therefore more reactive than the uncomplexed molecule toward the normal electron-rich dienes. The mechanism of the addition is still believed to be concerted, and high stereospecificity is observed.[12] Not only is the rate of cycloaddition increased, but Lewis acid catalysis usually increases the regioselectivity of the reaction.



Ref. 13

	"para"-like	*"meta"*-like
	Product ratio	
Uncatalyzed reaction: 120°C, 6 hr	70%	30%
Aluminum-chloride-catalyzed: 20°C, 3 hr	95%	5%

7.1.2. The Diels–Alder Reaction: Dienophiles

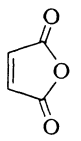
Examples of some compounds that exhibit a high level of dienophilic reactivity are collected in Table 7.1 and examples of Diels–Alder reactions of several of them

8. H. J. Backer, *Rec. Trav. Chim. Pays-Bas* **58**, 643 (1939).
9. P. Yates and P. Eaton, *J. Am. Chem. Soc.* **82**, 4436 (1960).
10. T. Inukai and M. Kasai, *J. Org. Chem.* **30**, 3567 (1965).
11. T. Inukai and T. Kojima, *J. Org. Chem.* **32**, 869, 872 (1967).
12. K. N. Houk, *J. Am. Chem. Soc.* **95**, 4094 (1973).
13. T. Inukai and T. Kojima, *J. Org. Chem.* **31**, 1121 (1966).

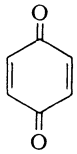
Table 7.1. Representative Dienophiles

A. Substituted Alkenes

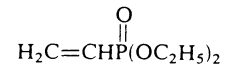
1[a] Maleic anhydride



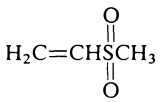
2[h] Benzoquinone



3[c] Diethyl vinylphosphonate



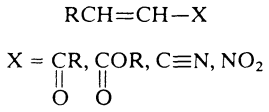
4[d] Methyl vinyl sulfone



5[e] Tetracyanoethylene

$(NC)_2C{=}C(CN)_2$

6[f] Vinyl ketones, acrolein, acrylate esters, acrylonitrile, nitroalkenes, etc.



B. Substituted Alkynes

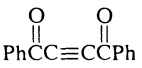
7[f] Esters of acetylenedicarboxylic acid

$H_3CO_2CC{\equiv}CCO_2CH_3$

8[g] Hexafluoro-2-butyne

$F_3CC{\equiv}CCF_3$

9[h] Dibenzoylacetylene



10[i] Dicyanoacetylene

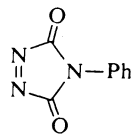
$N{\equiv}CC{\equiv}CC{\equiv}N$

C. Heteroatomic Dienophiles

11[j] Esters of azodicarboxylic acid

$H_3CO_2CN{=}NCO_2CH_3$

12[k] 4-phenyl-1,2,4-triazoline-3,5-dione



13[l] Iminourethanes

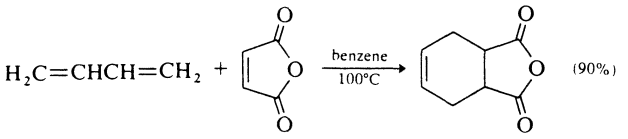
$RCH{=}NCO_2C_2H_5$

a. M. C. Kloetzel, *Org. React.* **4**, 1 (1948).
b. L. W. Butz and A. W. Rytina, *Org. React.* **5**, 136 (1949).
c. W. M. Daniewski and C. E. Griffin, *J. Org. Chem* **31**, 3236 (1966).
d. J. C. Philips and M. Oku, *J. Org. Chem.* **37**, 4479 (1972).
e. W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Krespan, *J. Am. Chem. Soc.* **80**, 2783 (1958); E. Ciganek, W. J. Linn, and O. W. Webster, *The Chemistry of the Cyano Group*, Z. Rappoport (ed.), Interscience, New York (1970), pp. 423–638.
f. H. L. Holmes, *Org. React.* **4**, 60 (1948).
g. R. E. Putnam, R. J. Harder, and J. E. Castle, *J. Am. Chem. Soc.* **83**, 391 (1961); C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Am. Chem. Soc.* **83**, 3428 (1961).
h. J. D. White, M. E. Mann, H. D. Kirshenbaum, and A. Mitra, *J. Org. Chem.* **36**, 1048 (1971).
i. C. D. Weis, *J. Org. Chem.* **28**, 74 (1963).
j. B. T. Gillis and P. E. Beck, *J. Org. Chem.* **28**, 3177 (1963).
k. B. T. Gillis and J. D. Hagarty, *J. Org. Chem.* **32**, 330 (1967).
l. M. P. Cava, C. K. Wilkins, Jr., D. R. Dalton, and K. Bessho, *J. Org. Chem.* **30**, 3772 (1965); G. Krow, R. Rodebaugh, R. Carmosin, W. Figures, H. Pannella, G. DeVicaris, and M. Grippi, *J. Am. Chem. Soc.* **95**, 5273 (1973).

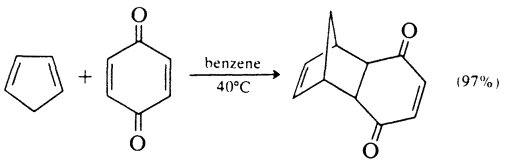
are presented in Scheme 7.1. All of these compounds bear at least one strongly electron-withdrawing substituent on a double or triple bond. Simple alkenes and alkynes such as ethylene and acetylene are notoriously poor dienophiles.

Scheme 7.1. Diels–Alder Reactions of Some Representative Dienophiles

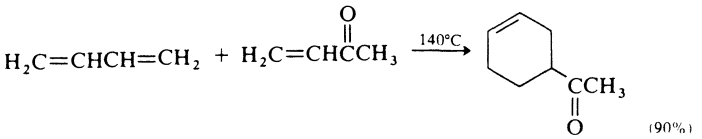
1[a] Maleic Anhydride



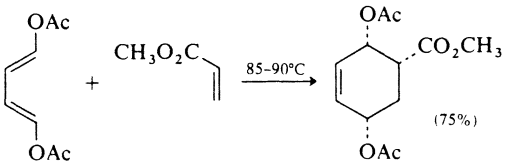
2[b] Benzoquinone



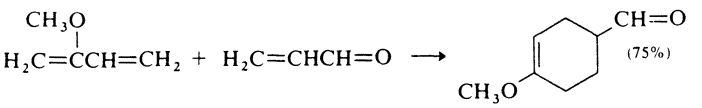
3[c] Methyl Vinyl Ketone



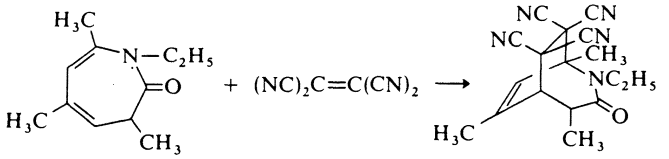
4[d] Methyl Acrylate



5[e] Acrolein

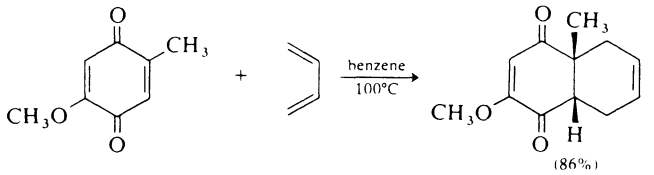


6[f] Tetracyanoethylene



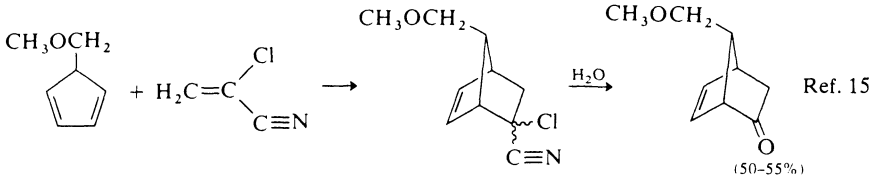
a. L. F. Fieser and F. C. Novello, *J. Am. Chem. Soc.* **64**, 802 (1942).
b. A. Wassermann, *J. Chem. Soc.*, 1511 (1935).
c. W. K. Johnson, *J. Org. Chem.* **24**, 864 (1959).
d. R. McCrindle, K. H. Overton, and R. A. Raphael, *J. Chem. Soc.* 1560 (1960); R. K. Hill and G. R. Newkome, *Tetrahedron Lett.*, 1851 (1968).
e. J. I. DeGraw, L. Goodman, and B. R. Baker, *J. Org. Chem.* **26**, 1156 (1961).
f. L. A. Paquette, *J. Org. Chem.* **29**, 3447 (1964).

Functionalized dienophiles have long played a prominent role in synthetic organic chemistry. Cycloaddition of a substituted benzoquinone to 1,3-butadiene, for example, was the first step in one of the early syntheses of steroids and served to introduce the required angular methyl group in a molecule containing appropriate functionality for further elaboration.



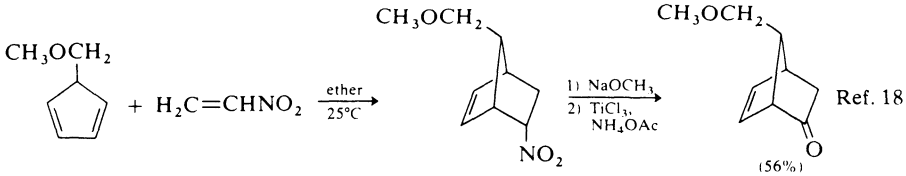
Ref. 14

The synthetic utility of the Diels–Alder reaction has been significantly expanded in recent years by development of dienophiles which contain *masked functionalities* and are the synthetic equivalents of unreactive or inaccessible species. For example, α-chloroacrylonitrile shows satisfactory reactivity as a dienophile. The α-chloronitrile function in the adduct can be hydrolyzed to a carbonyl group. Thus, α-chloroacrylonitrile is serving as a ketene ($CH_2=C=O$) equivalent. Ketene itself is not suitable as a dienophile since it has a tendency to react with dienes in a [2 + 2]-cycloaddition rather than the desired [4 + 2] fashion.



Ref. 15

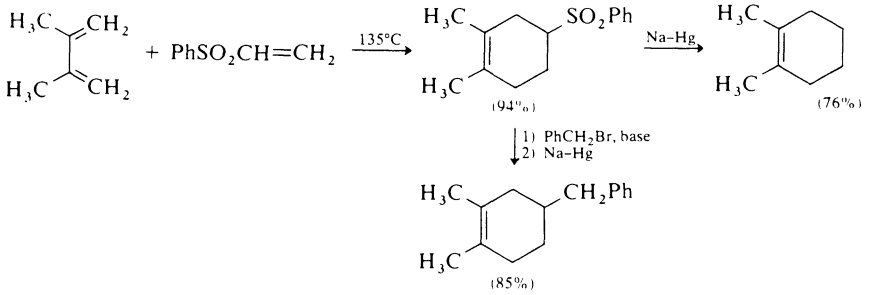
The variety of transformations available to a nitro group permits Diels–Alder adducts of nitroethylene to serve as precursors to a number of useful structural types.[16] One of these transformations converts a nitro group to a carbonyl. Thus, nitroethylene can also be used as a ketene equivalent.[17]



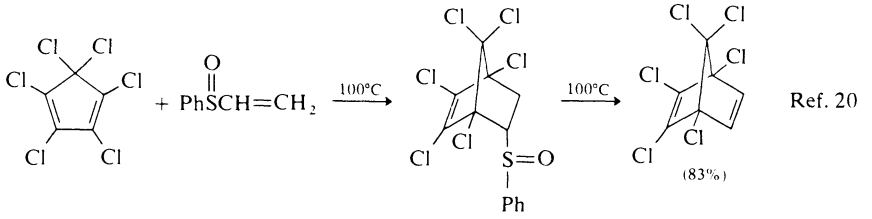
Ref. 18

14. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.* **74**, 4223 (1952).
15. E. J. Corey, N. M. Weinshenker, T. K. Schaff, and W. Huber, *J. Am. Chem. Soc.* **91**, 5675 (1969).
16. D. Ranganathan, C. B. Rao, S. Ranganathan, A. K. Mehrotra, and R. Iyengar, *J. Org. Chem.* **45**, 1185 (1980).
17. For a review of ketene equivalents, see S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *Synthesis*, 289 (1977).
18. S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *J. Am. Chem. Soc.* **96**, 5261 (1974).

Vinyl sulfones are reactive as dienophiles. The sulfonyl group can be removed reductively with sodium amalgam. In this two-step reaction sequence, the vinyl sulfone functions as an ethylene equivalent. Because the sulfonyl group also permits alkylation of the α-carbon, via the carbanion, a three-step sequence permits a vinyl sulfone to serve as the synthetic equivalent of a terminal alkene.[19]

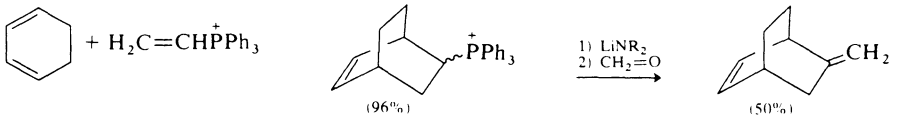


Acetylene is not only dangerous to handle at high temperatures and pressures, but is a poor dienophile. A potentially useful acetylene equivalent is phenyl vinyl sulfoxide. Its merits are that it is a reasonably good dienophile and that its Diels–Alder adducts eliminate benzenesulfenic acid readily, often under the conditions of their formation.



Ref. 20

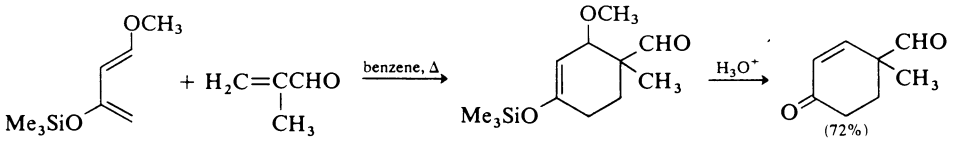
The Diels–Alder adducts of vinylphosphonium salts may be deprotonated with base to give ylides. Subsequent reaction with a carbonyl compound introduces an exocyclic carbon–carbon double bond. This sequence of reactions thus corresponds to a Diels–Alder reaction employing a substituted allene as the dienophile.[21]



19. R. V. C. Carr and L. A. Paquette, *J. Am. Chem. Soc.* **102**, 853 (1980).
20. L. A. Paquette, R. E. Moerck, B. Harirchian, and P. D. Magnus, *J. Am. Chem. Soc.* **100**, 1597 (1978).
21. R. Bonjouklian and R. A. Ruden, *J. Org. Chem.* **42**, 4095 (1977).

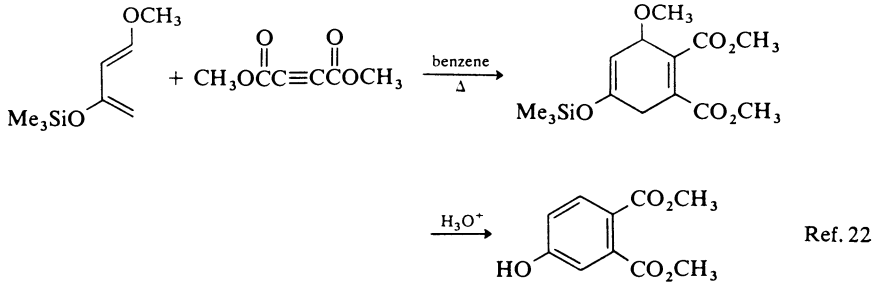
7.1.3. The Diels–Alder Reaction: Dienes

Simple dienes react readily with good dienophiles in Diels–Alder reactions. As discussed earlier, steric effects can play a role in their reactivity. Functionalized dienes have become increasingly important in organic synthesis, just as have functionalized dienophiles. One which illustrates the versatility of such reagents is 1-methoxy-3-trimethylsiloxy-1,3-butadiene ("Danishefsky's diene").[22] Its Diels–Alder adducts are enol trimethylsilyl ethers which are readily hydrolyzable to ketones. The methoxy group is lost during hydrolysis by elimination. Reaction of



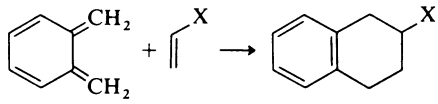
Ref. 22

Danishefsky's diene with methyl acetylenedicarboxylate gives the phenol, dimethyl 4-hydroxy-*o*-phthalate on hydrolysis.



Ref. 22

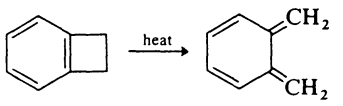
Dienes can also be generated under the conditions of the Diels–Alder reaction from precursors. The most useful examples of this type of diene are the so-called quinodimethanes. These are exceedingly reactive as dienes because the Diels–Alder



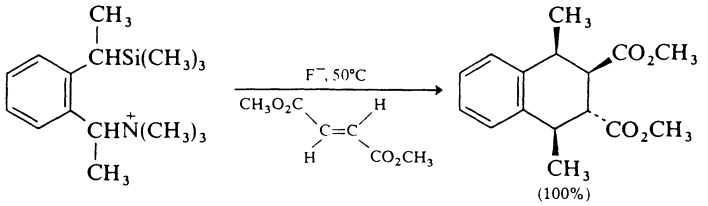
quinodimethane

reaction reestablishes a benzenoid ring with the resulting gain of aromatic stabilization.[23,24] There are three useful general routes to quinodimethanes. These include pyrolysis of benzocyclobutenes,[25]

22. S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.* **96**, 7807 (1974).
23. W. Oppolzer, *Angew. Chem. Int. Ed. Engl.* **16**, 10 (1977); T. Kametani and K. Fukumoto, *Heterocycles* **3**, 29 (1975); J. J. McCullough, *Acc. Chem. Res.* **13**, 270 (1980).
24. W. Oppolzer, *Synthesis*, 793 (1978).
25. For reviews of the chemistry of benzocyclobutenes, see M. P. Cava and M. J. Mitchell, *Cyclobutadiene and Related Compounds*, Academic Press, New York (1967), Chap. 6; I. L. Klundt, *Chem. Rev.* **70**, 471 (1970); R. P. Thummel, *Acc. Chem. Res.* **13**, 70 (1980).

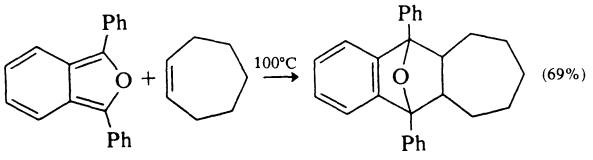


elimination processes involving α,α'-difunctionalized *o*-toluenes,[26]



and thermolysis of 1,3-dihydrobenzo[c]thiophene dioxide. This last method will be considered in Section 7.6.1. Quinodimethanes have been especially useful in intramolecular Diels–Alder reactions, as will be illustrated in Section 7.1.4.

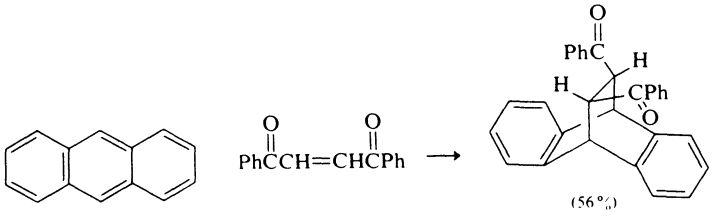
Another example of a diene with extraordinarily high reactivity is diphenylbenzo[c]furan (diphenylisobenzofuran).[27]



Ref. 28

Here again, the high reactivity can be traced to the gain of aromatic stabilization in the adduct.

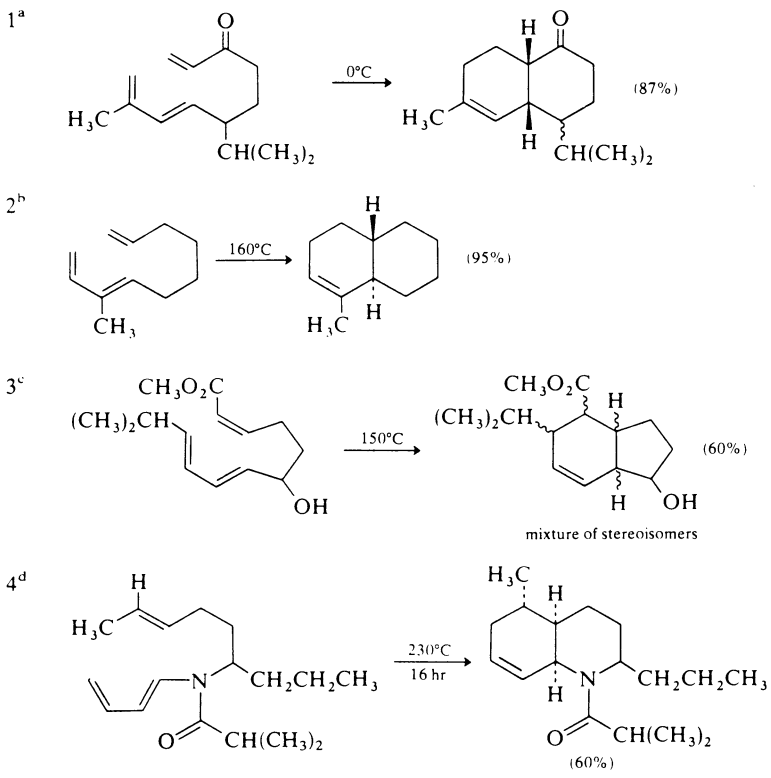
Polycyclic aromatics are moderately reactive as the diene component in Diels–Alder reactions. Anthracene forms adducts with a number of dienophiles. The addition occurs at the center ring. There is no loss of resonance stabilization, since the anthracene (resonance energy 1.60 eV) is replaced by two benzenoid rings (total delocalization energy $2 \times 0.87 = 1.74$ eV).[29]



Ref. 30

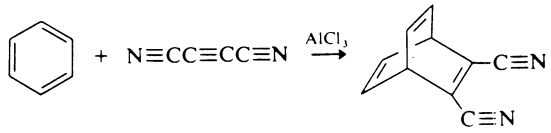
26. Y. Ito, M. Nakatsuka, and T. Saegusa, *J. Am. Chem. Soc.* **104**, 7609 (1982).
27. M. J. Haddadin, *Heterocycles*, **9**, 865 (1978); W. Friedrichsen, *Adv. Heterocycl. Chem.* **26**, 135 (1980).
28. G. Wittig and T. F. Burger, *Justus Liebigs Ann. Chem.* **632**, 85 (1960).
29. M. J. S. Dewar and D. de Llano, *J. Am. Chem. Soc.* **91**, 789 (1969).
30. D. M. McKinnon and J. Y. Wong, *Can. J. Chem.* **49**, 3178 (1971).

Scheme 7.2. Intramolecular

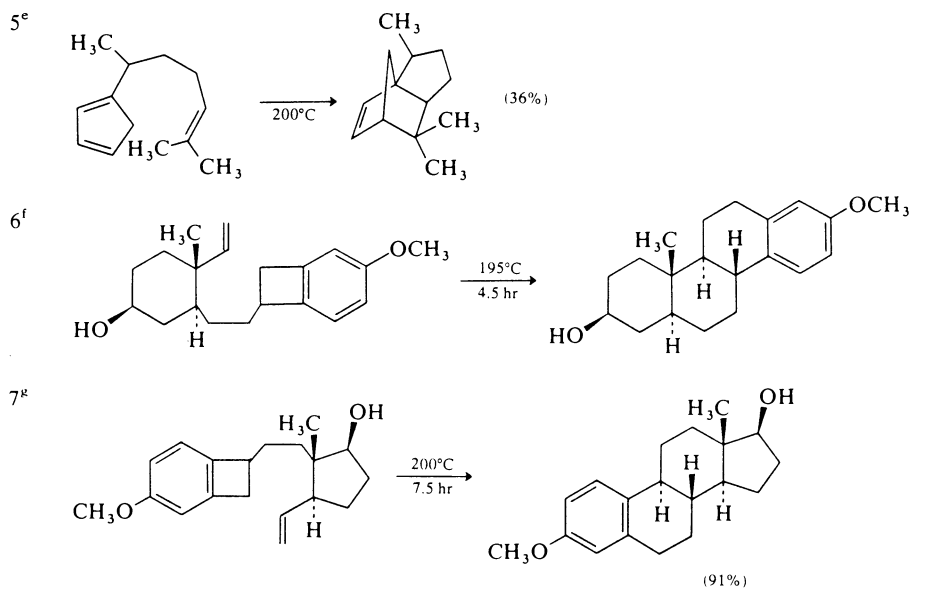


The naphthalene ring system is much less reactive. Polymethylnaphthalenes are considerably more reactive than the parent compound, and 1,2,3,4-tetramethylnaphthalene gives an adduct with maleic anhydride in 82% yield.[31] Reaction occurs exclusively at the substituted ring. It is believed that the steric repulsions between the methyl groups, which are relieved in the nonplanar adduct, exert an accelerating effect in the reaction.

With benzenoid compounds, Diels–Alder addition is rare and occurs only with powerful dienophiles. Formation of an adduct between benzene and dicyanoacetylene in the presence of $AlCl_3$ has been reported, however.[32]



31. A. Oku, Y. Ohnishi, and F. Mashio, *J. Org. Chem.* **37**, 4264 (1972).
32. E. Ciganek, *Tetrahedron Lett.* 3321 (1967).



a. D. F. Taber and B. P. Gunn, *J. Am. Chem. Soc.* **101**, 3992 (1979).
b. S. R. Wilson and D. T. Mao, *J. Am. Chem. Soc.* **100**, 6289 (1978).
c. W. R. Roush, *J. Am. Chem. Soc.* **102**, 1390 (1980).
d. W. Oppolzer and E. Flaskamp, *Helv. Chim. Acta.* **60**, 204 (1977).
e. E. G. Breitholle and A. G. Fallis, *J. Org. Chem.* **43**, 1964 (1978).
f. T. Kametani, K. Suzuki, and H. Nemoto, *J. Org. Chem.* **45**, 2204 (1980); *J. Am. Chem. Soc.* **103**, 2890 (1981).
g. P. A. Grieco, T. Takigawa, and W. J. Schillinger, *J. Org. Chem.* **45**, 2247 (1980).

Hexafluoro-2-butyne also gives Diels–Alder adducts with benzene, toluene, and other alkylbenzenes.[33]

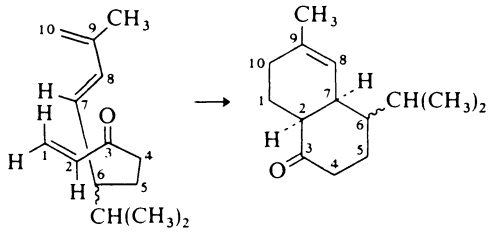
7.1.4. Intramolecular Diels–Alder Reactions

An area of Diels–Alder chemistry that has received a good deal of attention in the synthesis of polycyclic natural products is its intramolecular variant.[34] Some examples of intramolecular Diels–Alder reactions are given in Scheme 7.2.

In entry 1 of the scheme the dienophilic portion of the molecule bears a carbonyl substituent and cycloaddition occurs readily. Both stereoisomeric products

33. R. S. H. Liu, *J. Am. Chem. Soc.* **90**, 215 (1968); C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Am. Chem. Soc.* **83**, 3428 (1961).
34. For reviews, see (a) W. Oppolzer, *Angew. Chem. Int. Ed. Engl.* **16**, 10 (1977); (b) G. Brieger and J. N. Bennett, *Chem. Rev.* **80**, 63 (1980).

have *cis* ring fusions, an observation in keeping with the usual transition state geometry and the Alder rule favoring *endo*-like addition as shown.



In an analogous triene lacking a carbonyl group (entry 2), higher temperatures are required to bring about intramolecular cycloaddition, and conformational effects in the transition state favor the formation of the *trans*-ring-fused product. In entry 3, even though the dienophilic double bond bears an electron-withdrawing group, higher temperatures are required compared to entry 1 because the absence of one methylene group in the chain makes the transition state more strained. A mixture of diastereomers is obtained due to a conflict between the Alder rule favoring *endo* addition and conformational effects favoring *exo* addition. In general, conformational factors seem to play the dominant role in determining product structure in intramolecular Diels–Alder reactions.[35]

Intramolecular Diels–Alder reactions have been employed in the synthesis of heterocyclic (entry 4) and tricyclic (entry 5) ring systems. Entries 6 and 7 are examples of intramolecular Diels–Alder reactions based on quinodimethane intermediates.

7.1.5. Dipolar Cycloaddition Reactions

In Part A, Chapter 10, the relationship of 1,3-dipolar cycloaddition reactions to the general topic of concerted cycloaddition reactions was discussed briefly. It is useful to discuss this reaction in somewhat more detail at this point, since it constitutes a useful method for the synthesis of heterocyclic rings. Table 7.2 lists some classes of molecules that are capable of dipolar cycloaddition. These molecules, which are called *1,3-dipoles*, are isoelectronic with allyl anion and each has at least one charge-separated resonance structure with opposite charges in a 1,3-relationship. It is this structural feature which leads to the name *1,3-dipolar cycloaddition reactions* as the general name for the particular class of reaction which

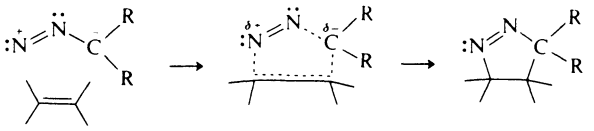
35. W. R. Roush, A. I. Ko, and H. R. Gillis, *J. Org. Chem.* **45**, 4264 (1980); R. K. Boeckman, Jr., and S. K. Ko, *J. Am. Chem. Soc.* **102**, 7146 (1980); W. R. Roush and S. E. Hall, *J. Am. Chem. Soc.* **103**, 5200 (1981).

Table 7.2. 1,3-Dipolar Compounds

$:\overset{+}{N}=\ddot{N}-\overset{-}{\ddot{C}}R_2 \leftrightarrow :N\equiv\overset{+}{N}-\overset{-}{\ddot{C}}R_2$	Diazoalkane
$:\overset{+}{N}=\ddot{N}-\overset{-}{\ddot{N}}R \leftrightarrow :N\equiv\overset{+}{N}-\overset{-}{\ddot{N}}R$	Azide
$R\overset{+}{C}=\ddot{N}-\overset{-}{\ddot{C}}R_2 \leftrightarrow RC\equiv\overset{+}{N}-\overset{-}{\ddot{C}}R_2$	Nitrile ylide
$R\overset{+}{C}=\ddot{N}-\overset{-}{\ddot{N}}R \leftrightarrow RC\equiv\overset{+}{N}-\overset{-}{\ddot{N}}R$	Nitrile imine
$R\overset{+}{C}=\ddot{N}-\overset{-}{\ddot{O}}: \leftrightarrow RC\equiv\overset{+}{N}-\overset{-}{\ddot{O}}:$	Nitrile oxide
$R_2\overset{+}{C}-\underset{R}{\ddot{N}}-\overset{-}{\ddot{C}}R_2 \leftrightarrow R_2C=\underset{R}{\overset{+}{\ddot{N}}}-\overset{-}{\ddot{C}}R_2$	Azomethine ylide
$R_2\overset{+}{C}-\underset{R}{\ddot{N}}-\overset{-}{\ddot{O}}: \leftrightarrow R_2C=\underset{R}{\overset{+}{\ddot{N}}}-\overset{-}{\ddot{O}}:$	Nitrone
$R_2\overset{+}{C}-\ddot{O}-\overset{-}{\ddot{O}}: \leftrightarrow R_2C=\overset{+}{\ddot{O}}-\overset{-}{\ddot{O}}:$	Carbonyl oxide

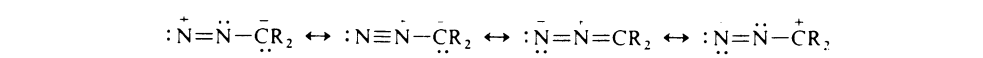
these substances undergo.[36] The other reactant in a dipolar cycloaddition, usually an alkene or alkyne, is referred to as the *dipolarophile*. Other multiply bonded species, such as imines and azo and nitroso compounds can also act as dipolarophiles.

Mechanistic studies have shown that the transition state for cycloaddition of 1,3-dipoles to carbon–carbon multiple bonds is not very polar. The rate of reaction is not strongly sensitive to solvent polarity, and this is in agreement with viewing the addition as a concerted process.[37] The formal destruction of charge that is indicated is more apparent than real, because most 1,3-dipoles are not highly polar

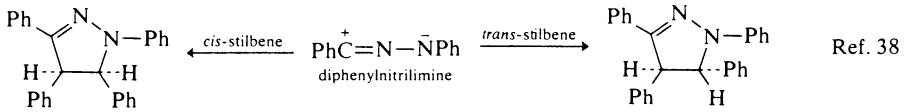


36. A comprehensive review of 1,3-dipolar cycloaddition reactions is that of G. Bianchi, C. DeMicheli, and R. Gandolfi, in *The Chemistry of Double Bonded Functional Groups, Part 1, Supplement A*, S. Patai (ed.), John Wiley and Sons, New York (1977), pp. 369–532. For a review of intramolecular 1,3-dipolar cycloaddition reactions, see A. Padwa, *Angew. Chem. Int. Ed. Engl.* **15**, 123 (1976).
37. P. K. Kadaba, *Tetrahedron* **25**, 3053 (1969); R. Huisgen, G. Szeimies, and L. Mobius, *Chem. Ber.* **100**, 2494 (1967); P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Am. Chem. Soc.* **87**, 306 (1965).

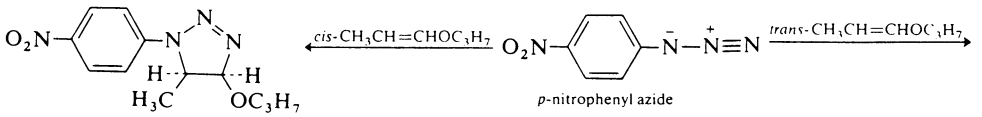
substances. The high polarity implied by any single structure is balanced by other contributing structures.

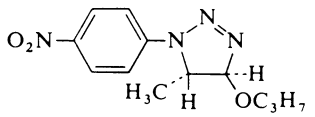


Two questions are of principal interest for predicting the structure of reaction products of 1,3-dipolar addition: (1) Is the reaction stereospecific? (2) Is the reaction regioselective? The answer to the first question is yes with respect to the dipolarophile. Many specific examples demonstrate that the cyclic product results from a stereospecific *syn* addition to olefins. The stereospecific addition that is observed is exactly what would be expected on the basis of a concerted mechanism.



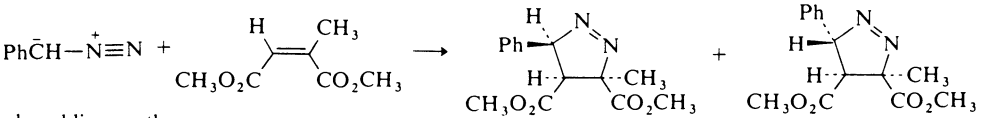
Ref. 38





Ref. 39

With some 1,3-dipoles, two possible stereoisomers can be formed by *syn* additions differing in the relative orientation of the reacting molecules. For example, when diazoalkanes add to unsymmetrical alkenes, mixtures of diastereomers are obtained.[40] This is comparable to the competing *endo* and *exo* stereoselectivities which characterize Diels–Alder cycloadditions.



phenyldiazomethane

Each 1,3-dipole exhibits its own characteristic regioselectivity toward different types of dipolarophiles. The dipolarophiles can be classified as were dienophiles, depending on the electron-donating or electron-withdrawing characteristics of substituent groups. The regioselectivity can then be interpreted in terms of frontier orbital interactions. Depending on the relative energy of the orbitals in the 1,3-dipole and the dipolarophile, the strongest interaction may be between the HOMO

38. R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron* **17**, 3 (1962).
39. R. Huisgen and G. Szeimies, *Chem. Ber.* **98**, 1153 (1965).
40. R. Huisgen and P. Eberhard, *Tetrahedron Lett.*, 4343 (1971).

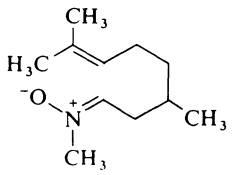
of the dipole and the LUMO of the dipolarophile or vice versa. In some circumstances the magnitudes of the two interactions may be comparable.[41] Usually for dipolarophiles with electron-attracting groups the dipole HOMO–dipolarophile LUMO interaction is dominant. The reverse is true for dipolarophiles with donor substituents.

A complete analysis requires estimation or calculation of the energy of the orbitals which are involved. The orbital coefficients and energies for the most common systems have been summarized[41] and further qualitative predictions can be made by considering the effect of additional substituents on the 1,3-dipole and dipolarophile (see Section 10.3 of Part A for a discussion.)

In addition to the role of substituents in determining regioselectivity, several other structural features can affect the reactivity of dipolarophiles. Strain increases the reactivity of olefins. Norbornene, for example, is consistently more reactive than cyclohexene in 1,3-dipolar cycloadditions. Conjugated functional groups also increase reactivity. This increased reactivity has most often been demonstrated with electron-withdrawing substituents such as carbonyl and cyano groups, but enamines and vinyl ethers, which have electron-releasing amino and alkoxy groups, are also quite reactive. Reactivity data for a series of olefins with a few typical 1,3-dipoles are summarized in Table 7.3. Scheme 7.3 gives some examples of 1,3-dipolar cycloaddition reactions.

Dipolar cycloadditions are important as a means of synthesis of heterocyclic molecules. Diazo compounds react with alkenes to form pyrazolines as shown in entry 3. Pyrazolines undergo thermal and photochemical loss of nitrogen to yield cyclopropanes. This reaction is considered, along with eliminations of nitrogen for other heterocycles, in Section 7.6.2.

Among the most synthetically useful 1,3-dipolar cycloaddition reactions are those involving nitrones.[42] The nitrone shown in entry 4 is the condensation product of benzaldehyde and *N*-methylhydroxylamine. It reacts with alkenes to yield isoxazolines. Entry 6 shows an intramolecular cycloaddition proceeding via *in situ* formation of nitrone **A**.



A

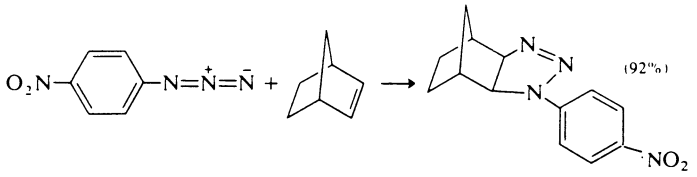
The oxygen–nitrogen bond of isoxazolines can be cleaved by reduction and a number of imaginative syntheses have employed isoxazoline formation and cleavage

41. K. N. Houk, J. Sims, B. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.* **95**, 7287 (1973); I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John Wiley, New York (1977); K. N. Houk, in *Pericyclic Reactions*, Vol. II, A. P. Marchard and R. E. Lehr (eds.), Academic Press, New York (1977), pp. 181–271.
42. For reviews, see (a) D. St. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, 205 (1975); (b) J. J. Tufariello, *Acc. Chem. Res.* **12**, 396 (1979).

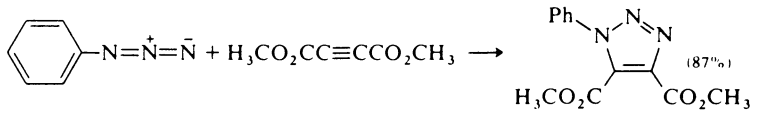
Scheme 7.3. Typical 1,3-Dipolar

A. Intermolecular Cycloaddition

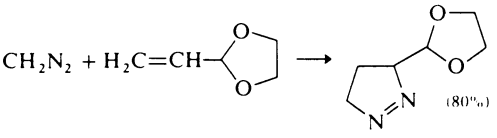
1[a]



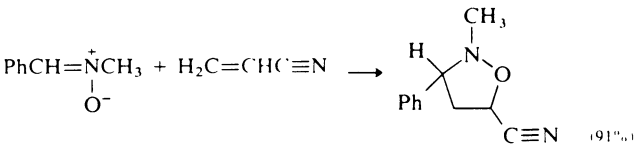
2[b]



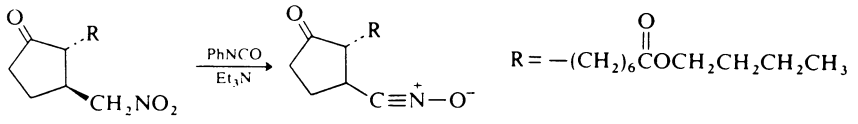
3[c]



4[d]



5[c]

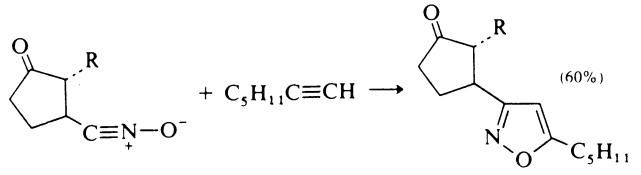


a. P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Am. Chem. Soc.* **87**, 306 (1965).
b. R. Huisgen, R. Knorr, L. Mobius, and G. Szeimies, *Chem. Ber.* **98**, 4014 (1965).
c. J. M. Stewart, C. Carlisle, K. Kem, and G. Lee, *J. Org. Chem.* **35**, 2040 (1970).
d. R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.* **101**, 2568 (1968).

as key steps. Entry 7 shows the application of this approach to the synthesis of pseudotropine. The proper stereochemical orientation of the hydroxyl group in pseudotropine is dictated by its origin in isoxazoline formation and cleavage. Entry 8 portrays an intramolecular cycloaddition, followed by reduction, used in the early stages of a synthesis of biotin.

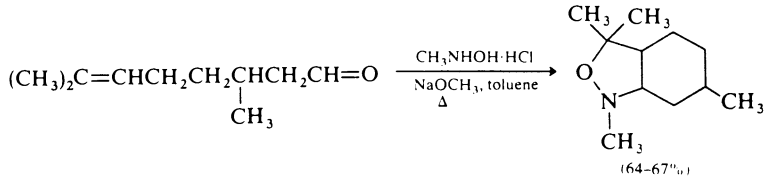
Nitrile oxides, obtained by formal dehydration of nitroalkanes, react with alkynes to produce isoxazoles (entry 5). In the example shown, the isoxazole ring was subsequently elaborated to a prostaglandin side chain.

An interesting variation of the 1,3-dipolar cycloadditions involves generation of 1,3-dipoles from strained-ring compounds. As an example, aziridines **1** and **2**

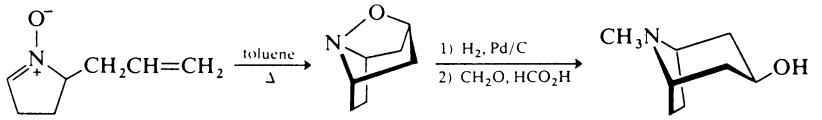


B. Intramolecular Cycloaddition

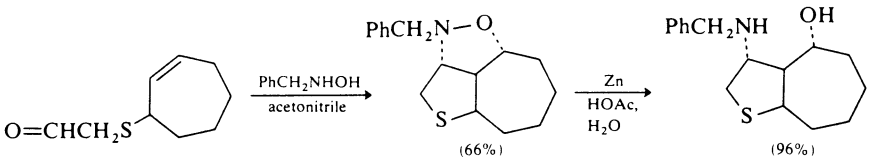
6[f]



7[g]

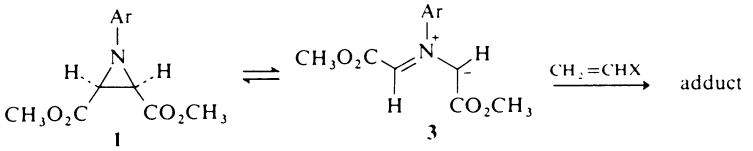


8[h]



e. A. Barco, S. Benetti, G. P. Pollini, P. G. Baraldi, M. Guarneri, D. Simoni, and C. Gandolfi, *J. Org. Chem.* **46**, 4518 (1981).
f. N. A. LeBel and D. Hwang, *Org. Synth.* **58**, 106 (1978).
g. J. J. Tufariello, G. B. Mullen, J. J. Tegeler, E. J. Trybulski, S. C. Wong, and S. A. Ali, *J. Am. Chem. Soc.* **101**, 2435 (1979).
h. P. N. Confalone, G. Pizzolato, D. L. Confalone, and M. R. Uskokovic, *J. Am. Chem. Soc.* **102**, 1954 (1980).

give adducts apparently derived from the reaction of 1,3-dipoles **3** and **4**, respectively, with a variety of dipolarophiles.[43] The evidence for the involvement of

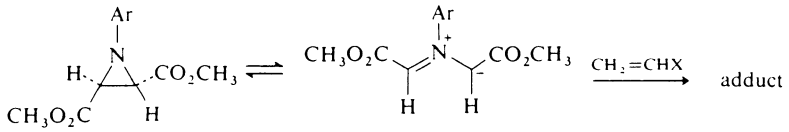


43. R. Huisgen and H. Mader, *J. Am. Chem. Soc.* **93**, 1777 (1971).

Table 7.3. Relative Reactivity of Substituted Alkenes Toward Some 1,3-Dipoles[a,b]

Substituted alkene	Ph_2CN_2	PhN_3	$PhN^+=N-\bar{N}Ph$	$PhC\equiv\overset{+}{N}-\bar{O}$	$PhC(H)=\overset{+}{N}(O^-)-CH_3$
Dimethyl fumarate	100	31	283	94	18.3
Dimethyl maleate	27.8	1.25	7.9	1.61	6.25
Norbornene	1.15	700	3.1	97	0.13
Ethyl acrylate	28.8	36.5	48	66	11.1 (methyl ester)
Butyl vinyl ether	—	1.5	—	15	—
Styrene	0.57	1.5	1.6	9.3	0.32
Ethyl crotonate	1.0	1.0	1.0	1.0	1.0
Cyclopentene	—	6.9	0.13	1.04	0.022
Terminal alkene	—	0.89 (heptene)	0.15 (heptene)	2.6 (hexene)	0.072 (heptene)
Cyclohexene	—	—	0.011	0.055	—

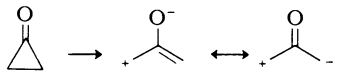
a. Data are selected from those compiled by R. Huisgen, R. Grashey, and J. Sauer, in *Chemistry of Alkenes*, S. Patai (ed.), Interscience, New York (1964), pp. 806–877.
b. Conditions such as solvent and temperature vary for each 1,3-dipole, so comparison from dipole to dipole is not possible. Following Huisgen, Grashey, and Sauer,[a] ethyl crotonate is assigned reactivity = 1.0 for each 1,3-dipole.



2 4

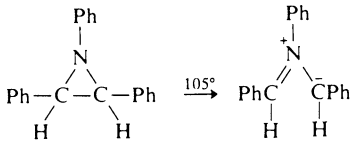
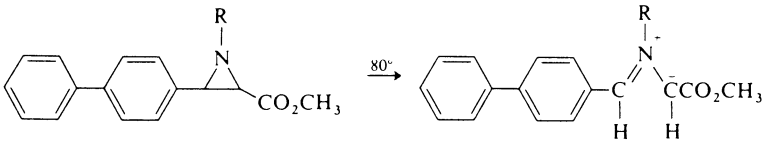
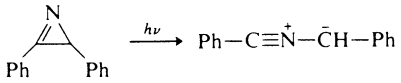
dipoles as discrete intermediates includes the observation that the reaction rates are independent of dipolarophile concentration, a result consistent with ring opening being the rate-determining step in the reaction. This ring-opening reaction appears to be most facile for aziridines that have an electron-attracting substituent capable of stabilizing the carbanionic center in the dipole.

Cyclopropanones are also reactive toward cycloadditions of various types. It is suspected that a dipolar species resulting from reversible cleavage of the cyclopropanone ring may be the reactive species.[44]



44. N. J. Turro, S. S. Edelson, J. R. Williams, T. R. Darling, and W. B. Hammond, *J. Am. Chem. Soc.* **91**, 2283 (1969); S. S. Edelson and N. J. Turro, *J. Am. Chem. Soc.* **92**, 2770 (1970); N. J. Turro, *Acc. Chem. Res.* **2**, 25 (1969).

Table 7.4. Generation of Dipolar Intermediates from Small Rings

1[a]		
2[b]		
3[c]		

a. H. W. Heine, R. Peavy, and A. J. Durbetaki, *J. Org. Chem.* **31**, 3924 (1966).
b. P. B. Woller and N. H. Cromwell, *J. Org. Chem.* **35**, 888 (1970).
c. A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *J. Am. Chem. Soc.* **95**, 1945, 1954 (1973).

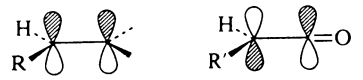
Illustrations of other 1,3-dipoles that are believed to form from ring-opening of strained rings are given in Table 7.4.

7.1.6. 2 + 2 Cycloadditions and other Reactions Leading to Cyclobutanes

Among the cycloaddition reactions that have been shown to have some generality and synthetic utility are the 2 + 2 cycloadditions of ketenes with alkenes.[45] Cyclobutanones are the products of these reactions as illustrated by the examples in Scheme 7.4. The stereoselectivity of ketene cycloadditions can be rationalized on the basis of steric effects. According to the Woodward–Hoffmann rules,[46] addition must be suprafacial to one component and antarafacial to the other if the process is to be concerted. Figure 7.4 illustrates this mode of cycloaddition for the case of an alkene and a ketene. The ketene, through its low-lying LUMO, is the antarafacial component and interacts with the HOMO of the alkene. Minimizing steric interactions in the transition state (between substituents R and R′ in Figure 7.4) leads to a cyclobutanone product in which these substituents are *cis*. In entry 4 of Scheme 7.4 the major stereoisomer has the larger methyl substituent

45. For a review, see W. T. Brady, in *The Chemistry of Ketenes, Allenes, and Related Compounds*, S. Patai (ed.), John Wiley and Sons, New York (1980), Chap. 8.
46. R. B. Woodward and R. Hoffman, *Angew. Chem. Int. Ed. Engl.* **8**, 781 (1969).

(a) Frontier orbitals of alkene and ketene.



HOMO of alkene LUMO of ketene

(b) Suprafacial addition to alkene and antarafacial addition to ketene require transition state geometry which leads to R and R′ in *cis* orientation in cyclobutanone product.

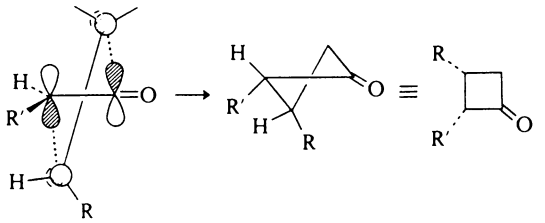


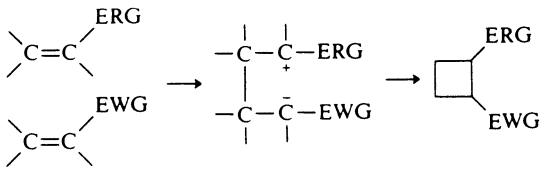
Figure 7.4. HOMO–LUMO interactions in the 2 + 2 cycloaddition of an alkene and a ketene.

in the more crowded *endo* orientation of the product in agreement with the transition state arrangement of Figure 7.4.

Ketenes are especially reactive in 2 + 2 cycloadditions because they offer a low degree of steric hindrance at one center—the carbonyl group—and a low-energy LUMO.

A few other types of compounds can react with alkenes to give cyclobutanes, but many of these reactions are believed to involve diradical intermediates, rather than being concerted.[47] The best substrates for such additions are fluoroalkenes and allenes. Either alkynes or alkenes can serve as the other reactive component. Dienes and other conjugated compounds are more reactive than are simple alkenes. Some examples of this class of reactions are given in Scheme 7.5.

Cyclobutanes can also be formed by nonconcerted processes involving zwitterionic intermediates. The combination of an electron-rich alkene (enamines, enol ethers) and an electrophilic one (nitroalkenes, cyano-substituted alkenes) is required for such processes.

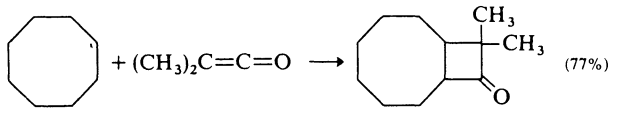


ERG = electron-releasing group (—OR, —NR_2)
EWG = electron-withdrawing group (—NO_2, —C≡N)

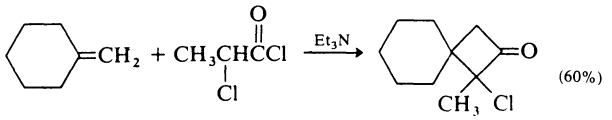
47. J. D. Roberts and C. M. Sharts, *Org. React.* **12**, 1 (1962); P. D. Bartlett, *Q. Rev. Chem. Soc.* **24**, 473 (1970).

Scheme 7.4. 2 + 2 Cycloadditions of Ketenes

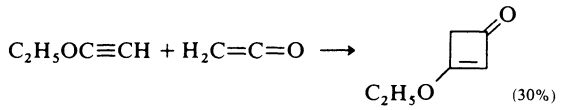
1[a]



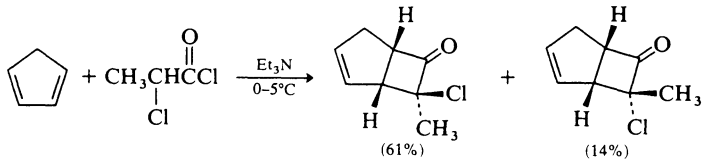
2[b]



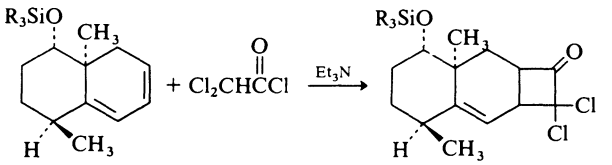
3[c]



4[d]

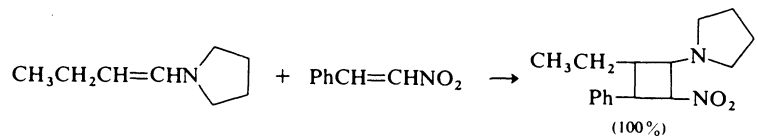


5[e]

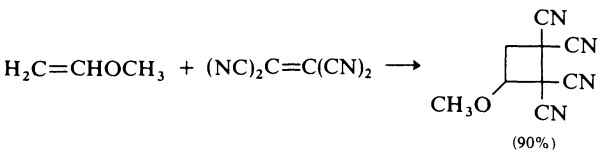


a. A. P. Krapcho and J. H. Lesser, *J. Org. Chem.* **31**, 2030 (1966).
b. W. T. Brady and A. D. Patel, *J. Org. Chem.* **38**, 4106 (1973).
c. H. H. Wasserman, J. U. Piper, and E. V. Dehmlow, *J. Org. Chem.* **38**, 1451 (1973).
d. W. T. Brady and R. Roe, *J. Am. Chem. Soc.* **93**, 1662 (1971).
e. P. A. Grieco, T. Oguri, and S. Gilman, *J. Am. Chem. Soc.* **102**, 5886 (1980).

Two examples of this reaction type are



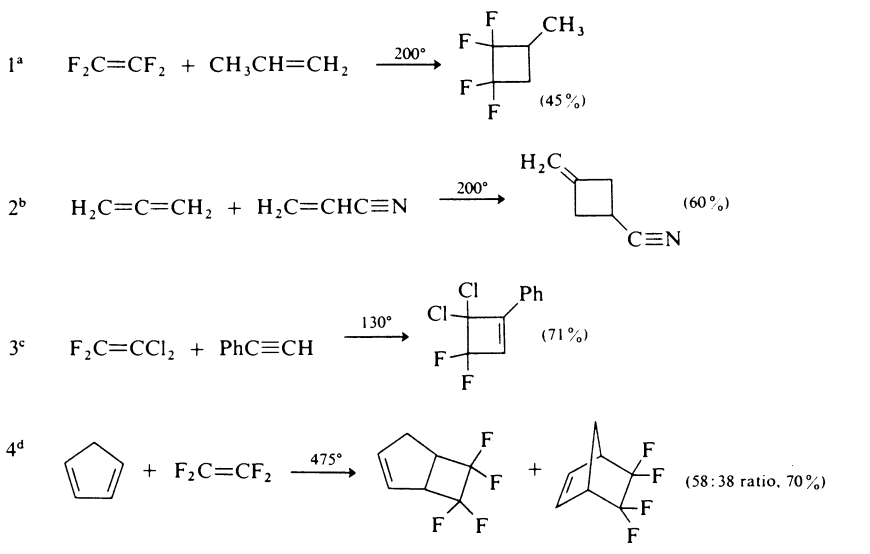
Ref. 48



Ref. 49

48. M. E. Kuehne and L. Foley, *J. Org. Chem.* **30**, 4280 (1965).
49. J. K. Williams, D. W. Wiley, and B. C. McKusick, *J. Am. Chem. Soc.* **84**, 2210 (1962).

Scheme 7.5. Formation of Cyclobutanes in Thermal Addition Reactions



a. D. D. Coffman, P. L. Barrick, R. D. Cramer, and M. S. Raasch, *J. Am. Chem. Soc.* **71**, 490 (1949).
b. H. N. Cripps, J. K. Williams, and W. H. Sharkey, *J. Am. Chem. Soc.* **81**, 2723 (1959).
c. J. D. Roberts, G. B. Kline, and H. E. Simmons, Jr., *J. Am. Chem. Soc.* **75**, 4765 (1953).
d. J. J. Drysdale, W. W. Gilbert, H. K. Sinclair, and W. H. Sharkey, *J. Am. Chem. Soc.* **80**, 3672 (1958).

In reactions with tetracyanoethylene, the stereochemistry of the double bond of an enol ether is retained in the cyclobutane product when the reaction is carried out in nonpolar solvents. In polar solvents, cycloaddition is nonstereospecific in accordance with a longer lifetime for the zwitterionic intermediate.[50]

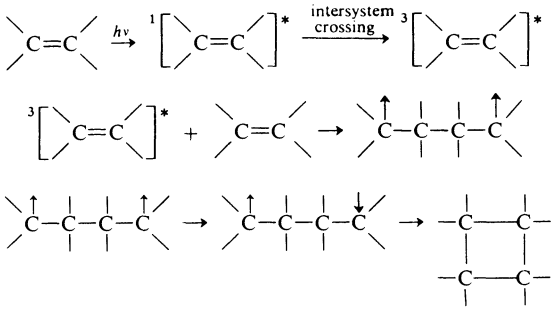
7.2. Photochemical Cycloaddition Reactions

Photochemical cycloadditions provide a method that is often complementary to thermal cycloadditions with regard to the types of compounds that can be prepared. The theoretical basis for this complementary relationship between thermal and photochemical modes of reaction lies in orbital-symmetry relationships and was discussed in detail in Part A, Chapter 10.

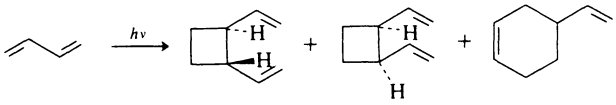
The reaction types permitted by photochemical excitation that are particularly useful for synthesis are 2 + 2 additions between two carbon–carbon double bonds, and 2 + 2 addition of alkenes with carbonyl compounds leading to oxetanes. Many

50. R. Huisgen, *Acc. Chem. Res.* **10**, 117, 199 (1977).

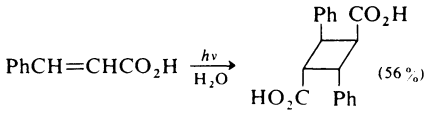
examples of intramolecular cycloadditions involving two alkene groups have been reported, and this now constitutes an important method for constructing compounds containing four-membered rings.[51] 2 + 2 Photochemical cycloadditions are not always concerted processes, the reason being that the reactive photochemical excited state is often a triplet. In this case, the intermediate adduct, which is also a triplet, must undergo spin inversion before the cycloaddition can be completed. As a result, photochemical 2 + 2 cycloadditions are not always stereospecific, in contrast to concerted thermal cycloadditions such as the Diels–Alder reaction. Stereospecificity is lost if the intermediate 1,4-diradical undergoes bond rotation faster than ring closure.



Intermolecular addition of alkenes can be carried out by photosensitization with mercury or directly with short-wavelength sources.[52] Relatively little preparative use has been made of simple alkenes, however. Dienes can be photosensitized using such materials as benzophenone, butane-2,3-dione, and acetophenone.[53] Under these conditions, preparatively useful yields of stereoisomeric mixtures of dimers are obtained. Usually, some 4 + 2 adduct accompanies the dominant 2 + 2 adduct.



The photodimerizations of cinnamic acids were among the earliest photochemical reactions to be studied.[54] These compounds give good yields of dimers

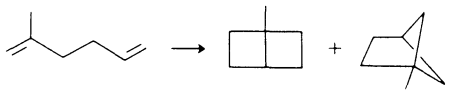


Ref. 55

51. P. de Mayo, *Acc. Chem. Res.* **4**, 41 (1971).
52. H. Yamazaki and R. J. Cvetanovic, *J. Am. Chem. Soc.* **91**, 520 (1969).
53. G. S. Hammond, N. J. Turro, and R. S. H. Liu, *J. Org. Chem.* **28**, 3297 (1963).
54. A. Mustafa, *Chem. Rev.* **51**, 1 (1952).
55. D. G. Farnum and A. J. Mostashari, *Org. Photochem. Synth.* **1**, 103 (1971).

when irradiation is carried out in the crystalline state. In solution, *cis–trans* isomerization is the dominant reaction.

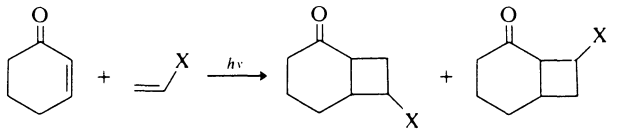
Cycloaddition of carbon–carbon double bonds can also occur intramolecularly. Direct irradiation of simple dienes leads to cyclobutanes.[56] This is a singlet-state process and is concerted. The stereochemistry of the cyclobutane can be predicted on the basis of orbital-symmetry rules (Part A, Section 10.1). Nonconjugated dienes can also undergo photochemical cyclization employing mercury or carbonyl compounds as sensitizers. Cyclobutane formation is usually unfavorable with 1,4-dienes because it would result in a very strained ring system. When the alkene units are separated by at least two carbon atoms, cyclization becomes more favorable sterically:



Ref. 57

The most widely exploited photochemical 2 + 2 cycloadditions of alkenes are intramolecular reactions that have been used to effect synthesis of a variety of complex "cage" skeletons. Cyclization is facilitated in these molecules by the proximity of the two carbon–carbon double bonds. Several examples are given in Scheme 7.6.

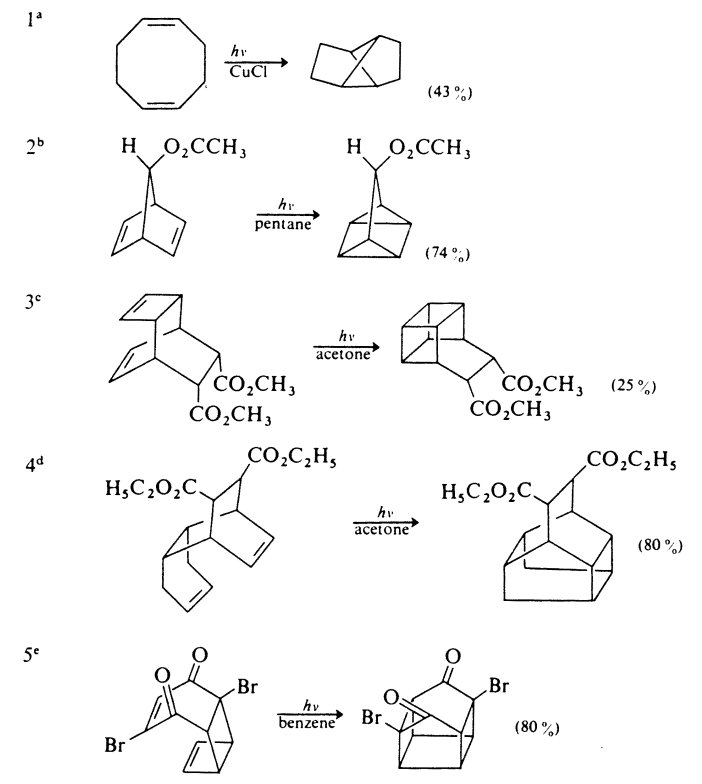
Another class of molecules that are quite prone to undergo photochemical cycloadditions are α,β-unsaturated carbonyl compounds. The reactive state in photochemical cycloadditions of α,β-unsaturated ketones is believed to be the n–π^* triplet.[58] Conservation of spin then implies that the initial intermediate is a triplet diradical, and the reaction need not be stereospecific with respect to the alkene component.[59] The reaction has been most thoroughly studied in the case of cyclopentenones and cyclohexenones. The excited states of acyclic enones and larger ring compounds can be deactivated by *cis–trans* isomerization and do not add readily to alkenes. Isomerization is not possible in cyclopentenones or cyclohexenones because of the restraint of the ring. Alkynes can serve in the addition reaction in place of alkenes.[60,61] Unsymmetrical alkenes can undergo two modes of addition. The factors governing regioselectivity in such reactions are not entirely



clear at this point. Scheme 7.7 records some examples of photochemical cycloaddition of enones and alkenes.

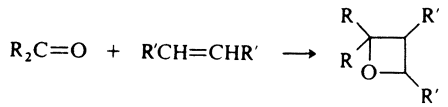
56. R. Srinivasan, *J. Am. Chem. Soc.* **84**, 4141 (1962); **90**, 4498 (1968).
57. J. Meinwald and G. W. Smith, *J. Am. Chem. Soc.* **89**, 4923 (1967); R. Srinivasan and K. H. Carlough, *J. Am. Chem. Soc.* **89**, 4932 (1967).
58. P. E. Eaton, *Acc. Chem. Res.* **1**, 50 (1968).
59. E. J. Corey, J. D. Bass, R. Le Mahieu, and R. B. Mitra, *J. Am. Chem. Soc.* **86**, 5570 (1964).
60. R. L. Cargill, T. Y. King, A. B. Sears, and M. R. Willcott, *J. Org. Chem.* **36**, 1423 (1971).
61. W. C. Agosta and W. W. Lowrance, Jr., *J. Org. Chem.* **35**, 3851 (1970).

Scheme 7.6. Intramolecular 2 + 2 Photochemical Cycloaddition Reactions of Dienes



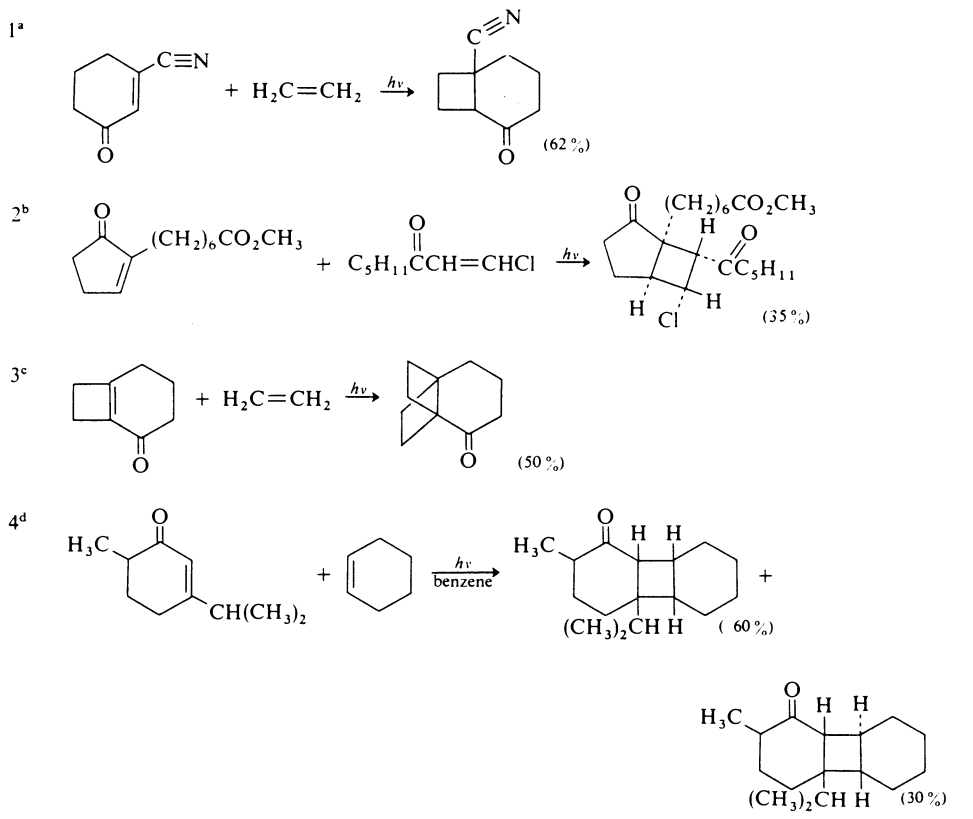
a. P. Srinivasan, *Org. Photochem. Synth.* **1**, 101 (1971); *J. Am. Chem. Soc.* **86**, 3318 (1964).
b. P. G. Gassman and D. S. Patton, *J. Am. Chem. Soc.* **90**, 7276 (1968).
c. W. G. Dauben, C. H. Schallhorn, and D. L. Whalen, *J. Am. Chem. Soc.* **93**, 1446 (1971).
d. B. M. Jacobson, *J. Am. Chem. Soc.* **95**, 2579 (1973).
e. J. C. Barborak, L. Watts, and R. Pettit, *J. Am. Chem. Soc.* **88**, 1328 (1966).

With saturated carbonyl compounds, and especially with aromatic carbonyl compounds, reaction between the photoexcited carbonyl chromophore and alkenes results in the formation of four-membered cyclic ethers (oxetanes). The addition of carbonyl compounds to alkenes to give oxetanes is often referred to as the *Paterno–Buchi reaction.*[62] The reaction is stereospecific for at least some aliphatic



62. D. R. Arnold, *Adv. Photochem.* **6**, 301 (1968).

Scheme 7.7. Photochemical Cycloaddition



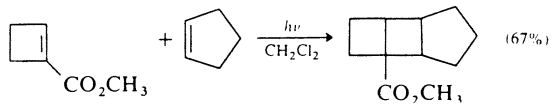
carbonyl compounds, but not for aromatic systems.[63] This result suggests that the reactive excited carbonyl compound is the singlet species for aliphatics, but a triplet for aromatics. With aromatic ketones, the predominant mode of addition can usually be predicted on the basis that the more stable of the two possible diradical intermediates will be formed by bonding of the oxygen to the less substituted end of the carbon–carbon double bond. Many successful examples have been reported

$$Ar_2C{=}O + CH_2{=}C(CH_3)_2 \xrightarrow{h\nu} Ar_2\dot{C}{-}O{-}CH_2\dot{C}(CH_3)_2 \rightarrow \underset{\text{favored}}{Ar_2C(O{-}CH_2)C(CH_3)_2}$$

and tabulated.[62] Yields are best for aromatic ketones and aldehydes. Some examples are given in Scheme 7.8.

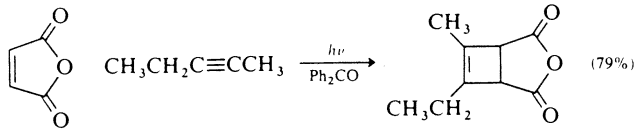
63. N. C. Yang and W. Eisenhardt, *J. Am. Chem. Soc.* **93**, 1277 (1971); D. R. Arnold, R. L. Hinman, and A. H. Glick, *Tetrahedron Lett.*, 1425 (1964); N. J. Turro and P. A. Wriede, *J. Am. Chem. Soc.* **90**, 6863 (1968); J. A. Barltrop and H. A. J. Carless, *J. Am. Chem. Soc.* **94**, 8761 (1972).

5[e]



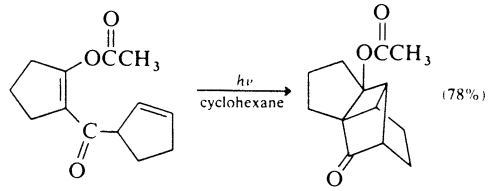
(67%)

6[f]



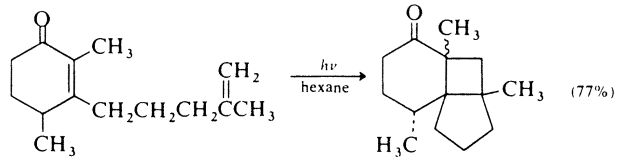
(79%)

7[g]



(78%)

8[h]



(77%)

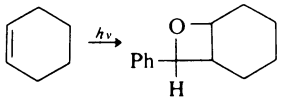
a. W. C. Agosta and W. W. Lowrance, Jr., *J. Org. Chem.* **35**, 3851 (1970).
b. J. F. Bagli and T. Bogri, *J. Org. Chem.* **37**, 2132 (1972).
c. P. E. Eaton and K. Nyi, *J. Am. Chem. Soc.* **93**, 2786 (1971).
d. P. Singh, *J. Org. Chem.* **36**, 3334 (1971).
e. P. A. Wender and J. C. Lechleiter, *J. Am. Chem. Soc.* **99**, 267 (1977).
f. R. M. Scarborough, Jr., B. H. Toder, and A. B. Smith, III, *J. Am. Chem. Soc.* **102**, 3904 (1980).
g. W. Oppolzer and T. Godel, *J. Am. Chem. Soc.* **100**, 2583 (1978).
h. M. C. Pirrung, *J. Am. Chem. Soc.* **101**, 7130 (1979).

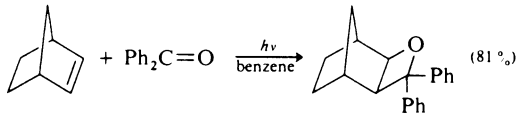
7.3. [3,3]-Sigmatropic Rearrangements: Cope and Claisen Rearrangements

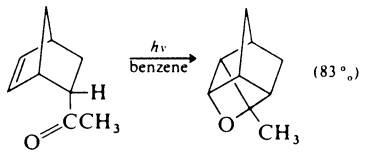
The mechanistic basis and terminology of sigmatropic rearrangements were considered in Part A, Chapter 10. The sigmatropic process that has become most firmly established as a useful tool in synthetic methodology is the [3,3]-sigmatropic rearrangement. The principles of orbital-symmetry conservation establish that concerted suprafacial [3,3]-sigmatropic rearrangements are allowed processes. Based on these principles and the results of numerous experiments, their stereochemistry is highly predictable. Some of the various kinds of [3,3]-sigmatropic rearrangements which have been exploited to synthetic advantage are presented in general terms in Table 7.5.[64]

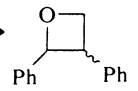
64. For recent reviews of synthetic aspects of these reactions, see (a) G. B. Bennett, *Synthesis*, 589 (1977); (b) F. E. Ziegler, *Acc. Chem. Res.* **10**, 227 (1977).

Scheme 7.8. Photochemical Cycloaddition Reactions of Carbonyl Compounds with Alkenes

1[a] PhCH=O +  (38 %)

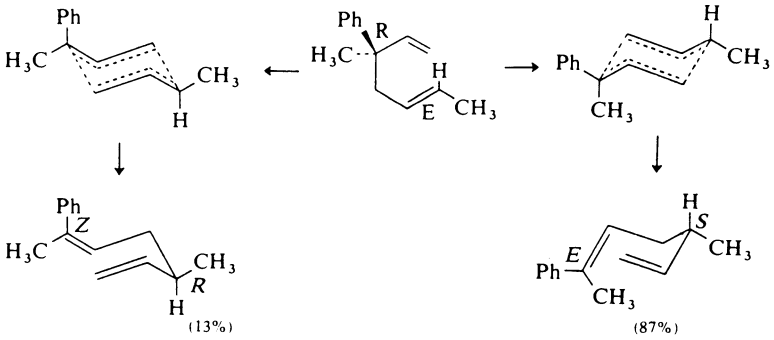
2[b]  (81 %)

3[c]  (83 %)

4[d] PhCH=O + PhCH=CH$_2$ $\xrightarrow{h\nu}$  (31%)

a. J. S. Bradshaw, *J. Org. Chem.* **31**, 237 (1966).
b. D. R. Arnold, A. H. Glick, and V. Y. Abraitys, *Org. Photochem. Synth.* **1**, 51 (1971).
c. R. R. Sauers, W. Schinski, and B. Sickles, *Org. Photochem. Synth* **1**, 76 (1971).
d. H. A. J. Carless, A. K. Maitra, and H. S. Trivedi, *J. Chem. Soc. Chem. Commun.*, **984** (1979).

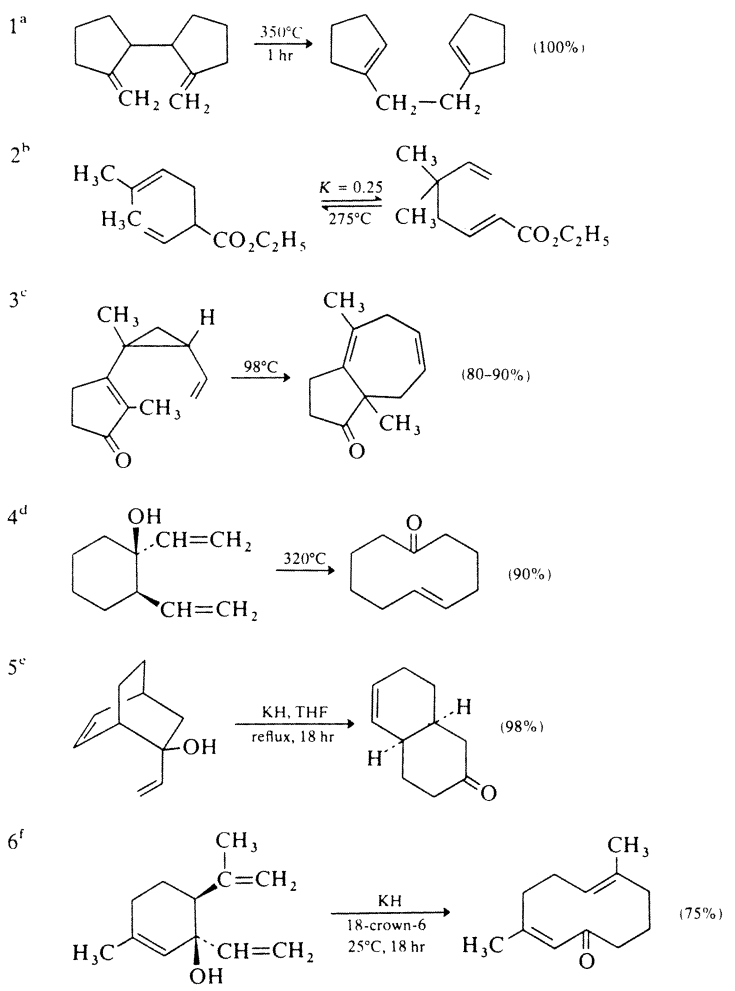
Cope rearrangements of 1,5-dienes were discussed from a mechanistic perspective in Part A, Section 10.2. A chairlike transition state in which substituents occupy equatorial sites is preferred. The stereospecificity of the rearrangement is clearly evident in the reaction shown[65]:



Both the configuration of the new chiral center and the new double bond correspond to those expected on the basis of chair-like transition states. Of four

65. R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967).

Scheme 7.9. Cope Rearrangements of 1,5-Dienes



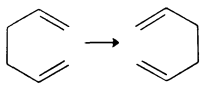
a. K. J. Shea and R. B. Phillips, *J. Am. Chem. Soc.* **102**, 3156 (1980).
b. F. E. Zeigler and J. J. Piwinski, *J. Am. Chem. Soc.* **101**, 1612 (1979).
c. P. A. Wender, M. A. Eissenstat, and M. P. Filosa, *J. Am. Chem. Soc.* **101**, 2196 (1979).
d. E. N. Marvell and W. Whalley, *Tetrahedron Lett.*, 509 (1970).
e. D. A. Evans, A. M. Golob, N. S. Mandel, and G. S. Mandel, *J. Am. Chem. Soc.* **100**, 8170 (1978).
f. W. C. Still, *J. Am. Chem. Soc.* **99**, 4186 (1977).

possible stereoisomeric products in this example, only two are formed. The major product is the one derived from a chairlike transition state in which the phenyl substituent is equatorial. The preferred double-bond geometry in the product usually has the more bulky substituent *trans* to the main carbon chain since this is the stereochemistry which arises from an equatorial-like orientation in the transition state.

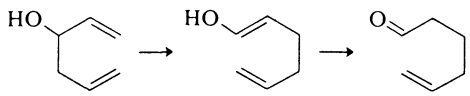
Cope rearrangements are generally reversible processes, and there are no changes in the number of single and double bonds as a result of the reaction,

Table 7.5. [3,3]-Sigmatropic

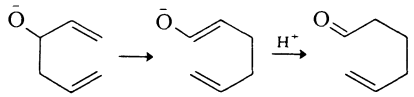
1[a] Cope Rearrangement



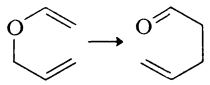
2[b] Oxy-Cope Rearrangement



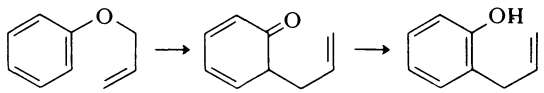
3[c] Anionic Oxy-Cope Rearrangement



4[d] Claisen Rearrangement of Allyl Vinyl Ethers



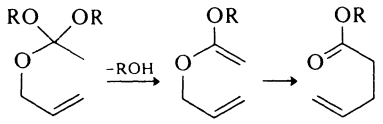
5[d] Claisen Rearrangement of Allyl Phenyl Ethers



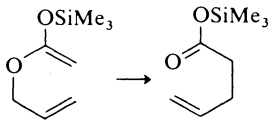
so to a rough approximation the total bond energy is unchanged. The position of the final equilibrium is governed by the relative stability of the starting materials and the products. The equilibrium is favorable in the example just cited because the double bond in the product is stabilized by conjugation with the phenyl substituent. Entry 1 in Scheme 7.9 is an example of a strongly biased equilibrium in which two terminal double bonds of the starting diene are converted to two internal, more highly substituted, double bonds in the rearranged product. In entry 2 the gain in conjugation is offset by the formation of a less highly substituted double bond leading to an equilibrium mixture which contains significant quantities of the two dienes. When ring strain is relieved, Cope rearrangements occur at much lower temperatures and with complete conversion to ring-opened products. The classic example of such a process is the conversion of cis-divinylcyclopropane to 1,4-cycloheptadiene, a reaction that occurs readily at temperatures below −40°C.[66]

66. W. von E. Doering and W. R. Roth, *Tetrahedron* **19**, 715 (1963).

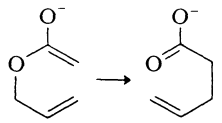
6[e] Orthoester Claisen Rearrangement



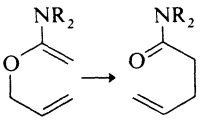
7[f] Claisen Rearrangement of *O*-Allyl-*O'*-trimethylsilyl Ketene Acetals



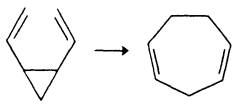
8[g] Ester Enolate Claisen Rearrangement



9[h] Claisen Rearrangement of *O*-Allyl-*N,N*-dialkyl Ketene Aminals



a. S. J. Rhoads and N. R. Raulins, *Org. React.* **22**, 1 (1975).
b. J. A. Berson and M. Jones, Jr., *J. Am. Chem. Soc.* **86**, 5019 (1964).
c. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.* **97**, 4765 (1975).
d. D. S. Tarbell, *Org. React.* **2**, 1 (1944).
e. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.* **92**, 741 (1970).
f. R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.* **94**, 5898 (1972).
g. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.* **98**, 2868 (1976).
h. D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chem. Acta.* **52**, 1030 (1969).



Entry 3 in Scheme 7.9 illustrates the application of a *cis*-divinylcyclopropane rearrangement to the preparation of an intermediate in the synthesis of pseudoguiane natural products.

When there is a hydroxyl substituent at C-3 of the diene system, the Cope rearrangement product is an enol, which is, of course, converted to the carbonyl compound. This reaction, which is called the *oxy-Cope rearrangement*, thus has a driving force resulting from the formation of the carbonyl group.[67] As entry 4 indicates, oxy-Cope rearrangements have found use in the synthesis of medium-

67. A. Viola, E. J. Iorio, K. K. Chen, G. M. Glover, U. Nayak, and P. J. Kocienski, *J. Am. Chem. Soc.* **89**, 3462 (1967).

sized rings. An important discovery made by Evans,[68] was that oxy-Cope rearrangements are markedly catalyzed by bases. When the C-3 hydroxyl group of a 1,5-diene is converted to its alkoxide ion, the anionic oxy-Cope rearrangement leads to an enolate ion, and rate accelerations of 10^{10}–10^{17} are observed. Anionic oxy-Cope rearrangements, such as those presented in entries 5 and 6, take place under relatively mild conditions.

The [3,3]-sigmatropic rearrangement of allyl vinyl ethers is known as the *Claisen rearrangement.* Allylic alcohols can be converted to allyl vinyl ethers by mercuric-ion-catalyzed exchange with ethyl vinyl ether.[69] The allyl vinyl ether need not be isolated but is usually prepared under conditions which lead to its rearrangement. The simplest of all Claisen rearrangements, conversion of allyl vinyl ether to 4-pentenal, typifies the process.

$$CH_2{=}CHCH_2OH + CH_2{=}CHOCH_2CH_3 \xrightarrow[\Delta]{Hg(OAc)_2}$$

$$[CH_2{=}CHCH_2OCH{=}CH_2] \xrightarrow[(96\%)]{} CH_2{=}CHCH_2CH_2\overset{\overset{O}{\|}}{C}H$$

Ref. 70

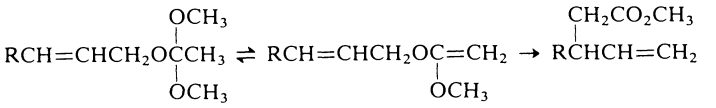
Entry 1 in Scheme 7.10 depicts one application of the Claisen rearrangement, the introduction of substituent groups at the "angular" position at the junction of two six-membered rings. Introduction of a substituent at such a position is frequently necessary in the synthesis of steroids and terpenes.

Numerous variants of the Claisen rearrangement are known which have increased its versatility and made it a powerful synthetic tool. Increased complexity in the vinyl ether portion can be tolerated. Claisen rearrangement using isopropenyl methyl ether in place of ethyl vinyl ether has been used in the preparation of unsaturated ketones as shown in entry 2. A version of the Claisen rearrangement that utilizes 3-methoxyisoprene as the alkyl vinyl ether has proved valuable as a method for introduction of isoprene units in the synthesis of natural products (entry 3).

The ortho ester modification of the Claisen rearrangement allows carboalkoxyalkyl groups to be introduced.[71] A mixed ortho ester is formed as an intermediate which undergoes sequential elimination and rearrangement.

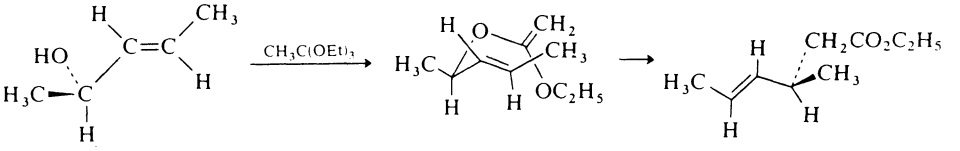
$$RCH{=}CHCH_2OH + CH_3C(OC_2H_5)_3 \rightleftharpoons RCH{=}CHCH_2O\overset{\overset{OCH_3}{|}}{\underset{\underset{OCH_3}{|}}{C}}CH_3$$

68. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.* **97**, 4765 (1975); D. A. Evans, D. J. Baillargeon, and J. V. Nelson, *J. Am. Chem. Soc.* **100**, 2242 (1978).
69. W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.* **79**, 2828 (1957).
70. S. E. Wilson, *Tetrahedron Lett.*, 4651 (1975).
71. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.* **92**, 741 (1970).



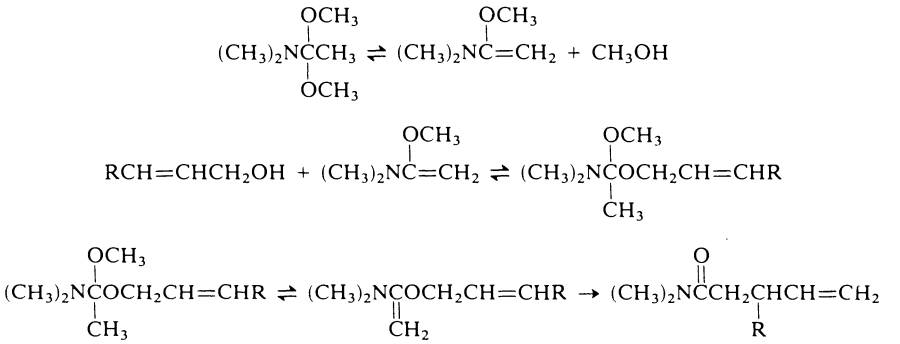
Both exchange and elimination are catalyzed by addition of a small amount of a weak acid, such as propionic acid. Ortho ester Claisen rearrangements have found frequent use in synthesis. Entries 5–8 in Scheme 7.10 are representative examples of this process.

High levels of chirality transfer have been observed in ortho ester Claisen rearrangements. Treatment of (2*R*,3*E*)-3-penten-2-ol with ethyl orthoacetate gave the ethyl ester of (3*R*,4*E*)-3-methyl-4-hexenoic acid in 90% optical yield.[72] The



stereochemistry at the new chiral center is that predicted by a chairlike transition state having quasiequatorial placement of methyl groups.

A reaction related to the ortho ester Claisen rearrangement utilizes *N*,*N*-dimethylacetamide dimethyl acetal and an allylic alcohol and produces *N*,*N*-dimethyl amides. The reaction can be carried out by heating the allyl alcohol with the *N*,*N*-dimethylacetamide dimethyl acetal, or with its elimination product 1-dimethylamino-1-methoxyethene, which can be prepared separately.[73] The stereospecificity of this process is identical to that of the ortho ester Claisen rearrangement.[72,74]

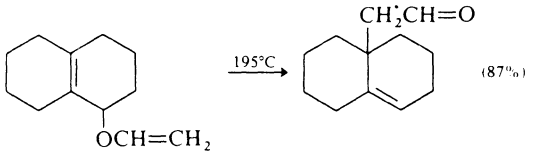


Esters of allylic alcohols can be rearranged to γ,δ-unsaturated carboxylic acids via the trimethylsilyl derivative of the ester enolate.[75] This rearrangement takes

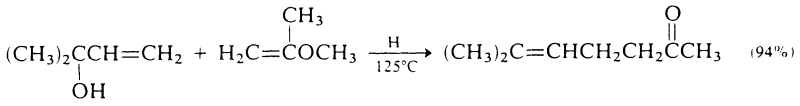
72. R. K. Hill, R. Soman, and S. Sawada, *J. Org. Chem.* **37**, 3737 (1972); **38**, 4218 (1973).
73. A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta.* **47**, 2425 (1964); D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta.* **52**, 1030 (1969).
74. W. Sucrow, M. Slopianka, and P. P. Calderia, *Chem. Ber.* **108**; 1101 (1975).
75. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.* **98**, 2868 (1976).

Scheme 7.10. Claisen

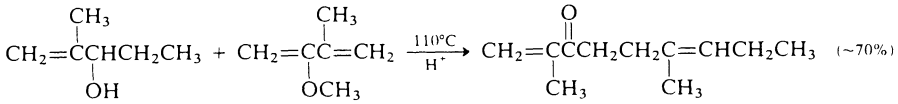
1[a]



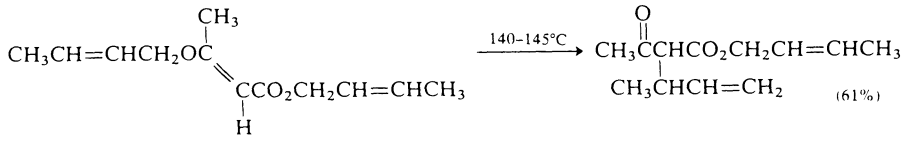
2[b]



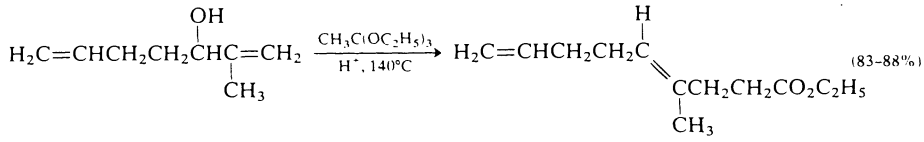
3[c]



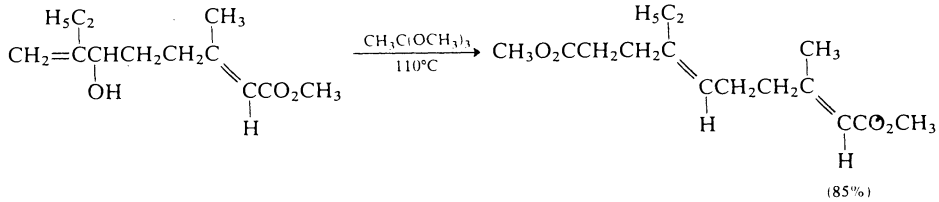
4[d]



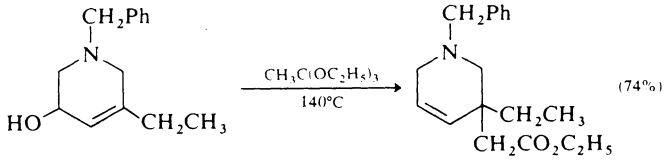
5[e]



6[f]

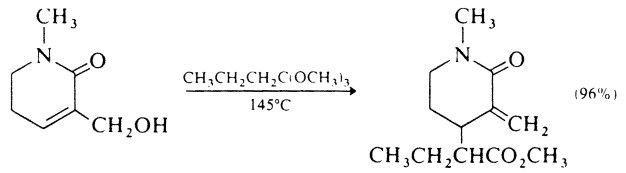


7[g]

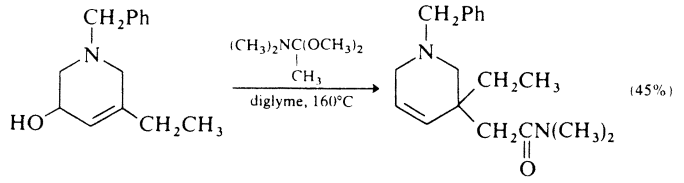


a. A. W. Burgstahler and I. C. Nordin, *J. Am. Chem. Soc.* **83**, 198 (1961).
b. G. Saucy and R. Marbet, *Helv. Chim. Acta.* **50**, 2091 (1967).
c. D. J. Faulkner and M. R. Petersen, *J. Am. Chem. Soc.* **95**, 553 (1973).
d. J. W. Ralls, R. E. Lundin, and G. F. Bailey, *J. Org. Chem.* **28**, 3521 (1963).
e. R. I. Trust and R. E. Ireland, *Org. Synth.* **53**, 116 (1973).
f. C. A. Henrick, R. Schaub, and J. B. Siddall, *J. Am. Chem. Soc.* **94**, 5374 (1972).
g. F. E. Ziegler and G. B. Bennett, *J. Am. Chem. Soc.* **95**, 7458 (1973).

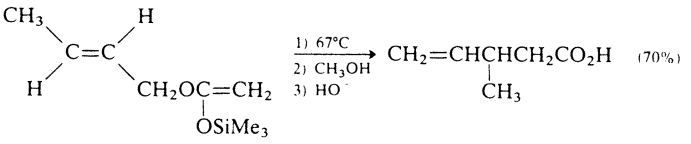
8[h]



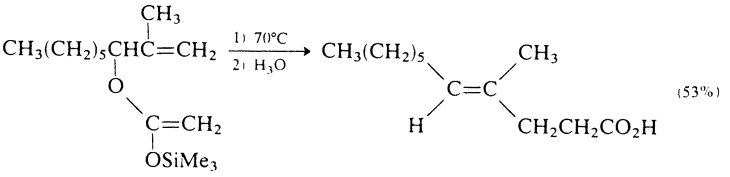
9[g]



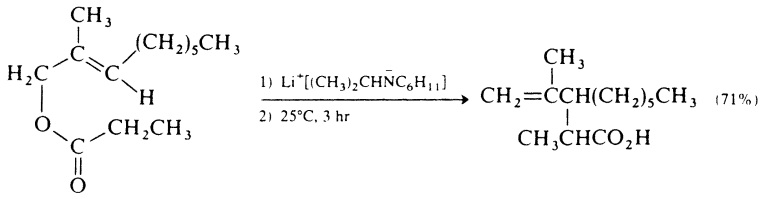
10[i]



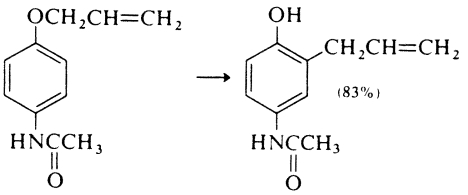
11[i]



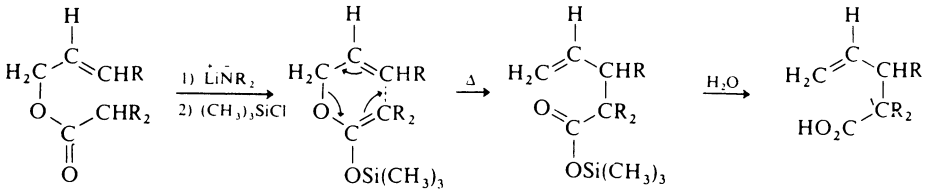
12[i]



13[k]

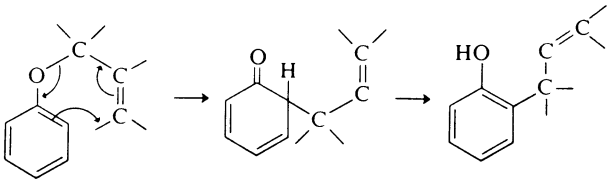


h. J. J. Plattner, R. D. Glass, and H. Rapoport, *J. Am. Chem. Soc.* **94**, 8614 (1972).
i. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.* **98**, 2868 (1976).
j. J. A. Katzenellenbogen and K. J. Christy, *J. Org. Chem.* **39**, 3315 (1974).
k. J. H. Burkhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Am. Chem. Soc.* **70**, 1363 (1948).

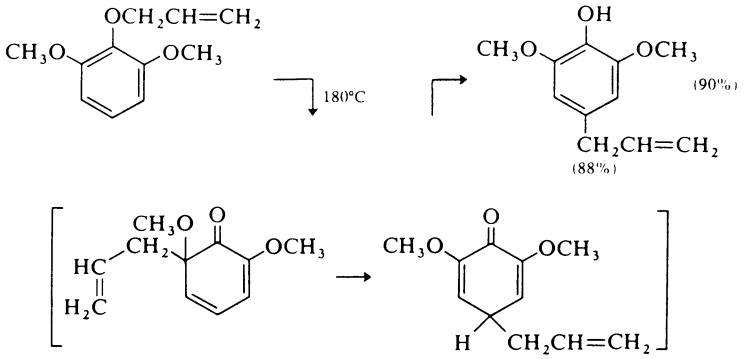


place quite rapidly slightly above room temperature. The mild conditions employed allow Claisen rearrangements to be carried out on acid-sensitive or thermally unstable molecules. Entries 10 and 11 in Scheme 7.10 are examples of this procedure. Interestingly, as shown in entry 12, ester enolates of allylic alcohols themselves undergo Claisen rearrangement at moderate temperatures. Chairlike transition states are involved here as well.[75]

Claisen rearrangements of allyl phenyl ethers to *ortho*-allylphenols were thoroughly studied before the analogous rearrangements of allyl vinyl ethers.[76] Entry 13 in Scheme 7.10 illustrates this type of Claisen rearrangement. The rearrangement step is a concerted one and leads to a cyclohexadienone, which then enolizes to an *ortho*-allylphenol.



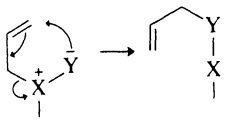
When both *ortho* positions are substituted, the allyl group undergoes a second migration via a concerted sigmatropic mechanism, giving the *para*-substituted phenol:



Ref. 77

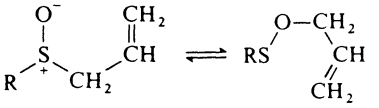
76. S. J. Rhoads, in *Molecular Rearrangements*, Vol. 1, P. de Mayo (ed.), Interscience, New York (1963), pp. 655-684.
77. I. A. Pearl, *J. Am. Chem. Soc.* **70**, 1746 (1948).

A class of [2,3]-sigmatropic rearrangements may be represented as

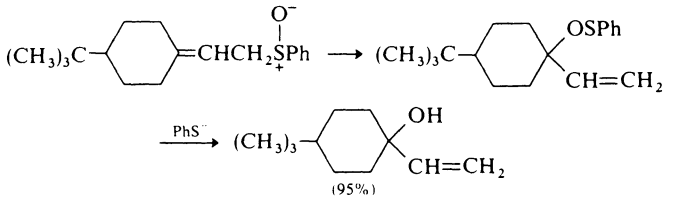


where X is sulfur or selenium and Y is oxygen or a carbanionic site.

The rearrangement of allyl sulfoxides to allyl sulfenates first received careful study in connection with the mechanism of racemization of optically active aryl sulfoxides.[78] While the allyl sulfoxide is strongly favored at equilibrium, rearrangement to the allyl sulfenate provides a low-energy pathway for racemization *via* an

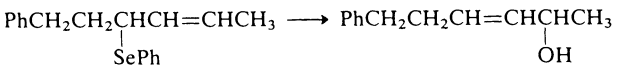


achiral intermediate. The utility of the allyl sulfoxide–allyl sulfenate rearrangement in synthesis stems from the fact that the O–S bond in the allyl sulfenate may be cleaved by a number of reagents, including sulfur nucleophiles and trimethyl phosphite, yielding an allylic alcohol with 1,3 transposition of sulfur and oxygen substituents.[79]



Ref. 80

A comparable transposition occurs with allyl selenoxides when they are generated *in situ* by oxidation of allyl selenoethers.[81,82]

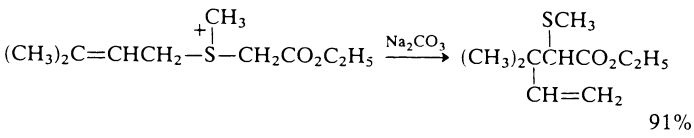


The ylide analogs of allyl sulfoxides readily undergo a [2,3]-sigmatropic rearrangement.[83]

78. R. Tang and K. Mislow, *J. Am. Chem. Soc.* **92**, 2100 (1970).
79. D. A. Evans and G. C. Andrews, *Acc. Chem. Res.* **7**, 147 (1974).
80. D. A. Evans, G. C. Andrews, and C. L. Sims, *J. Am. Chem. Soc.* **93**, 4956 (1971).
81. H. J. Reich, *J. Org. Chem.* **17**, 2570 (1975).
82. D. L. J. Clive, G. Chittatu, N. J. Curtis, and S. M. Menchen, *Chem. Commun.*, 770 (1978).
83. J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *Chem. Commun.* 537 (1968).

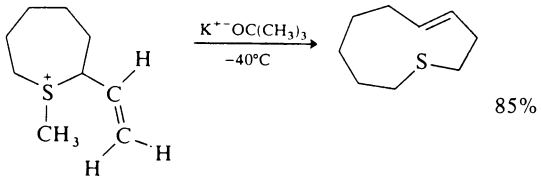
Scheme 7.11. Carbon–Carbon Bond Formation via [2,3]-Sigmatropic Rearrangements of Sulfur and Nitrogen Ylides

1[a]



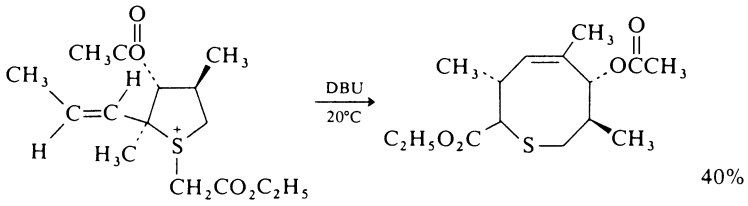
91%

2[b]



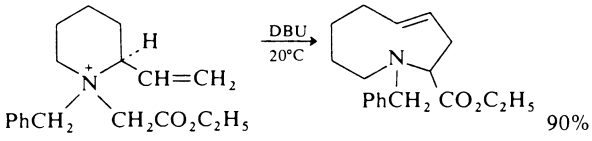
85%

3[c]



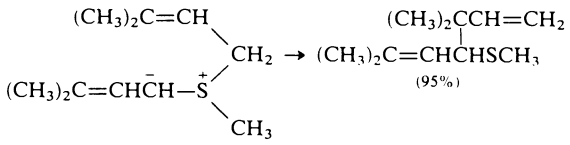
40%

4[d]



90%

a. K. Ogura, S. Furukawa, and G. Tsuchihashi, *J. Am. Chem. Soc.*, **102**, 2125 (1980).
b. V. Cere, C. Paolucci, S. Pollicino, E. Sandri, and A. Fava, *J. Org. Chem.*, **43**, 4826 (1978).
c. E. Vedejs and M. J. Mullins, *J. Org. Chem.*, **44**, 2947 (1979).
d. E. Vedejs, M. J. Arco, D. W. Powell, J. M. Renga, and S. P. Singer, *J. Org. Chem.*, **43**, 4831 (1978).



Since this reaction results in carbon–carbon bond formation, it has seen some application in synthesis, particularly for ring-expansion sequences which generate medium-sized rings. The reaction proceeds best when the ylide carbon has a second stabilizing group. Scheme 7.11 gives some examples of [2,3]-sigmatropic rearrangements of sulfur and nitrogen ylides.

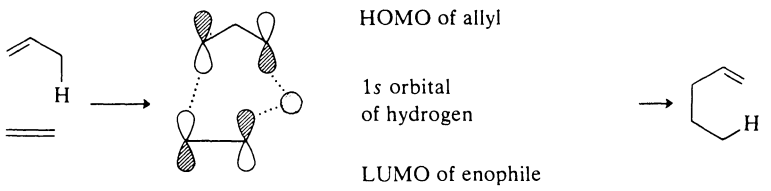
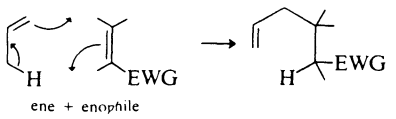


Figure 7.5. A concerted ene reaction corresponds to the interaction of a hydrogen atom with the HOMO of an allyl radical and the LUMO of the enophile and is allowed.

7.5. Ene Reactions

Electrophilic alkenes of the kind we are accustomed to seeing function as dienophiles in Diels–Alder reactions can undergo a different reaction with alkenes which have allylic hydrogens. This reaction leads to carbon–carbon bond formation, double-bond migration, and hydrogen transfer. It is called the *ene reaction.*[84] The electrophilic alkene is referred to as the *enophile.*



Concerted ene reactions are allowed by the Woodward–Hoffmann rules (Figure 7.5) but occur relatively slowly. For example, an electrophilic alkene will undergo Diels–Alder cycloaddition to a diene which bears allylic hydrogens rather than an ene reaction. Nonconcerted free-radical formation of ene products can sometimes compete with their formation by the concerted process.

Scheme 7.12 presents some ene reactions. Entries 1 and 2 illustrate the process; β-pinene is particularly prone to ene reactions and reacts with maleic anhydride in refluxing xylene. Unstrained alkenes such as isobutene require more extreme conditions to undergo ene reactions (entry 2).

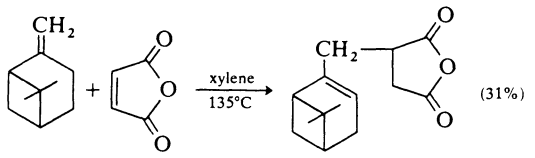
Alkenes can react with formaldehyde under conditions of acid catalysis in an ene process where protonated formaldehyde ($CH_2{=}\overset{+}{O}H$) or its equivalent acts as a highly electrophilic enophile (entry 3).

Many ene reactions can be catalyzed by Lewis acids, particularly aluminum chloride and ethylaluminum chloride.[85] Coordination of aluminum with the carbonyl group of an enophile increases its electrophilicity, making it possible to carry out ene reactions at room temperatures. Entry 4 illustrates this point.

84. For a review of ene reactions, see H. M. R. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **8**, 556 (1969).
85. B. B. Snider, *Acc. Chem. Res.* **13**, 426 (1980).

Scheme 7.12. Ene Reactions

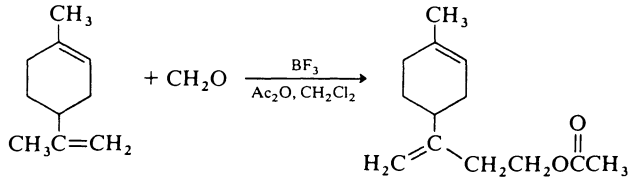
1[a]



(31%)

2[b] $(CH_3)_2C{=}CH_2 + CH_2{=}CHCCCH_3 \xrightarrow[\text{pressure}]{300°C} CH_3CCH_2CH_2CH_2C{=}CH_2$ (27%)

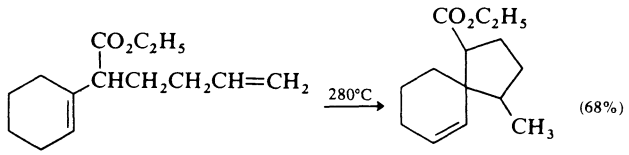
3[c]



(84%)

4[d] $(CH_3)_2C{=}CH_2 + HC{\equiv}CCO_2CH_3 \xrightarrow[25°C]{AlCl_3} CH_2{=}CCH_2CH{=}CHCO_2CH_3$ (61%)

5[e]



(68%)

(mixture of stereoisomers)

a. R. T. Arnold and J. S. Showell, *J. Am. Chem. Soc.* **79**, 419 (1957).
b. C. J. Albisetti, N. G. Fisher, M. J. Hogsed, and R. M. Joyce, *J. Am. Chem. Soc.* **78**, 2637 (1956).
c. A. T. Blomquist and R. J. Himics, *J. Org. Chem.* **33**, 1156 (1968).
d. B. B. Snider, D. J. Rodini, R. S. E. Conn, and S. Sealfon, *J. Am. Chem. Soc.* **101**, 5283 (1979).
e. W. Oppolzer, K. K. Mahalanabis, and K. Battig, *Helv. Chim. Acta.* **60**, 2388 (1977).

Intramolecular ene reactions are known (entry 5) and this aspect has been reviewed.[86]

7.6. Unimolecular Thermal Elimination Reactions

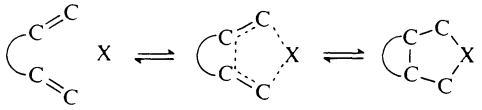
There is an important group of thermal elimination reactions which find use in synthesis. Some of these are concerted processes. When these processes are

86. W. Oppolzer and V. Snieckus, *Angew. Chem. Int. Ed. Engl.* **17**, 476 (1978).

concerted, their relative transition state energies are governed by the same orbital symmetry considerations as are cycloadditions and sigmatropic processes. These concerted reactions are highly stereospecific. There are also nonconcerted eliminations which generate intermediates that subsequently form a new bond to close a ring. A final group of synthetically important thermal reactions are unimolecular β-eliminations which proceed through cyclic transition states. These reactions, which will be considered in Section 7.6.3, usually exhibit predictable stereochemistry. Consideration of conformational and other steric features of the transition state usually provide a basis for understanding the stereoselectivity of such processes.

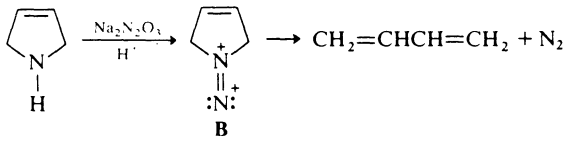
7.6.1. Cheletropic Eliminations

Just as cycloaddition reactions can be interpreted in terms of orbital-symmetry considerations, elimination reactions which are concerted also require appropriate alignment of orbitals for continuous bonding. The principles of orbital symmetry can then specify what processes can occur in concerted fashion and identify the stereochemical restrictions which are imposed by the concerted process. The number of elimination reactions that have been studied in detail is not large, but there is sufficient information to establish that orbital-symmetry controls are indeed operating. Cheletropic processes are defined as reactions in which two bonds are broken (or formed) to a single atom.



We are interested here in the elimination process. In these reactions the atom X is bound to other atoms in such a way that it is part of a small stable molecule. The most common examples involve five-membered cyclic transition states, although the term *cheletropic* is not restricted with respect to ring size so long as the process can be concerted.

A good example of a concerted elimination is the reaction that takes place on treatment of 3-pyrrolines with *N*-nitrohydroxylamine. The reactive intermediate **B** is capable of elimination of molecular nitrogen. The reaction has been shown to

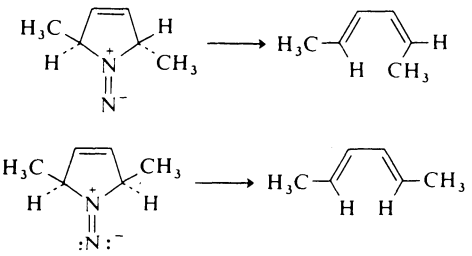


B

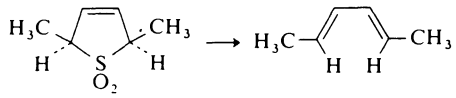
be completely stereospecific.[87] Furthermore, the groups at carbon atoms 2 and 5

87. D. M. Lemal and S. D. McGregor, *J. Am. Chem. Soc.* **88**, 1335 (1966).

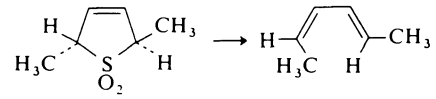
rotate in opposite senses in going to product (disrotatory). This stereochemistry is consistent with predictions based on conservation of orbital symmetry.



A synthetically useful type of a cheletropic reaction involves 2,5-dihydrothiophene-1-1-dioxides (sulfolene dioxides). These compounds can either be made by independent synthetic routes or made by cycloaddition reactions from dienes and sulfur dioxide. At elevated temperatures the ring fragments to sulfur dioxide and a diene.[88] For example, the two dimethyl derivatives **5** and **6** fragment to sulfur dioxide and *trans,trans*-2,4-hexadiene and *cis,trans*-2,4-hexadiene, respectively, at temperatures of 100–150°C. The cleavages are stereospecific and involve disrotatory motion of the substituents at C-2 and C-5 similar to the pyrroline decomposition described previously.[89] This reaction has proven to be a satisfactory

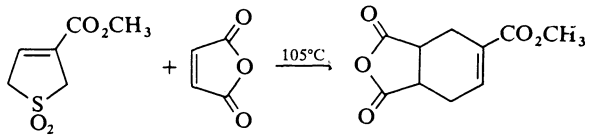


5



6

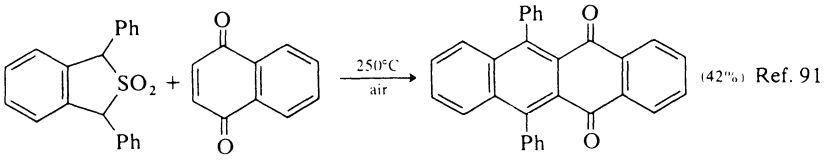
route for generating dienes which subsequently undergo Diels–Alder reactions. This concept of generating a diene from cyclic sulfones is especially valuable in the

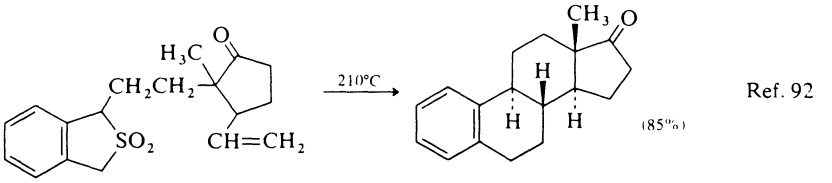


Ref. 90

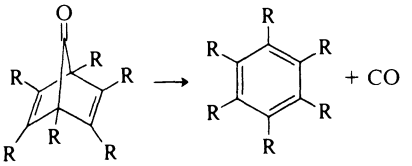
88. W. L. Mock, in *Pericyclic Reactions*, Vol. II, A. P. Marchard and R. E. Lehr (eds.), Academic Press, New York (1977), Chap. 3.
89. W. L. Mock, *J. Am. Chem. Soc.* **88**, 2857 (1966); S. D. McGregor and D. M. Lemal, *J. Am. Chem. Soc.* **88**, 2858 (1966).
90. J. M. McIntosh and R. A. Sieler, *J. Org. Chem.* **43**, 4431 (1978).

formation of highly unstable dienes such as *o*-quinodimethanes and there have been several examples of subsequent Diels–Alder reactions, both intermolecular and intramolecular.



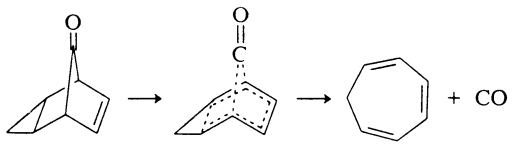


The elimination of carbon monoxide from certain cyclic ketones can occur by a concerted process. Facile thermal expulsion of carbon monoxide occurs only in molecules which permit a concerted bond making and bond breaking. The elimination of carbon monoxide from bicyclo[2.2.1]heptadien-7-ones can occur by a concerted mechanism. In fact, generation of bicyclo[2.2.1]-heptadien-7-ones is usually accompanied by spontaneous elimination of CO. The most general route



to this ring system is by Diels–Alder reaction of a substituted cyclopentadienone with an acetylene. The reaction is of some utility for the synthesis of highly substituted benzene rings.[93] Higher temperatures are required to eliminate CO from related systems that cannot lead directly to an aromatic ring. An example is the conversion of bicyclo[2.2.1]hept-2-en-7-ones to cyclohexadienes.[94] The nature of the substituents on the ring system determines the ease of elimination in this case, but the temperatures required are often above 100–150°C. Exceptionally facile elimination of CO also takes place from structure **7**, in which homoaromaticity can stabilize the transition state:

91. M. P. Cava, M. J. Mitchell, and A. A. Deana, *J. Org. Chem.* **25**, 1481 (1960).
92. K. C. Nicolaou, W. E. Barnette, and P. Ma, *J. Org. Chem.* **45**, 1463 (1980).
93. M. A. Ogliaruso, M. G. Romanelli, and E. I. Becker, *Chem. Rev.* **65**, 261 (1965).
94. B. Halton, M. A. Battiste, R. Rehberg, C. L. Deyrup, and M. E. Brennan, *J. Am. Chem. Soc.* **89**, 5964 (1967); S. C. Clarke and B. L. Johnson, *Tetrahedron* **27**, 3555 (1971).

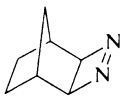


7

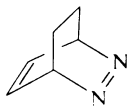
7.6.2. Decomposition of Cyclic Azo Compounds

Another significant family of elimination reactions involve processes in which a small molecule is eliminated and a bond is reclosed to form a ring. The most widely studied process of this type is the elimination of nitrogen from cyclic azo compounds.[95] This is a useful reaction, especially for the synthesis of certain strained-ring systems. The elimination of nitrogen from cyclic azo compounds can be carried out either photochemically or thermally. Although this reaction generally does not proceed by a concerted mechanism, we will first consider some special instances where concerted thermal elimination is possible, and then proceed to consider the mechanism and synthetic aspects of the more general case.

An interesting illustration that orbital-symmetry considerations are as applicable to eliminations as to cycloadditions is the contrasting stability of the azo compounds **8** and **9**. Compound **8** decomposes to norbornene and nitrogen only

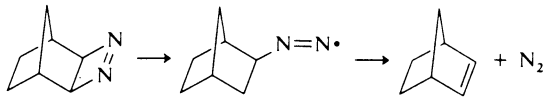


8



9

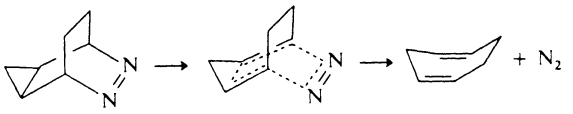
above 100°C. In contrast **9** decomposes immediately on preparation even at −78°C,[96] even though it is less strained than **8**. The reason for this difference is that if **8** were to undergo a concerted elimination, it would have to follow the high-energy (2 + 2) pathway. For **9**, the elimination can take place by a concerted (4 + 2) cycloreversion. The temperature range at which **8** decomposes is fairly typical of strained azo compounds, and it is presumably proceeding by a nonconcerted biradical mechanism. Because a C–N bond must be broken without concomitant



compensation by carbon–carbon double-bond formation, the activation energy is much higher than for the concerted process.

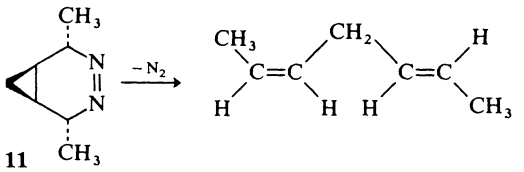
95. P. S. Engel, *Chem. Rev.* **80**, 99 (1980).
96. N. Rieber, J. Alberts, J. A. Lipsky, and D. M. Lemal, *J. Am. Chem. Soc.* **91**, 5668 (1969).

Another example of an azo compound for which a concerted elimination mechanism is available is **10**.[97] Here, the electrons of the cyclopropane ring participate in a smooth electronic reorganization associated with elimination of nitrogen. This azo compound also eliminates nitrogen at room temperature:

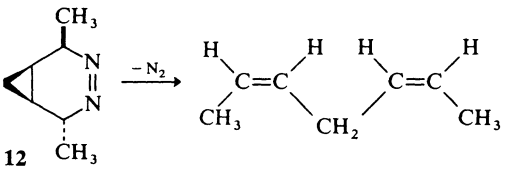


10

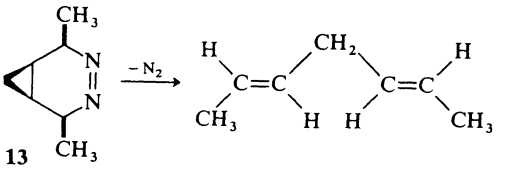
Further evidence that a concerted mechanism is operative comes from a study of the stereochemistry of the elimination of nitrogen from **11–13**.[98] In each case, the reaction is highly stereospecific and the diene produced is that expected from a concerted reaction. The transition state is of relatively low energy because of its homoaromatic nature. These azo compounds are all unstable at room temperature.



11

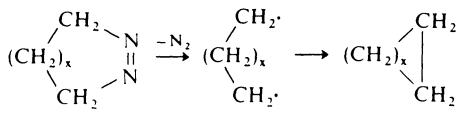


12



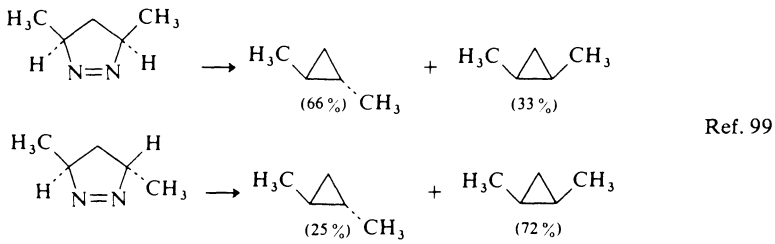
13

Although the concerted mechanism described in the preceding paragraphs is available only to those azo compounds with appropriate orbital arrangements, the decomposition by nonconcerted mechanisms occurs at low enough temperatures to be synthetically useful. Most often, the principal product from decomposition of a cyclic azo compound is the hydrocarbon formed by bond formation between the two radical centers generated when nitrogen is eliminated. The decomposition can be carried out thermally or photochemically.

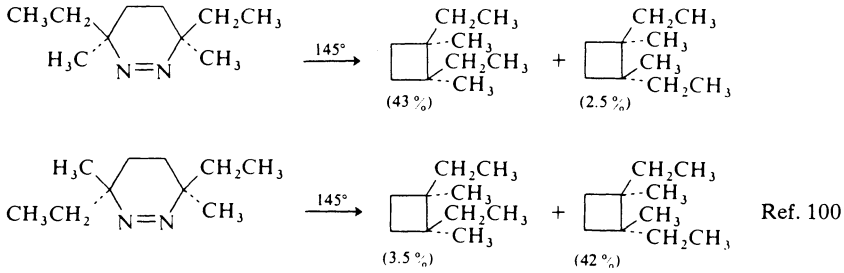


97. E. L. Allred, J. C. Hinshaw, and A. L. Johnson, *J. Am. Chem. Soc.* **91**, 3382 (1969); E. L. Allred and K. J. Voorhees, *J. Am. Chem. Soc.* **95**, 620 (1973).
98. J. A. Berson and S. S. Olin, *J. Am. Chem. Soc.* **91**, 777 (1969).

The stereochemistry of these nonconcerted reactions has been a topic of considerable discussion. Frequently, there is not complete stereorandomization as would be expected for a diradical intermediate. Although the details vary from



Ref. 99



Ref. 100

case to case, the general situation evidently involves a competition between rapid conformational changes and the equally rapid recombination of the diradical intermediates. When recombination is very rapid some stereospecificity is noted.

The principal synthetic value of these reactions is for the formation of cyclopropanes. The required pyrazoline intermediate can often be made by cycloaddition of diazoalkanes to an appropriate dipolarophile. Scheme 7.13 provides some specific examples. Entries 4–7 illustrate the use of photochemical methods to generate highly strained molecules, which would be difficult to obtain under thermal conditions.

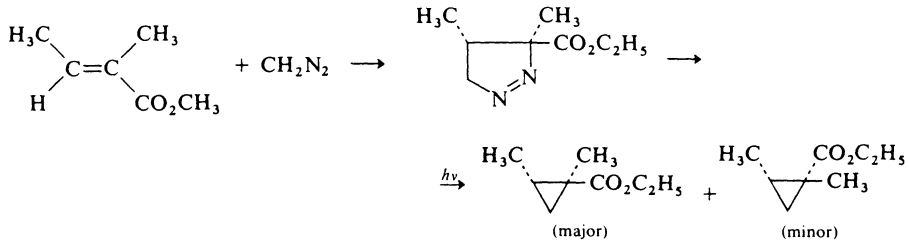
7.6.3. β-Eliminations Involving Cyclic Transition States

Another important family of elimination reactions has as a mechanistic feature cyclic transition states in which there is an intramolecular transfer of hydrogen accompanied by departure of a small molecule and formation of an olefin. Scheme 7.14 depicts the most important examples of this family of reactions. These processes are thermal, unimolecular reactions and do not require acidic or basic catalysts. There is, however, wide variation in the temperatures at which the reactions proceed at convenient rates.

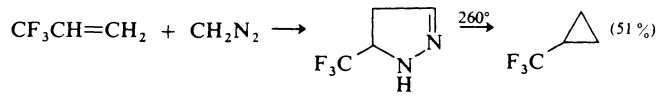
99. R. J. Crawford and A. Mishra, *J. Am. Chem. Soc.* **88**, 3963 (1966).
100. P. D. Bartlett and N. A. Porter, *J. Am. Chem. Soc.* **90**, 5317 (1968).

Scheme 7.13. Photochemical and Thermal Decomposition of Cyclic Azo Compounds

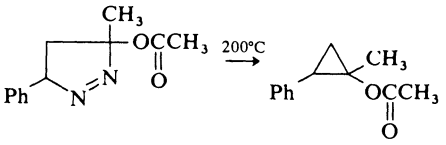
1[a]



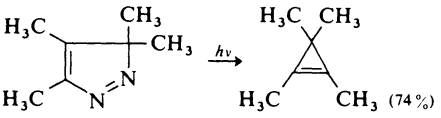
2[b]



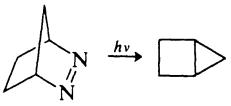
3[c]



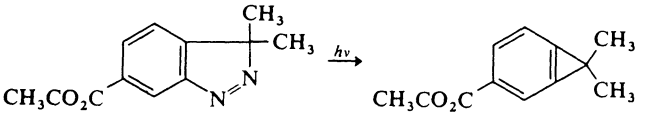
4[d]



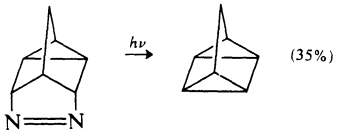
5[e]



6[f]

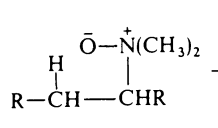
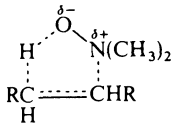
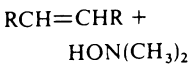
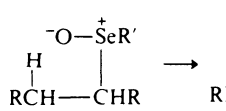
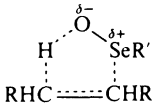
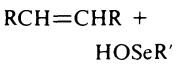
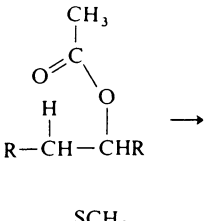
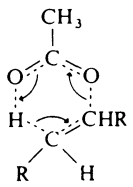
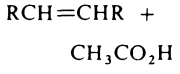
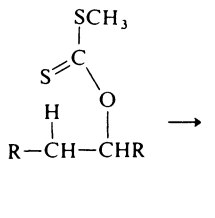
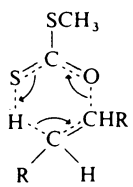
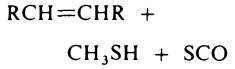


7[g]



a. T. V. Van Auken and K. L. Rinehart, Jr., *J. Am. Chem. Soc.* **84**, 3736 (1962).
b. F. Misani, L. Speers, and A. M. Lyon, *J. Am. Chem. Soc.* **78**, 2801 (1956).
c. J. P. Freeman, *J. Org. Chem.* **29**, 1379 (1964).
d. G. L. Closs, W. A. Böll, H. Heyn, and V. Dev, *J. Am. Chem. Soc.* **90**, 173 (1968).
e. C. G. Overberger, N. R. Byrd, and R. B. Mesrobian, *J. Am. Chem. Soc.* **78**, 1961 (1956).
f. R. Anet and F. A. L. Anet, *J. Am. Chem. Soc.* **86**, 525 (1964).
g. F. M. Moriarty, *J. Org. Chem.* **28**, 2385 (1963).

Scheme 7.14. Eliminations via Cyclic Transition States

Substrate	Transition state	Product	Temp. range	Ref.
			100–150°C	a
			0–100°C	b
			400–600°C	c
			150–250°C	d

a. A. C. Cope and E. R. Trumbull, *Org. React.* **11**, 317 (1960).
b. D. L. J. Clive, *Tetrahedron* **34**, 1049 (1978).
c. C. H. De Puy and R. W. King, *Chem. Rev.* **60**, 431 (1961).
d. H. R. Nace, *Org. React.* **12**, 57 (1962).

The cyclic nature of the transition states in these reactions dictate that elimination will proceed with *syn* stereochemistry. A cyclic transition state involving only five or six atoms cannot accommodate an *anti* stereochemical relationship at the site of elimination. For this reason, this family of reactions is often referred to as *thermal syn eliminations.*

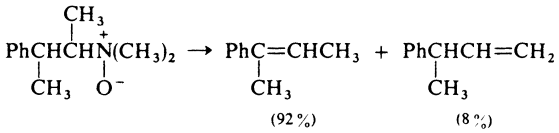
Amine oxide pyrolysis occurs at temperatures of 100–150°C. The reaction will proceed at room temperature for some amine oxides in dimethyl sulfoxide.[101] If more than one type of β-hydrogen is present in the amine oxide, a mixture of olefins will generally result. The amine oxides are prepared from tertiary amines by oxidation with peroxycarboxylic acids or hydrogen peroxide. Some typical examples are shown in Section A of Scheme 7.15.

101. D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Am. Chem. Soc.* **84**, 1734 (1962).

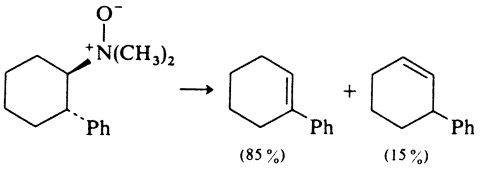
Scheme 7.15. Thermal Eliminations via Cyclic Transition States

A. Amine Oxide Pyrolyses

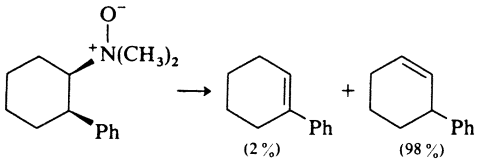
1[a]



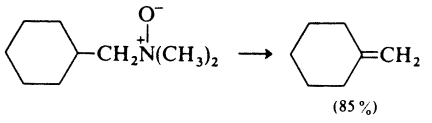
2[b]



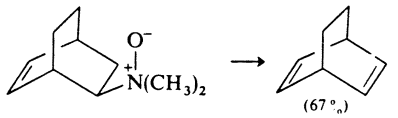
3[c]



4[d]



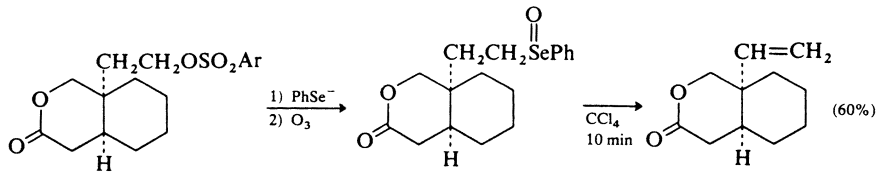
5[e]



6[f] $CH_3(CH_2)_6CH_2\overset{+}{N}(CH_3)_2 \longrightarrow CH_3(CH_2)_5CH{=}CH_2$ (87%)

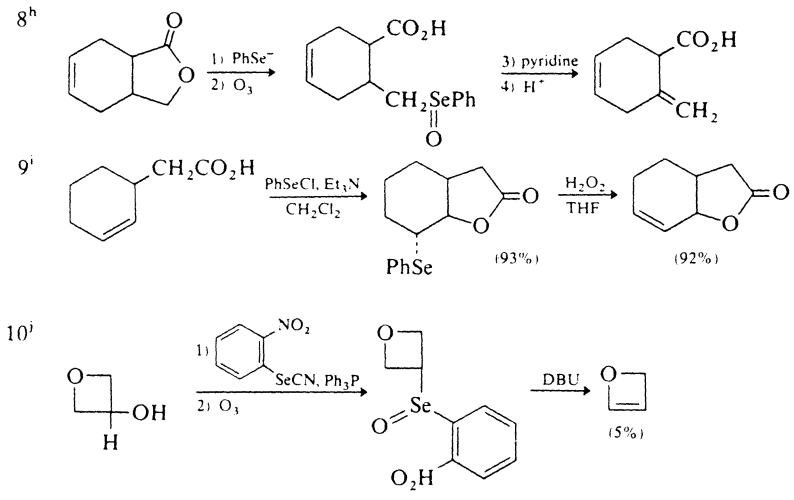
B. Selenoxide Elimination

7[g]

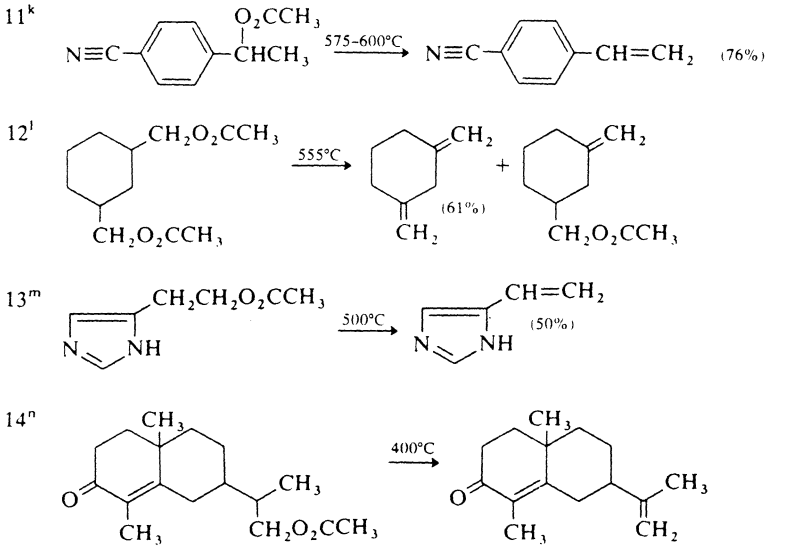


a. D. J. Cram and J. E. McCarty, *J. Am. Chem. Soc.* **76**, 5740 (1954).
b. A. C. Cope and C. L. Bumgardner, *J. Am. Chem. Soc.* **79**, 960 (1957).
c. A. C. Cope, C. L. Bumgardner, and E. C. Schweizer, *J. Am. Chem. Soc.* **79**, 4729 (1957).
d. A. C. Cope, E. Ciganek, and N. A. LeBel, *J. Am. Chem. Soc.* **81**, 2799 (1959).
e. A. C. Cope and C. L. Bumgardner, *J. Am. Chem. Soc.* **78**, 2812 (1956).
f. J. I. Roberts, P. S. Borromeo, and C. C. Poulter, *Tetrahedron Lett.* 1299 (1977).
g. R. D. Clark and C. H. Heathcock, *J. Org. Chem.* **41**, 1396 (1976).

Scheme 7.15—*continued.*



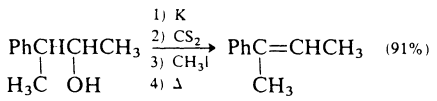
C. Acetate Pyrolyses

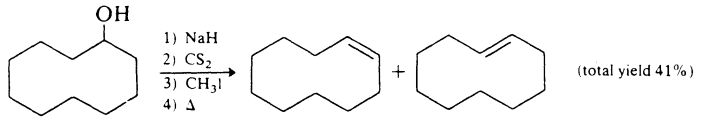


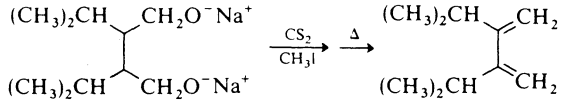
h. D. Liotta and H. Santiesteban, *Tetrahedron Lett.* 4369 (1977); R. M. Scarborough, Jr. and A. B. Smith, III, *Tetrahedron Lett.* 4361 (1977).
i. K. C. Nicolaou and Z. Lysenko, *J. Am. Chem. Soc.* **99**, 3185 (1977).
j. L. E. Friedrich and P. Y. S. Lam, *J. Org. Chem.* **46**, 306 (1981).
k. C. G. Overberger and R. E. Allen, *J. Am. Chem. Soc.* **68**, 722 (1946).
l. W. J. Bailey and J. Economy, *J. Org. Chem.* **23**, 1002 (1958).
m. C. G. Overberger and N. Vorchheimer, *J. Am. Chem. Soc.* **85**, 951 (1963).

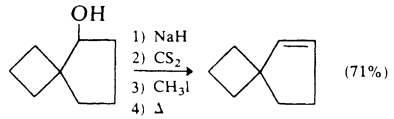
Scheme 7.15—*continued*

D. Xanthate Ester Pyrolyses

15[n] 

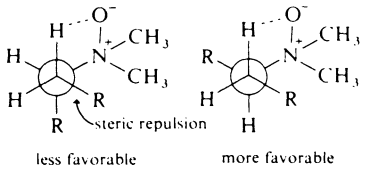
16[p] 

17[q] 

18[r] 

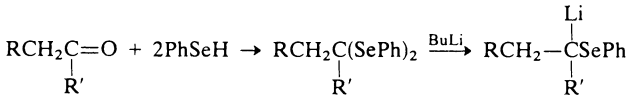
n. E. Piers and K. F. Cheng, *Can. J. Chem.* **46**, 377 (1968).
o. D. J. Cram, *J. Am. Chem. Soc.* **71**, 3883 (1949).
p. A. T. Blomquist and A. Goldstein, *J. Am. Chem. Soc.* **77**, 1001 (1955).
q. A. de Groot, B. Evenhuis, and H. Wynberg, *J. Org. Chem.* **33**, 2214 (1968).
r. C. F. Wilcox, Jr. and G. C. Whitney, *J. Org. Chem.* **32**, 2933 (1967).

Under the mild conditions of the reaction, there is no equilibration of the alkenes, so the product composition is governed by the relative stabilities of the various transition states. Usually, more of the *trans* olefin than of its *cis* isomer is formed, presumably because partial eclipsing raises the energy of the transition state leading to *cis* olefin. The selectivity is not high, however, since the ratio of *trans*:*cis* from some simple cases is in the range 3:1 to 2:1. In cyclic systems, conformational effects and the requirement for a cyclic transition state are the most

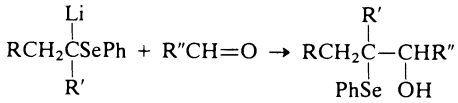


important factors in determining product composition. Elimination to give an olefin conjugated with an aromatic ring is especially favorable. The increased acidity of the hydrogen alpha to the phenyl group and the conjugation that develops in the transition state are believed to be responsible for this effect. Entry 1 in Scheme 7.14 is an example of the importance of this factor in determining product composition.

Selenoxides are even more reactive than amine oxides. In fact, many types decompose spontaneously on generation at room temperature. Synthetic procedures based on selenoxide eliminations usually involve synthesis of the corresponding selenide followed by oxidation and elimination. We have already discussed examples of these procedures in Chapter 4 where the synthesis of α,β-unsaturated carbonyl compounds (Section 4.7) was considered. In addition to the electrophilic addition of selenenyl halides and related compounds to alkenes and enolate selenenation, which was discussed in Section 4.5, selenides can be readily formed by nucleophilic displacement on halides, tosylates, or epoxides.[102] Selenium is also capable of stabilizing an adjacent carbanion so that α-selenenylcarbanions are accessible carbon nucleophiles. One versatile procedure involves conversion of ketone to *bis*-selenoketals which are then cleaved by butyllithium.[103] These carbanions

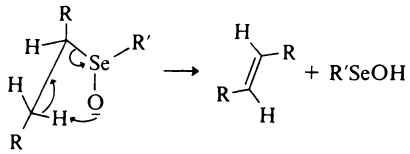


in turn can react with carbonyl compounds to make accessible a variety of β-hydroxyselenides.[104]



Alcohols can be converted to *o*-nitrophenylselenides by reaction with *o*-nitrophenyl selenocyanate and tri(*n*-butylphosphine).[105] Several oxidants have been employed to convert selenides to selenoxides and bring about elimination. Hydrogen peroxide, sodium metaperiodate, peroxycarboxylic acids, *tert*-butyl hydroperoxide, and ozone have been used most frequently.

Selenoxide eliminations usually favor formation of the (*E*) isomer in acyclic systems. This stereoselectivity reflects the fact that the cyclic transition state which minimizes steric interferences corresponds to *E*-alkene geometry. In cyclic systems



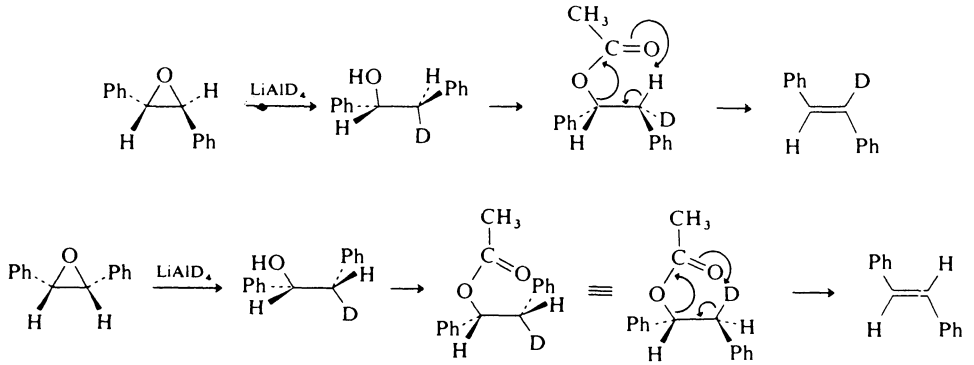
interplay of geometric considerations and the requirements for a cyclic transition state permit prediction and rationalization of stereochemical results.

102. D. L. J. Clive, *Tetrahedron* **34**, 1049 (1978).
103. W. Dumont, P. Bayet and A. Krief, *Angew. Chem. Int. Ed. Engl.* **13**, 804 (1974).
104. D. Van Ende, W. Dumont and A. Krief, *Angew. Chem. Int. Ed. Engl.* **14**, 700 (1975); W. Dumont, and A. Krief, *Angew. Chem. Int. Ed. Engl.* **14**, 350 (1975).
105. P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.* **41**, 1485 (1976).

The rate of selenoxide elimination depends upon the relationship to adjacent functionality. Selenoxide groups α or β to carbonyl groups undergo spontaneous eliminations at room temperature or below. Primary alkyl selenoxides are the least reactive systems. These eliminations can be catalyzed by amines or by alumina.[106] Section B of Scheme 7.14 gives some examples of selenoxide eliminations. Additional examples involving elimination as part of procedures for α,β dehydrogenation of carbonyl compounds were given in Scheme 4.5.

A third category of *syn* elimination involves pyrolytic decomposition of esters with elimination of a carboxylic acid. The pyrolysis of esters has usually been done with acetate esters. The energy requirement for the reaction is very high, with temperatures above 400°C being required. The pyrolysis is therefore usually a vapor-phase reaction. In the laboratory, this can be carried out using a glass tube heated with a small furnace. The reacting vapors and product are swept through the hot chamber at an appropriate rate by an inert gas such as nitrogen, and into a cold trap or other system for condensation. Similar reactions occur with esters derived from long-chain acids; if the boiling point of the ester is high enough, the reaction can be carried out in the liquid phase. Vapor-phase acetate pyrolysis is, however, the most generally used procedure.

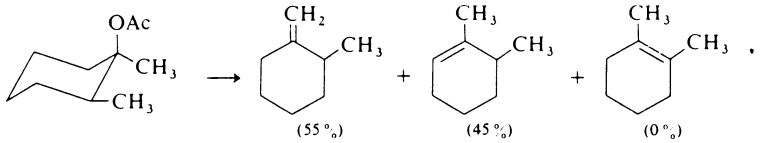
That the elimination is *syn* has been established by use of deuterium labels. Deuterium was introduced stereospecifically by $LiAlD_4$ reduction of *cis*- and *trans*-stilbene oxide. The product of the subsequent ester pyrolysis is *trans*-stilbene because of eclipsing effects in the transition state. The *syn* elimination is demonstrated by retention of deuterium in the olefin from a *trans*-stilbene oxide and its absence in the olefin from *cis*-stilbene oxide.[107] An alternative view of the mechanism has been presented. Although recognizing the existence of the concerted cyclic



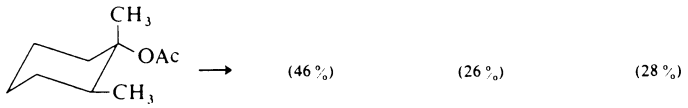
elimination, it is proposed that most preparative pyrolyses proceed *via* a surface-catalyzed mechanism.[108]

106. D. Labar, L. Hevesi, W. Dumont, and A. Krief, *Tetrahedron Lett.*, 1141 (1978).
107. D. Y. Curtin and D. B. Kellom, *J. Am. Chem. Soc.* **75**, 6011 (1953).
108. D. H. Wertz and N. L. Allinger, *J. Org. Chem.* **42**, 698 (1977).

As with the amine oxides, mixtures of olefins are obtained when more than one type of β-hydrogen is present. In noncyclic compounds, the olefin composition often approaches that expected on a statistical basis from the number of each type of hydrogen. The *trans* olefin usually predominates over the *cis* for a given isomeric pair. In cyclic systems, conformational features, ring strain, and related factors usually distort the mixture from that expected on a statistical basis. Elimination in a direction in which the *syn* mechanism can operate is strongly preferred over elimination in a direction where this is impossible. Alcohols can be dehydrated via



Ref. 109



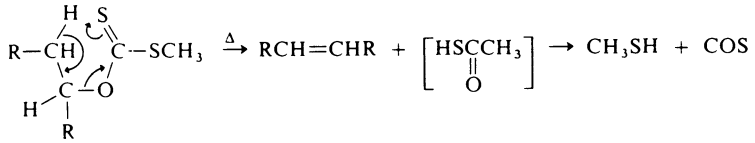
xanthate esters at temperatures much lower than those required for acetate pyrolysis. The preparation of xanthate esters involves reaction of the sodium alkoxide

$$ROH + Na \rightarrow RO^-Na^+$$

$$RO^-Na^+ + CS_2 \rightarrow ROCS^-Na^+$$

$$ROCS^- + CH_3I \rightarrow ROCSCH_3$$

with carbon disulfide. The resulting salt is alkylated with methyl iodide to complete the transformation. The elimination step is often effected by simple distillation:



As with the other *syn* thermal eliminations, there are no intermediates prone to undergo skeletal rearrangement. The principal application of the xanthate method has been in situations in which acid-catalyzed alcohol dehydration would be accompanied by skeletal rearrangement, or in which a very sensitive olefin is being produced.

109. D. H. Froemsdorf, C. H. Collins, G. S. Hammond, and C. H. DePuy, *J. Am. Chem. Soc.* **81**, 643 (1959).

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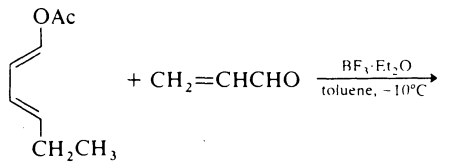
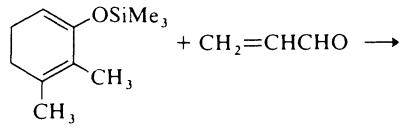
T. S. Stevens and W. E. Watts, *Selected Molecular Rearrangements*, Van Nostrand Reinhold, London (1973), Chapter 8.
H.-J. Hansen, in *Mechanisms of Molecular Migrations*, Vol. 3, B. S. Thyagarajan (ed.), Wiley-Interscience, New York (1971), pp. 177–236.
W. H. Saunders, Jr., and A. F. Cockerill, *Mechanisms of Elimination Reactions*, Wiley, New York (1973), Chap. VIII.

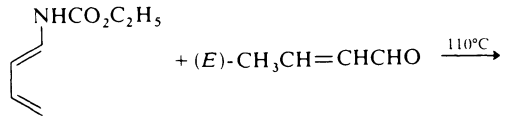
Problems

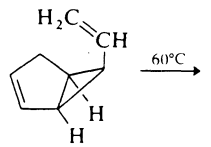
(*References for these problems will be found on page 626.*)

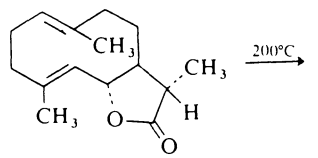
1. Predict the product of each of the following reactions, clearly showing stereochemistry where appropriate:

(a) 

(b) 

(c) 

(d) 

(e) 

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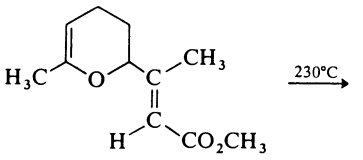
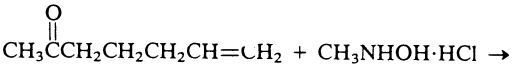


(g)



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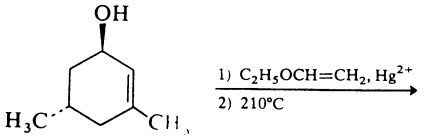
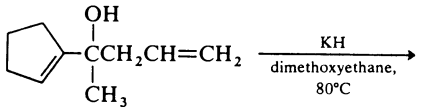


(i)



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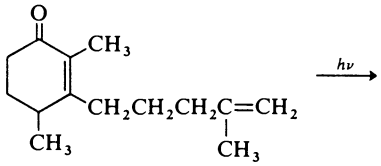

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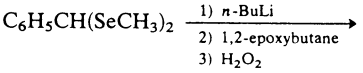

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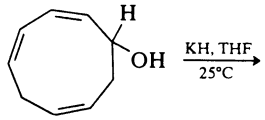
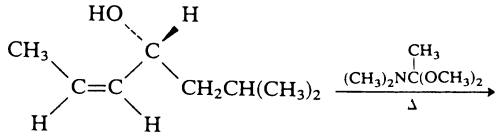
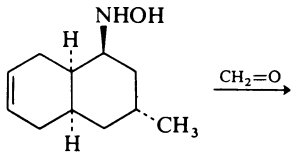


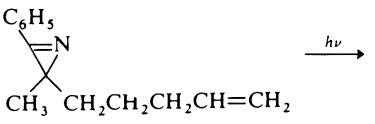
(m)

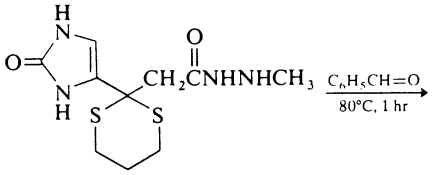


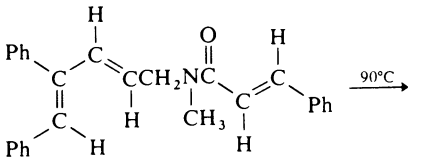
2. Intramolecular cycloaddition reactions occur under the reaction conditions specified for each of the following substrates. Show the structure of the product, including all aspects of its stereochemistry, and indicate the structures of any intermediates which are involved in the reactions.

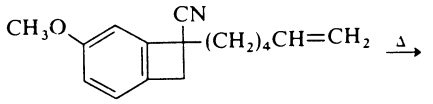
(a)

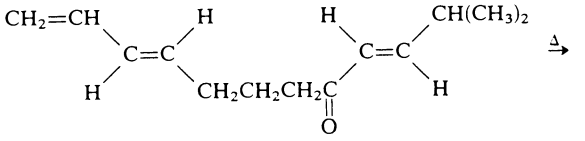


(b) 

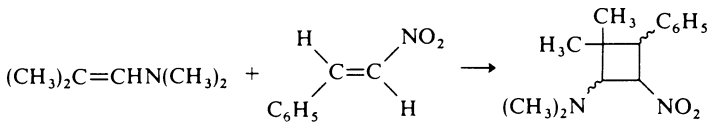
(c) 

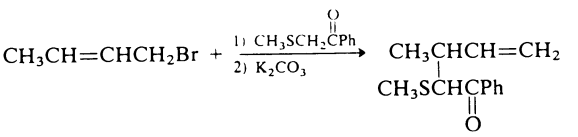
(d) 

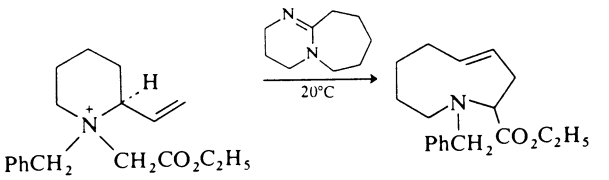
(e) 

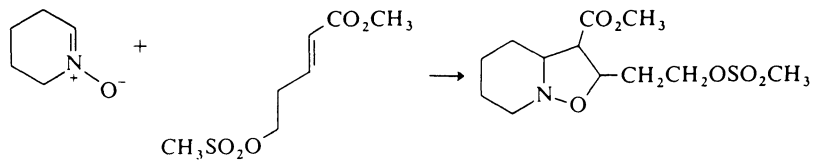
(f) 

3. Indicate the mechanistic type to which each of the following reactions belongs.

(a) 

(b) 

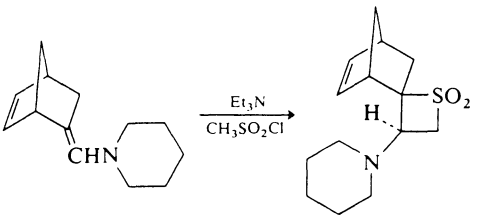
(c) 

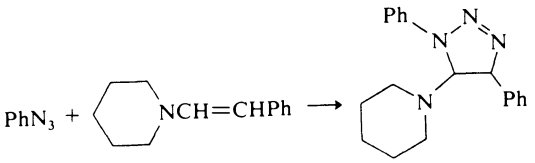
(d) 

(e) $CH_2{=}CHCH_2CH_3 + C_2H_5O_2CN{=}NCO_2C_2H_5 \rightarrow CH_3CH{=}CHCH_2\underset{\displaystyle CO_2C_2H_5}{\overset{\displaystyle |}{N}}NHCO_2C_2H_5$

(f) $(CH_3)_2C{=}CHCH_2CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}HCH_2CH_2CO_2CH_3 + HC{\equiv}CCO_2CH_3$

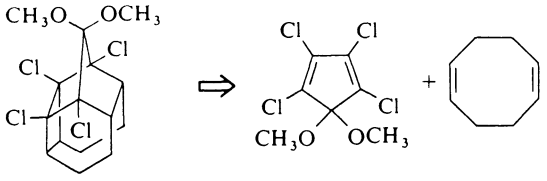
$\xrightarrow{AlCl_3}$ $CH_2{=}\underset{\displaystyle CH{=}CHCO_2CH_3}{\overset{\displaystyle |}{C}}CHCH_2CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}HCH_2CH_2CO_2CH_3$

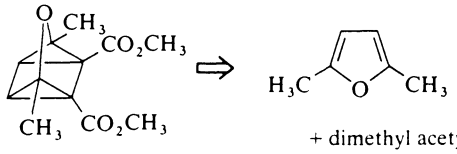
(g) 

(h) 

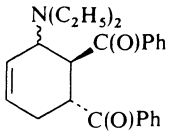
(i) $(CH_3)_2CH\underset{\displaystyle CN}{\overset{\displaystyle |}{C}}HOCH_2CH{=}C(CH_3)_2 \xrightarrow[2)\ H_3O^+]{1)\ LiNR_2} (CH_3)_2CHC(=O)\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}CCH{=}CH_2$

4. By applying the principles of retrosynthetic analysis, show how each of the indicated target molecules could be prepared from the starting material(s) given. No more than three separate transformations are necessary in any of the syntheses.

(a) 

(b) 

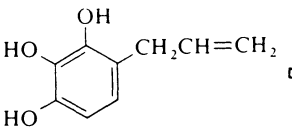
+ dimethyl acetylenedicarboxylate

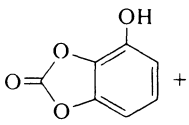
(c) 

⇨ acrolein, diethylamine, and *trans*-1,2-dibenzoylethylene

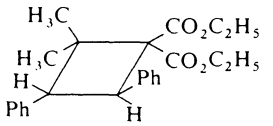
(d) $CH_3CH_2C{\equiv}CCH{=}CHCH_2CH_2CO_2CH_3$ ⇨

$CH_3CH_2C{\equiv}CH + CH_2{=}CHCHO + CH_3C(OCH_3)_3$

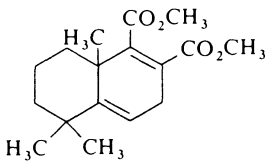
(e) 

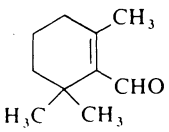
⇨ 

+ $H_2C{=}CHCH_2Br$

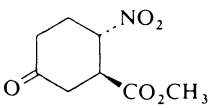
(f) 

⇨ *trans*-stilbene, diethyl malonate, and acetone

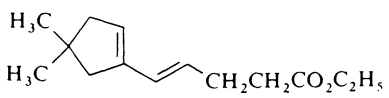
(g) 

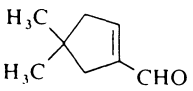
⇨ 

and any other necessary reagents

(h) 

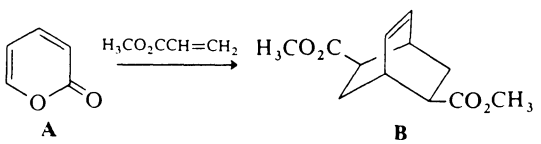
⇨ (*E*)-$O_2NCH{=}CHCO_2CH_3$ and any other necessary reagents

(i) 

⇨ 

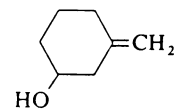
and any other necessary reagents

5. Reaction of α-pyrone (**A**) with methyl acrylate at reflux for extended periods gives a mixture of **B** and other isomers. Account for the formation of this product.

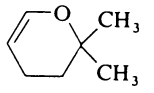


A **B**

6. When 2-methylpropene and acrolein are heated at 300°C under pressure, 3-methylenecyclohexanol and 6,6-dimethyldihydropyran are formed. Explain the formation of these products.

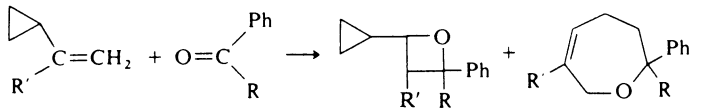


3-methylenecyclohexanol



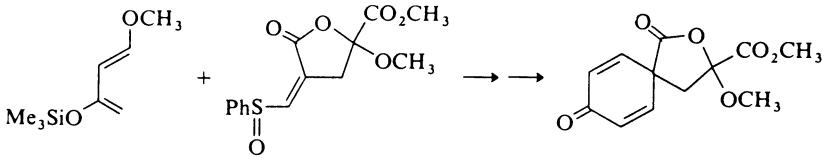
6,6-dimethyldihydropyran

7. Vinylcyclopropane, when irradiated with benzophenone or benzaldehyde, gives a mixture of two types of products. Suggest the mechanism by which product of type **C** is formed.

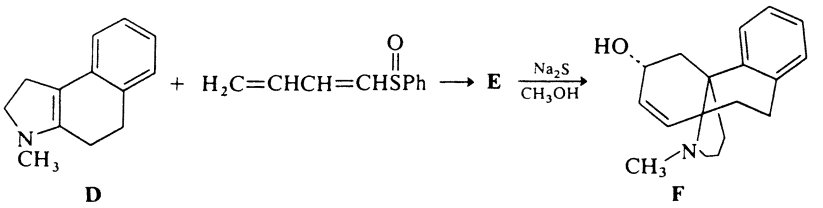


C

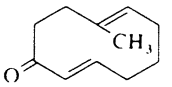
8. The addition reaction of tetracyanoethylene and ethyl vinyl ether in acetone gives 94% of the 2 + 2 adduct and 6% of an adduct having the composition: tetracyanoethylene + ethyl vinyl ether + acetone. If the 2 + 2 adduct is kept in contact with acetone for several days, it is completely converted to the minor product. Suggest a structure for this product, and indicate its mode of formation (a) in the initial reaction and (b) on standing in acetone.
9. A convenient preparation of 2-allylcyclohexanone involves simply heating the diallyl ketal of cyclohexanone in toluene containing a trace of *p*-toluenesulfonic acid and collecting a distillate consisting of toluene and allyl alcohol. Distillation of the residue gives a 90% yield of 2-allylcyclohexanone. Outline the mechanism of this reaction.
10. The preparation of a key intermediate in an imaginative synthesis of prephenic acid is depicted below. Write a series of equations showing the important steps and intermediates in this process. Indicate the reagents required to bring about the desired transformations where other than thermal reactions are involved.



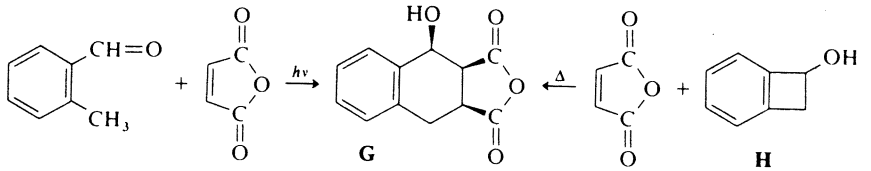
11. A route to hasubanan alkaloids has been described involving reaction of 1-butadienyl phenyl sulfoxide with the tetrahydrobenzindole **D**. Treatment of the resulting adduct with sodium sulfide in refluxing methanol gave **F**. Suggest a structure for **E**, and rationalize the formation of **F** from **E**.



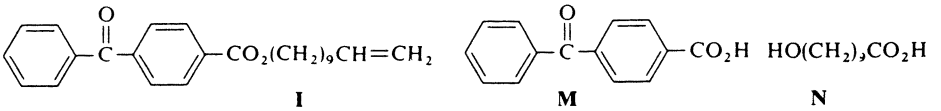
12. A solution of but-2-enal, 2-acetoxypropene, and dimethyl acetylenedicarboxylate refluxed in the presence of a small amount of an acidic catalyst gives an 80% yield of dimethyl phthalate. Explain the course of this reaction.
13. Irradiation of the dienone shown generates three isomeric saturated ketones, all of which contain cyclobutane rings. Postulate reasonable structures.



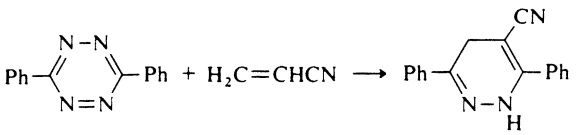
14. Irradiation of *o*-methylbenzaldehyde in the presence of maleic anhydride gives **G**. The same compound is obtained when **H** is heated with maleic anhydride. Both reactions give only the stereoisomer shown. Formulate a mechanism.



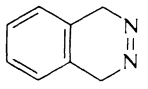
15. Photolysis of **I** gives an isomeric compound **J** in 83% yield. Alkaline hydrolysis of **J** affords a hydroxy carboxylic acid **K**, $C_{25}H_{32}O_4$. Treatment of **J** with silica gel in hexane yields **L** $C_{24}H_{28}O_2$. **L** is converted by sodium periodate–potassium permanganate to a mixture of **M** and **N**. What are the structures of **J**, **K**, and **L**?



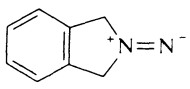
16. (a) 1,2,4,5-Tetrazines react with alkenes to give dihydropyridazines, as illustrated in the equation below. Suggest a mechanism.



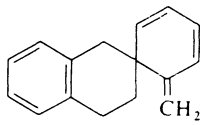
(b) Compounds **O** and **P** are both unstable toward loss of nitrogen at room temperature. Both compounds give **Q** as the product of decomposition. Account for the formation of **Q**.



O

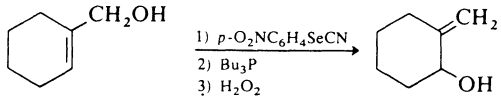


P

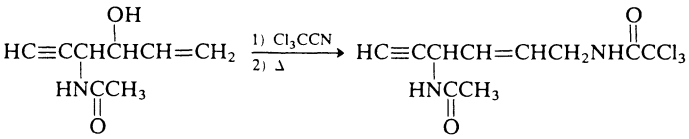


Q

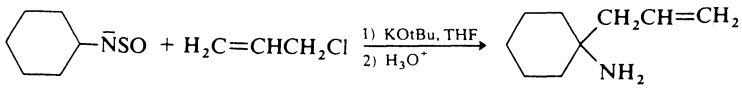
17. A procedure has been described for the "transposition" of functionality in allylic alcohols as shown in the following example. Suggest a reasonable mechanism for this process.



18. A procedure for oxygen–nitrogen transposition with allylic rearrangement involves treating an allylic alcohol with trichloroacetonitrile, then heating the derived trichloroacetimidate. Rationalize this transformation.

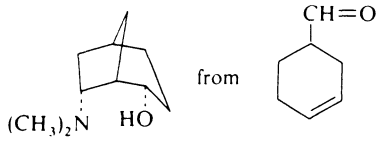


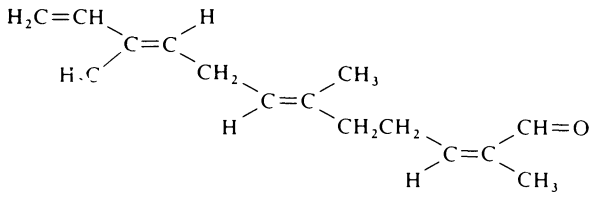
19. The anions formed by deprotonation of *N*-sulfinylamines do not react with *alkyl* halides but are alkylated readily by *allylic* halides as shown. Suggest an explanation for this apparent selectivity.

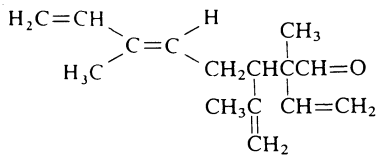


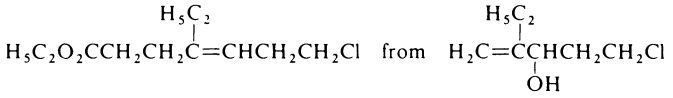
20. Suggest sequences of reactions for accomplishing each of the following synthetic transformations:
    (a) squalene from succinaldehyde, isopropyl bromide, and 3-methoxy-2-methyl-1,3-butadiene

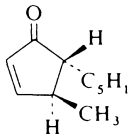
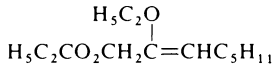
(b)

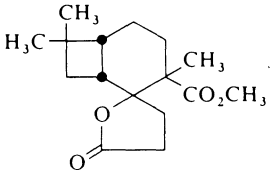
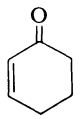


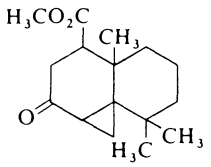
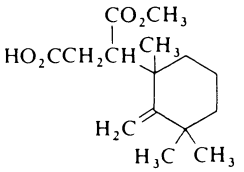
(c) 

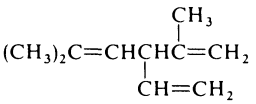
from 

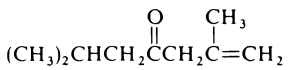
(d) 

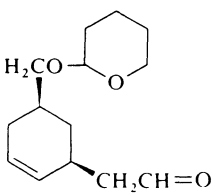
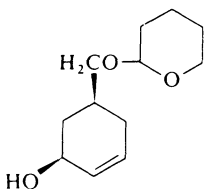
(e)  from 

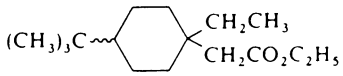
(f)  from 

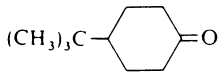
(g)  from 

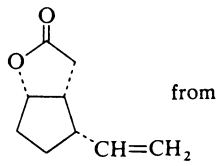
(h)  from $(CH_3)_2C{=}CHCH{=}CHCH_2OH$

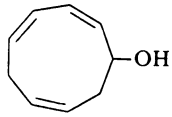
(i)  from $H_2C{=}CHOCH_2CH{=}CH_2$ and $(CH_3)_2CHBr$

(j)  from 

(k) 

from 

(l) 

from 

8

Aromatic Substitution Reactions

This chapter is concerned with reactions that introduce or interchange substituent groups on aromatic rings. The most important group of such reactions are the electrophilic aromatic substitutions, but there are also significant reactions that take place by nucleophilic mechanisms, and still others that involve radical processes. Examples of synthetically important reactions from each group will be discussed. Electrophilic aromatic substitution has also been studied in great detail from the point of view of reaction mechanism and structure-reactivity relationships; these mechanistic studies received considerable attention in Part A, Chapter 9. In this chapter, the synthetic aspects of electrophilic aromatic substitutions will be emphasized.

8.1. Electrophilic Aromatic Substitution

8.1.1. Nitration

Aromatic nitration has been an important reaction, from the standpoint both of synthesis and of understanding reaction mechanisms, since the early days of organic chemistry. Synthetically, it provides a route for introduction of amino groups onto aromatic rings, since the nitro group can be readily reduced to the amino function. As will be seen in Section 8.2.1, the amino group, in turn, provides an entry for many other important functional groups. From the point of view of reaction mechanism, nitration was important in the early work that established the patterns of substituent-directing effects and in determining the effect of substituents on reaction rates.

There are several reagent systems that are capable of effecting nitration. A major factor in the choice of reagent is the reactivity of the aromatic ring to be nitrated. Concentrated nitric acid can effect nitration, but it is not nearly so reactive as mixtures of nitric acid with sulfuric acid. In both media, the active nitrating species is the nitronium ion NO_2^+. A variety of physical measurements provide evidence for the existence of this species.[1,2] The nitronium ion is formed by protonation and dissociation of nitric acid, a reaction which is driven to the right in strongly acidic media.

$$HNO_3 + 2H^+ \rightleftarrows H_3O^+ + NO_2^+$$

It is possible to prepare and characterize solid salts containing the nitronium ion, for example, $NO_2^+ClO_4^-$.[3]

Nitration can also be carried out in organic solvents, of which acetic acid and nitromethane are perhaps the most common examples. In such solvents, the rate constants for nitration are often found to be zero order in the aromatic substrate. The rate-controlling step is formation of the active nitrating species, the nitronium ion[4]:

$$2\,HNO_3 \rightleftarrows H_2NO_3^+ + NO_3^-$$

$$H_2NO_3^+ \xrightarrow{\text{slow}} NO_2^+ + H_2O$$

$$ArH + NO_2^+ \xrightarrow{\text{fast}} ArNO_2 + H^+$$

Another useful medium for nitration is a solution prepared by dissolving nitric acid in acetic anhydride. This is believed to generate acetyl nitrate:

$$HNO_3 + (CH_3CO)_2O \rightleftarrows CH_3\overset{\overset{O}{\|}}{C}ONO_2 + CH_3CO_2H$$

A useful feature of this reagent is that high ratios of *ortho* to *para* products are found for some substituted aromatics.[5] It is possible to use nitronium ion salts for nitration.[6] Nitronium fluoroborate has been the most extensively studied. The trifluoromethanesulfonate salt is also readily prepared and is an active nitrating agent in both organic solvents and strong acids.[7]

1. R. J. Gillespie, J. Graham, E. D. Hughes, C. K. Ingold, and E. R. A. Peeling, *J. Chem. Soc.*, 2504 (1950).
2. C. K. Ingold, D. J. Millen, and H. G. Poole, *J. Chem. Soc.*, 2576 (1950).
3. D. R. Goddard, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2559 (1950); D. J. Millen, *J. Chem. Soc.*, 2606 (1950).
4. E. D. Hughes, C. K. Ingold, and R. I. Reed, *J. Chem. Soc.*, 2400 (1950); J. G. Hoggett, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 1 (1969).
5. A. K. Sparks, *J. Org. Chem.* **31**, 2299 (1966).
6. S. J. Kuhn and G. A. Olah, *J. Am. Chem. Soc.* **83**, 4564 (1961); G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.* **84**, 3684 (1962).
7. C. L. Coon, W. G. Blucher, and M. E. Hill, *J. Org. Chem.* **38**, 4243 (1973).

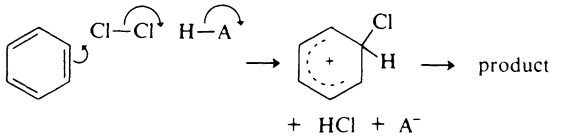
Certain aromatic heterocycles, in particular, pyridine and quinoline, form *N*-nitro salts when allowed to react with NO_2BF_4.[8] These reagents react by "transfer nitration." That is, the nitronium group is transferred directly to the aromatic substrate and free NO_2^+ groups are not involved. These reagents are somewhat more selective than the free NO_2^+ ion but, in general, show similar $o:m:p$ ratios.

Nitration is a very general reaction and satisfactory conditions can normally be developed for both activated and deactivated aromatic substrates. Since each successive nitro group decreases the reactivity of the ring it is usually possible to control conditions to obtain mononitration or multiple nitration as desired. Scheme 8.1 gives some specific examples.

8.1.2. Halogenation

The introduction of the halogens onto the aromatic ring by electrophilic substitution is an important synthetic procedure. Chlorine and bromine are reactive toward aromatic hydrocarbons, although catalysts are needed to achieve desirable rates. Fluorine reacts too violently to be useful under normal laboratory conditions. Iodine itself can effect substitution of only very reactive aromatic compounds, but synthetic methods involving other iodinating reagents have been developed.

Rate studies of chlorination of typical aromatics often reveal acid catalysis although the kinetics are frequently complex.[9] This behavior has been interpreted in terms of acid-catalyzed cleavage of the Cl–Cl bond in a chlorine–substrate complex. Chlorination is much more rapid in polar than in nonpolar solvents.[10] Bromination also tends to exhibit complex kinetics in acetic acid and other solvents, with terms ranging from first- to third-order in bromine being observed.

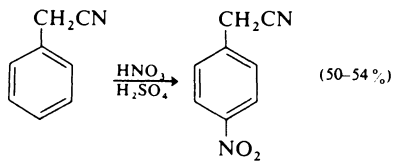


For preparative reactions, the catalytic effect of Lewis acids is often utilized. Zinc chloride or ferric chloride is used in chlorinations, and metallic iron, which generates $FeBr_3$, is often added to bromination mixtures. The Lewis acid takes the role of facilitating the cleavage of the halogen–halogen bond.

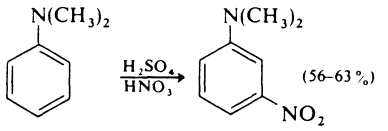
8. G. A. Olah, S. C. Narang, J. A. Olah, R. L. Pearson, and C. A. Cupas, *J. Am. Chem. Soc.* **102**, 3507 (1980).
9. L. M. Stock and F. W. Baker, *J. Am. Chem. Soc.* **84**, 1661 (1962); L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.* **81**, 1063 (1959); R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc* **82**, 4547 (1960); L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.* **79**, 5169 (1957).
10. L. M. Stock and A. Himoe, *J. Am. Chem. Soc.* **83**, 4605 (1961).

Scheme 8.1. Aromatic Nitration

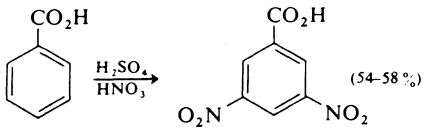
1[a]



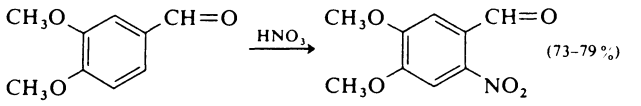
2[b]



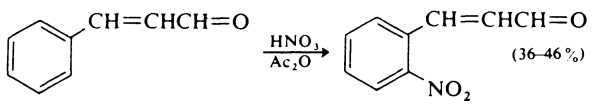
3[c]



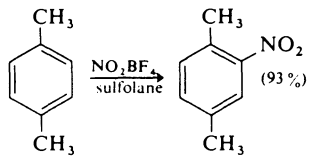
4[d]



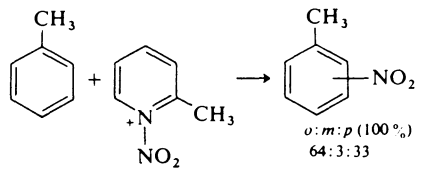
5[e]



6[f]

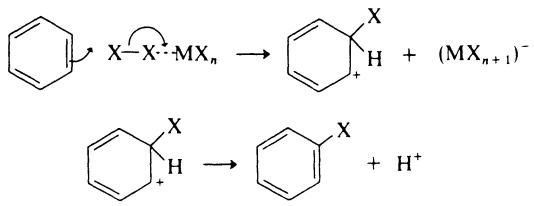


7[g]



a. G. R. Robertson, *Org. Synth.* **I**, 389 (1932).
b. H. M. Fitch, *Org. Synth.* **III**, 658 (1955).
c. R. Q. Brewster, B. Williams, and R. Phillips, *Org. Synth.* **III**, 337 (1955).
d. C. A. Fetscher, *Org. Synth.* **IV**, 735 (1963).
e. R. E. Buckles and M. P. Bellis, *Org. Synth.* **IV**, 722 (1963).
f. S. J. Kuhn and G. A. Olah, *J. Am. Chem. Soc.* **83**, 4564 (1961).
g. C. A. Cupas and R. L. Pearson, *J. Am. Chem. Soc.* **90**, 4742 (1968).

$$MX_n + X_2 \rightleftharpoons X{-}X\cdots MX_n$$

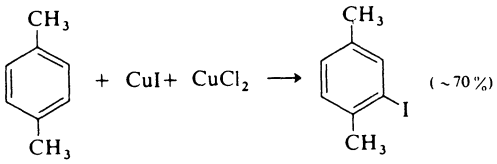


It is possible to brominate a wide variety of aromatic substrates. Anilines and phenols are highly reactive, and bromination at all positions *ortho* and *para* to the activating group occurs readily. Amido, alkyl, and halobenzenes can be brominated satisfactorily, and the usual *ortho-para*-directing effect of these substituents is noted. Use of Lewis acid catalysts permits bromination of aromatic rings carrying such strongly electron-attracting substituents as nitro or cyano. Use of dibromoisocyanuric acid in concentrated sulfuric acid is another effective method for brominating unreactive substrates[11] (entry 5, Scheme 8.2).

Halogenations are also strongly catalyzed by certain other metal ions, particularly Hg(II) and Ag(I). In solutions containing halogen and mercuric carboxylate salts, the dominant halogenating agent is the acyl hypohalite. The trifluoroacetyl hypohalites are very reactive halogenating agents. Even nitrobenzene, for example, is readily brominated by trifluoroacetyl hypobromite.[12]

$$Hg(O_2CR)_2 + X_2 \rightleftarrows HgX(O_2CR) + RCO_2X$$

Iodination can be carried out in the presence of cupric salts.[13] The cupric salt appears to act both as a Lewis acid catalyst and as an oxidant for converting iodide to iodine. The latter function is readily evident, since iodide salts are effective as iodinating agents in the presence of cupric chloride. Iodination of moderately



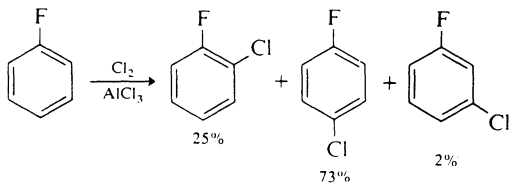
reactive aromatics can be effected by reaction with mixtures of iodine and silver or mercury salts, with the reaction presumably involving hypoiodites as the reactive iodinating species.[14] Examples of synthetically useful halogenations are given in Scheme 8.2.

11. A. R. Leed, S. D. Boettger, and B. Ganem, *J. Org. Chem.* **45**, 1098 (1980).
12. J. R. Barnett, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.* **94**, 6129 (1972).
13. W. C. Baird, Jr. and J. H. Surridge, *J. Org. Chem.* **35**, 3436 (1970).
14. A. R. Leed, S. D. Boettger, and B. Ganem, *J. Org. Chem.* **45**, 1098 (1980).

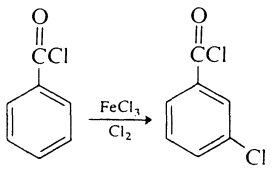
Scheme 8.2. Aromatic

A. Chlorination

1[a]

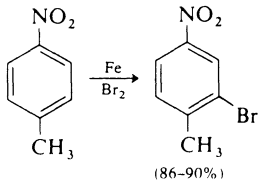


2[b]

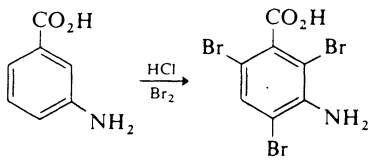


B. Bromination

3[c]



4[d]

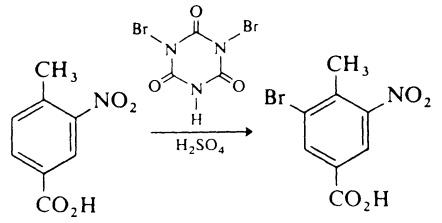


a. G. A. Olah, S. J. Kuhn, and B. A. Hardie, *J. Am. Chem. Soc.* **86**, 1055 (1964).
b. E. Hope and G. F. Riley, *J. Chem. Soc.* **121**, 2510 (1922).
c. M. M. Robison and B. L. Robison, *Org. Synth.* **IV**, 947 (1963).
d. W. A. Wisansky and S. Ansbacher, *Org. Synth.* **III**, 138 (1955).

8.1.3. Friedel–Crafts Alkylations and Acylations

Friedel–Crafts reactions are one of the most important methods for introducing carbon substituents on aromatic rings. The reactive electrophiles are various intermediates having a positive charge or positive polarization at a carbon atom. In some reactions, discrete carbonium ions or acylium ions are involved; in other cases, however, the electrophile no doubt consists of the alkyl or acyl group still bonded to a potential leaving group, which is displaced in the substitution step. Whether discrete carbonium ions are involved depends primarily on the stability of the potential carbonium ion.

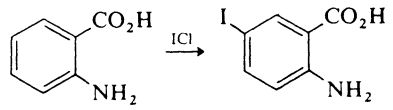
5[e]



(98%)

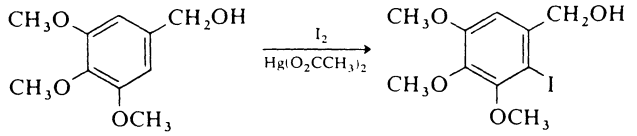
C. Iodination

6[f]



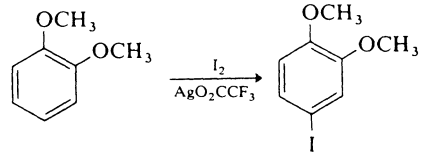
(76–84%)

7[g]



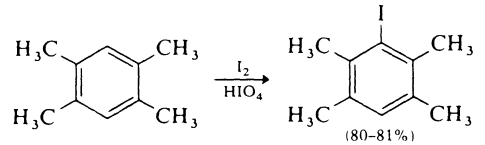
(76%)

8[h]



(85–91%)

9[i]



(80–81%)

e. A. R. Leed, S. D. Boettger, and B. Ganem, *J. Org. Chem.* **45**, 1098 (1980).
f. V. H. Wallingord and P. A. Krueger, *Org. Synth.* **II**, 349 (1943).
g. F. E. Ziegler and J. A. Schwartz, *J. Org. Chem.* **43**, 985 (1978).
h. D. E. Janssen and C. V. Wilson, *Org. Synth.* **IV**, 547 (1963).
i. H. Suzuki, *Org. Synth.* **51**, 94 (1971).

The choice of potential alkylating agents is quite wide. Complexes of alkyl halides with Lewis acids, especially $AlCl_3$, protonated alcohols, and protonated alkenes can all provide carbonium ions or other reactive alkylating agents:

$$R{-}X + AlCl_3 \rightleftharpoons R{-}\overset{+}{X}{-}\overset{-}{Al}Cl_3 \rightleftharpoons R^+ + X\overset{-}{Al}Cl_3$$

$$R{-}OH + H^+ \rightleftharpoons R{-}\overset{+}{\underset{H}{O}}H \rightleftharpoons R^+ + H_2O$$

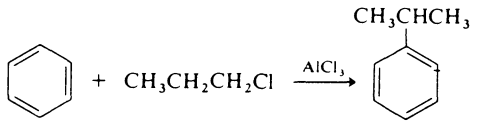
$$RCH{=}CH_2 + H^+ \rightleftharpoons R\overset{+}{C}HCH_3$$

Table 8.1. Relative Activity of Friedel–Crafts Catalysts[a]

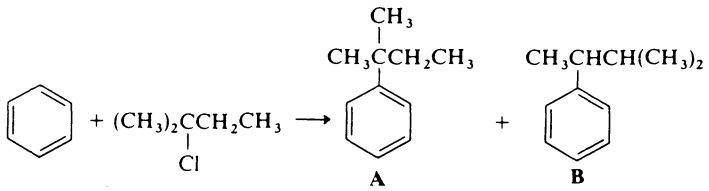
Very active	Moderately active	Weak
$AlCl_3$, $AlBr_3$, $GaCl_3$, $GaCl_2$, SbF_5, $MoCl_5$	$InCl_3$, $LnBr_3$, $SbCl_5$, $FeCl_3$, $AlCl_3$–CH_3NO_2, SbF_5–CH_3NO_2	BCl_3, $SnCl_4$, $TiCl_4$, $TiBr_4$, $FeCl_2$

a. G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.* **94**, 7448 (1972).

Because of the involvement of carbonium ions and related intermediates, Friedel–Crafts reactions are often accompanied by rearrangements in the alkylating agent. For example, isopropyl groups are often introduced when *n*-propyl compounds are used as reactants.[15] Under a variety of reaction conditions, alkylation



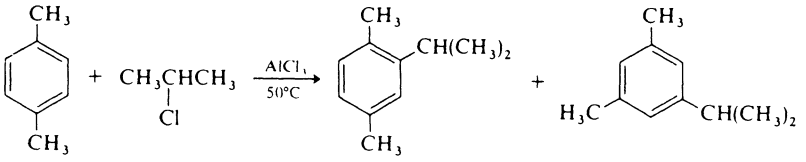
of benzene with either 2-chloro or 3-chloropentane gives rise to a mixture which is between 2 : 1 and 3 : 1 in favor of 2-pentylbenzene over 3-pentylbenzene.[16] Even at −20°C isomerization of the halides is competitive with alkylation. Rearrangement can also occur after the initial alkylation. The reaction of 2-chloro-2-methylbutane with benzene under Friedel–Crafts conditions is an example of this behavior.[17] With relatively mild Friedel–Crafts catalysts such as BF_3 and $FeCl_3$ the main product is **A**. With $AlCl_3$ equilibration of **A** and **B** favors **B**. Thus the apparent rearrangement of a tertiary carbonium ion to a less stable secondary one actually is the result



of product equilibration. Migration of groups from one position to another can

15. S. H. Sharman, *J. Am. Chem. Soc.* **84**, 2945 (1962).
16. R. M. Roberts, S. E. McGuire, and J. R. Baker, *J. Org. Chem.* **41**, 659 (1976).
17. A. A. Khalaf and R. M. Roberts, *J. Org. Chem.* **35**, 3717 (1970); R. M. Roberts and S. E. McGuire, *J. Org. Chem.* **35**, 102 (1970).

also occur.[18] Such migrations are thermodynamically controlled and proceed in the direction of minimizing steric interactions between the substituent groups.



The relative reactivity of the various Friedel–Crafts catalysts cannot be described in a quantitative way but comparative studies using a series of benzyl halides has resulted in the qualitative grouping shown in Table 8.1. Proper choice of catalyst can minimize subsequent product equilibration, provided the catalyst is sufficiently reactive to promote the desired alkylation.

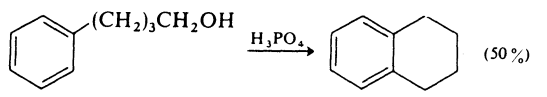
The Friedel–Crafts alkylation reaction does not proceed successfully with aromatic substrates having electron-attracting groups. A further limitation is that the alkyl group introduced in the reaction increases the reactivity of the aromatic ring toward further substitution, so that polyalkylation can occur. Polyalkylation is usually minimized in practice by using the aromatic substrate in excess.

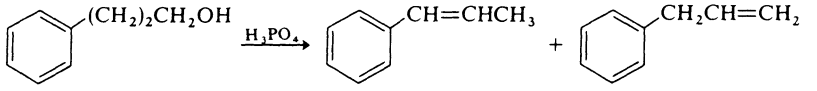
Besides the alkyl halide–Lewis acid combination, two other routes to carbonium ions are quite widely used in synthesis. Alcohols can serve as sources of carbonium ions in strongly acidic media such as sulfuric acid and phosphoric acid. The alkylation of aromatic rings by alcohols is also catalyzed by BF_3 and $AlCl_3$.[19]

Alkenes are also sources of carbonium ions for alkylations. Protic acids—especially sulfuric acid, phosphoric acid, and hydrogen fluoride—and Lewis acids, such as BF_3 and $AlCl_3$, are used as catalysts.[20] Insofar as comparisons have been made, such factors as position selectivity and tendency toward isomerism of the alkyl group to more stable structures are similar to those described with alkyl halides as alkylating agents.[21]

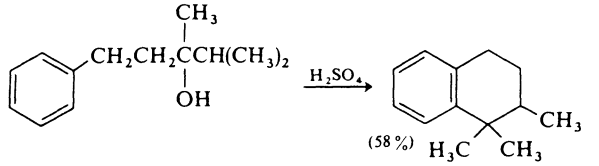
Friedel–Crafts alkylation can also occur intramolecularly, in which case a new ring is formed. It is somewhat easier to form six-membered rings than five-membered rings in such reactions. Thus, while 4-phenyl-1-butanol gives a 50% yield of cyclized product in phosphoric acid, 3-phenyl-1-propanol gives mainly dehydration to alkene.[22] If a potential carbonium ion intermediate can undergo a

18. R. M. Roberts and D. Shiengthong, *J. Am. Chem. Soc.* **86**, 2851 (1964).
19. A. Schriesheim, in *Friedel-Crafts and Related Reactions*, Vol. II, G. Olah (ed.), Interscience, New York (1964), Chap. XVIII.
20. S. H. Patinkin and B. S. Friedman, in *Friedel-Crafts and Related Reactions*, Vol. II, G. Olah (ed.), Interscience, New York (1964), Chap. XIV.
21. R. H. Allen and L. D. Yats, *J. Am. Chem. Soc.* **83**, 2799 (1961).
22. A. A. Khalaf and R. M. Roberts, *J. Org. Chem.* **34**, 3571 (1969).





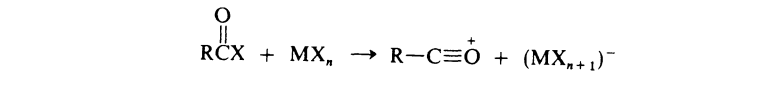
hydride or alkyl shift, this shift will occur in preference to closure of the five-membered ring:

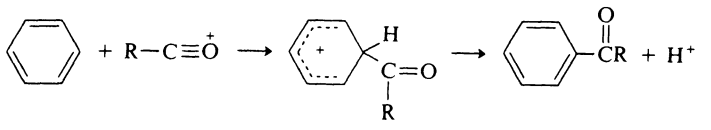


Ref. 23

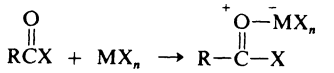
An important use of the intramolecular Friedel–Crafts reaction is in construction of the polycyclic hydrocarbon framework of terpenes and steroids. Entry 5 in Scheme 8.3 is an example of this type of application.

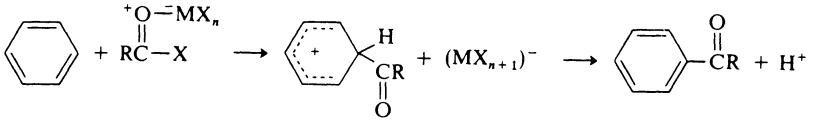
Friedel–Crafts acylation generally involves reaction of an acid halide with a Lewis acid catalyst such as $AlCl_3$, SbF_5, or BF_3. Acid anhydrides are employed in some cases. As in alkylations, the reaction intermediate may be a dissociated organic cation (acylium ion) or a complex of the acid chloride and Lewis acid.[24]





or

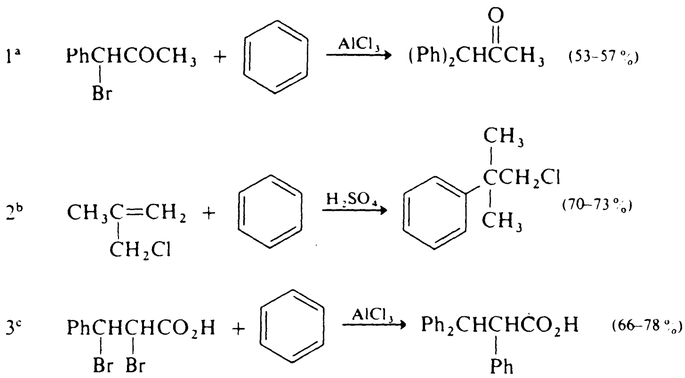




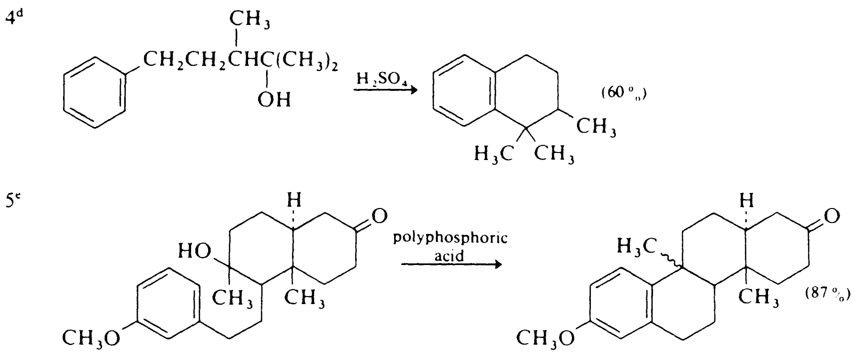
23. A. A. Khalaf and R. M. Roberts, *J. Org. Chem.* **37**, 4227 (1972).
24. F. R. Jensen and G. Goldman, in *Friedel-Crafts and Related Reactions*, Vol. III, G. Olah (ed.), Interscience, New York (1964), Chap. XXXVI.

Scheme 8.3. Friedel–Crafts Alkylation Reactions

A. Intermolecular Reactions



B. Intramolecular Friedel–Crafts Cyclizations

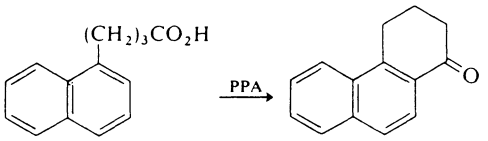


a. E. M. Schultz and S. Mickey, *Org. Synth.* **III**, 343 (1955).
b. W. T. Smith, Jr., and J. T. Sellas, *Org. Synth.* **IV**, 702 (1963).
c. C. P. Krimmel, L. E. Thielen, E. A. Brown, and W. J. Heidtke, *Org. Synth.* **IV**, 960 (1963).
d. A. A. Khalaf and R. M. Roberts, *J. Org. Chem.* **37**, 4227 (1972).
e. R. E. Ireland, S. W. Baldwin, and S. C. Welch, *J. Am. Chem. Soc.* **94**, 2056 (1972).

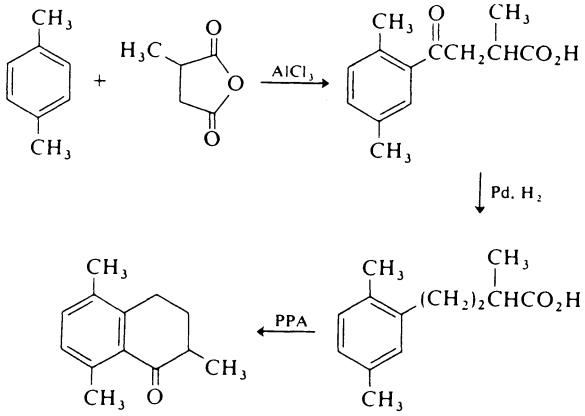
Orientation of the incoming acyl group in Friedel–Crafts acylations can be quite sensitive to the reaction solvent and other procedural variables.[25] In general, however, *para* attack predominates for alkylbenzenes. The percentage of *ortho* attack increases with the electrophilicity of the acylium ion and approaches 1 : 1 with such less selective species as formyl and 2,4-dinitrobenzoyl ions.[26] For simple alkanoyl and benzoyl halides, the *o* : *p* ratio is usually 1 : 20 or higher.[27]

25. For example, See L. Friedman and R. J. Honour, *J. Am. Chem. Soc.* **91**, 6344 (1969).
26. G. A. Olah and S. Kobayashi, *J. Am. Chem. Soc.* **93**, 6964 (1971).
27. H. C. Brown, G. Marino, and L. M. Stock, *J. Am. Chem. Soc.* **81**, 3310 (1959); H. C. Brown and G. Marino, *J. Am. Chem. Soc.* **81**, 5611 (1959); G. A. Olah, M. E. Moffatt, S. J. Kuhn, and B. A. Hardie, *J. Am. Chem. Soc.* **86**, 2198 (1964).

Intramolecular acylations are quite common. The normal Friedel–Crafts procedure involving an acid halide and Lewis acid is frequently used, but there are alternatives. One useful method for inducing intramolecular acylations is to dissolve the carboxylic acid in polyphosphoric acid (PPA) and heat to effect cyclization. The mechanism probably involves formation of a mixed carboxylic–phosphoric anhydride.[28] Cyclizations of this type can also be carried out using "polyphosphate ester," an esterified oligomer of phosphoric acid that is soluble in solvents such as chloroform.[29]



A procedure of long standing for introduction of a fused ring onto a benzene skeleton utilizes succinic anhydride or a derivative. An intermolecular acylation is followed by reduction and then an intramolecular acylation. The reduction is necessary to convert the deactivating acyl substituent to a more favorable alkyl substituent before the final cyclization.

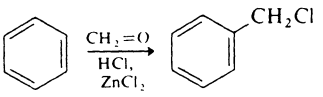


Scheme 8.4 records some typical Friedel–Crafts acylation reactions.

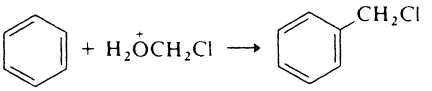
Certain other reactions of aromatic molecules are closely related to the Friedel–Crafts reaction. The introduction of chloromethyl groups is brought about by formaldehyde in concentrated hydrochloric acid in the presence of halide salts, especially zinc chloride.[31] The reaction is restricted in scope to benzene and

28. W. E. Bachmann and W. J. Horton, *J. Am. Chem. Soc.* **69**, 58 (1947).
29. Y. Kanaoka, O. Yonemitsu, K. Tanizawa, and Y. Ban, *Chem. Pharm. Bull. (Japan)* **12**, 773 (1964); T. Kametani, S. Takano, S. Hibino, and T. Terui, *J. Heterocycl. Chem.* **6**, 49 (1969).
30. E. J. Eisenbraun, C. W. Hinman, J. M. Springer, J. W. Burnham, T. S. Chou, P. W. Flanagan, and M. C. Hamming, *J. Org. Chem.* **36**, 2480 (1971).
31. R. C. Fuson and C. H. McKeever, *Org. React.* **1**, 63 (1942); G. A. Olah and S. H. Yu, *J. Am. Chem. Soc.* **97**, 2293 (1975).

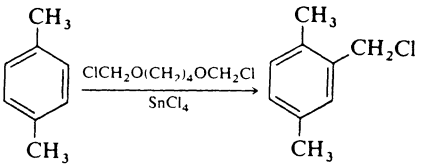
derivatives with electron-releasing substituents. Several mechanistic pathways could be operative in the chloromethylation reaction, but the active electrophile is probably protonated chloromethyl alcohol. Chloromethylation of benzene and



$$CH_2{=}O + HCl + H^+ \rightleftharpoons H_2\overset{+}{O}CH_2Cl$$



alkylbenzenes can also be carried out using various chloromethyl ethers with $SnCl_4$ catalyst.[32]



Carbon monoxide, hydrogen cyanide, and nitriles also react with aromatic compounds in the presence of strong acids or other Friedel–Crafts catalysts. These reactions are quite useful for synthetic purposes, since the products are formyl- or acyl-substituted aromatics. These electron-withdrawing groups retard any further electrophilic substitutions. The general outlines of the mechanism of these reactions are given below:

a. Formylation with carbon monoxide:

$$\bar{C}{\equiv}\overset{+}{O} + H^+ \rightleftharpoons H{-}C{\equiv}\overset{+}{O}$$

$$ArH + HC{\equiv}\overset{+}{O} \rightarrow ArCH{=}O + H^+$$

b. Formylation with hydrogen cyanide:

$$H{-}C{\equiv}N + H^+ \rightleftharpoons H{-}C{\equiv}\overset{+}{N}{-}H$$

$$ArH + H{-}C{\equiv}\overset{+}{N}{-}H \rightarrow \underset{\displaystyle H}{\underset{|}{ArC}}{=}\overset{+}{N}H_2 \xrightarrow{H_2O} ArCH{=}O$$

c. Acylation with nitriles:

$$R{-}C{\equiv}N + H^+ \rightleftharpoons R{-}C{\equiv}\overset{+}{N}{-}H$$

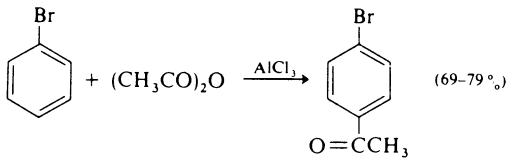
$$ArH + R{-}C{\equiv}\overset{+}{N}{-}H \rightarrow \underset{\displaystyle Ar}{\underset{|}{R{-}C}}{=}\overset{+}{N}H_2 \xrightarrow{H_2O} Ar\overset{\displaystyle O}{\overset{\|}{C}}R$$

32. G. A. Olah, D. A. Beal, and J. A. Olah, *J. Org. Chem.* **41**, 1627 (1976); G. A. Olah, D. A. Beal, S. H. Yu, and J. A. Olah, *Synthesis*, 560 (1974).

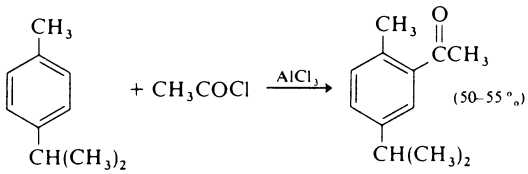
Scheme 8.4. Friedel–Crafts

A. Intermolecular Reactions

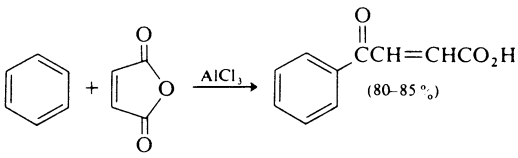
1[a]



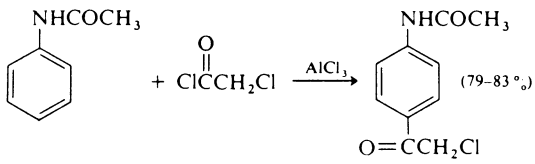
2[b]



3[c]



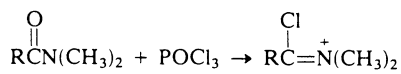
4[d]



a. R. Adams and C. R. Noller, *Org. Synth.* **I**, 109 (1941).
b. C. F. H. Allen, *Org. Synth.* **II**, 3 (1943).
c. O. Grummitt, E. I. Becker, and C. Miesse, *Org. Synth.* **III**, 109 (1955).
d. J. L. Leiserson and A. Weissberger, *Org. Synth.* **III**, 183 (1955).

Many specific examples of these reactions can be found in reviews in the *Organic Reactions* series.[33]

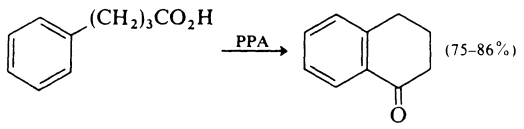
Dichloromethyl ethers are also precursors of the formyl group via alkylation catalyzed by $SnCl_4$.[34] Another useful method of introducing formyl and acyl groups is by the Vilsmeier–Haack reaction.[35] An *N,N*-dialkylamide and phosphorus oxychloride give rise to a chloroiminium ion which acts as the reactive electrophile.



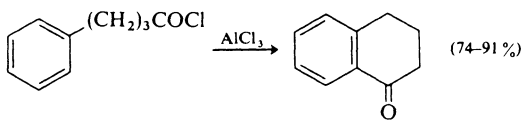
33. N. N. Crounse, *Org. React.* **5**, 290 (1949); W. E. Truce, *Org. React.* **9**, 37 (1957); P. E. Spoerri and A. S. DuBois, *Org. React.* **5**, 387 (1949).
34. P. E. Sonnet, *J. Med. Chem.* **15**, 97 (1972).
35. G. Martin and M. Martin, *Bull. Soc. Chim. France*, 1637 (1963).

B. Intramolecular Friedel–Crafts Acylations

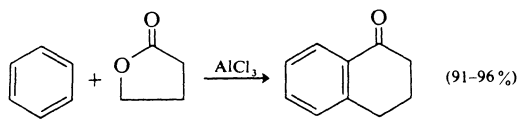
5[e]



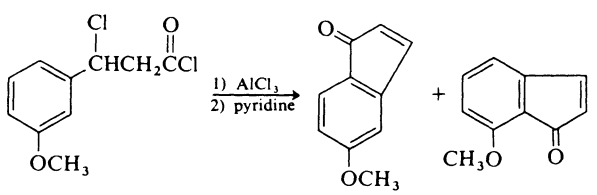
6[f]



7[g]



8[h]



e. L. Arsenijevic, V. Arsenijevic, A. Horeau, and J. Jacques, *Org. Synth.* **53**, 5 (1973).
f. E. L. Martin and L. F. Fieser, *Org. Synth.* **II**, 569 (1943).
g. C. E. Olson and A. F. Bader, *Org. Synth.* **IV**, 898 (1963).
h. M. B. Floyd and G. R. Allen, Jr., *J. Org. Chem.* **35**, 2647 (1970).

This species is more reactive as an electrophile than an acid chloride because of the positively charged nitrogen, and activated aromatics are substituted without need for Lewis acid catalysts. The reactivity of the electrophile is such that only rings with activating substituents react effectively.

Scheme 8.5 gives some specific examples of these electrophilic substitutions.

8.1.4. Electrophilic Metalation

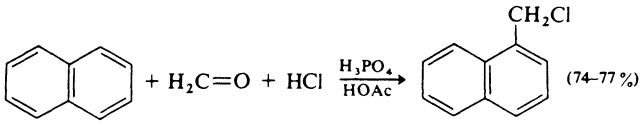
Aromatic compounds react with mercuric salts to give arylmercury compounds.[36] The reaction shows substituent effects characteristic of electrophilic

36. W. Kitching, *Organomet. Chem. Rev.* **3**, 35 (1968).

Scheme 8.5. Other Electrophilic Aromatic

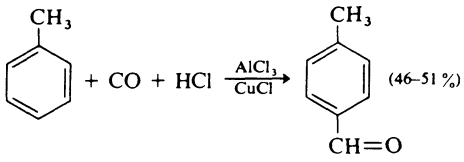
Chloromethylation

1[a]



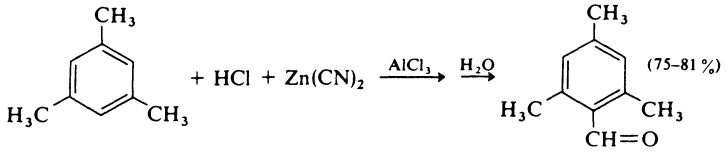
Formylation with Carbon Monoxide

2[b]

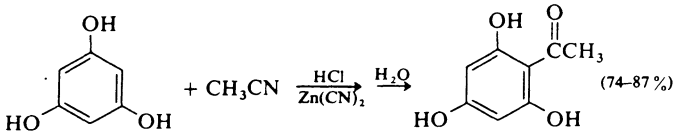


Acylation with Cyanide and Nitriles

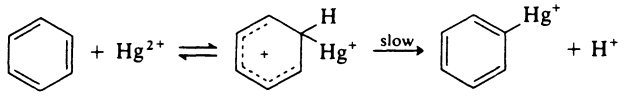
3[c]



4[d]



substitution, and is accelerated by electron-releasing substituents.[37] Mercuration is one of the few electrophilic aromatic substitutions in which proton loss from the σ complex is rate determining. The reactions exhibit an isotope effect of about $k_H/k_D = 6$.[38] This indicates that the σ complex must be reversibly formed. A

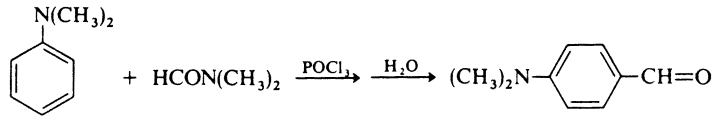


variety of mercury species are present under typical mercuration conditions. The reactive species are usually considered to be ion pairs of Hg^{2+} or HgX^+.[39] Undissoci-

37. H. C. Brown and C. W. McGary, Jr., *J. Am. Chem. Soc.* **77**, 2300, 2306, 2310 (1955); A. J. Kresge and H. C. Brown, *J. Org. Chem.* **32**, 756 (1967).
38. C. Perrin and F. H. Westheimer, *J. Am. Chem. Soc.* **85**, 2773 (1963); A. J. Kresge and J. F. Brennan, *J. Org. Chem.* **32**, 752 (1967).
39. A. J. Kresge, M. Dubeck, and H. C. Brown, *J. Org. Chem.* **32**, 745 (1967).

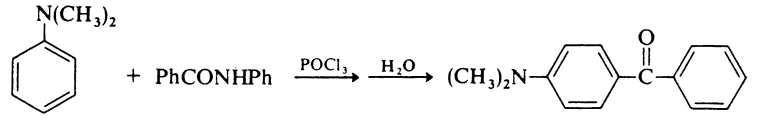
Vilsmeier–Haack Acylation

5[e]



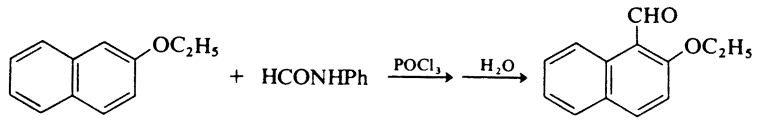
(80–84 %)

6[f]



(72–77 %)

7[g]



(74–84 %)

a. O. Grummitt and A. Buck, *Org. Synth.* **III**, 195 (1955).
b. G. H. Coleman and D. Craig, *Org. Synth.* **II**, 583 (1955).
c. R. C. Fuson, E. C. Horning, S. P. Rowland, and M. L. Ward, *Org. Synth.* **III**, 549 (1955).
d. K. C. Gulati, S. R. Seth, and K. Venkataraman, *Org. Synth.* **II**, 522 (1943).
e. E. Campaigne and W. L. Archer, *Org. Synth.* **IV**, 331 (1963).
f. C. D. Hurd and C. N. Webb, *Org. Synth.* **I**, 217 (1941).
g. J. H. Wood and R. W. Bost, *Org. Synth.* **IV**, 98 (1955).

ated species such as $Hg(OAc)_2$ are less reactive. It has been found that trifluoroacetic acid is an excellent solvent for electrophilic mercuration.[40] In this medium mercuration gives clean second-order kinetics with benzene and its simple alkyl derivatives.

The synthetic utility of the mercuration reaction derives from subsequent transformations of the arylmercury derivatives. As indicated in Chapter 6, arylmercury compounds are only weakly nucleophilic but the carbon–mercury is reactive toward various electrophiles. The nitroso group can be introduced by reaction with nitrosyl chloride[41] or nitrosonium tetrafluoroborate[42] as the electrophile. Arylmercury compounds are intermediates in nitrations carried out in nitric acid using mercuric acetate as a catalyst.[42]

40. H. C. Brown and R. A. Wirkkala, *J. Am. Chem. Soc.* **88**, 1447, 1453, 1456 (1966).
41. L. I. Smith and F. L. Taylor, *J. Am. Chem. Soc.* **57**, 2460 (1935); S. Terabe, S. Kuruma, and R. Konaka, *J. Chem. Soc., Perkin Trans. 2*, 1252 (1973).
42. L. M. Stock and T. L. Wright, *J. Org. Chem.* **44**, 3467 (1979).

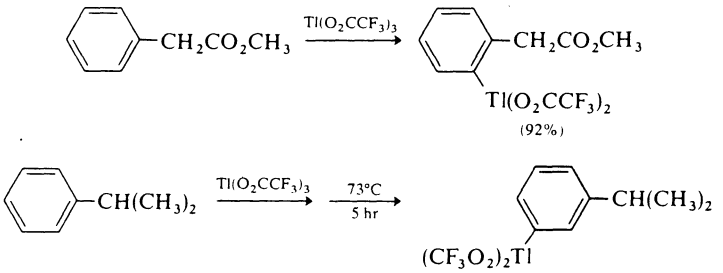
The arylmercury compounds prepared by metalation are also useful intermediates for a variety of synthetic processes which involve exchange with other metal ions such as Pd(II). These reactions were discussed in Chapter 6.

Thallium(III), particularly as its trifluoroacetate salt, is also a reactive metallating species and a variety of synthetic schemes based on arylthallium intermediates have been devised.[43] Arylthallium compounds are converted to chlorides or bromides by reaction with the appropriate cupric halide.[44] Reaction with potassium iodide gives excellent yields of iodides.[45] Fluorides are prepared by successive treatment with potassium fluoride followed by boron trifluoride.[46]

$$ArTl(O_2CCF_3)_2 \xrightarrow{KF} ArTlF_2 \xrightarrow{BF_3} ArF$$

Procedures for converting arylthallium compounds to nitriles[47,48] and phenols[48] have also been described.

The thallium intermediates can be useful in directing substitution to a specific position, if the site of thallation can be controlled in an advantageous way. The two principal means of control are chelation and the ability to effect thermal equilibration of arylthallium intermediates. Oxygen-containing groups normally



direct thallation to the *ortho* position, whereas the thermodynamically favored position in the absence of chelating effects is the *meta* position. For alkyl-substituted benzenes a predominance of the *meta* substituted product is obtained by heating the initial kinetically-controlled thallation product.[49]

43. E. C. Taylor and A. McKillop, *Acc. Chem. Res.* **3**, 338 (1970).
44. S. Uemura, Y. Ikeda, and K. Ichikawa, *Tetrahedron* **28**, 5499 (1972).
45. A. McKillop, J. D. Hunt, M. J. Zelesko, J. S. Fowler, E. C. Taylor, G. McGillivray, and F. Kienzle, *J. Am. Chem. Soc.* **93**, 4841 (1971).
46. E. C. Taylor, E. C. Bigham, and D. K. Johnson, *J. Org. Chem.* **42**, 362 (1977).
47. S. Uemura, Y. Ikeda, and K. Ichikawa, *Tetrahedron* **28**, 3025 (1972).
48. E. C. Taylor, H. W. Altland, R. H. Danforth, G. McGillivray, and A. McKillop, *J. Am. Chem. Soc.* **92**, 3520 (1970).
49. A. McKillop, J. D. Hunt, M. J. Zelesko, J. S. Fowler, E. C. Taylor, G. McGillivray, and F. Kienzle, *J. Am. Chem. Soc.* **93**, 4841 (1971).

8.2. Nucleophilic Aromatic Substitution

Many synthetically important aromatic substitutions are effected by nucleophilic reagents. Unlike nucleophilic substitution at saturated carbon, aromatic substitution rarely, if ever, occurs as a single step. Rather, intermediates are involved. Three broad mechanistic classes can be recognized: addition–elimination, elimination–addition, and radical or electron-transfer processes. Undoubtedly the most broadly useful substrates for nucleophilic aromatic substitution are the aryldiazonium salts and these compounds will be the first topic.

8.2.1. Diazonium Ion Intermediates

Aryl diazonium ions are usually prepared by reaction of an aniline with nitrous acid generated *in situ* from a nitrite salt.[50] Unlike aliphatic diazonium ions, which decompose very rapidly to molecular nitrogen and a carbonium ion, aryl diazonium ions are stable enough to exist in solution at room temperature or below and some can be isolated as salts with nonnucleophilic counterions. The steps in forming a diazonium ion involve addition of ^{+}NO to the nucleophilic amino group, followed by elimination of water.

$$ArNH_2 + HONO \xrightarrow{H^+} Ar\overset{H}{\underset{|}{N}}{-}N{=}O + H_2O$$

$$Ar\overset{H}{\underset{|}{N}}{-}N{=}O \rightarrow ArN{=}N{-}OH \xrightarrow{H^+} Ar\overset{+}{N}{\equiv}N + H_2O$$

In alkaline solution diazoate anions are formed.[51]

$$Ar\overset{+}{N}{\equiv}N + 2^{-}OH \rightarrow ArN{=}N{-}O^{-} + H_2O$$

In addition to the classical techniques for diazotization in aqueous solution, diazonium ions can be generated by reaction with alkyl nitrites. This method is frequently used for *in situ* formation of diazonium intermediates in organic solvents.

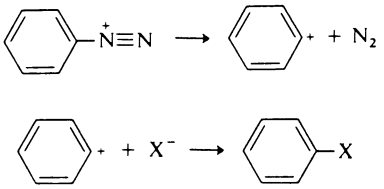
$$RO{-}N{=}O + ArNH_2 \rightarrow Ar\overset{H}{\underset{|}{N}}{-}N{=}O + ROH$$

$$Ar\overset{H}{\underset{|}{N}}{-}N{=}O \rightleftharpoons ArN{=}N{-}OH \xrightarrow{H^+} Ar\overset{+}{N}{\equiv}N + H_2O$$

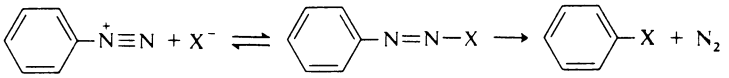
The great usefulness of aryl diazonium ions as synthetic intermediates results from the excellence of N_2 as a leaving group. There are at least three basic mechanisms by which substitution can occur. One involves first-order decomposition of the diazonium ion, followed by capture of the resulting aryl cation by nucleophiles present in solution. This cation is very unstable since the vacant orbital is in the

50. H. Zollinger, *Azo and Diazo Chemistry*, Interscience, New York (1961); S. Patai (ed.), *The Chemistry of Diazonium and Diazo Groups*, Wiley, New York (1978), Chaps. 8, 11 and 14.
51. E. S. Lewis and M. P. Hanson, *J. Am. Chem. Soc.* **89**, 6268 (1967).

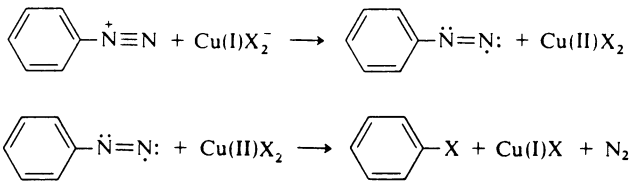
plane of the ring and not aligned for delocalization of the charge into the π system.



Nevertheless, several kinetic studies have shown that certain nucleophilic substitution reactions of aryl diazonium ions are first order and independent of the concentration of the nucleophilic species.[52] Solvent effects, isotope effects, and substituent effects are also in agreement with a rate-determining unimolecular decomposition of the aryl diazonium ion. In other reactions, an adduct of the nucleophile and diazonium ion is a distinct intermediate. Substitution results when nitrogen is eliminated from the adduct. Finally, substitution can occur via radical



reactions initiated by electron transfer. This mechanism is particularly likely to operate in reactions where copper catalysts are used[54]:



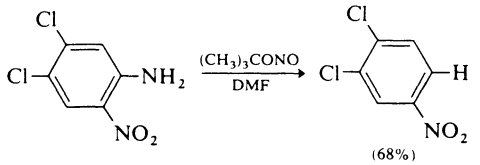
Examples of the three mechanisms are, respectively, (a) hydrolysis of aryl diazonium salts to phenols,[55] (b) reaction of aryl diazonium ions with N_3^- to give the aryl azides,[56] and (c) the Sandmeyer reaction, involving cuprous chlorides and bromides, for synthesis of aryl halides.[57] In the paragraphs which follow, the synthetically useful reactions of diazonium intermediates are considered with the organization being on the basis of the group which is introduced by the reaction, rather than the mechanistic pattern.

52. These studies are summarized by H. G. Richey and J. M. Richey, in *Carbonium Ions*, Vol. II, G. A. Olah and P. von R. Schleyer (eds.), Wiley-Interscience, New York (1970), pp. 922–931.
53. C. G. Swain, J. E. Sheats, and K. G. Harbison, *J. Am. Chem. Soc.* **97**, 783 (1975).
54. T. Cohen, R. J. Lewarchik, and J. Z. Tarino, *J. Am. Chem. Soc.* **96**, 7753 (1974).
55. E. S. Lewis, L. D. Hartung, and B. M. McKay, *J. Am. Chem. Soc.* **91**, 419 (1969).
56. C. D. Ritchie and D. J. Wright, *J. Am. Chem. Soc.* **93**, 2429 (1971); C. D. Ritchie and P. O. I. Virtanen, *J. Am. Chem. Soc.* **94**, 4966 (1972).
57. J. K. Kochi, *J. Am. Chem. Soc.* **79**, 2942 (1957); S. C. Dickerman, K. Weiss, and A. K. Ingberman, *J. Am. Chem. Soc.* **80**, 1904 (1958).

Replacement of a nitro or amino group by hydrogen is sometimes a required sequel to synthetic operations in which the group has been used to control orientation in another substitution reaction. Originally this was done by heating in an alcohol but later H_3PO_2[58] and $NaBH_4$[59] were found to be more effective reductants. Aryl diazenes are probably intermediates.[60] The reduction by hypophosphorous acid is substantially improved by catalysis with cuprous oxide.[61] The thermal

$$Ar-\overset{+}{N}\equiv N \xrightarrow{[H]} Ar-N=NH \rightarrow ArH + N_2$$

decomposition in alcohol solvents often gives product mixtures because of competition between ionic (leading to incorporation of the alcohol as a nucleophile) and homolytic mechanisms.[62] An alternative method for reductive removal of amino groups involves *in situ* diazotization with alkyl nitrites in dimethylformamide.[63] The solvent dimethylformamide acts as the hydrogen atom donor under these conditions.



Ref. 63

Diazonium compounds can be converted to phenols by hydrolysis under conditions where formation of the aryl cation takes place.

$$Ar\overset{+}{N}\equiv N \rightarrow Ar^+ \xrightarrow{H_2O} ArOH$$

This reaction is usually accomplished synthetically by heating an aqueous solution of the diazonium salt. Because the aryl cation which is generated is highly reactive it can capture other nucleophiles present in solution and lead to the corresponding by-products. In fact, it has been shown by appropriate isotopic labeling studies that the cation can even recapture nitrogen under certain experimental conditions.[64]

An alternative redox mechanism leads to formation of phenols under rather milder conditions.[65] The reaction is initiated by cuprous oxide, which effects reductive formation of an aryl radical. In the presence of Cu(II) salts the radical

58. N. Kornblum, *Org. React.* **2**, 262 (1944).
59. J. B. Hendrickson, *J. Am. Chem. Soc.* **83**, 1251 (1961).
60. C. E. McKenna and T. G. Traylor, *J. Am. Chem. Soc.* **93**, 2313 (1971).
61. S. Korzeniowski, L. Blum, and G. W. Gokel, *J. Org. Chem.* **42**, 1469 (1977).
62. T. J. Broxton, J. F. Bunnet, and C. H. Paik, *J. Org. Chem.* **42**, 643 (1977); I. Szele and H. Zollinger, *Helv. Chim. Acta* **61**, 1721 (1978).
63. M. P. Doyle, J. F. Dellaria, Jr., B. Siegfried, and S. W. Bishop, *J. Org. Chem.* **42**, 3494 (1977).
64. I. Szele and H. Zollinger, *J. Am. Chem. Soc.* **100**, 2811 (1978); Y. Hashida, R. G. M. Landells, G. E. Lewis, I. Szele, and H. Zollinger, *J. Am. Chem. Soc.* **100**, 2816 (1978).
65. T. Cohen, A. G. Dietz, Jr., and J. R. Miser, *J. Org. Chem.* **42**, 2053 (1977).

is oxidized to the phenol by a reaction presumably taking place in the copper coordination sphere. For preparative purposes, the reaction is run in the presence

$$ArN^{+}\equiv N + Cu(I) \rightarrow Ar^{\cdot} + N_2 + Cu(II)$$

$$Ar^{\cdot} + Cu(II) \rightarrow [Ar{-}Cu]^{2+} \xrightarrow{H_2O} ArOH + Cu(I) + H^{+}$$

of excess Cu(II) salts to permit efficient oxidative capture of the phenyl radicals. The reaction is very rapid and gives good yields of phenols over a range of structural types.

Replacement of diazonium groups by halide is a very valuable synthetic alternative to direct halogenation for preparation of aryl halides. There are three broad types of procedures: decomposition of aryl diazonium–halide adducts with expulsion of nitrogen, copper-mediated redox processes, and thermal processes proceeding *via* aryl radicals. The first type of process is probably involved in the reaction of aryl diazonium salts with iodide ion. Smooth high-yield transformation takes place in the absence of any metal catalyst. The mechanism of the reaction

$$ArN^{+}\equiv N + I^{-} \rightarrow ArN{=}N{-}I \rightarrow ArI + N_2$$

has not been studied in detail but the intermediate adduct suggested is similar to those demonstrated in other facile nucleophilic displacements on aryl diazonium ions.[66]

Aryl bromides and iodides are usually prepared from diazonium salts by a copper-catalyzed process, a reaction commonly known as the *Sandmeyer reaction.* Under the classic conditions of the Sandmeyer reaction, the diazonium salt is added to a hot acidic solution of the cuprous halide.[67] It is also possible to convert anilines to aryl halides by generating the diazonium ion *in situ.* Reaction of anilines with alkyl nitrites and cuprous halides in acetonitrile gives good yields of aryl bromides by a copper-mediated process which is mechanistically similar to that occurring under the usual Sandmeyer conditions.[68] Diazonium salts can also be converted to

$$ArNH_2 + RONO \rightarrow ArN^{+}\equiv N + ROH + {}^{-}OH$$

$$ArN^{+}\equiv N + [CuX_2]^{-} \rightarrow Ar{-}CuX_2 + N_2$$

$$Ar{-}CuX_2 \rightarrow ArX + CuX$$

halides by processes which involve aryl free radicals. In basic solution aryl diazonium ions decompose to phenyl radicals via diazooxides.[69] This reaction can be particularly efficiently carried out using aryldiazonium tetrafluoroborates and crown

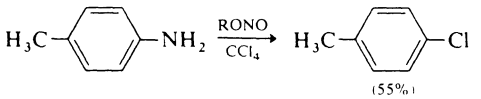
66. C. D. Ritchie and D. J. Wright, *J. Am. Chem. Soc.* **93**, 2429, 6574 (1971).
67. W. A. Cowdrey and D. S. Davies, *Q. Rev. Chem. Soc.* **6**, 358 (1952); H. H. Hodgson, *Chem. Rev.* **40**, 251 (1947).
68. M. P. Doyle, B. Siegfried, and J. F. Dellaria, Jr., *J. Org. Chem.* **42**, 2426 (1977).
69. C. Ruchardt and B. Freudenberg, *Tetrahedron Lett.*, 3623 (1964); C. Ruchardt and E. Merz, *Tetrahedron Lett.*, 2431 (1964).

$$2ArN^{+}\equiv N + 2^{-}OH \rightarrow ArN{=}N{-}O{-}N{=}NAr + H_2O$$

$$ArN{=}N{-}O{-}N{=}NAr \rightarrow ArN{=}N{-}O^{\cdot} + Ar^{\cdot} + N_2$$

$$Ar^{\cdot} + S{-}X \rightarrow ArX + S^{\cdot}$$

ether or polyether catalysts under phase-transfer conditions.[70] In the presence of solvents which can act as halogen atom donors, the reaction proceeds to the aryl halide. Bromotrichloromethane, for example, gives bromides and methyl iodide gives iodides.[71] Conditions for *in situ* generation of the diazonium species from the aniline and an alkyl nitrite have also been developed.[72] Bromoform or bromotrichloromethane serve as bromine donors, while carbon tetrachloride is the best chlorine donor.



Ref. 72

Fluorine can also be introduced onto aromatic rings via diazonium ions. One procedure is to isolate aryl diazonium tetrafluoroborates. These thermally decompose to give aryl fluorides presumably by formation of the aryl cation which abstracts fluoride from the anion.[73] Hexafluorophosphate salts behave similarly.[74] The

$$ArN^{+}\equiv N + BF_4^{-} \rightarrow ArF + N_2 + BF_3$$

diazonium tetrafluoroborates can be prepared either by precipitation of diazonium ions from an aqueous diazotization medium using fluoroboric acid[75] or by anhydrous diazotization in ether, THF, or acetonitrile using *t*-butyl nitrite and boron trifluoride.[76]

The cyano and azido groups are also readily introduced via diazonium ions. The former reaction occurs by a copper-catalyzed process analogous to the Sandmeyer reaction. Reaction of diazonium salts with azide ion gives adducts which smoothly decompose to nitrogen and the azide. Scheme 8.6 gives some representative examples of substitution reactions proceeding via diazonium salts.

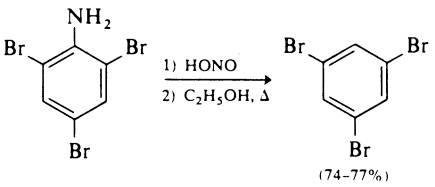
Aryl diazonium ions can also be used to form certain types of carbon–carbon bonds. The reaction of diazonium salts with certain conjugated alkenes results in

70. S. H. Korzeniowski and G. W. Gokel, *Tetrahedron Lett.*, 1637 (1977).
71. S. H. Korzeniowski and G. W. Gokel, *Tetrahedron Lett.*, 3519 (1977); R. A. Bartsch and I. W. Wang, *Tetrahedron Lett.*, 2503 (1979).
72. J. I. G. Cadogan, D. A. Roy, and D. M. Smith, *J. Chem. Soc. C*, 1249 (1966).
73. A. Roe, *Org. React.* **5**, 193 (1949); C. G. Swain and R. J. Rogers, *J. Am. Chem. Soc.* **97**, 799 (1975).
74. M. S. Newman and R. H. B. Galt, *J. Org. Chem.* **25**, 214 (1960).
75. E. B. Starkey, *Org. Synth.* **II**, 225 (1943); G. Schiemann and W. Winkelmuller, *Org. Synth.* **II**, 299 (1943).
76. M. P. Doyle and W. J. Bryker, *J. Org. Chem.* **44**, 1572 (1979).

Scheme 8.6. Aromatic

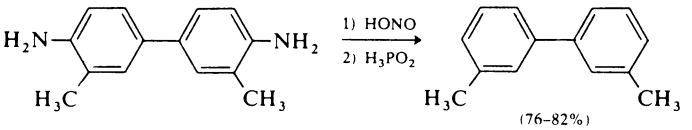
A. Replacement by Hydrogen

1[a]



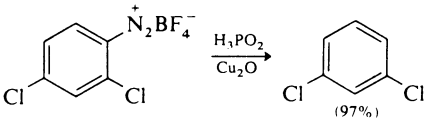
(74–77%)

2[b]



(76–82%)

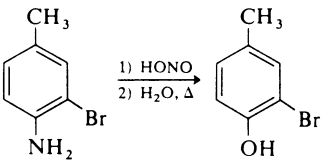
3[c]



(97%)

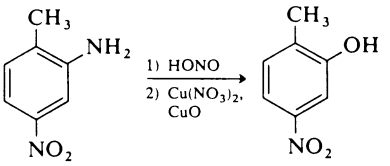
B. Replacement by Hydroxyl

4[d]



(80–92%)

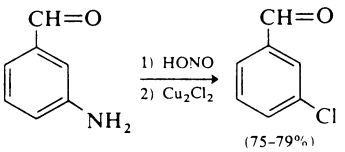
5[e]



(95%)

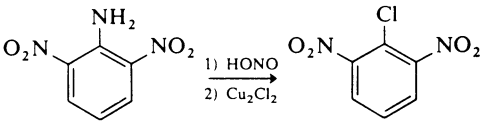
C. Replacement by Halogen

6[f]



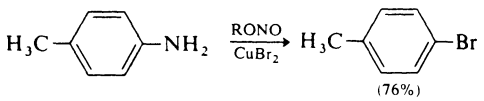
(75–79%)

7[g]



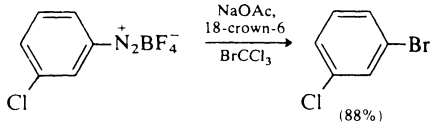
(71–74%)

8[h]



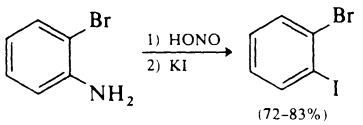
(76%)

9[i]



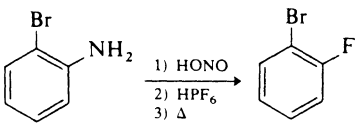
(88%)

10[j]



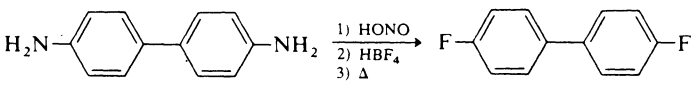
(72–83%)

11[k]



(73–75%)

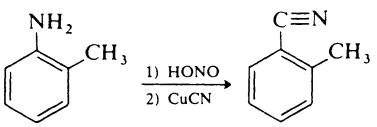
12[l]



(54–56%)

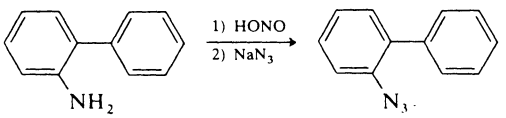
D. Replacement by Other Anions

13[m]



(64–70%)

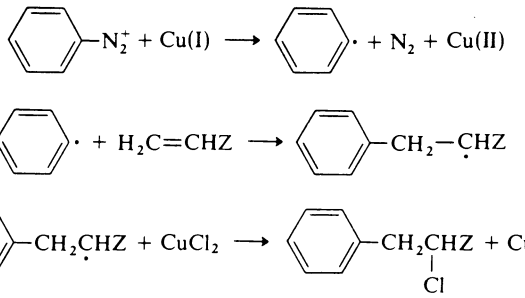
14[n]



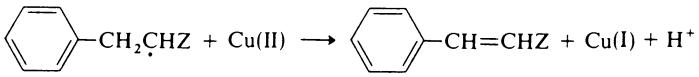
(88%)

a. G. H. Coleman and W. F. Talbot, *Org. Synth.* **II**, 592 (1943).
b. N. Kornblum, *Org. Synth.* **III**, 295 (1955).
c. S. H. Korzeniowski, L. Blum, and G. W. Gokel, *J. Org. Chem.* **42**, 1469 (1977).
d. H. E. Ungnade and E. F. Orwoll, *Org. Synth.* **III**, 130 (1955).
e. T. Cohen, A. G. Dietz, Jr., and J. R. Miser, *J. Org. Chem.* **42**, 2053 (1977).
f. J. S. Buck and W. S. Ide, *Org. Synth.* **II**, 130 (1943).
g. F. D. Gunstone and S. H. Tucker, *Org. Synth.* **IV**, 160 (1963).
h. M. P. Doyle, B. Siegfried, and J. F. Dellaria, Jr., *J. Org. Chem.* **42**, 2426 (1977).
i. S. H. Korzeniowski and G. W. Gokel, *Tetrahedron Lett.*, 3519 (1977).
j. H. Heaney and I. T. Millar, *Org. Synth.* **40**, 105 (1960).
k. K. G. Rutherford and W. Redmond, *Org. Synth.* **43**, 12 (1963).
l. G. Schiemann and W. Winkelmuller, *Org. Synth.* **II**, 188 (1943).
m. H. T. Clarke and R. R. Read, *Org. Synth.* **I**, 514 (1941).
n. P. A. S. Smith and B. B. Brown, *J. Am. Chem. Soc.* **73**, 2438 (1957).

arylation of the alkene. This is known as the *Meerwein arylation reaction.*[77] A redox sequence is initiated by reductive decomposition of the diazonium salt. The



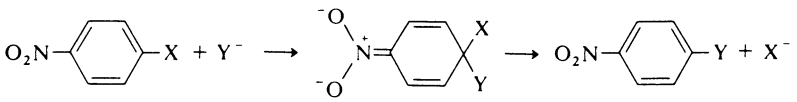
final step is an oxidative ligand transfer which takes place in the copper coordination sphere. An alternative course is oxidative elimination of a proton to give a styrene derivative. The reaction gives better yields with dienes, styrenes, or alkenes sub-



stituted with radical stabilizing substituents such as cyano or ester groups than with simple alkenes. These groups improve the efficiency of the capture of the aryl radicals. The standard conditions for the arylation reaction employ an aqueous solution of diazonium salt prepared in the usual way. An organic cosolvent and the alkene are then added followed by the copper salt. Conditions for *in situ* diazotization by *t*-butyl nitrite in the presence of $CuCl_2$ and acrylonitrile or styrene have also been found effective.[78] Scheme 8.7 illustrates some typical reactions.

8.2.2. Addition–Elimination Mechanism

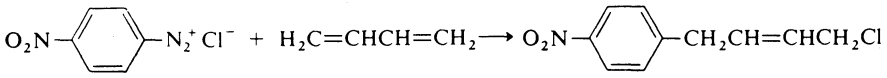
The addition of a nucleophile to an aromatic ring, followed by elimination of a substituent, results in nucleophilic substitution. The major energetic requirement for this mechanism is the formation of the addition intermediate. The addition step is greatly facilitated by strongly electron-attracting substituents, so that nitroaromatics are the best substrates for nucleophilic aromatic substitution. Other electron-withdrawing groups such as cyano, acetyl, and trifluoromethyl also increase reactivity, but to a lesser extent than the nitro group. The intermediate adducts can



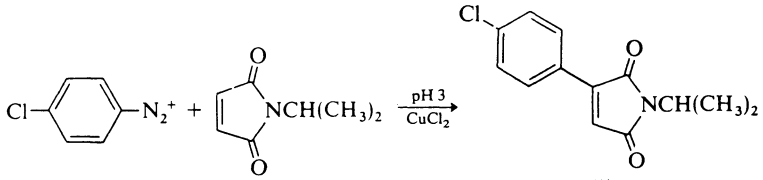
77. C. S. Rondestvedt, Jr., *Org. React.* **24**, 225 (1976); *Org. React.* **11**, 189 (1960).
78. M. P. Doyle, B. Siegfried, R. C. Elliot, and J. F. Dellaria, Jr., *J. Org. Chem.* **42**, 2431 (1977).

Scheme 8.7. Meerwein Arylation Reactions

1[a]

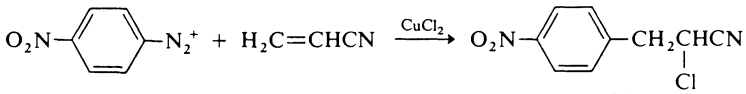


2[b]



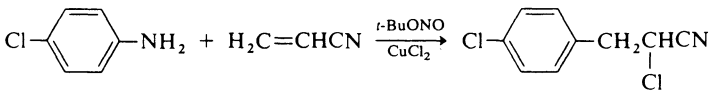
(51%)

3[c]



(48%)

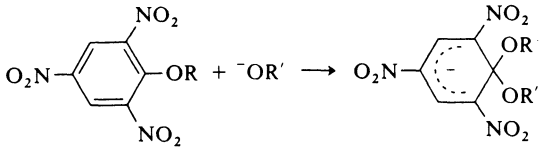
4[d]



(71%)

a. G. A. Ropp and E. C. Coyner, *Org. Synth.* **IV**, 727 (1963).
b. C. S. Rondestvedt, Jr., and O. Vogl, *J. Am. Chem. Soc.* **77**, 2313 (1955).
c. C. F. Koelsch, *J. Am. Chem. Soc.* **65**, 57 (1943).
d. M. P. Doyle, B. Siegfried, R. C. Elliott, and J. F. Dellaria, Jr., *J. Org. Chem.* **42**, 2431 (1977).

have appreciable stability under certain conditions, and are frequently referred to as *Meisenheimer complexes.*[79] Those derived from nitroaromatics are highly colored. Good examples are the compounds obtained by reaction of alkoxide ions with alkyl 2,4,6-trinitrophenyl ethers:



A wide variety of such compounds have been characterized involving nucleophiles such as cyanide, amines, thiolates, and enolates.

Nucleophilic substitution occurs through similar intermediates when the aromatic ring contains a potential leaving group. The most common case involves displacement of halide, but alkoxy, nitro and cyano groups can also be displaced by the addition–elimination mechanism. It is noteworthy that leaving-group ability

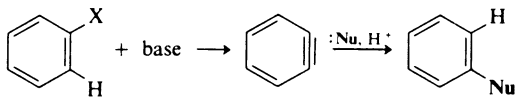
79. M. J. Strauss, *Chem. Rev.* **70**, 667 (1970).

in such reactions does not parallel that found for nucleophilic substitution at saturated carbon. As a particularly striking example, fluoride is often a better leaving group than the other halogens in nucleophilic aromatic substitution. The relative reactivity of the *p*-halonitrobenzenes toward sodium methoxide at 50°C is F(312) ≫ Cl(1) > Br(0.74) > I(0.36).[80] A principal reason for the order I > Br > Cl > F in S_N2 reactions is the carbon–halogen bond strength, which increases from I to F. This bond strength is not an important factor in nucleophilic aromatic substitution, because bond breaking is not ordinarily part of the rate-determining step. Furthermore, the highly electronegative fluorine stabilizes the addition transition state more effectively than the other halogens.

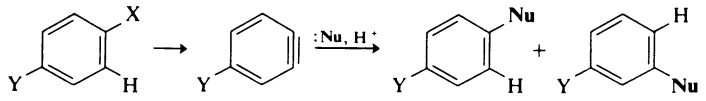
There have been a large number of detailed studies, especially involving kinetic measurements, that have helped to establish the finer details of aromatic nucleophilic substitutions proceeding via the addition–elimination mechanism.[81] Carbanions, alkoxides, and amines are all reactive in nucleophilic aromatic substitution and provide most of the cases in which this reaction has been used preparatively. Some examples are given in Scheme 8.8.

8.2.3. Elimination–Addition Mechanism

The elimination–addition mechanism involves a highly unstable intermediate, which is referred to as *dehydrobenzene* or *benzyne*:[82]



A characteristic feature of this mechanism is the substitution pattern in the product. The entering nucleophile need not always enter the ring at the carbon to which the leaving group was bound:

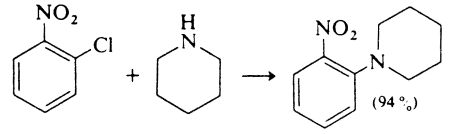


Benzyne has been observed spectroscopically in an inert solid matrix at very low temperatures.[83] For these studies, the molecule was generated photolytically:

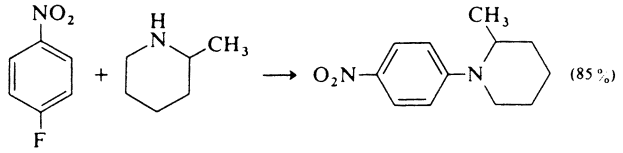
80. G. P. Briner, J. Miller, M. Liveris, and P. G. Lutz, *J. Chem. Soc.*, 1265 (1954).
81. J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, New York (1968); F. Pietra, *Q. Rev.* **23**, 504 (1969); C. F. Bernasconi, in *Aromatic Compounds*, H. Zollinger (ed.), University Park Press, Baltimore, Maryland (1973), Chap. 2; C. F. Bernasconi, *Acc. Chem. Res.* **11**, 147 (1978); G. Bartoli and P. E. Todesco, *Acc. Chem. Res.* **10**, 125 (1977).
82. R. W. Hoffmann, *Dehydrobenzene and Cycloalkynes*, Academic Press, New York (1967).
83. O. L. Chapman, K. Mattes, C. L. McIntosh, J. Pacansky, G. V. Calder, and G. Orr, *J. Am. Chem. Soc.* **95**, 6134 (1973).

Scheme 8.8. Nucleophilic Aromatic Substitution

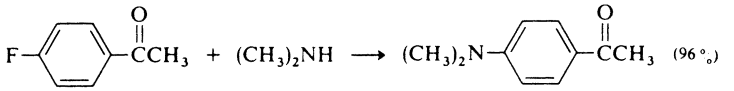
1[a]



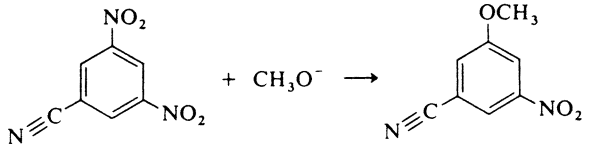
2[b]



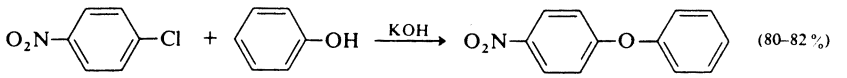
3[c]



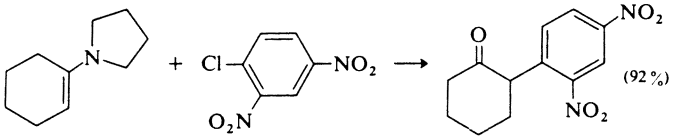
4[d]



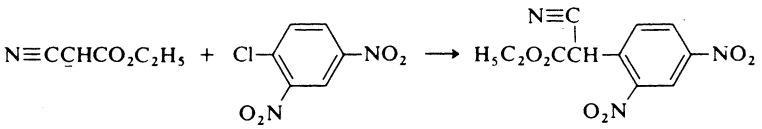
5[e]



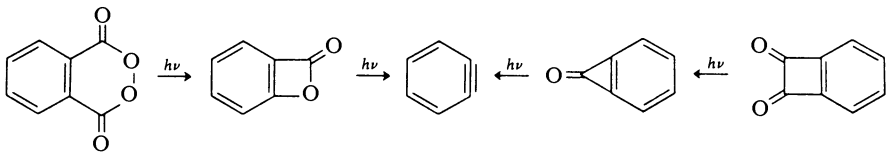
6[f]



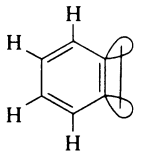
7[g]



a. S. D. Ross and M. Finkelstein, *J. Am. Chem. Soc.* **85**, 2603 (1963).
b. F. Pietra and F. Del Cima, *J. Org. Chem.* **33**, 1411 (1968).
c. H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*.**31**, 2319 (1966).
d. E. J. Fendler, J. H. Fendler, N. L. Arthur, and C. E. Griffin, *J. Org. Chem.* **37**, 812 (1972).
e. R. O. Brewster and T. Groening, *Org. Synth.* **II**, 445 (1943).
f. M. E. Kuehne, *J. Am. Chem. Soc.* **84**, 837 (1962).
g. H. R. Snyder, E. P. Merica, C. G. Force, and E. G. White, *J. Am. Chem. Soc.* **80**, 4622 (1958).

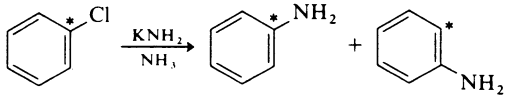


There have been several structural representations of benzyne. The one most generally used represents benzyne as similar to benzene, but with a weak π bond in the plane of the ring formed using two sp^2 orbitals.[84] Molecular-orbital calculations indicate that there is additional bonding between the "dehydro" carbons,



though the strength of the bond is much less than a normal triple bond.[85] Analysis of the infrared spectrum gives a bond length of 1.35 Å, about 0.05 Å shorter than normal aromatic C–C bond lengths.[86]

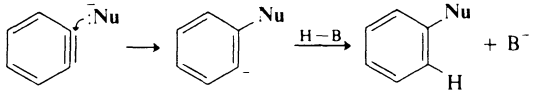
An early case in which the existence of benzyne as a reaction intermediate was established was in the reaction of chlorobenzene with potassium amide. ^{14}C-label in the starting material was found to be distributed in the aniline as expected for a benzyne intermediate.[87]



The elimination–addition mechanism is facilitated by electronic effects that favor removal of a hydrogen from the ring as a proton. Relative reactivity also depends on the halide. The order Br > I > Cl ≫ F has been established in the reaction of aryl halides with KNH_2 in liquid ammonia.[88] This order has been interpreted as representing a balance of two effects. The inductive order favoring proton removal would be F > Cl > Br > I, but this is largely overwhelmed by the order of leaving-group ability I > Br > Cl > F, which reflects bond strengths. With organometallic bases in aprotic solvents, the acidity of the hydrogen is the dominant factor, and the reactivity order is F > Cl > Br > I.[89]

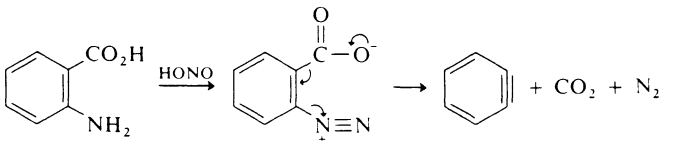
84. H. E. Simmons, *J. Am. Chem. Soc.* **83**, 1657 (1961).
85. R. Hoffmann, A. Imamura, and W. J. Hehre, *J. Am. Chem. Soc.* **90**, 1499 (1968); D. L. Wilhite and J. L. Whitten, *J. Am. Chem. Soc.* **93**, 2858 (1971).
86. J. W. Laing and R. S. Berry, *J. Am. Chem. Soc.* **98**, 660 (1976).
87. J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Am. Chem. Soc.* **78**, 601 (1956).
88. F. W. Bergstrom, R. E. Wright, C. Chandler, and W. A. Gilkey, *J. Org. Chem.* **1**, 170 (1936).
89. R. Huisgen and J. Sauer, *Angew. Chem.* **72**, 91 (1960).

Addition of nucleophiles such as ammonia or alcohols or their conjugate bases to benzynes takes place very rapidly. These nucleophilic additions are believed to involve capture of the nucleophile by benzyne, followed by protonation to give the substituted benzene.[90] Some evidence for the two-step mechanism can be drawn from the effect of substituent groups on the direction of nucleophilic addition.

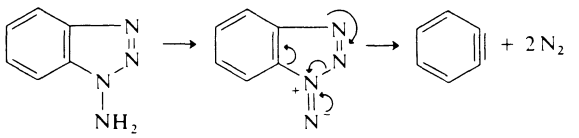


Electron-attracting groups tend to favor addition of the nucleophile at the more distant end of the "triple bond," since this permits maximum stabilization of the developing negative charge. Selectivity is usually not high, however, and formation of both possible products from monosubstituted benzynes is common.[91]

There are several methods for generation of benzyne in addition to base-catalyzed elimination of hydrogen halide from a halobenzene, and some of these are more generally applicable for preparative work. Probably the most useful method is diazotization of *o*-aminobenzoic acids.[92] Concerted loss of nitrogen and carbon dioxide follows diazotization and generates benzyne. Benzyne can be formed in this manner in the presence of a variety of compounds with which it reacts rapidly. Some specific examples will be given shortly.

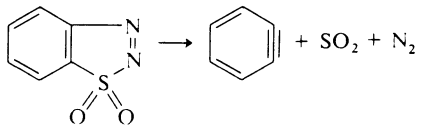


Oxidation of 1-aminobenzotriazole also serves as a source of benzyne under mild conditions. An oxidized intermediate decomposes with loss of two molecules of nitrogen.[93]

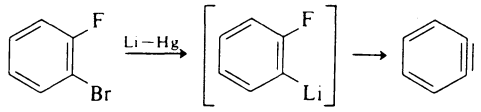


Another heterocyclic molecule that can serve as a benzyne precursor is benzothiadiazole-1,1-dioxide, which decomposes with elimination of nitrogen and sulfur dioxide.[94]

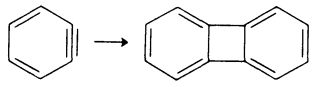
90. J. F. Bunnett, D. A. R. Happer, M. Patsch, C. Pyun, and H. Takayama, *J. Am. Chem. Soc.* **88**, 5250 (1966); J. F. Bunnett and J. K. Kim, *J. Am. Chem. Soc.* **95**, 2254 (1973).
91. E. R. Biehl, E. Nieh, and K. C. Hsu, *J. Org. Chem.* **34**, 3595 (1969).
92. M. Stiles, R. G. Miller, and U. Burckhardt, *J. Am. Chem. Soc.* **85**, 1792 (1963); L. Friedman and F. M. Logullo, *J. Org. Chem.* **34**, 3089 (1969).
93. C. D. Campbell and C. W. Rees, *J. Chem. Soc. C*, 742, 752 (1969).
94. G. Wittig and R. W. Hoffmann, *Org. Synth.* **47**, 4 (1967); G. Wittig and R. W. Hoffmann, *Chem. Ber.* **95**, 2718, 2729 (1962).



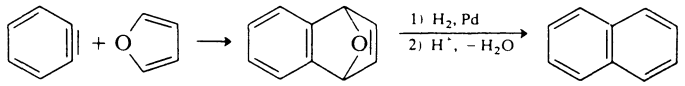
Benzyne can also be generated from *o*-dihaloaromatics. Reaction with lithium-amalgam (or magnesium) results in the formation of a transient organometallic compound that decomposes with elimination of lithium halide. *o*-Fluorobromobenzene is the usual starting material in this procedure.[95]



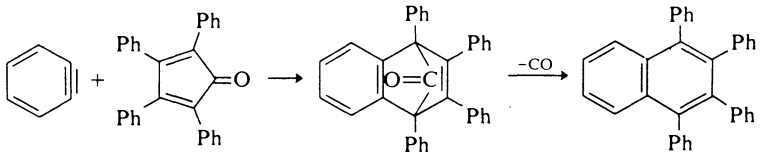
When benzyne is generated in the presence of unsaturated molecules, additions at the highly strained "triple bond" are observed. Benzyne is capable of dimerization, so that in the absence of either nucleophiles or a reactive unsaturated



compound, biphenylene is formed.[96] Among the types of compounds which give 4 + 2 cycloaddition products with benzyne are furans and cyclopentadienones.[97]

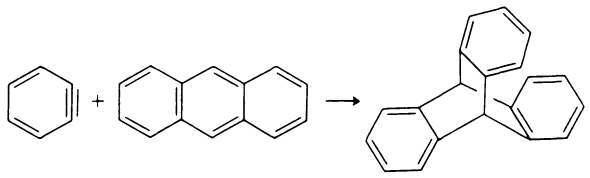


Ref. 97a



Ref. 97b

The adducts can be used to build up polycyclic aromatic rings. Anthracene also gives the cycloaddition product, triptycene.



Ref. 98

95. G. Wittig and L. Pohmer, *Chem. Ber.* **89**, 1334 (1956); G. Wittig, *Org. Synth.* **IV**, 964 (1963).
96. F. M. Logullo, A. H. Seitz, and L. Friedman, *Org. Synth.* **48**, 12 (1968).
97. a. G. Wittig and L. Pohmer, *Angew. Chem.* **67**, 348 (1955).
b. L. F. Fieser and M. J. Haddadin, *Org. Synth.* **46**, 107 (1966).
98. L. Friedman and F. M. Logullo, *J. Org. Chem.* **34**, 3089 (1969).

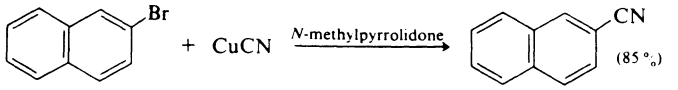
The stereochemistry of both 2 + 2 and 2 − 4 cycloadditions has been investigated. For dichloroethylenes, the 2 + 2 addition is not stereospecific; for dienes, however, the 4 + 2 addition is a stereospectfic *cis* addition. Benzyne thus shows behavior parallel to ground state ethyleneson undergoing concerted 2 + 4 cycloaddition, but nonconcerted 2 + 2 additions.[99]

Scheme 8.9 illustrates some of the types of compounds that can be prepared via benzyne intermediates.

8.2.4. Copper-Catalyzed Reactions

It has been known for a long time that the nucleophilic substitution of aromatic halides is strongly catalyzed by the presence of certain copper salts. Perhaps the most useful of the synthetic procedures based on this observation is the synthesis of aryl nitriles by reaction of aryl bromides with cuprous cyanide. The reaction is usually accomplished in dimethylformamide or a similar solvent. More recently,

Ref. 100



Ref. 101

the mechanistic basis of this reaction has become clearer and as a result the scope of the reaction has been expanded. A general mechanistic treatment of the copper-promoted reactions pictures an oxidative addition of Cu(I) followed by collapse of the arylcopper intermediate with transfer of a copper ligand to the aryl ring.[102]

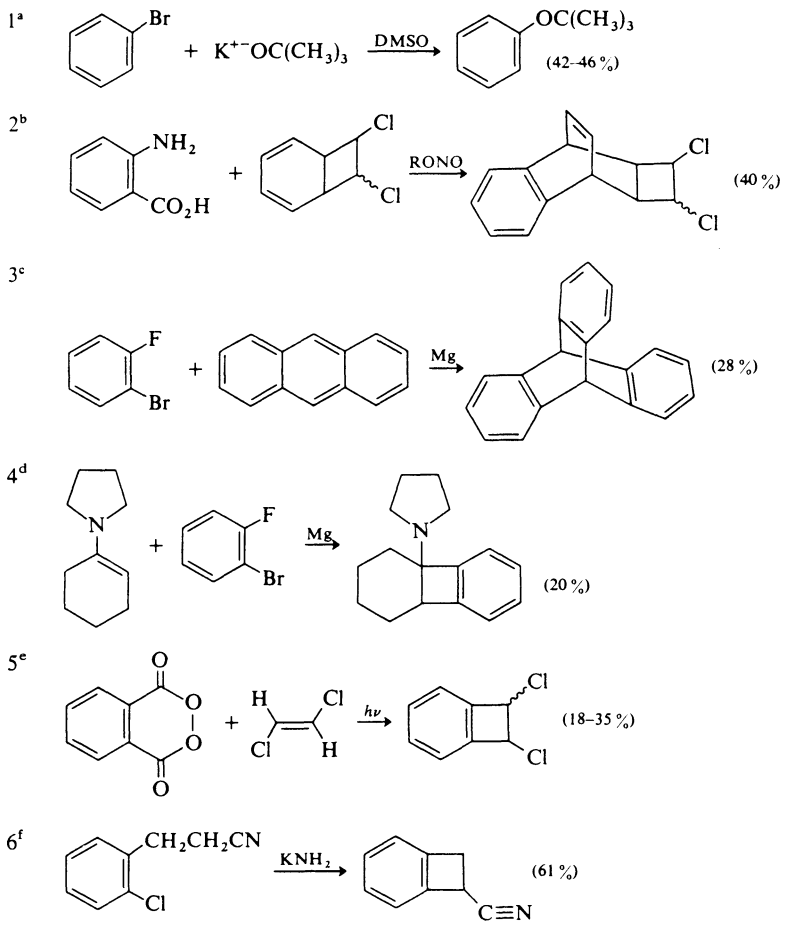
$$\mathrm{Ar{-}X + Cu(I)Z \rightarrow Ar{-}\underset{\displaystyle X}{\underset{|}{Cu}}{-}Z \rightarrow Ar{-}Z + CuX}$$

X = halide
Z = nucleophile

Among the nucleophiles which can be introduced by this reaction are carboxylate ions,[103] phthalimide anions,[104] alkoxide ions,[105] and acetylide groups.[106] In many of these reactions there is competitive reduction of the aryl halide to the arene.

99. M. Jones, Jr. and R. H. Levin, *J. Am. Chem. Soc.* **91**, 6411 (1969).
100. L. Friedman and H. Shechter, *J. Org. Chem.* **26**, 2522 (1961).
101. M. S. Newman and H. Boden, *J. Org. Chem.* **26**, 2525 (1961).
102. T. Cohen, J. Wood, and A. G. Dietz, *Tetrahedron Lett.*, 3555 (1974).
103. T. Cohen and A. H. Lewin, *J. Am. Chem. Soc.* **88**, 4521 (1966).
104. R. G. R. Bacon and A. Karim, *J. Chem. Soc. Perkin Trans. 1*, 272 (1973).
105. R. G. R. Bacon and S. C. Rennison, *J. Chem. Soc. C*, 312 (1969).
106. C. E. Castro, R. Havlin, V. K. Honwad, A. Malte, and S. Moje, *J. Am. Chem. Soc.* **91**, 6464 (1969).

Scheme 8.9. Some Syntheses via Benzyne Intermediates



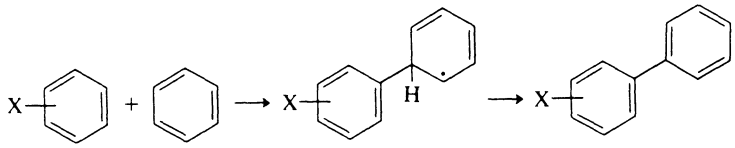
a. M. R. Sahyun and D. J. Cram, *Org. Synth.* **45**, 89 (1965).
b. L. A. Paquette, M. J. Kukla, and J. C. Stowell, *J. Am. Chem. Soc.* **94**, 4920 (1972).
c. G. Wittig, *Org. Synth.* **IV**, 964 (1963).
d. M. E. Kuehne, *J. Am. Chem. Soc.* **84**, 837 (1962).
e. M. Jones, Jr. and M. R. DeCamp, *J. Org. Chem.* **36**, 1536 (1971).
f. J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.* **27**, 3836 (1962).

This is attributed to protonolysis of the arylcopper intermediate. Protonolysis can become the dominant reaction under conditions where protonation is favorable. Most of these reactions are carried out under heterogeneous conditions but homogeneous conditions can be obtained with certain soluble copper(I) salt, particularly copper(I) trifluoromethanesulfonate.[107]

107. T. Cohen and J. G. Tirpak, *Tetrahedron Lett.*, 143 (1975).

8.3. Free-Radical and Electron-Transfer Processes

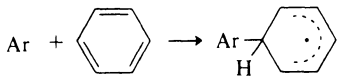
Perhaps the most important preparative use of aryl free radicals is in the synthesis of biaryls. If an aryl free radical is generated in the presence of a second aromatic compound, substitution leading to the biaryl is observed.[108] Yields in this

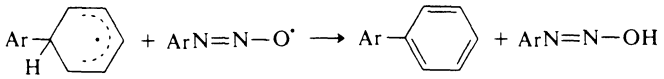


reaction are usually only modest and its utility is restricted because of the low regioselectivity of aryl substitution by radical mechanisms.[109] The reaction is usually practical only for substrates, such as benzene, where the position of substitution is immaterial. The best sources of aryl radicals in solution are aryl diazonium ions and *N*-nitrosoacetanilides. In the presence of base, diazonium ions form diazooxides which decompose to aryl radicals.[110] One convenient way of

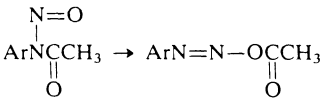
$$ArN{\equiv}N + 2^{-}OH \rightarrow ArN{=}N{-}O{-}N{=}NAr + H_2O$$

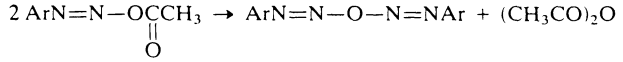
$$ArN{=}N{-}O{-}N{=}NAr \rightarrow Ar^{\cdot} + N_2 + {}^{\cdot}O{-}N{=}NAr$$





effecting this reaction involves potassium acetate as the base and a crown ether solubilizing agent.[111] The classical reaction conditions involve addition of strong base to a two-phase mixture of diazonium ion and an excess of the aromatic which is to be substituted. *N*-nitrosoacetanilides can rearrange to a diazoacetate which then leads to the diazooxide.[112]

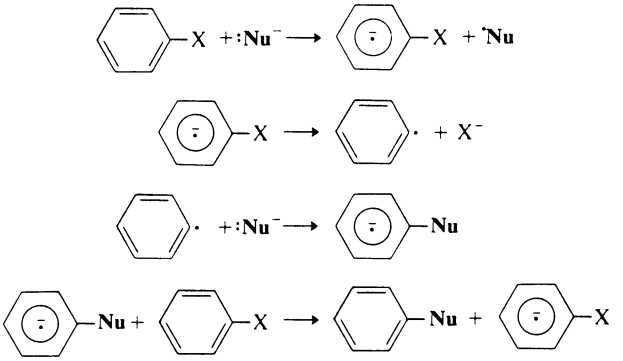




108. W. E. Bachmann and R. A. Hoffman, *Org. React.* **2**, 224 (1944).
109. D. H. Hey, *Adv. Free-Radical Chem.* **2**, 47 (1966).
110. C. Ruchardt and B. Freudenberg, *Tetrahedron Lett.*, 3623 (1964); C. Ruchardt and E. Merz, *Tetrahedron Lett.*, 2431 (1964).
111. S. H. Korzeniowski, L. Blum, and G. W. Gokel, *Tetrahedron Lett.*, 1871 (1977).
112. J. I. G. Cadogan, *Acc. Chem. Res.* **4**, 186 (1971); *Adv. Free Radical Chem.* **6**, 185 (1980).

A procedure for arylation involving *in situ* diazotization has also been reported.[113] Scheme 8.10 gives some representative preparative examples.

Recent mechanistic investigations have defined a group of nucleophilic aromatic substitutions which proceed by a pathway described as $S_{RN}1$.[114] The key is an electron transfer from the nucleophile to an aryl halide. The process is a chain



reaction. The reaction has not been widely used as yet in preparative practice but several types of synthetically important nucleophiles show reactivity toward aryl bromides. These include the enolate of acetone and other ketones,[116] 2,4-pentanedione dianion,[117] pentadienyl anion,[118] diethyl phosphite anion,[119] and thiolates.[120] The reaction proceeds with either aryl bromides or iodides and can be carried out in the presence of alkoxy and acyl substituents on the benzene ring. Chloropyridines and chloroquinolines are also excellent substrates for the reaction.[121] These reactions are usually initiated by light and can be inhibited by substances which interrupt the chain reaction. Some examples of the preparative use of the reaction are given in Scheme 8.11.

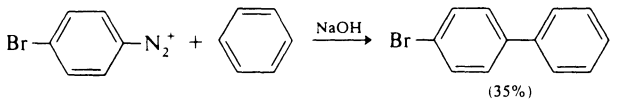
8.4. Reactivity of Polycyclic Aromatic Compounds

The polycyclic aromatic hydrocarbons, particularly naphthalene, anthracene and phenanthrene, as well as simple substituted derivatives, generally undergo the

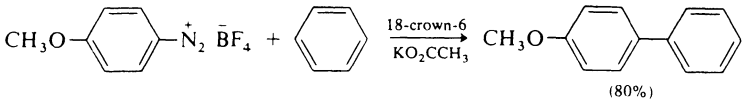
113. J. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962).
114. J. F. Bunnett, *Acc. Chem. Res.* **11**, 413 (1978).
115. R. A. Rossi and J. F. Bunnett, *J. Org. Chem.* **38**, 1407 (1973).
116. M. F. Semmelhack and T. Bargar, *J. Am. Chem. Soc.* **102**, 7765 (1980).
117. J. F. Bunnett and J. E. Sundberg, *J. Org. Chem.* **41**, 1702 (1976).
118. R. A. Rossi and J. F. Bunnett, *J. Org. Chem.* **38**, 3020 (1973).
119. J. F. Bunnett and X. Creary, *J. Org. Chem.* **39**, 3612 (1974).
120. J. F. Bunnett and X. Creary, *J. Org. Chem.* **39**, 3173, 3611 (1974), *J. Org. Chem.* **40**, 3740 (1975).
121. J. V. Hay, T. Hudlicky, and J. F. Wolfe, *J. Am. Chem. Soc.* **97**, 374 (1975); J. V. Hay and J. F. Wolfe, *J. Am. Chem. Soc.* **97**, 3702 (1975); A. P. Komin and J. F. Wolfe, *J. Org. Chem.* **42**, 2481 (1977).

Scheme 8.10. Biaryls by Radical Substitution

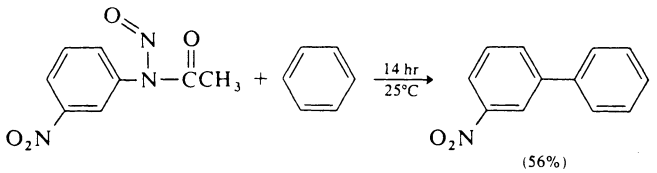
1[a]



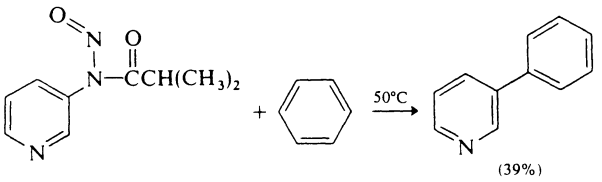
2[b]



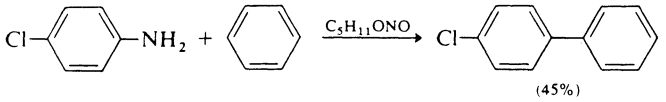
3[c]



4[d]

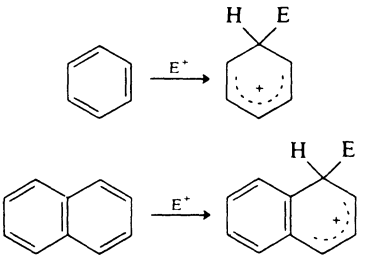


5[e]



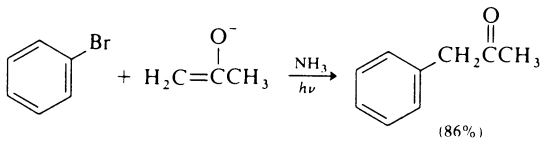
a. M. Gomberg and W. E. Bachmann, *Org. Synth.* **I**, 113 (1941).
b. S. H. Korzeniowski, L. Blum, and G. W. Gokel, *Tetrahedron Lett.*, 1871 (1977).
c. W. E. Bachmann and R. A. Hoffman, *Org. React.* **2**, 249 (1944).
d. H. Rapoport, M. Look, and G. J. Kelly, *J. Am. Chem. Soc.* **74**, 6293 (1952).
e. J. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962).

various types of aromatic substitution discussed in the preceding sections. In fact, the polycyclic compounds are generally more reactive toward both electrophilic and nucleophilic processes because the activation energies of the initial steps are lower than for benzene. This is because more of the aromatic stabilization is retained in intermediates having fused rings. Molecular orbital calculations provide estimates

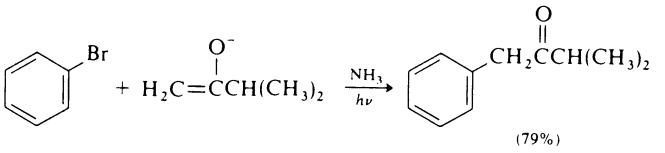


Scheme 8.11. Aromatic Substitution by the $S_{RN}1$ Process

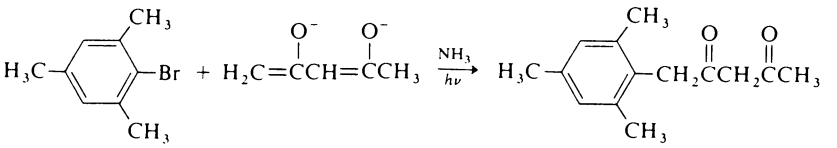
1[a]



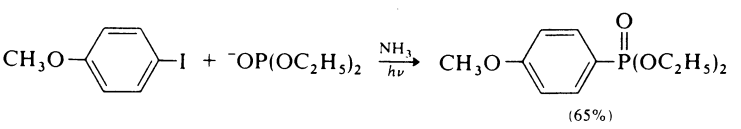
2[b]



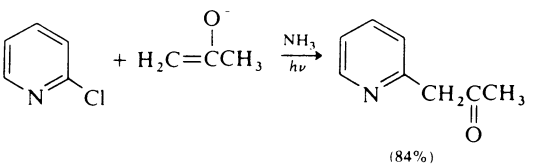
3[c]



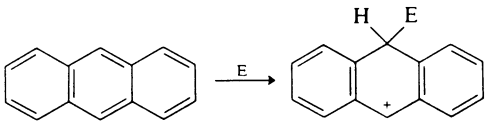
4[d]



5[e]



a. R. A. Rossi and J. F. Bunnett, *J. Org. Chem.* **38**, 1407 (1973).
b. M. F. Semmelhack and T. Bargar, *J. Am. Chem. Soc.* **102**, 7765 (1980).
c. J. F. Bunnett and J. E. Sundberg, *J. Org. Chem.* **41**, 1702 (1976).
d. J. F. Bunnett and X. Creary, *J. Org. Chem.* **39**, 3612 (1974).
e. A. P. Komin and J. F. Wolfe, *J. Org. Chem.* **42**, 2481 (1977).

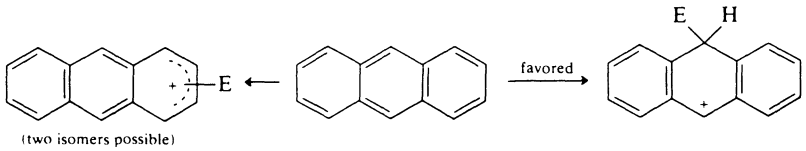


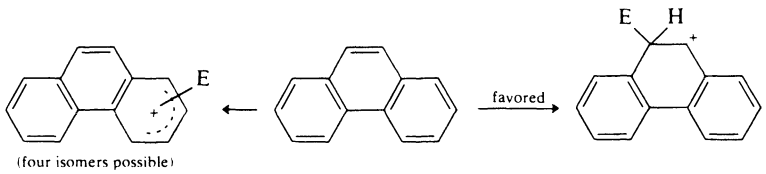
of the "localization energy," that is, the loss of conjugative stabilization caused by removing one carbon from the aromatic system. For electrophilic substitution in benzene, naphthalene, and anthracene these are, respectively, 1.58, 0.67, and 0.36 eV.[122]

122. A. Streitwieser, Jr., P. C. Mowery, R. G. Jesaitis, and A. Lewis, *J. Am. Chem. Soc.* **92**, 6529 (1970).

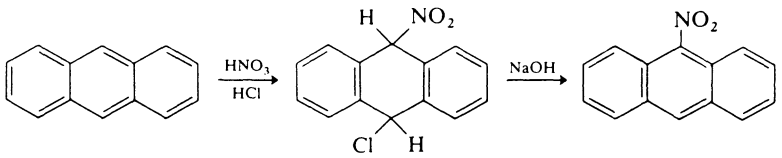
The relative stability of the intermediates determines the position of substitution under kinetically-controlled conditions. For naphthalene the preferred site for electrophilic attack is the 1-position. Two factors can result in dominant substitution at C-2. If the electrophile is very bulky, the hydrogen on the adjacent ring may cause a steric preference for attack at C-2. Under conditions of reversible substitution, where thermodynamic stability is the controlling factor, 2-substitution is preferred. This factor is illustrated by the outcome of sulfonation, where low-temperature reaction gives the 1-sulfonic acid, but high-temperature conditions give the 2-isomer.

Phenanthrene and anthracene are both much more reactive than benzene, and there is a preference for substitution to occur in the center ring. That this behavior would be expected is evident even from simple resonance considerations. The σ-complexes that result from substitution in the center ring have two intact benzene rings. The total resonance stabilization of this intermediate is larger than that of the naphthalene system that results if substitution occurs in one of the terminal rings.





Both phenanthrene and anthracene have a tendency to undergo addition reactions under the conditions involved in certain electrophilic substitutions. Halogenation and nitration may proceed in part via addition intermediates.[123] For example, in the nitration of anthracene in the presence of hydrochloric acid an intermediate addition product is isolated.[124]



Cycloaddition reactions are also favorable for anthracene since the resonance stabilization of two benzene rings is comparable to that of the anthracene ring.

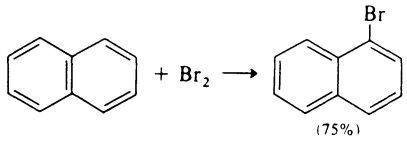
123. P. B. D. delaMare and J. H. Ridd, *Aromatic Substitution*, Academic Press, New York (1959), p. 174.

124. C. E. Braun, C. D. Cook, C. Merritt, Jr., and J. E. Rousseau, *Org. Synth.* **IV**, 711 (1965).

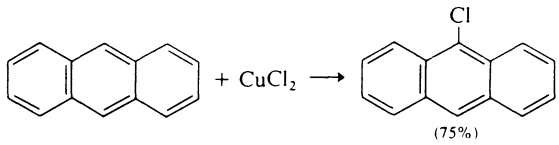
Scheme 8.12. Reactions of Polycyclic Aromatic Hydrocarbons

A. Electrophilic Substitution

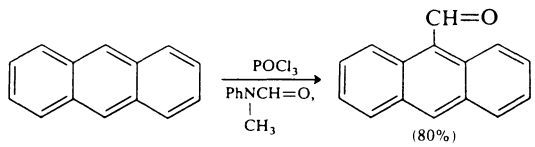
1[a]



2[b]

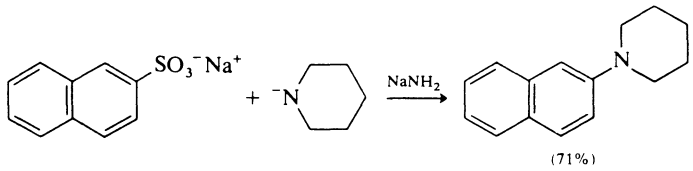


3[c]

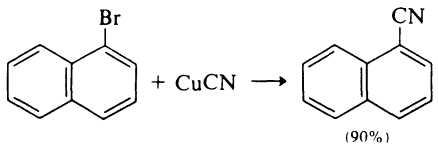


B. Nucleophilic Substitution

4[d]

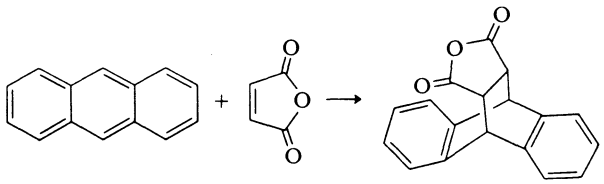


5[e]

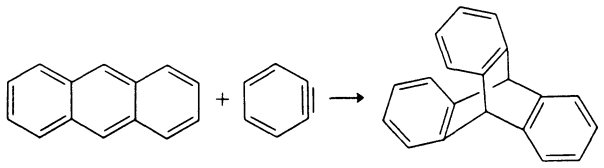


C. Addition

6[f]



7[g]



a. H. T. Clarke and M. R. Brethren, *Org. Synth.* **I**, 116 (1932).
b. D. C. Nonhebel, *Org. Synth.* **V**, 206 (1973).
c. L. F. Fieser, J. J. Hartwell, and J. E. Jones, *Org. Synth.* **III**, 98 (1955).
d. J. F. Bunnett, T. K. Brotherton, and S. M. Williamson, *Org. Synth.* **V**, 816 (1973).
e. M. S. Newman, *Org. Synth.* **III**, 631 (1955).
f. W. E. Bachmann and M. C. Kloetzel, *J. Am. Chem. Soc.* **60**, 481 (1938).
g. G. Wittig, *Org. Synth.* **IV**, 964 (1963).

Reactive dienophiles such as maleic anhydride, benzoquinone, and benzene give cycloaddition products.[125]

Scheme 8.12 gives some typical reactions of the polycyclic aromatic hydrocarbons.

General References

Electrophilic Substitution

G. A. Olah, *Friedel–Crafts Chemistry*, Wiley Interscience, New York (1973).
G. A. Olah (ed.), *Friedel–Crafts and Related Reactions*, Vols. I–IV, Interscience, New York (1962–1964).
R. O. C. Norman and R. Taylor, *Electrophilic Substitution in Benzenoid Compounds*, Elsevier, Amsterdam (1965).
L. M. Stock, *Aromatic Substitution Reactions*, Prentice-Hall, Englewood Cliffs, New Jersey (1968).
J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. S. Schofield, *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge (1971).

Nucleophilic Substitutions

H. Zollinger, *Azo and Diazo Chemistry*, Interscience, New York (1961).
S. Patai (ed.), *The Chemistry of Diazonium and Diazo Groups*, Wiley, New York (1978).
J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam (1968).
R. W. Hoffman, *Dehydrobenzene and Cycloalkynes*, Academic Press, New York (1967).

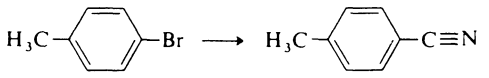
Polycyclic Aromatics

E. Clar, *Polycyclic Hydrocarbons*, Academic Press, New York (1964).

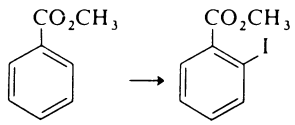
Problems

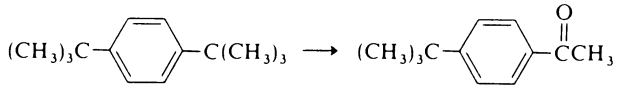
(*References for these problems will be found on page 627.*)

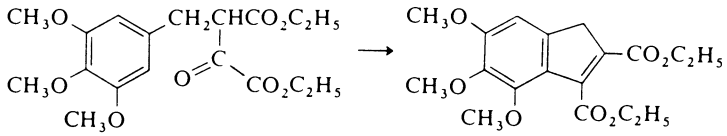
1. Give reaction conditions that would accomplish each of the following transformations. Multistep schemes are not necessary. Be sure to choose conditions that would afford the desired isomer as the principal product.

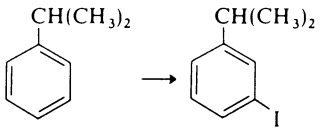
(a) 

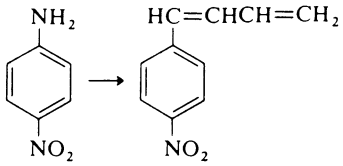
125. W. E. Bachmann and L. B. Scott, *J. Am. Chem. Soc.* **70**, 1458 (1948); P. D. Bartlett and F. D. Greene, *J. Am. Chem. Soc.* **76**, 1088 (1954).

(b) 

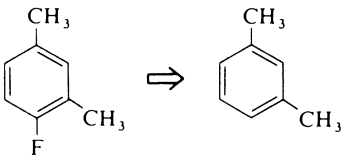
(c) 

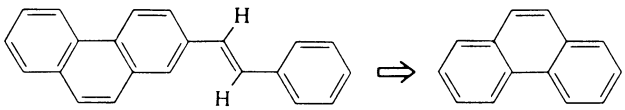
(d) 

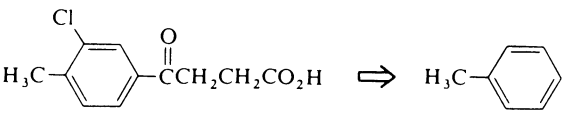
(e) 

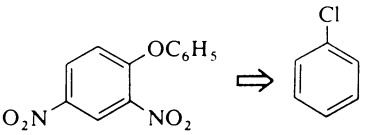
(f) 

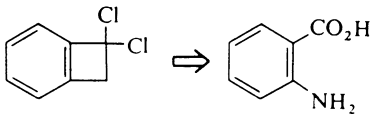
2. Suggest a short series of reactions which could be expected to transform the material on the right into the desired product shown on the left.

(a) 

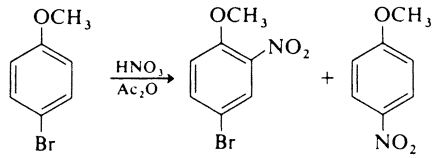
(b) 

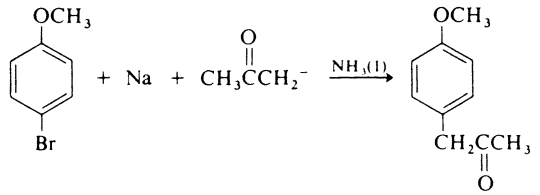
(c) 

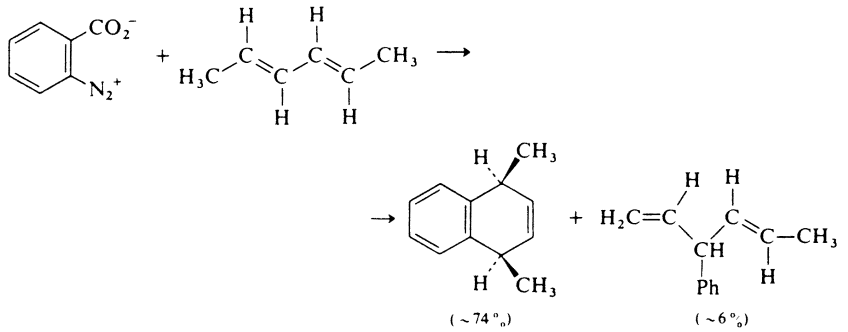
(d) 

(e) 

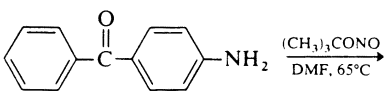
3. Write mechanisms that would account for the following reactions:

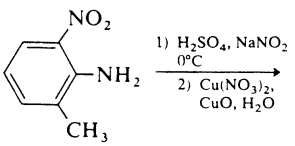
(a) 

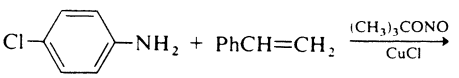
(b) 

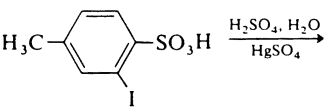
(c) 

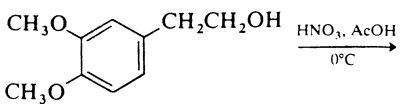
4. Predict the product(s) of the following reactions. If more than one product is expected indicate which will be major and which will be minor.

(a) 

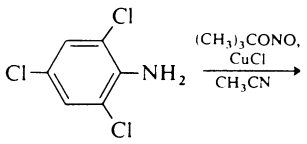
(b) 

(c) 

(d) 

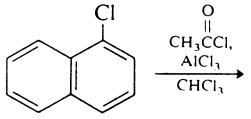
(e) 

(f)

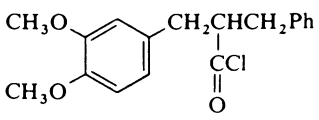


(g)

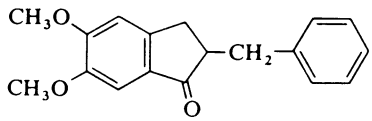
(h)



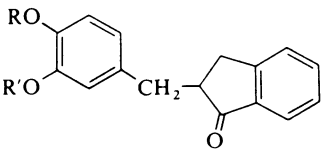
5. Suggest efficient syntheses of *ortho*-, *meta*-, and *para*-fluoropropiophenone from benzene and any other necessary organic or inorganic reagents.
6. Treatment of compound **A** in dibromomethane with one equivalent of aluminum bromide yielded **B** as the only product in 78% yield. When three equivalents of aluminum bromide were used, however, compounds **C** and **D** were obtained in a combined yield of 97%. Suggest an explanation for these observations.



A



B



C R = CH_3, R' = H
D R = H, R' = CH_3

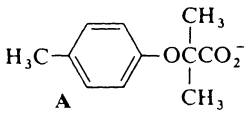
7. Some data for the alkylation of naphthalene by isopropyl bromide under various conditions are given.

Reaction medium A: $AlCl_3$–CS_2
Reaction medium B: $AlCl_3$–CH_3NO_2

	$\alpha:\beta$ Ratio	
Reaction time (min)	A	B
5	4:96	83:17
15	2.5:97.5	74:26
45	2:98	70:30

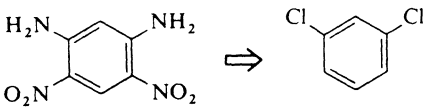
What factors are responsible for the difference in the product ratio for the two reaction media and why does the ratio change with reaction time?

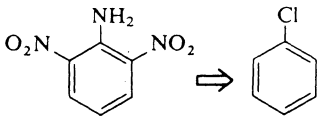
8. Addition of a solution of bromine and potassium bromide to a solution of the carboxylate salt **A** results in the precipitation of a neutral compound having the formula $C_{11}H_{13}BrO_3$. Various spectroscopic data show that the compound is nonaromatic. Suggest a structure and discuss the significance of the formation of this product.

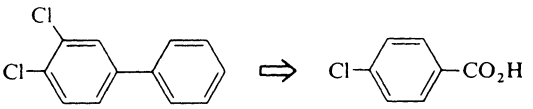


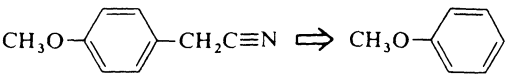
A

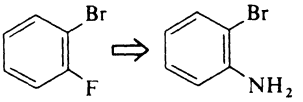
9. Benzaldehyde, benzyl methyl ether, benzoic acid, methyl benzoate, and phenylacetic acid all undergo thallation initially in the *ortho* position. Explain this observation.
10. Suggest reaction sequences that would permit synthesis of the following aromatic compounds from the starting material indicated on the right.

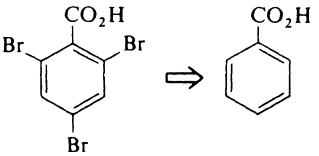
(a) 

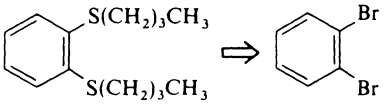
(b) 

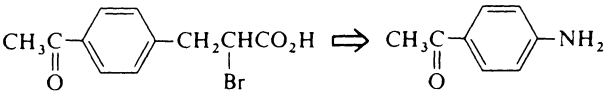
(c) 

(d) 

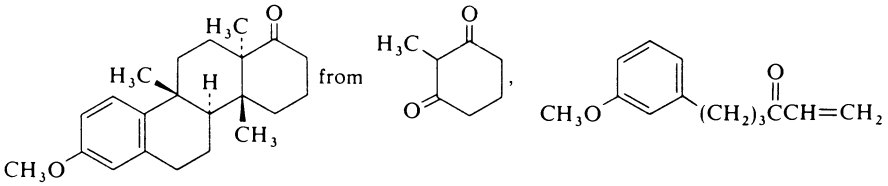
(e) 

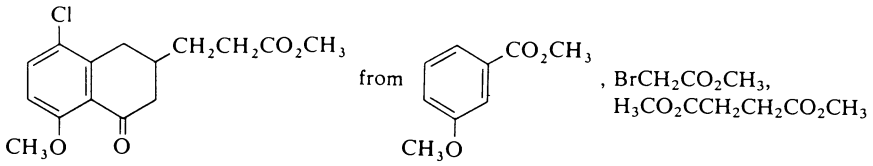
(f) 

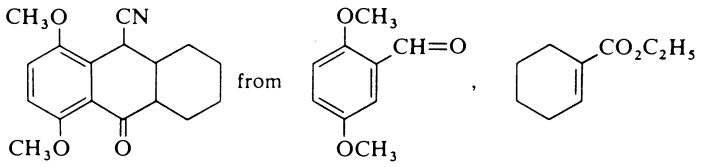
(g) 

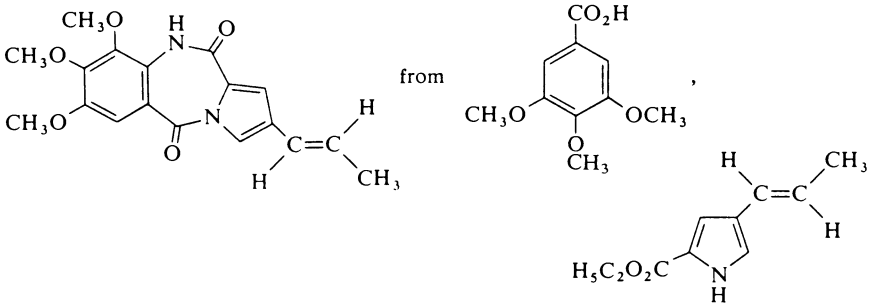
(h) 

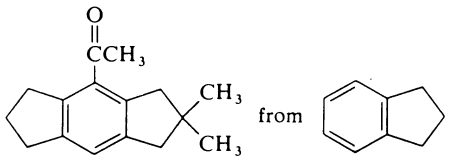
11. Aromatic substitution reactions are key steps in multistep synthetic sequences that effect the following transformations. Suggest reaction sequences that might accomplish the desired syntheses.

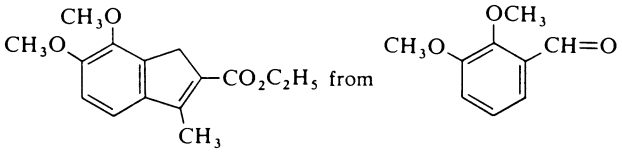
(a) 

(b) 

(c) 

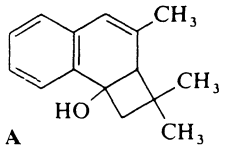
(d) 

(e) 

(f) 

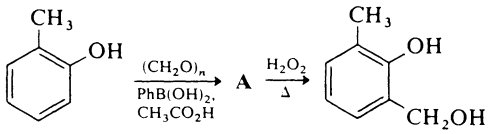
12. Reaction of 3,5,5-trimethylcyclohex-2-enone with $NaNH_2$ (3 equiv) in THF generates its enolate. When bromobenzene is then added to this solution

and stirred for 4 hr, the product **A** is isolated in 30% yield. Formulate a mechanism for this transformation.



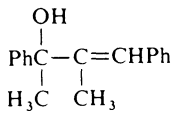
A

13. Various phenols can be selectively hydroxymethylated at the *ortho* position by heating with paraformaldehyde and phenylboronic acid.

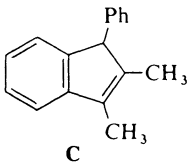


An intermediate **A**, having the formula $C_{14}H_{13}O_2B$ for the case above, can be isolated after the first step. Postulate a structure for the intermediate and comment on its role in the reaction.

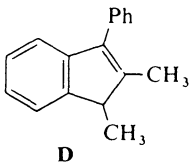
14. When compound **B** is dissolved in FSO_3H at $-78°C$, nmr shows that a carbonium ion is formed. If the solution is then allowed to warm to $-10°C$, a different ion forms. The first ion gives compound **C** when quenched with base, while the second gives **D**. What are the structures of the two carbonium ions and why do they give different products on quenching?



B



C

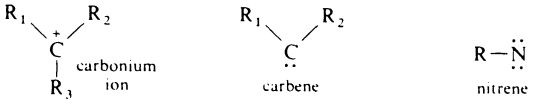


D

9

Reactions of Electron-Deficient Intermediates

The reactions to be described in this chapter have in common the formal involvement of even-electron intermediates having unfilled orbitals of low energy. The most familiar of these intermediates are carbonium ions. Sections 9.4 and 9.6 contain examples of reactions of carbonium ions that are of synthetic value; the discussion of these reactions supplements the more mechanistically-oriented discussion presented in Part A, Chapter 5. Also important are the neutral divalent carbon and monovalent nitrogen species, carbenes and nitrenes, respectively.

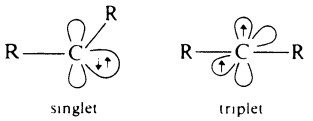


Current organic chemical thought recognizes that many of the reactions ascribed to carbenes and nitrenes may also be available to various intermediates of higher coordination, which are grouped under the nonspecific terms *carbenoids* and *nitrenoids*. It is often difficult to determine exactly the nature of the actual intermediate in a particular process, and a number of the reactions to be encountered are subject to this ambiguity. Moreover, some of the reactions to be discussed have been shown not to involve free carbenes or nitrenes, but are included here because the reactivity pattern is closely analogous, and the net structural changes are identical to reactions involving the free intermediates.

9.1. Carbenes

9.1.1. Structure and Reactivity

A carbene may exist as a singlet or a triplet, depending on whether the two nonbonded electrons are, respectively, in the same molecular orbital with paired spins, or in two orbitals of identical energy with parallel spins. Depending upon the mode of generation, a carbene may initially be formed in either state, no matter which is the lower in energy. These two electronic configurations should be reflected

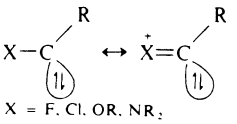


in differing geometries and chemical reactivity, as well as in the important physical property that the singlet is diamagnetic while the triplet is paramagnetic. The triplet may therefore be observed by electron spin resonance spectroscopy.

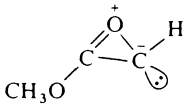
A rough picture of the bonding in the singlet assumes sp^2 hybridization at carbon, with the two electrons in an sp^2-hybridized orbital leaving an unoccupied p orbital. The R_1CR_2 angle would be expected to be contracted slightly from the normal 120° angle (provided R_1 and R_2 are small), because the interorbital repulsions will be greatest for the more diffuse lone-pair orbital. The triplet carbene would bind the ligands to carbon sp-hybridized orbitals in a linear array, with the unpaired electrons in two mutually orthogonal p orbitals. Both theoretical and experimental studies have provided a more detailed picture of carbene structure. Molecular-orbital calculations lead to the prediction of HCH angles for methylene (CH_2) of ~135° for the triplet and ~105° for the singlet, with the triplet lying about 8 kcal/mol lower in energy than the singlet.[1] Experimental determinations of the geometry of CH_2 tend to confirm the theoretical predictions. The HCH angle of the triplet state as determined by analysis of its esr spectrum is 125–140°. The HCH angle of the singlet state is determined by electronic spectroscopy as 102°. All the available physical and chemical evidence is consistent with the triplet as the ground state.

Substituents have the effect of perturbing the relative energies of the singlet and triplet states. In general, alkyl groups resemble hydrogen as a substituent, and dialkylcarbenes are ground state triplets. Lone-pair donors can stabilize the singlet state more than the triplet state by π donation into the empty p orbital.[2] Electronegative substituents, particularly fluorine and oxygen, stabilize the singlet state.[3]

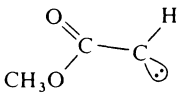
1. J. F. Harrison, *Acc. Chem. Res.* **7**, 378 (1974); R. K. Lengel and R. N. Zare, *J. Am. Chem. Soc.* **100**, 7495 (1978); C. W. Bauschlicher, Jr., and I. Shavitt, *J. Am. Chem. Soc.* **100**, 739 (1978).
2. N. C. Baird and K. F. Taylor, *J. Am. Chem. Soc.* **100**, 1333 (1978).
3. J. F. Harrison, R. C. Liedtke and J. F. Liebman, *J. Am. Chem. Soc.* **101**, 7162 (1979).



The presence of more complex substituent groups quickly complicates the theoretical description of carbene structure. Furthermore, since carbenes are high-energy species, structural entities which would be unrealistic for more stable species, must be considered. As a case in point, one set of MO calculations[4] arrives at structure **A** as a better description of carbomethoxycarbene than the conventional structure **B**.



A



B

From the point of view of both synthetic and mechanistic interest, much attention has been focused on the addition reaction between carbenes and alkenes, which gives cyclopropanes. Characterization of the reactivity of individual substituted carbenes in addition reactions has focused on stereochemistry and selectivity. The reactivity of the singlet and triplet states should be different. The triplet state is a diradical, and would be expected to exhibit a selectivity in its reactions toward olefins similar to that of other species having unpaired electrons. The singlet state, with its unfilled *p* orbital, should be electrophilic and exhibit reactivity toward olefins similar to that of other electrophilic species. Also, the triplet addition must go through an intermediate which has two unpaired electrons of the same spin. It would be expected that single-bond rotations could occur competitively with spin inversion. In contrast, a singlet carbene can go to a cyclopropane in a single concerted step (see Fig. 9.1). As a result it was predicted[5] that singlet species would add to alkenes in a stereospecific manner while triplets would not. This prediction has been confirmed and stereospecificity of addition to alkenes has therefore come to be used as a test for the involvement of the singlet versus triplet carbenes in specific reactions.[6]

The radical versus electrophilic character of triplet and singlet carbenes, respectively, also shows up in relative reactivity patterns. The relative reactivity of singlet dibromocarbene toward selected olefins (Table 9.1) can be seen to be more in accord with the electrophilic models (bromination, epoxidation) than with the radical model (addition of $\cdot CCl_3$). Carbene reactivity is strongly affected by substituent groups.[7] Various singlet carbenes have been characterized as nucleophilic,

4. R. Noyori and M. Yamanaka, *Tetrahedron Lett.*, 2851 (1980).
5. P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.* **78**, 5430 (1956).
6. R. C. Woodworth and P. S. Skell, *J. Am. Chem. Soc.* **81**, 3383 (1959).
7. A comprehensive review of this topic is given by R. A. Moss, in *Carbenes*, M. Jones, Jr., and R. A. Moss (eds.), John Wiley and Sons, New York (1973), pp. 153–304.

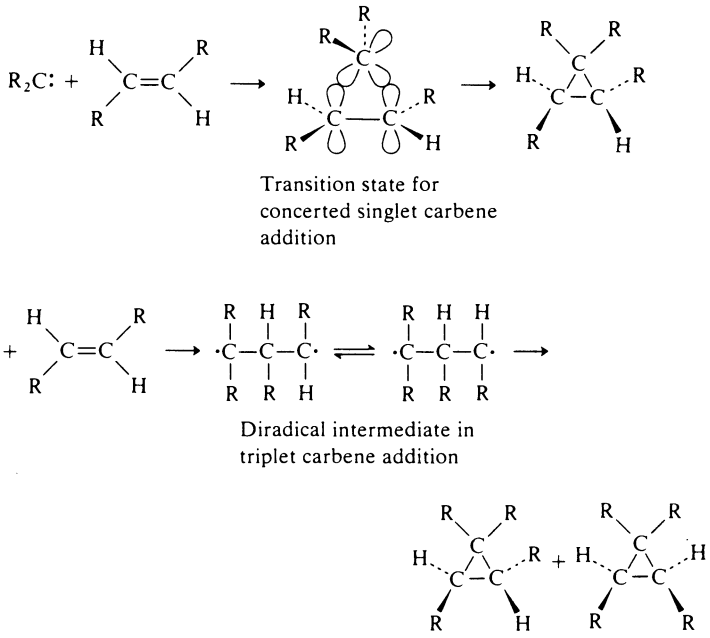
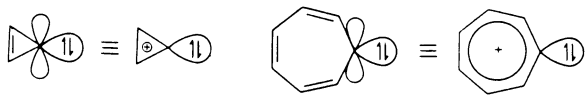


Figure 9.1. Mechanisms for addition of singlet and triplet carbenes to alkenes.

ambiphilic, and electrophilic as shown in Table 9.2. The classification is based on relative reactivity toward a series of different alkenes containing both nucleophilic alkenes such as tetramethylethylene and electrophilic alkenes such as acrylonitrile. The principal structural feature which determines the reactivity of the carbene is the ability of the substituent to act as a π donor. Thus in dimethoxycarbene, which is devoid of electrophilicity toward alkenes,[8] the electrophilicity of the empty π orbital has been reduced by electron donation by the adjacent oxygens.

$$CH_3-\ddot{O}-\dot{C}-\ddot{O}-CH_3 \longleftrightarrow CH_3-\overset{+}{\ddot{O}}=\bar{C}-\ddot{O}-CH_3 \longleftrightarrow CH_3-\ddot{O}-\bar{C}=\overset{+}{\ddot{O}}-CH_3$$

π-Delocalization involving divalent carbon in conjugated cyclic systems has been studied as in the case of the interesting species cyclopropenylidene (**C**) and cycloheptatrienylidene (**D**). In these molecules, since the empty orbital is part of the π-system, the electron deficiency is distributed over the entire aromatic ring.



C **D**

8. D. M. Lemal, E. P. Gosselink, and S. D. McGregor, *J. Am. Chem. Soc.* **88**, 582 (1966).

Table 9.1. Relative Rates of Addition to Alkenes[a]

Alkene	$\cdot CCl_3$	$:CBr_2$	Br_2	Epoxidation
Isobutylene	1.00	1.00	1.00	1.00
Styrene	>19	0.4	0.6	0.1
2-Methylbutene	0.17	3.2	1.9	13.5

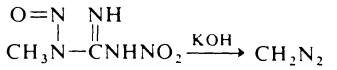
a. P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.* **78**, 5430 (1956).

These carbenes could be described as the conjugate bases of the aromatic cyclopropenium and tropylium ions, respectively. The carbene cyclopropenylidene (**C**) has not yet been generated, although its diphenyl derivative has been.[9] Cycloheptatrienylidene has been generated, however, and its reactivity seems to confirm that the delocalized carbene is not strongly electrophilic. It reacts best with alkenes bearing electron-attracting groups; in reactions with styrenes, the ρ value is about 1.0, indicating that the carbene is acting as a nucleophilic species.[10]

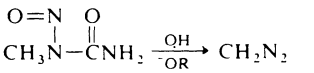
9.1.2. Generation of Carbenes

There are numerous ways of generating carbene intermediates. The most general are summarized in Scheme 9.1, and will be discussed individually in succeeding paragraphs. This discussion will serve to establish some of the limits on the generality of the various procedures.

Decomposition of diazo compounds to carbenes is a quite general reaction. Examples include the simplest diazo compound, diazomethane, as well as diaryldiazomethanes and diazo compounds in which one or both of the substituents is an acyl group. The inability to synthesize the required diazo compound is sometimes a limitation on the method. The low-molecular-weight diazoalkanes are toxic and unstable, and are usually prepared and used *in situ* rather than isolated. The simple aliphatic diazo compounds are synthesized from derivatives of the corresponding amine. All the common precursors of diazomethane, for example, are derivatives of methylamine. The details of the base-catalyzed decompositions vary somewhat



Ref. 11



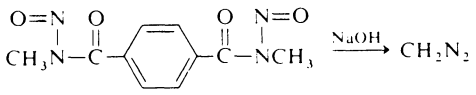
Ref. 12

9. W. M. Jones, M. E. Stowe, E. E. Wells, Jr., and E. W. Lester, *J. Am. Chem. Soc.* **90**, 1849 (1968).
10. L. W. Christensen, E. E. Waali, and W. M. Jones, *J. Am. Chem. Soc.* **94**, 2118 (1972).
11. M. Neeman and W. S. Johnson, *Org. Synth.* **V**, 245 (1973).
12. F. Arndt, *Org. Synth.* **II**, 165 (1943).

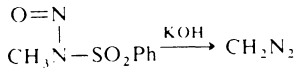
Table 9.2. Classification of Carbenes on the Basis of Reactivity Toward Alkenes[a]

Nucleophilic	Ambiphilic	Electrophilic
$CH_3O\ddot{C}OCH_3$	$CH_3O\ddot{C}Cl$	$Cl\ddot{C}Cl$
$CH_3O\ddot{C}N(CH_3)_2$	$CH_3O\ddot{C}F$	$Ph\ddot{C}Cl$
		$CH_3\ddot{C}Cl$
		$Br\ddot{C}CO_2C_2H_5$

a. R. A. Moss and R. C. Munjal, *Tetrahedron Lett.*, 4721 (1979); R. A. Moss, *Acc. Chem. Res.* **13**, 58 (1980).

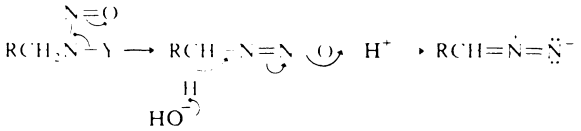


Ref. 13

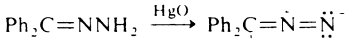


Ref. 14

from case to case, but involve two essential steps.[15] The initial substrate undergoes a base-catalyzed elimination to form an alkyl diazoate. This is followed by a deprotonation of the α-carbon and elimination of the oxygen. Another route to

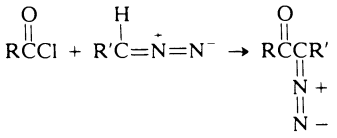


diazo compounds is by oxidation of the corresponding hydrazone. This route is most frequently employed when at least one of the substituents is an aromatic group.



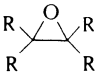
Ref. 16

When an α-diazoketone is needed, the usual synthesis starts with an acid halide. Reaction with a diazoalkane gives the diazoketone as a result of nucleophilic attack, with displacement of the chloride ion:



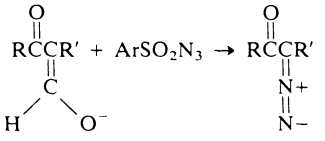
13. Th. J. de Boer and H. J. Backer, *Org. Synth.* **IV**, 250 (1963).
14. J. A. Moore and D. E. Reed, *Org. Synth.* **V**, 351 (1973).
15. W. M. Jones, D. L. Muck, and T. K. Tandy, Jr., *J. Am. Chem. Soc.* **88**, 68 (1966); W. M. Jones and D. L. Muck, *J. Am. Chem. Soc.* **88**, 3798 (1966); R. A. Moss, *J. Org. Chem.* **31**, 1082 (1966); D. E. Applequist and D. E. McGreer, *J. Am. Chem. Soc.* **82**, 1965 (1960); S. M. Hecht and J. W. Kozarich, *J. Org. Chem.* **38**, 1821 (1973).
16. L. I. Smith and K. L. Howard, *Org. Synth.* **III**, 351 (1955).

Scheme 9.1. General Methods for Generation of Carbenes

	Precursor	Condition	Products
1[a]	$R_2C{=}\overset{+}{N}{=}N^-$ Diazoalkanes	Photolysis, thermolysis, or metal-ion catalysis	$R_2C: + N_2$
2[b]	$R_2C{=}N{-}\overset{-}{N}SO_2Ar$ Salts of sulfonylhydrazones	Photolysis or thermolysis: diazoalkanes are intermediates	$R_2C: + N_2 + ArSO_2^-$
3[c]	 Diazirines	Photolysis	$R_2C: + N_2$
4[d]	 Epoxides	Photolysis	$R_2C: + R_2C{=}O$
5[e]	$R_2CH{-}X$ Halides	Strong base or organometallic compounds	$R_2C: + BH + X^-$
6[f]	$R_2C(X)HgR'$ α-Halomercury compounds	Thermolysis	$R_2C: + R'HgX$

a. W. J. Baron, M. R. DeCamp, M. E. Hendrick, M. Jones, Jr., R. H. Levin, and M. B. Sohn, in *Carbenes*, M. Jones, Jr., and R. A. Moss (eds.), John Wiley and Sons, New York (1973), pp. 1–151.
b. W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).
c. H. M. Frey, *Adv. Photochem.* **4**, 225 (1966); R. A. G. Smith and J. R. Knowles, *J. Chem. Soc. Perkin Trans. 2*, 686 (1975).
d. G. W. Griffin and N. R. Bertoniere, in *Carbenes*, M. Jones, Jr., and R. A. Moss (eds.), John Wiley and Sons, New York (1973), pp. 318–332.
e. W. Kirmse, *Carbene Chemistry*, Academic Press, New York (1971), pp. 96–109, 129–149.
f. D. Seyferth, *Acc. Chem. Res.* **5**, 65 (1972).

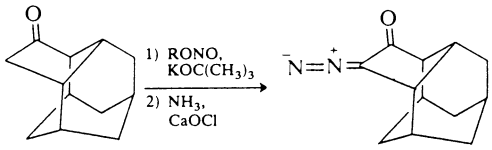
Under the usual conditions one equivalent of the diazoalkane is consumed by the liberated acid but this can be avoided by use of an added base such as triethylamine.[17] Cyclic α-diazoketones, which are not available from acid chloride, can be prepared by reaction of a nucleophilic derivative such as the α-hydroxymethylene enolate with arylsulfonyl azides. Several combinations of carbon nucleophile and sulfonyl



azide are possible. These include generation of an enolate with an appropriate

17. M. S. Newman and P. Beall, III, *J. Am. Chem. Soc.* **71**, 1506 (1949); M. Berebom and W. S. Fones, *J. Am. Chem. Soc.* **71**, 1629 (1949); L. T. Scott and M. A. Minton, *J. Org. Chem.* **42**, 3757 (1977).

base[18] or conversion of the ketone to a dialkylaminomethylene derivative.[19] *p*-Toluenesulfonyl azide is commonly used as the azide but *p*-carboxybenzenesulfonyl azide[20] and polymer-bound *p*-toluenesulfonyl azide[21] have also been used to advantage. The introduction of diazo functions from sulfonyl azides is called a "diazo-transfer" reaction and is generally applicable to the synthesis of diazo compounds from compounds that are capable of forming stabilized carbanions. α-Diazoketones can also be made by nitrosation of the ketone to the α-oximino derivative, followed by reaction of the oxime with chloramine.[22]



(70%)

Ref. 23

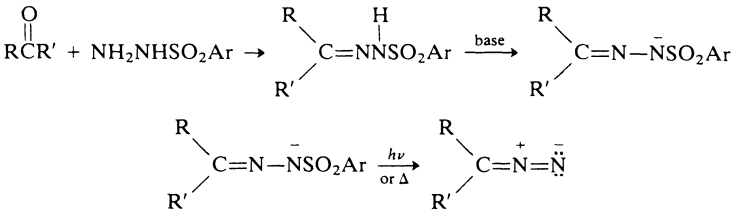
The driving force for decomposition of diazo compounds to carbenes is the formation of the very stable nitrogen molecule. Activation energies for the process with diazoalkanes in the gas phase are in the neighborhood of 30 kcal/mol. The requisite energy can also be supplied by photochemical excitation. It is often possible to control the photochemical process to give predominantly singlet or triplet carbene. Direct photolysis leads primarily to the singlet intermediate, the reason being that dissociation of the excited diazoalkene is more rapid than intersystem crossing to the triplet state. It cannot be assumed, however, that the triplet intermediate is always excluded in direct photolysis experiments. In studies of several types of diazo compounds, the conclusion has been reached that the triplet intermediate is responsible for up to 15–20% of the product on direct photolysis.[24] The triplet carbene is the principal intermediate in photosensitized decomposition. Aromatic ketones are frequently employed as photosensitizers.

Addition of certain copper salts to solutions of diazo compounds also leads to evolution of nitrogen and formation of products of the same general types as those formed in thermal and photochemical decompositions of diazoalkanes. The weight of the evidence, however, indicates that free carbene intermediates are not involved in such reactions.[25] Instead, complexes of the carbene unit with the metallic catalyst

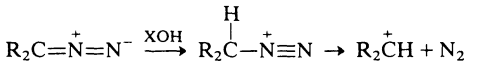
18. M. Regitz and G. Heck, *Chem. Ber.* **97**, 1482 (1964); M. Regitz, *Angew. Chem. Int. Ed. Engl.* **6**, 733 (1967).
19. M. Rosenberger, P. Yates, J. B. Hendrickson, and W. Wolf, *Tetrahedron Lett.*, 2285 (1964); K. B. Wiberg, B. L. Furtek, and L. K. Olli, *J. Am. Chem. Soc.* **101**, 7675 (1979).
20. J. B. Hendrickson and W. A. Wolf, *J. Org. Chem.* **33**, 3610 (1968).
21. W. R. Roush, D. Feitler, and J. Rebek, *Tetrahedron Lett.*, 1391 (1974).
22. T. N. Wheeler and J. Meinwald, *Org. Synth.* **52**, 53 (1972).
23. T. Sasaki, S. Eguchi, and Y. Hirako, *J. Org. Chem.* **42**, 2981 (1977).
24. C. S. Elliott and H. M. Frey, *Trans. Faraday Soc.* **64**, 2352 (1968); C. D. Gutsche, G. L. Bachman, and R. S. Coffey, *Tetrahedron.* **18**, 617 (1962).
25. W. R. Moser, *J. Am. Chem. Soc.* **91**, 1135, 1141 (1969).

seem to be the actual reactants. Such complexes are examples of carbenoid species. Although the products are the result of a carbene-like reactivity, other evidence rules out completely free carbenes of the type generated by photochemical expulsion of a molecule of nitrogen. Several other metal ions exert a useful degree of catalysis on the decomposition of diazo compounds and this reaction will be discussed further in Section 9.1.3.

The second method in Scheme 9.1, thermal or photochemical decomposition of salts of arenesulfonylhydrazones, is actually a variation on the diazoalkane method, since diazo compounds are intermediates. It is an important and useful method, however, since the ultimate starting materials are ketones, and also because the procedure avoids isolation of the potentially dangerous diazoalkanes. The conditions of the decomposition are usually such that the diazo compound reacts soon after formation, and high concentrations do not build up.[26] The nature of the solvent mixture plays an important role in the outcome of tosylhydrazone decompositions. In the presence of proton donors, the diazoalkane intermediates can be



diverted to a carbonium ion pathway by protonation.[27] Aprotic solvents such as dimethoxyethane favor decomposition via the carbene pathway:

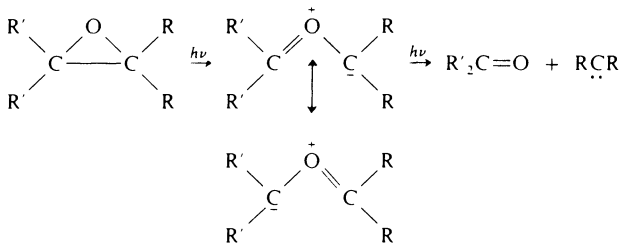


The diazirines (entry 3, Scheme 9.1) are cyclic isomers of diazo compounds. The strain of the small ring, along with the potential for formation of molecular nitrogen, makes these compounds highly reactive toward loss of nitrogen on photoexcitation. Little work has been done on their thermal decomposition. They are, in general, somewhat more difficult to synthesize than either diazo compounds or arenesulfonylhydrazones,[28] and this problem limits their use for synthetic purposes.

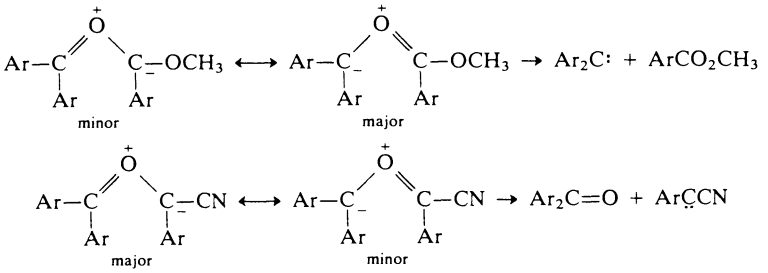
Carbenes are also generated when aryl epoxides are photolyzed (entry 4, Scheme 9.1). The other product formed is a carbonyl compound. The photodecomposition of epoxides is not a single-step process; highly colored intermediate

26. G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, and H. Shechter, *J. Am. Chem. Soc.* **87**, 935 (1965).
27. J. H. Bayless, L. Friedman, F. B. Cook, and H. Shechter, *J. Am. Chem. Soc.* **90**, 531 (1968).
28. For a review of available synthetic methods, see E. Schmitz, *Dreiringe mit Zwei Heteroatomen*, Springer Verlag, Berlin (1967), pp. 114–121.

species have been detected.[29] The structure assigned these intermediates is the carbonyl ylide, a dipolar valence isomer of the epoxide ring.[30] It is believed that the decomposition of the ylide is also a photoreaction.



It can be seen that an unsymmetrical epoxide can conceivably give rise to two carbenes and two carbonyl compounds. The nature of the substituent groups ordinarily favors one possible mode of cleavage over the other. When R = aryl and R′ = alkyl, the aliphatic ketone is generated, and the aryl-substituted carbon is released as the carbene fragment. Electron-withdrawing substituents such as cyano or carbomethoxy favor carbene formation, but an electron-releasing methoxy substituent directs carbene formation to the other oxirane carbon. These substituent effects can be understood by considering which of the two possible resonance structures will be the principal contributor to the carbonyl ylide structure. The relative contribution from each resonance structure is reflected in the bond order of the C–O bonds. The C–O bond with the greatest double-bond character becomes the carbonyl group, while the weaker C–O is cleaved.



The α elimination of hydrogen halide induced by strong base (entry 5, Scheme 9.1) was the first of the methods for generation of carbenes to receive thorough modern study. The efficient generation of carbenes by α elimination from halides is, however, restricted to substrates without β-hydrogen, since dehydrohalogenation by β-elimination dominates when it can occur. Classic examples of this method are the generation of dichlorocarbene from chloroform, the formation of chlorocarbene from methylene chloride, and the formation of aryl carbenes from benzyl halides:

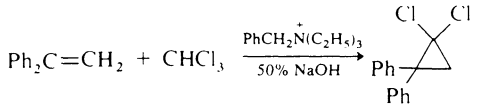
29. R. S. Becker, R. O. Bost, J. Kolc, N. R. Bertoniere, R. L. Smith, and G. W. Griffin, *J. Am. Chem. Soc.* **92**, 1302 (1970).
30. T. Do-Minh, A. M. Trozzolo, and G. W. Griffin, *J. Am. Chem. Soc.* **92**, 1402 (1970).

$$HCCl_3 + {}^{-}OR \rightleftharpoons :\bar{C}Cl_3 \rightarrow :CCl_2 + Cl^{-} \qquad \text{Ref. 31}$$

$$H_2CCl_2 + RLi \rightarrow RH + LiCHCl_2 \rightarrow :CHCl + LiCl \qquad \text{Ref. 32}$$

$$ArCH_2X + RLi \rightarrow RH + Ar\overset{Li}{C}HX \rightarrow Ar\ddot{C}H + LiX \qquad \text{Ref. 33}$$

Both phase transfer and crown ether catalysts have been used to promote α eliminations from chloroform and other haloalkanes.[34a] Various trialkylammonium hydroxides catalyze formation of dichlorocarbene in the organic phase of two phase systems consisting of $CHCl_3$ and 50% sodium hydroxide solution.



Ref. 34b

Highly hindered lithium dialkylamides can generate aryl carbenes from benzyl halides.[35a] The generation of phenylbromocarbene and phenylchlorocarbene from the corresponding α,α-dihalotoluenes using potassium *t*-butoxide and 18-crown-6 as catalyst has been reported.[35b] Under these conditions the usual addition reactions are observed with typical alkenes and furthermore, the relative reactivity data suggests that the carbenes generated under these conditions are "free." The potassium cation would be expected to be strongly solvated by the crown ether and therefore would not participate in the carbene generating step.

Halogenated carbenes are also generated by reaction of dihalomethanes with organolithium reagents. The exact formulation of the reactive intermediate in α-elimination reactions using organolithium compounds as bases has been difficult. Apart from the carbene, various carbenoids are possible, including the α-haloorganolithium formed on metalation, and carbene–lithium halide complexes of various degrees of association.[36] In the case of the dichlorocarbene–trichloromethyllithium

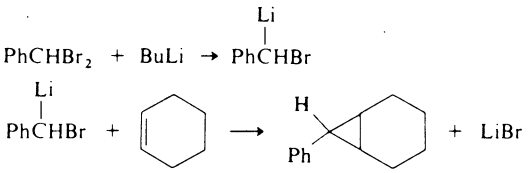
$$Cl_3CLi \rightleftharpoons Cl_2C: + LiCl$$

equilibrium, the equilibrium lies heavily to the side of trichloromethyllithium at $-100°C$.[37] Reaction with alkenes to afford 1,1-dichlorocyclopropanes, however,

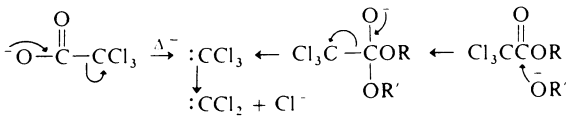
31. J. Hine, *J. Am. Chem. Soc.* **72**, 2438 (1950); J. Hine and A. M. Dowell, Jr., *J. Am. Chem. Soc.* **76**, 2688 (1954).
32. G. Köbrich, H. Trapp, K. Flory, and W. Drischel, *Chem. Ber.* **99**, 689 (1966); G. Köbrich and H. R. Merkle, *Chem. Ber.* **99**, 1782 (1966).
33. G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.* **82**, 5723 (1960).
34a. W. P. Weber and G. W. Gokel, *Phase Transfer Catalysis in Organic Synthesis*, Springer Verlag, New York (1977), Chaps. 2–4.
b. E. V. Dehmlow and J. Schönefeld, *Liebigs Ann. Chem.* **744**, 42 (1971).
35a. R. A. Olofson and C.M. Dougherty, *J. Am. Chem. Soc.* **95**, 581 (1973).
b. R. A. Moss and F. G. Pilkiewicz, *J. Am. Chem. Soc.* **96**, 5632 (1974).
36. G. Köbrich, *Angew. Chem. Int. Ed. Engl.* **6**, 41 (1967).
37. W. T. Miller, Jr., and D. M. Whalen, *J. Am. Chem. Soc.* **86**, 2089 (1964); D. F. Hoeg, D. I. Lusk, and A. L. Crumbliss, *J. Am. Chem. Soc.* **87**, 4147 (1965).

appears to involve only $:CCl_2$, and not Cl_3CLi, since the pattern of reactivity versus alkene structure is identical to that observed for free $:CCl_2$ generated in the gas phase.[38]

A general approach to the problem of distinguishing "free" carbenes from carbenoids is to compare product distribution and stereochemistry in reactions involving several carbene sources, including unequivocal methods such as diazoalkene decomposition. By such comparisons, it has been concluded, for example, that the intermediate generated from α,α-dibromotoluene and butyllithium is not the free carbene but, instead, a carbenoid reagent in which the incipient carbene remains attached to the elements of LiBr.[39] LiBr is eliminated only when reaction with the substrate occurs.



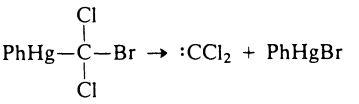
A method that provides an alternative route to dichlorocarbene is the decarboxylation of trichloroacetic acid.[40] In essence, this simply constitutes an alternative route to the trichloromethyl anion. Treatment of alkyl trichloroacetates with alkoxide ions is still another way of generating the same carbanion:



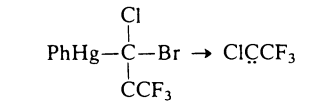
The applicability of these methods is restricted to polyhalogenated compounds, since the inductive effect of the three halogen atoms is necessary both for easy decarboxylation and for elimination of a carbanion from the tetrahedral intermediate generated in the alkoxide-cleavage procedure.

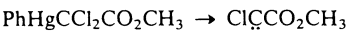
The principle underlying the use of organomercury compounds for carbene generation (entry 6, Scheme 9.1) is again the α-elimination mechanism. The carbon–mercury bond is much more covalent than the C–Li bond, however, so that the mercury reagents are generally stable at room temperature and easily isolated. They then decompose to the carbene when heated in solution with an appropriate alkene.[41] The decomposition appears to be a reversible unimolecular reaction, and the rate is not greatly influenced by the alkene. This observation implies that a

38. P. S. Skell and M. S. Cholod, *J. Am. Chem. Soc.* **91**, 6035, 7131 (1969); *J. Am. Chem. Soc.* **92**, 3522 (1970).
39. G. L. Closs and R. A. Moss, *J. Am. Chem. Soc.* **86**, 4042 (1964).
40. W. E. Parham and E. E. Schweizer, *Org. React.* **13**, 55 (1963).
41. D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J. H. Treiber, and S. R. Dowd, *J. Am. Chem. Soc.* **87**, 4259 (1965).



free carbene is generated from the precursor.[42] Synthesis of a variety of organomercurials has provided compounds that are appropriate sources for substituted carbenes. For example, carbenes with a carbomethoxy or trifluoromethyl substituent can be generated from appropriate organomercury precursors.[43] The addition

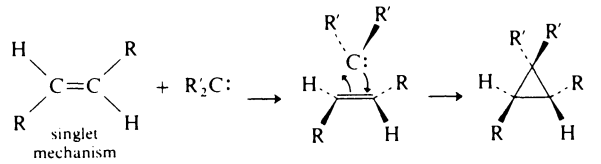


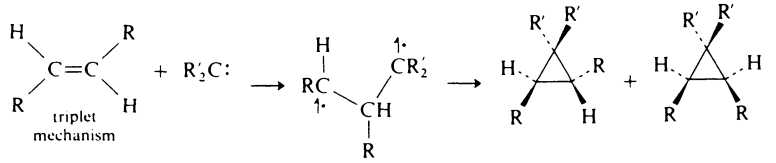


reaction of alkenes and phenylmercuric bromides typically occurs at 80°C. Higher reactivity is observed with phenylmercuric iodides and this may be advantageous for relatively unstable alkenes.[44]

9.1.3. Addition Reactions

The addition reaction with alkenes is the best-studied reaction of carbene intermediates, both from the point of view of understanding carbene mechanisms and for synthetic applications. The usual course of reaction of a carbene with an alkene results in the formation of a cyclopropane. This is true for both the singlet and the triplet state of most carbenes. The alternative electronic states show





characteristic differences in stereochemistry. A one-step mechanism is possible for singlet carbenes. As a result, the stereochemistry present in the alkene is retained in the cyclopropane. Calculations of the preferred orientation of approach of singlet

42. D. Seyferth, J. Y.-P. Mui, and J. M. Burlitch, *J. Am. Chem. Soc.* **89**, 4953 (1967).
43. D. Seyferth, D. C. Mueller, and R. L. Lambert, Jr., *J. Am. Chem. Soc.* **91**, 1562 (1969).
44. D. Seyferth and C. K. Haas, *J. Org. Chem.* **40**, 1620 (1975).

carbenes to alkenes have indicated that an unsymmetrical approach as illustrated in Figure 9.1 is favored.[45] With the triplet carbene, an intermediate diradical is involved. Closure to a ground state cyclopropane requires a spin inversion. The rate of spin inversion is slow relative to rotation about single bonds, so that the cyclopropane formed from a triplet carbene need not have the same stereochemistry as the starting olefin. Usually, the cyclopropanes formed from triplet carbenes are mixtures of the two possible stereoisomers.

Carbene addition reactions are expected to be very exothermic since two new σ bonds are formed and only a π bond is broken. The reactions are very rapid and, in fact, theoretical treatment of the reaction of methylene ($:CH_2$) with ethylene suggests that there is no activation barrier.[46] Thus the slow step in carbene addition reactions under most circumstances is generation of the carbene.

The addition of carbenes to alkenes is an important method for synthesis of many types of cyclopropanes and several of the methods for carbene generation listed in Scheme 9.1 have been adopted for use in synthesis. A number of specific synthetic examples are given in Scheme 9.2.

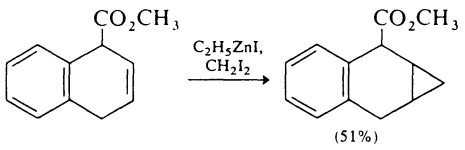
A very effective means for conversion of alkenes to cyclopropanes by transfer of a CH_2 unit involves the system methylene iodide and zinc–copper couple, commonly referred to as the *Simmons–Smith reagent.*[47] The active species is believed to be iodomethylzinc iodide in equilibrium with (bis)iodomethylzinc.[48]

$$2ICH_2ZnI \rightleftharpoons (ICH_2)_2Zn + ZnI_2$$

The transfer of methylene occurs from the organometallic and is stereospecific. Free $:CH_2$ is not an intermediate. It is also observed that in molecules with polar substituents, especially hydroxyl groups, the CH_2 unit is introduced on the side of the double bond in closer proximity to the hydroxyl group.[49] This observation implies that the attacking reagent may be complexed at the hydroxyl group before reaction with the carbon–carbon double bond. Entries 2 and 3 in Scheme 9.2 illustrate this stereodirective effect of the hydroxyl group.

An alternative reagent combination which effects alkene cyclopropanation involves alkylzinc reagents and methylene iodide.[50a]

45. R. Hoffmann, *J. Am. Chem. Soc.* **90**, 1475 (1968); W. A. Goddard, III, *J. Am. Chem. Soc.* **94**, 793 (1972).
46. B. Zurawski and W. Kutzelnigg, *J. Am. Chem. Soc.* **100**, 2654 (1978).
47. H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.* **80**, 5323 (1958); **81**, 4256 (1959); H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. React.* **20**, 1 (1973).
48. E. P. Blanchard and H. E. Simmons, *J. Am. Chem. Soc.* **86**, 1337 (1964); H. E. Simmons, E. P. Blanchard, and R. D. Smith, *J. Am. Chem. Soc.* **86**, 1347 (1964).
49. J. H.-H. Chan and B. Rickborn, *J. Am. Chem. Soc.* **90**, 6406 (1968); J. A. Staroscik and B. Rickborn, *J. Org. Chem.* **37**, 738 (1972).
50a. S. Sawada and Y. Inouye, *Bull. Chem. Soc. Japan* **42**, 2669 (1969); N. Kawabata, T. Nakagawa, T. Nakao, and S. Yamashita, *J. Org. Chem.* **42**, 3031 (1977); J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968).
b. J. S. Swenton, K. A. Burdett, D. M. Madigan, T. Johnson, and P. D. Rosso, *J. Am. Chem. Soc.* **97**, 3428 (1975).



Ref. 50b

A second reaction which is a formal carbene addition is the metal-ion-catalyzed decomposition of diazo compounds. Although this reaction was originally carried out primarily with copper salts[51] many other metal ions have been found to have related catalytic effects. Among those for which synthetic application have been developed are salts or complexes of Pd,[52a], Rh,[52b] Mo,[52c] and Ni.[52d] These reactions are of the carbenoid type. The initial reaction is between the diazo compound and metal ion to generate the reactive species. Since different metal ions, and therefore different intermediates, are involved in the various systems, they exhibit a range of efficiencies toward different types of alkenes. Entries 4–7 in Scheme 9.2 give some examples.

The haloalkylmercury compounds are also useful in synthesis. The organomercury reagents are generally prepared from an arylmercuric halide and a polyhalomethane by a base-catalyzed reaction.[53] Similar conditions are appropriate for

$$PhHgBr + HCBr_3 \xrightarrow[THF]{KOC(CH_3)_3} PhHgCBr_3$$

Ref. 53b

reaction of α-haloesters.[53c] The addition reactions are usually carried out by heating the organomercurial with the alkene. Two typical examples are given in Section C of Scheme 9.2.

α-Elimination reactions are also a means for generation of dichloro- and dibromocarbene. The procedures involving prior lithiation have been less generally used in synthesis. Section D of Scheme 9.2 gives a few typical examples.

Intramolecular carbene addition reactions have a special importance in the synthesis of strained ring compounds. Because of the high energy of carbene or carbenoid species, the formation of highly strained bonds is possible. The strategy

51a. Cu(I)Cl: W. von E. Doering and W. R. Roth, *Tetrahedron* **19**, 715 (1963); J. P. Chesick, *J. Am. Chem. Soc.* **84**, 3250 (1962).
b. $Cu(I)CF_3SO_3$: R. G. Salomon and J. K. Kochi, *J. Am. Chem. Soc.* **95**, 3300 (1973).
c. $Cu(II)(CH_3COCHCOCH_3)_2$: M. E. Alonso, P. Jano, and M. I. Hernandez, *J. Org. Chem.* **45**, 5299 (1980).

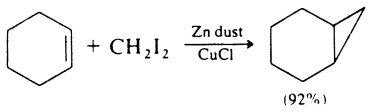
52a. R. Paulissen, A. J. Hubert and P. Teyssie, *Tetrahedron Lett.*, 1465 (1972); U. Mende, B. Radüchel, W. Skuballa, and H. Vorbrüggen, *Tetrahedron Lett.*, 629 (1975).
b. S. Bien and Y. Segal, *J. Org. Chem.* **42**, 1685 (1977); A. J. Anciaux, A. J. Hubert, A. F. Noels, N. Petiniot, and P. Teyssie, *J. Org. Chem.* **45**, 695 (1980).
c. M. P. Doyle and J. G. Davidson, *J. Org. Chem.* **45**, 1538 (1980).
d. A. Nakamura, T. Yoshida, M. Cowie, S. Otsuka, and J. A. Ibers, *J. Am. Chem. Soc.* **99**, 2108 (1977).

53a. D. Seyferth, *Acc. Chem. Res.* **5**, 65 (1972).
b. D. Seyferth and H. D. Simmons, Jr. *J. Organometal. Chem.*, **6**, 306 (1966).
c. D. Seyferth, D. C. Mueller, and R. L. Lambert, Jr., *J. Am. Chem. Soc.* **91**, 1562 (1969).

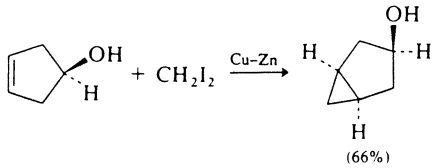
Scheme 9.2. Cyclopropane

A. Cyclopropanes by Methylene Transfer

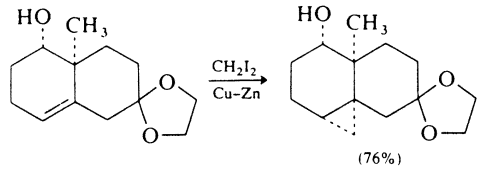
1[a]



2[b]

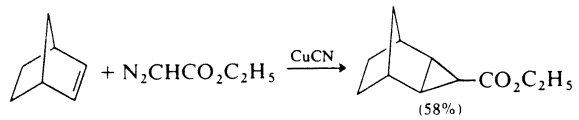


3[c]

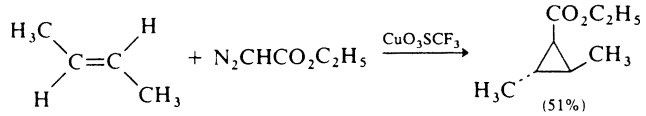


B. Catalytic Cyclopropanation by Diazo Compounds and Metal Salts

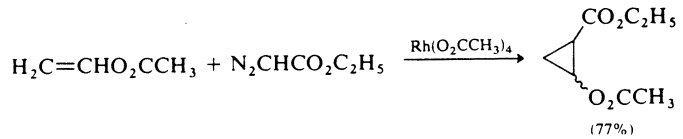
4[d]



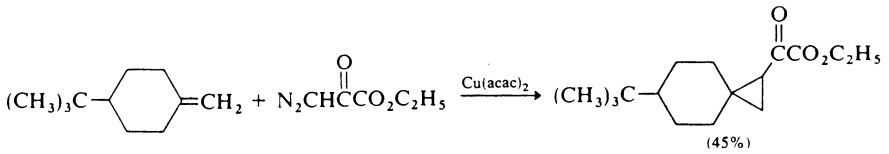
5[e]



6[f]

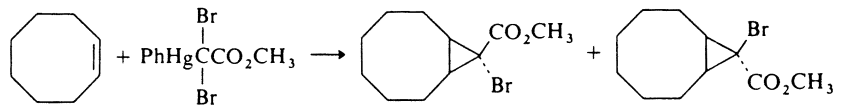


7[g]



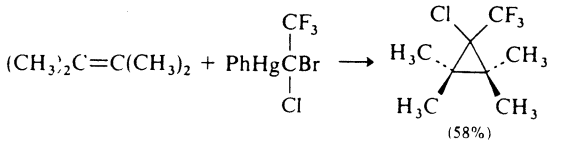
C. Cyclopropane Formation Using Haloalkylmercurials

8[h]



a. R. J. Rawson and I. T. Harrison, *J. Org. Chem.* **35**, 2057 (1970).
b. S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.* **83**, 3235 (1961).
c. P. A. Grieco, T. Oguri, C.-L. J. Wang, and E. Williams, *J. Org. Chem.* **42**, 4113 (1977).
d. R. R. Sauers and P. E. Sonnett, *Tetrahedron* **20**, 1029 (1964).
e. R. G. Salomon and J. K. Kochi, *J. Am. Chem. Soc.* **95**, 3300 (1973).
f. A. J. Anciaux, A. J. Hubert, A. F. Noels, N. Petiniot, and P. Teyssie, *J. Org. Chem.* **45**, 695 (1980).
g. M. E. Alonso, P. Jano, and M. I. Hernandez, *J. Org. Chem.* **45**, 5299 (1980).

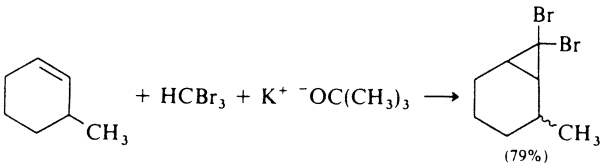
9[i]



(58%)

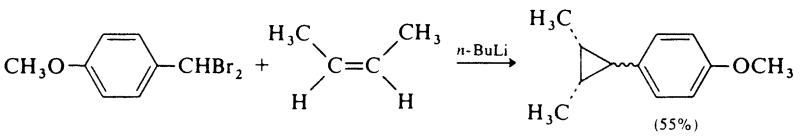
D. Reactions of Carbenes Generated by α-Elimination

10[j]



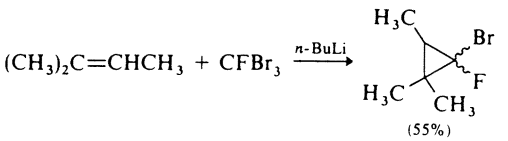
(79%)

11[k]



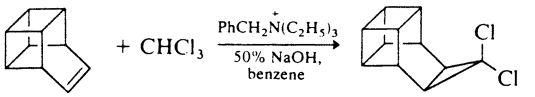
(55%)

12[l]



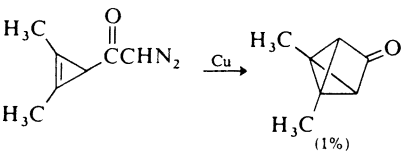
(55%)

13[m]



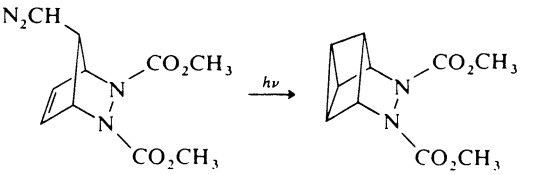
E. Intramolecular Addition Reactions

14[n]



(1%)

15[o]

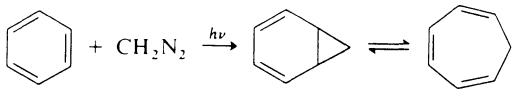


(50%)

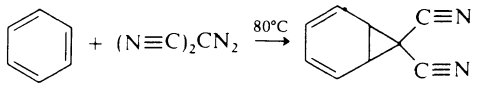
h. D. Seyferth, D. C. Mueller, and R. L. Lambert, Jr., *J. Am. Chem. Soc.* **91**, 1562 (1969).
i. D. Seyferth and D. C. Mueller, *J. Am. Chem. Soc.* **93**, 3714 (1971).
j. L. A. Paquette, S. E. Wilson, R. P. Henzel, and G. R. Allen, Jr., *J. Am. Chem. Soc.* **94**, 7761 (1972).
k. G. L. Closs and R. A. Moss, *J. Am. Chem. Soc.* **86**, 4042 (1964).
l. D. J. Burton and J. L. Hahnfeld, *J. Org. Chem.* **42**, 828 (1977).
m. T. T. Sasaki, K. Kanematsu, and N. Okamura, *J. Org. Chem.* **40**, 3322 (1975).
n. W. von E. Doering and M. Pomerantz, *Tetrahedron Lett.*, 961 (1964).
o. B. M. Trost, R. M. Cory, P. H. Scudder, and H. B. Neubold, *J. Am. Chem. Soc.* **95**, 7813 (1973).

for synthesis is to construct a potential carbene precursor, such as a diazo compound or di- or trihalo compound, in the proper position to form the desired molecule when the carbene is generated. Scheme 9.2 gives some representative examples.

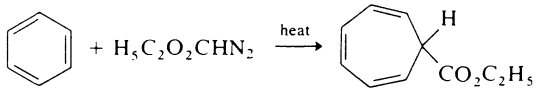
The high energy and reactivity of carbenes is also essential to another characteristic addition reaction of carbenes which has a specific synthetic use. This is the reaction which occurs when carbenes are generated in the presence of aromatic compounds.[54] The resulting adducts are in thermal equilibrium with the corresponding cycloheptatriene. The position of this equilibrium is a function of the substituents introduced via the carbene.



Ref. 55



Ref. 56



Ref. 57

9.1.4. Insertion Reactions

Insertion reactions are processes in which a reactive intermediate interposes itself into an existing bond. In terms of carbene chemistry this is of most interest with respect to insertion reactions involving C–H bonds. Carbenes are sufficiently high in energy that this reaction can occur as a one-step process. Such a one-step

$$CH_3{-}CH_2{-}CH_3 + {:}CH_2 \rightarrow CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_3$$

process is, however, only available to singlet carbenes. Analogous products can be derived by a two-step H· abstraction and recombination, which is more likely for triplet carbenes. It is frequently a difficult task to clearly distinguish between these

$$CH_3{-}CH_2{-}CH_3 + \cdot\dot{C}H_2 \rightarrow CH_3{-}CH{-}CH_3 + CH_3\cdot \rightarrow CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_3$$

mechanisms but stereochemical investigations provide one approach. The true one-step insertion must occur with retention of stereochemistry, whereas the two-step process is expected to suffer loss of stereochemical integrity at the reacting site.

54. E. Ciganek, *J. Am. Chem. Soc.* **93**, 2207 (1971).
55. G. A. Russell and D. G. Hendry, *J. Org. Chem.* **28**, 1933 (1963).
56. E. Ciganek, *J. Am. Chem. Soc.* **89**, 1454 (1967).
57. J. E. Baldwin and R. A. Smith, *J. Am. Chem. Soc.* **89**, 1886 (1967).

Because of the very high energy of the intermediates which are involved, carbene insertion reactions tend not to be very selective. The distribution of insertion products from heptane, for example, is almost exactly what would be calculated on a statistical basis.[58] Some increase in selectivity is observed with functionally

$$CH_3CH_2CH_2CH_2CH_2CH_2CH_3 \xrightarrow[h\nu]{CH_2N_2} \underset{(38\%)}{CH_3(CH_2)_6CH_3} + \underset{\underset{CH_3}{|}}{CH_3CH(CH_2)_4CH_3}\ {}_{(25\%)}$$

$$+ \underset{\underset{CH_3}{|}}{CH_3CH_2CH(CH_2)_3CH_3}\ {}_{(24\%)}$$

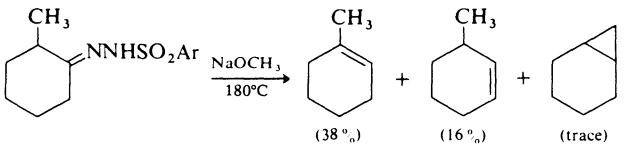
$$+ \underset{(13\%)}{(CH_3CH_2CH_2)_2CHCH_3}$$

substituted carbenes, but it is still not high enough to prevent formation of mixtures. Carbethoxycarbene, for example, inserts at tertiary C–H bonds about three times as fast as at primary C–H bonds in simple alkanes.[59] For this reason intermolecular insertion reactions are seldom a useful synthetic method.

Intermolecular insertion reactions can be of synthetic use. Particularly in instances where molecular geometry puts a potential insertion site close to the carbene site, good yields can be obtained. As with addition reactions, intramolecular insertions can provide routes to highly strained molecules or cage systems that would be difficult to approach in other ways. Scheme 9.3 gives some examples.

9.1.5. Rearrangement Reactions

The most common rearrangement reaction of carbenes is the shift of a hydrogen, generating an alkene. This mode of stabilization predominates to the exclusion of most intermolecular reactions of aliphatic and alicyclic carbenes, and often competes successfully with intramolecular insertion reactions. For example, the carbene generated by decomposition of the tosylhydrazone of 2-methylcyclohexanone gives mainly 1- and 3-methylcyclohexene, and only a trace of the intramolecular insertion product. Carbenes can also be stabilized by migration of

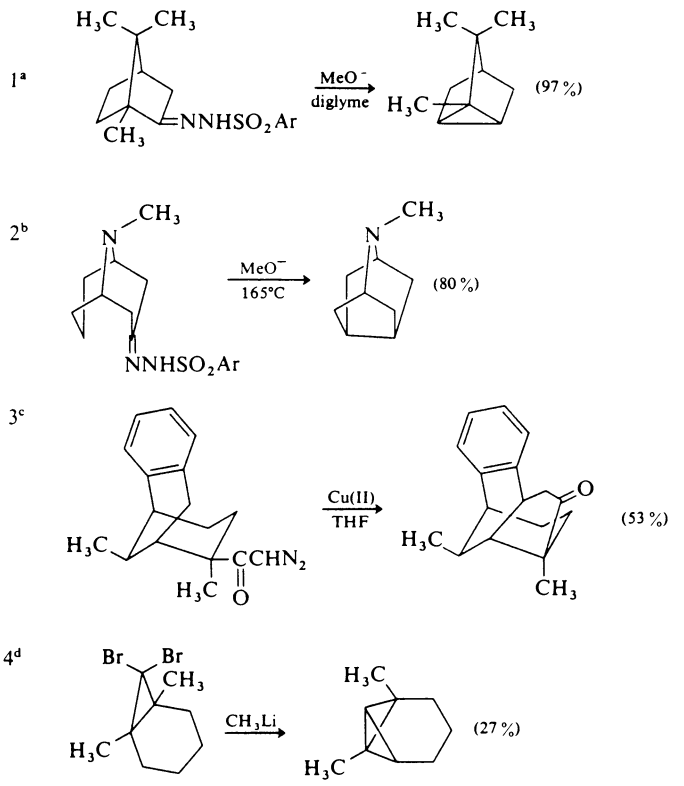


Ref. 60

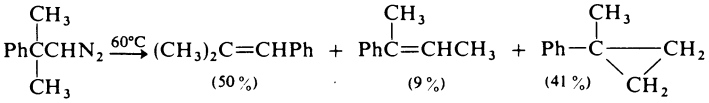
alkyl or aryl groups. 2-Methyl-2-phenyldiazopropane provides a case in which phenyl migration, methyl migration, and intramolecular insertion are all observed:

58. D. B. Richardson, M. C. Simmons, and I. Dvoretzky, *J. Am. Chem. Soc.* **83**, 1934 (1961).
59. W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.* **83**, 1989 (1961).
60. J. W. Wilt and W. J. Wagner, *J. Org. Chem.* **29**, 2788 (1964).

Scheme 9.3. Intramolecular Carbene-Insertion Reactions

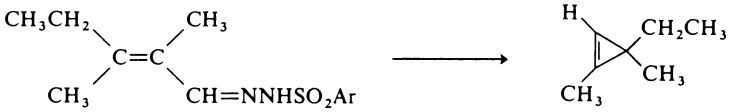


a. R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *J. Am. Chem. Soc.* **89**, 1442 (1967).
b. T. Sasaki, S. Eguchi, and T. Kiriyama, *J. Am. Chem. Soc.* **91**, 212 (1969).
c. U. R. Ghatak and S. Chakrabarty, *J. Am. Chem. Soc.* **94**, 4756 (1972).
d. L. A. Paquette, S. E. Wilson, R. P. Henzel, and G. R. Allen, Jr., *J. Am. Chem. Soc.* **94**, 7761 (1972).



Ref. 61

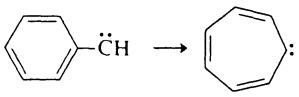
Carbene centers adjacent to double bonds (vinyl carbenes) cyclize to cyclopropenes.[62]



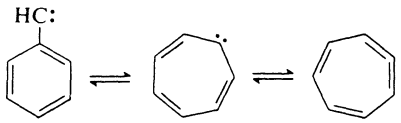
Ref. 62b

61. H. Philip and J. Keating, *Tetrahedron Lett.*, 523 (1961).
62a. G. L. Closs, L. E. Closs, and W. A. Böll, *J. Am. Chem. Soc.* **85**, 3796 (1963).
b. E. J. York, W. Dittmar, J. R. Stevenson, and R. G. Bergman, *J. Am. Chem. Soc.* **95**, 5680 (1973).

Phenylcarbene undergoes a rearrangement to cycloheptatrienylidene in the gas phase above 250°C.[63]

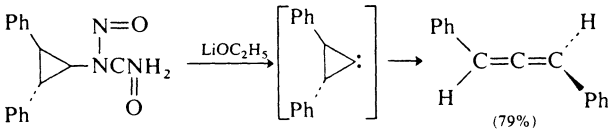


Further rearrangements of this carbene can be accounted for by interconversion among these carbenes and an isomeric, fully bonded, but highly strained, hydrocarbon, cycloheptatetraene.

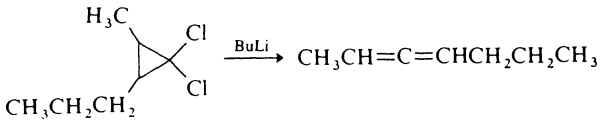


Question 14 involves a more detailed consideration of this interesting system.

Cyclopropylidenes, in which the divalent carbon is part of a cyclopropane ring, undergo a ring opening to give allenes. Reaction processes that would be expected to generate a cyclopropylidene therefore lead to allenes, often in preparatively useful yields.



Ref. 64



Ref. 65

9.1.6. Related Reactions

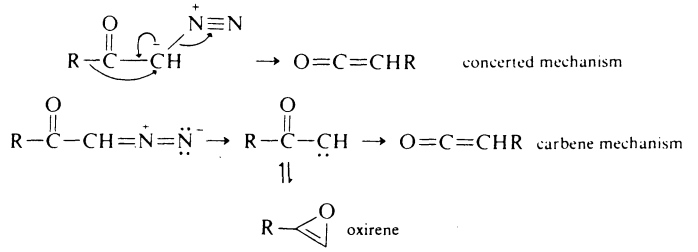
There are several reactions which are known which are conceptually related to carbene reactions but which in general do not actually involve carbenes or even carbenoid intermediates. Usually these reactions are processes in which the potential generation of a carbene is circumvented by a concerted rearrangement process. An important example of this type of reaction is the thermal and photochemical reactions of acyl diazo compounds. Examples of carbene reactivity of α-diazoesters

63. R. C. Joines, A. B. Turner, and W. M. Jones, *J. Am. Chem. Soc.* **91**, 7754 (1969); W. J. Baron, M. Jones, Jr., and P. P. Gaspar, *J. Am. Chem. Soc.* **92**, 4739 (1970).
64. W. M. Jones, J. W. Wilson, Jr., and F. B. Tutwiler, *J. Am. Chem. Soc.* **85**, 3309 (1963).
65. W. R. Moore and H. R. Ward, *J. Org. Chem.* **25**, 2073 (1960).

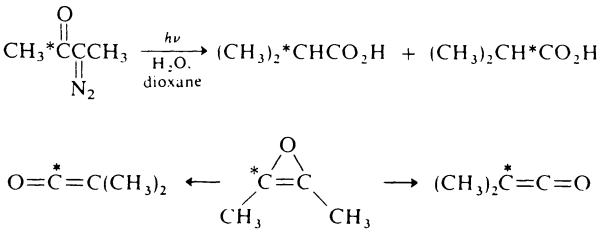
and other α-diazo compounds not having either an alkyl or aryl group on the carbonyl carbon were considered in Sections 9.1.2 and 9.1.3. When the diazo compound is an α-diazo ketone, thermal and metal-ion-catalyzed reactions usually result in rearrangement to ketenes. This reaction may proceed by a concerted process which avoids a carbene intermediate. The reaction is of synthetic importance as a convenient method for one-carbon homologation of carboxylic acids. The reaction is known as the *Wolff rearrangement.*[66] Mechanistic studies have been

$$RCO_2H \rightarrow RCOCl \xrightarrow{CH_2N_2} R\overset{O}{\overset{\|}{C}}CHN_2 \rightarrow RCH{=}C{=}O \xrightarrow{H_2O} RCH_2CO_2H$$

aimed at determining whether or not migration is concerted with loss of nitrogen. The conclusion that has emerged from these studies is that a carbene is generated



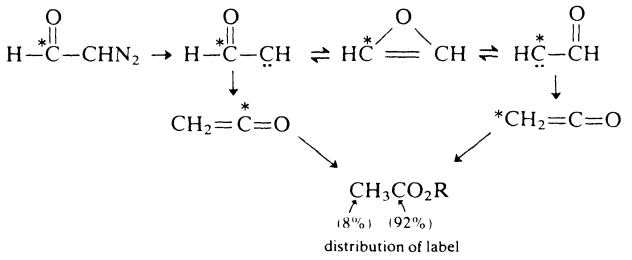
in photochemical reactions, but there is not general agreement about the thermal process. A related issue is whether the carbene, when involved, is in equilibrium with a ring-closed isomer, the oxirene. The existence of the acyl carbene–oxirene equilibrium has been established in the photochemical reactions.[67] This aspect of the mechanism has been demonstrated by isotopic labeling. The distribution of radioactive label between the two carbons is explained by the symmetrical oxirene intermediate. A carbene intermediate that did not reach the symmetrical oxirene



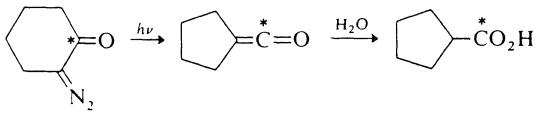
structure would be expected to give product labeled only in the carboxyl group. The extent to which the rearrangement occurs depends upon the particular structure.

66. W. E. Bachmann and W. S. Stuve, *Org. React.* **1**, 38 (1942); L. L. Rodina and I. K. Korobitsyna, *Russ. Chem. Rev.* (English trans.) **36**, 260 (1967); W. Ando, in *Chemistry of Diazonium and Diazo Groups*, S. Patai (ed.), John Wiley, New York (1978), pp. 458–475; H. Meier and K.-P. Zeller, *Angew. Chem. Int. Ed. Engl.* **14**, 32 (1975).
67. S. A. Matlin and P. G. Sammes, *J. Chem. Soc. Perkin Trans. 1*, 2623 (1972); J. Fenwick, G. Frater, K. Ogi, and O. P. Strausz, *J. Am. Chem. Soc.* **95**, 124 (1973).

The simplest acyl carbene, that derived from diazoacetaldehyde, undergoes 16% interconversion of the two carbenes upon photolysis in ether as determined by isotopic labeling.[68] The diphenyl analogs show about 20–30% migration of label.[69]



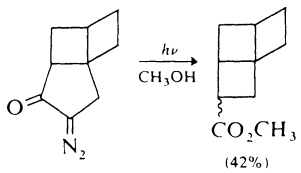
α-Diazocyclohexanone gives no evidence of the oxirene intermediate as all the label remains at the carbonyl carbon.[70] The extent of rearrangement for any



particular system will depend primarily on the relative rates of the intramolecular cyclization and the rearrangement reaction to give ketene. Very rapid trapping of the carbene by some system constituent can suppress the extent of involvement of the oxirene.

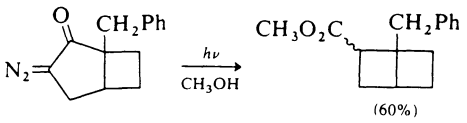
There are several experimental methods for effecting the Wolff rearrangement. The classical technique for preparation of acids or esters involves thermal decomposition in the presence of silver oxide in an aqueous solution (for acids) or an alcohol (for esters). At least for unsaturated diazoketones, the silver oxide seems to direct the reaction toward the rearrangement pathway in preference to carbenoid addition.[71] Photolysis in nonnucleophilic solvents generates the ketene, which can undergo subsequent reactions *in situ* or, if sufficiently stable, be isolated.

The photolysis of cyclic α-diazoketones results in ring contraction by a process which is analogous to the Wolff rearrangement. The ring contraction leads to a ketene intermediate, which is usually isolated as an ester.



Ref. 72

68. K.-P. Zeller, *Tetrahedron Lett.*, 707 (1977).
69. K.-P. Zeller, H. Meier, H. Kolshorn, and E. Müller, *Chem. Ber.* **105**, 1875 (1972).
70. U. Timm, K.-P. Zeller, and H. Meier, *Tetrahedron.* **33**, 453 (1977).
71. T. Hudlicky and J. P. Sheth, *Tetrahedron Lett.*, 2667 (1979).
72. K. B. Wiberg, L. K. Olli, N. Golembeski, and R. D. Adams, *J. Am. Chem. Soc.* **102**, 7467 (1980).

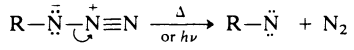


Ref. 73

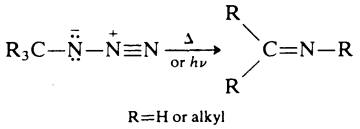
Scheme 9.4 gives some additional examples of the Wolff rearrangement.

9.2. Nitrenes

The nitrogen analogs of carbenes are called nitrenes. As with the carbenes, both singlet and triplet electronic states are possible. The triplet state is usually the ground state, but either species can be involved in reactions. By far the most commonly applied means of generating a nitrene is photolysis or thermolysis of an azide. This method is clearly analogous to formation of a carbene from a diazo compound. The types of azides in which the decomposition has been studied



extensively are those where R = alkyl,[74] aryl,[75] acyl,[76] and sulfonyl.[77] The characteristic reaction of alkyl nitrenes is migration of one of the substituents to nitrogen, giving an imine:

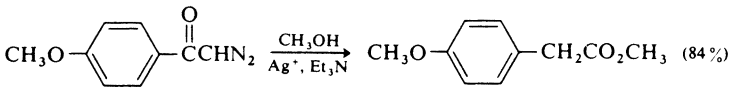


Intermolecular insertion and addition reactions are almost unknown for alkyl nitrenes. In fact, it is not clear that the nitrenes exist as discrete species. The conformation of the azide group seems to determine which substituent migrates in the decomposition of alkyl azides. This observation implies that migration begins before the nitrogen molecule has become completely detached from the incipient nitrene center,[78] since once the nitrogen has departed, the three potential migrating groups are all stereochemically equivalent.

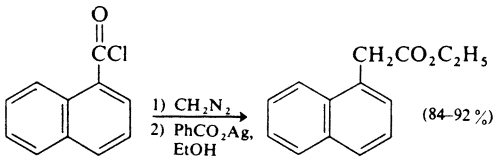
73. K. B. Wiberg, B. L. Furtek, and L. K. Olli, *J. Am. Chem. Soc.* **101**, 7675 (1979).
74. F. D. Lewis and W. H. Saunders, Jr., in *Nitrenes*, W. Lwowski (ed.), Interscience, New York (1970), pp. 47–98.
75. P. A. S. Smith, in *Nitrenes*, W. Lwowski (ed.), Interscience, New York (1970), pp. 99–162.
76. W. Lwowski, in *Nitrenes*, W. Lwowski (ed.), Interscience, New York (1970), pp. 185–224.
77. D. S. Breslow, in *Nitrenes*, W. Lwowski (ed.), Interscience, New York (1970), pp. 245–303; R. A. Abramovitch and R. G. Sutherland, *Fortschr. Chem. Forsch.* **16**, 1 (1970).
78. R. M. Moriarty and R. C. Reardon, *Tetrahedron.* **26**, 1379 (1970); R. A. Abramovitch and E. P. Kyba, *J. Am. Chem. Soc.* **93**, 1537 (1971); R. M. Moriarty and P. Serridge, *J. Am. Chem. Soc.* **93**, 1534 (1971).

Scheme 9.4. Wolff Rearrangement of α-Diazoketones

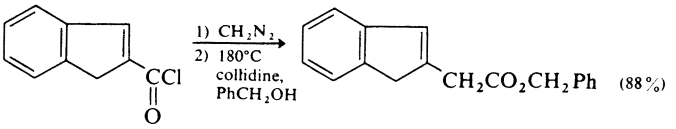
1[a]



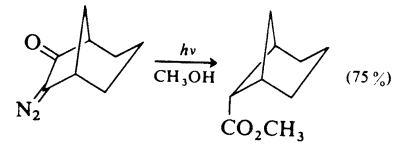
2[b]



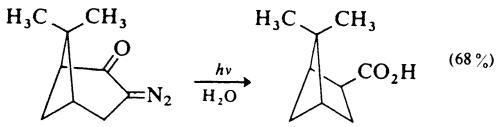
3[c]



4[d]

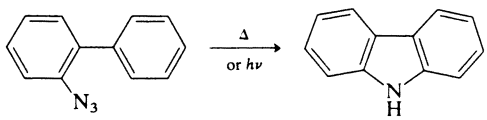


5[e]



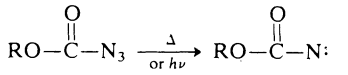
a. M. S. Newman and P. F. Beal, III, *J. Am. Chem. Soc.* **72**, 5163 (1956).
b. V. Lee and M. S. Newman, *Org. Synth.* **50**, 77 (1970).
c. E. D. Bergmann and E. Hoffmann, *J. Org. Chem.* **26**, 3555 (1961).
d. K. B. Wiberg and B. A. Hess, Jr., *J. Org. Chem.* **31**, 2250 (1966).
e. J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.* **82**, 2857 (1960).

Aryl nitrenes also generally rearrange rather than undergo addition or insertion reactions. A few intramolecular insertion reactions in aromatic systems go in good yield.[79]

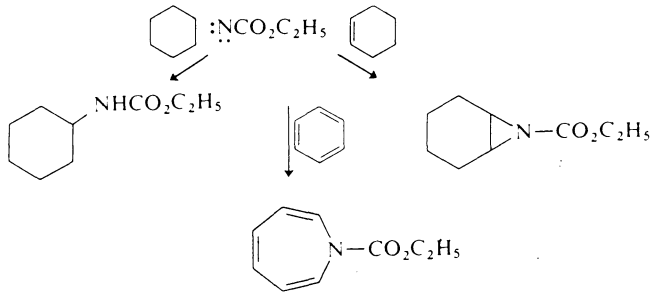


79. P. A. S. Smith and B. B. Brown, *J. Am. Chem. Soc.* **73**, 2435, 2438 (1951); J. S. Swenton, T. J. Ikeler, and B. H. Williams, *J. Am. Chem. Soc.* **92**, 3103 (1970).

The nitrenes which most consistently give addition and insertion reactions analogous to carbenes are the carboalkoxynitrenes generated from alkyl azidofor-

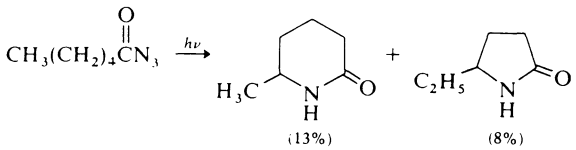


mates. These intermediates undergo addition reactions with alkenes and insertion reactions with saturated systems. Addition also occurs on reaction with benzene.[80]



This nitrene is somewhat more selective than simple carbenes, showing selectivities of roughly 1 : 10 : 40 for the primary, secondary, and tertiary positions in 2-methylbutane in insertion reactions. The relationship between nitrene multiplicity and stereospecificity in addition to alkenes is analogous to that described for carbenes. The singlet gives stereospecific addition, while the triplet gives nonstereospecific addition products.

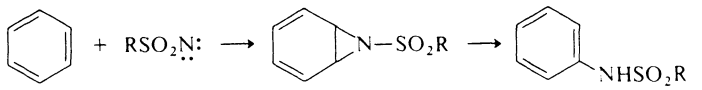
Acyl azides are well-known compounds. Their role in the thermal Curtius rearrangement, a reaction that apparently does not involve a nitrene, will be discussed in Section 9.3. Photochemical decomposition of acyl azides elicits nitrene reactivity. In particular, intramolecular C–H insertion reactions have been observed, but not usually in high yield.[81]



Ref. 82

Sulfonylnitrenes are formed by thermal decomposition of sulfonyl azides. Insertion reactions occur with saturated hydrocarbons.[83] With aromatic rings, addition is believed to occur, but the main products are sulfonanilides, which result from ring opening of the addition intermediate.

80. W. Lwowski, *Angew Chem. Int. Ed. Engl.* **6**, 897 (1967).
81. O. E. Edwards, in *Nitrenes*, W. Lwowski (ed.), Interscience, New York (1970), pp. 225–243.
82. I. Brown and O. E. Edwards, *Can. J. Chem.* **45**, 2599 (1967).
83. D. S. Breslow, M. F. Sloan, N. R. Newburg, and W. B. Renfrow, *J. Am. Chem. Soc.* **91**, 2273 (1969).

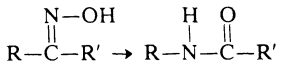


Ref. 84

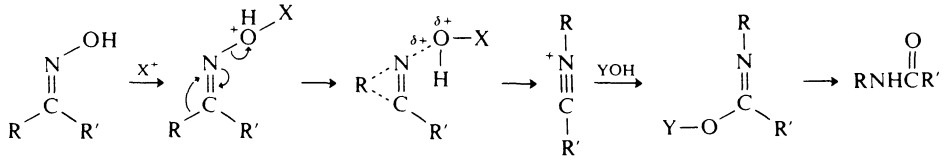
9.3. Rearrangement to Electron-Deficient Nitrogen

In contrast to the somewhat limited synthetic utility of nitrenes, there is an important group of reactions in which migration to an electron-deficient nitrogen occurs. These reactions, as a group, bear the same relationship to nitrene intermediates that the Wolff rearrangement bears to carbene intermediates. The most important reactions in this group are the *Beckmann rearrangement*, which converts oximes to amides; a family of reactions that convert carboxylic acid derivatives to amines with loss of the carbonyl group; and the reaction of ketones with hydrazoic acid to give amides (the *Schmidt reaction*).

The Beckmann rearrangement of oximes is a very general reaction that has been studied over a long period of time. A variety of protic and Lewis acids can cause the reaction to occur. Early studies established two significant points about



the stereochemistry of the reaction that provide an insight into the mechanism. First, the group that migrates is the one *anti* to the hydroxyl group on the C=N double bond, so that in the structure shown, R migrates in preference to R′. Second, the stereochemical configuration of the migrating group is retained. These stereochemical features are accounted for by a heterolytic rupture of the N–O bond with concerted migration of the *anti* group. The reaction is completed by addition of a nucleophile to the resulting nitrilium ion, and eventually, hydrolysis and tautomerism to the stable amide.[85]



A wide variety of reagents—including sulfuric acid, hydrochloric acid, polyphosphoric acid, phosphorus pentachloride, phosphorus oxychloride, and arenesulfonyl halides—can cause the rearrangement to occur. All function by converting

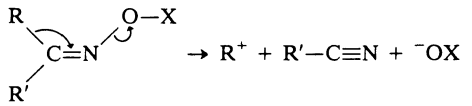
84. R. A. Abramovitch, G. N. Knaus, and V. Uma, *J. Org. Chem.* **39**, 1101 (1974).

85a. L. G. Donaruma and W. Z. Heldt, *Org. React.* **11**, 1 (1960); P. A. S. Smith, *Open Chain Nitrogen Compounds*, Vol. II, W. A. Benjamin, New York (1966), pp. 47–54.

b. P. A. Smith, in *Molecular Rearrangements*, Vol. 1, P. De Mayo (ed.) Interscience, New York (1973), pp. 483–507.

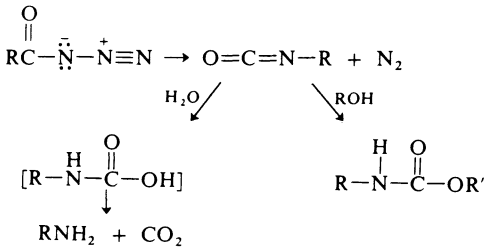
the —OH group to a more reactive leaving group, thereby facilitating rupture of the N–O bond. Under some conditions, inversion of oxime configuration is competitive with the rearrangement step. When this competition occurs, a mixture of amides is formed. The methods that are least likely to promote oxime isomerism, and resultant formation of a mixture of amides, are treatment of the oxime with phosphorus pentachloride or solvolysis of the *p*-toluenesulfonate ester of the oxime.[86,87] Catalysis of the rearrangement by protic acids is more likely to cause prior equilibration of the oxime isomers.

A variation in the Beckmann rearrangement occurs if one of the groups R or R′ can give rise to a relatively stable carbonium ion. In this circumstance, fragmentation of the molecule occurs, as will be discussed more fully in Section 9.7.

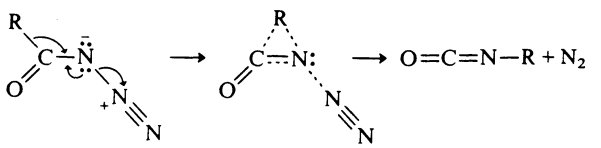


Scheme 9.5 records a number of examples of the Beckmann rearrangement. A review article in *Organic Reactions*[85a] contains an extensive survey of reactions reported prior to 1960.

A second useful reaction involving rearrangement to an electron-deficient nitrogen center is the thermal decomposition of acyl azides, known as the *Curtius rearrangement.* The initial product is an isocyanate that may be isolated or react further, depending on the reaction solvent. This rearrangement shares with the Beckmann rearrangement the feature that the migrating group retains its

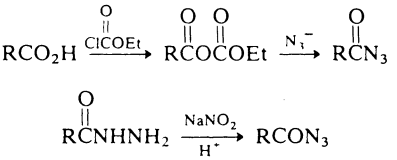


stereochemical configuration. The migration is usually considered to be concerted, with the loss of molecular nitrogen, because reactions attributable to a nitrene intermediate are not observed.[88] The temperatures required to bring about



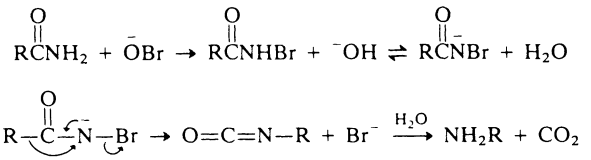
86. R. F. Brown, N. M. van Gulick, and G. H. Schmid, *J. Am. Chem. Soc.* **77**, 1094 (1955).
87. J. C. Craig and A. R. Naik, *J. Am. Chem. Soc.* **84**, 3410 (1962).
88. S. Linke, G. T. Tisue, and W. Lwowski, *J. Am. Chem. Soc.* **89**, 6308 (1967).

decomposition of acyl azides are quite low, usually being in the vicinity of 100°C.[89] The acyl azides are obtained either by a reaction of sodium azide with a reactive acylating agent or by diazotization of an acid hydrazide. An especially convenient variation of the former approach is to treat the carboxylic acid with ethyl chloroformate, which gives a mixed anhydride that reacts readily with azide ion[90]:

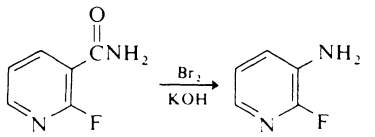


Some examples of the use of the Curtius reaction are given in Scheme 9.5.

Another reaction that is occasionally used for conversion of carboxylic acids to the corresponding amine with loss of carbon dioxide is the hypobromite oxidation of amides. The *N*-bromoamide is presumably an intermediate.[91] This reaction is known as the *Hofmann rearrangement.* The migration is believed to be concerted, with elimination of bromide ion. It can be used to replace carboxyl groups with



amino groups, a synthetically useful transformation, particularly for the synthesis of certain aromatic amines.



Ref. 92

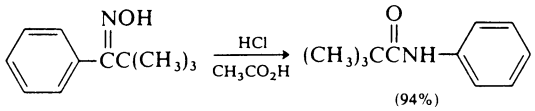
Carboxylic acids and esters can also be converted to amines with loss of the carbonyl group by reaction with hydrazoic acid, HN_3. This is known as the *Schmidt reaction.*[93] The mechanism of the process is related to that of the Curtius reaction, in that an electron-deficient center is developed by expulsion of nitrogen from an azido group. The intermediate is generated by addition of hydrazoic acid to the carbonyl group. The migrating group retains its configuration.

89. P. A. S. Smith, *Org. React.* **3**, 337 (1946); P. A. S. Smith, *Open Chain Nitrogen Compounds*, Vol. 2, W. A. Benjamin, New York (1966), pp. 219–221.
90. J. Weinstock, *J. Org. Chem.* **26**, 3511 (1961).
91. E. S. Wallis and J. F. Lane, *Org. React.* **3**, 267 (1946).
92. G. C. Finger, L. D. Starr, A. Roe, and W. J. Link, *J. Org. Chem.* **27**, 3965 (1962).
93. H. Wolff, *Org. React.* **3**, 307 (1946); P. A. S. Smith, in *Molecular Rearrangements*, P. de Mayo (ed.), Vol. 1, Interscience, New York (1963), pp. 507–527.

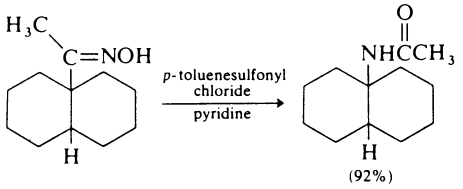
Scheme 9.5. Rearrangement to

A. Beckmann Rearrangement Reactions

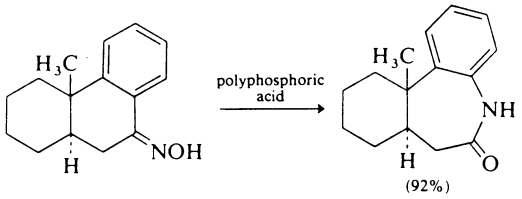
1[a]



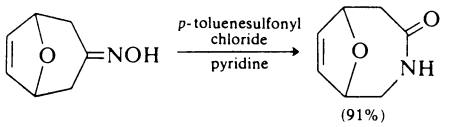
2[b]



3[c]



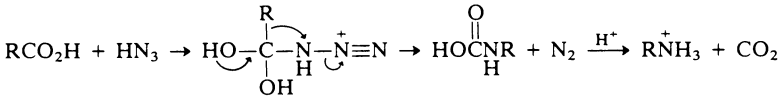
4[d]



B. Cutius Rearrangement Reactions

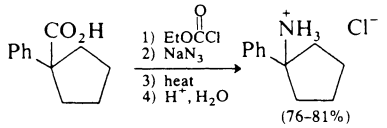
5[e] $CH_3(CH_2)_{10}\overset{O}{\overset{\|}{C}}Cl \xrightarrow[2)\ \text{benzene, } 70°C]{1)\ NaN_3} CH_3(CH_2)_{10}N{=}C{=}O$

6[f] $H_5C_2O_2C(CH_2)_4CO_2C_2H_5 \xrightarrow[2)\ HNO_2\ 3)\ \Delta\ 4)\ H^+, H_2O]{1)\ N_2H_4} Cl^-H_3\overset{+}{N}(CH_2)_4\overset{+}{N}H_3Cl^-$



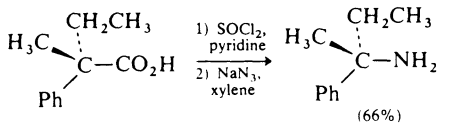
When the Schmidt reaction is applied to α,β-unsaturated carboxylic acids, the product of the rearrangement is an enamine, which hydrolyzes to the corresponding ketone. Reaction with hydrazoic acid converts ketones to amides, and is thus an alternative method for effecting the same transformation as the Beckmann rearrangement. A drawback of this method is that the features that determine which

7[g]



(76–81%)

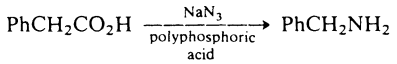
8[h]



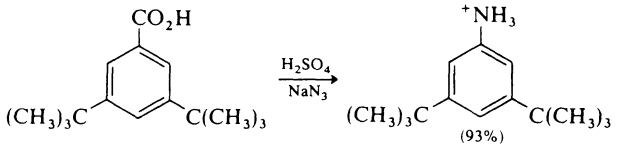
(66%)

C. Schmidt Reactions

9[i]

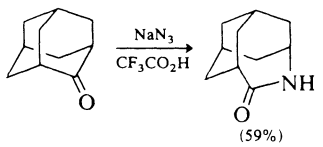


10[j]



(93%)

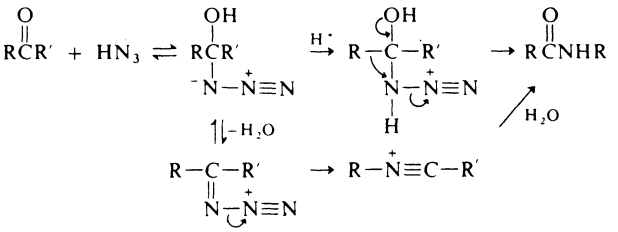
11[k]



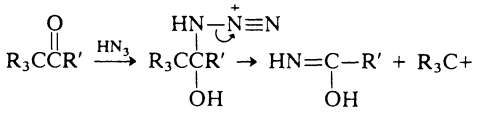
(59%)

a. R. F. Brown, N. M. van Gulick, and G. H. Schmid, *J. Am. Chem. Soc.* **77**, 1094 (1955).
b. R. K. Hill and O. T. Chortyk, *J. Am. Chem. Soc.* **84**, 1064 (1962).
c. R. A. Barnes and M. T. Beachem, *J. Am. Chem. Soc.* **77**, 5388 (1955).
d. S. R. Wilson, R. A. Sawicki, and J. C. Huffman, *J. Org. Chem.* **46**, 3887 (1981).
e. C. F. H. Allen and A. Bell, *Org. Synth.* **III**, 846 (1955).
f. P. A. S. Smith, *Org. Synth.* **IV**, 819 (1963).
g. C. Kaiser and J. Weinstock, *Org. Synth.* **51**, 48 (1971).
h. D. J. Cram and J. S. Bradshaw, *J. Am. Chem. Soc.* **85**, 1108 (1963).
i. R. M. Palmere and R. T. Conley, *J. Org. Chem.* **35**, 2703 (1970).
j. J. W. Elder and R. P. Mariella, *Can. J. Chem.* **41**, 1653 (1963).
k. T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.* **35**, 4109 (1970).

of the ketone branches will migrate are not completely understood. For this reason, the composition of the product mixture which is formed from unsymmetrical ketones cannot always be predicted. As in the case of carboxylic acids, the key intermediate is generated by addition of hydrazoic acid to the carbonyl group. The



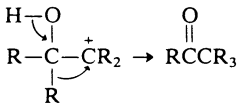
decomposition may, in some cases, be preceded by a dehydration step. Fragmentation to a nitrile and carbonium ion can occur when one of the ketone substituents is capable of generating a stable carbonium ion.[94]



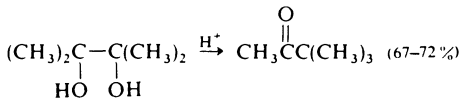
Some examples of the Schmidt reaction are given in Scheme 9.5.

9.4. Rearrangement of Carbonium Ion Intermediates

Like carbenes and nitrenes, carbonium ions can be stabilized by the migration of hydrogen, alkyl and aryl groups, and occasionally other substituents. A mechanistic discussion of these reactions was given in Section 5.11, Part A. Reactions involving rearrangement of simple alkyl carbonium ions are usually avoided in planning syntheses because of the great potential for complications resulting from competing rearrangement pathways. Carbonium ion rearrangements can become highly specific and, therefore reliable synthetic reactions, when the structural situation is such as to strongly favor a particular reaction. One case where this arises is in the reaction of carbonium ions having a hydroxyl group adjacent to the potential carbonium ion site. The formation of a carbonyl group is then possible and favorable under these conditions. One reaction which follows this pattern is



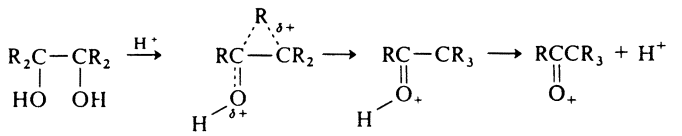
the acid-catalyzed conversion of diols to ketones. This reaction is sometimes referred to as the *pinacol rearrangement.*[95] The classic example of the reaction is the conversion of 2,3-dimethylbutane-2,3-diol (pinacol) to methyl *t*-butyl ketone (pinacolone):



Ref. 96

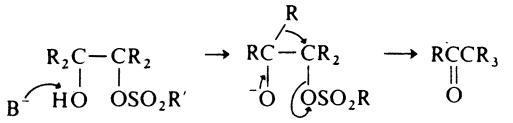
The mechanism involves carbonium ion formation and substituent migration, assisted by electron release from the remaining hydroxyl group:

94. R. K. Hill, R. T. Conley, and O. T. Chortyk, *J. Am. Chem. Soc.* **87**, 5646 (1965); R. M. Palmere, R. T. Conley, and J. L. Rabinowitz, *J. Org. Chem.* **37**, 4095 (1972); R. T. Conley and B. E. Nowak, *J. Org. Chem.* **26**, 692 (1961).
95. C. J. Collins, *Q. Rev.* **14**, 357 (1960).
96. G. A. Hill and E. W. Flosdorf, *Org. Synth.* **I**, 451 (1932).



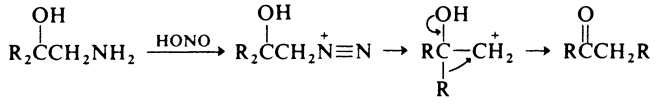
The traditional conditions for carrying out the pinacol rearrangement have involved treating the glycol with a strong acid. Under these conditions, the more easily ionized C–O bond generates the carbonium ion, and migration of one of the groups from the adjacent carbinol site ensues. Both stereochemistry and "migratory aptitude" can be factors in determining the extent of migration of two unlike groups.

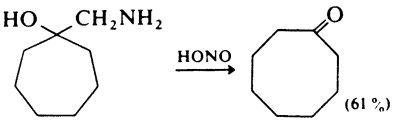
Another method for carrying out the same net rearrangement involves synthesis of a glycol monosulfonate ester. These compounds rearrange under the influence of base. This method can be used to change the nature of rearrangement from that



expected in an acid-catalyzed reaction of the corresponding glycol. In the case of a glycol that contains one secondary and one tertiary hydroxyl, for example, the secondary group will be preferentially sulfonylated. In contrast, the tertiary hydroxyl will be more easily ionized under the acid-catalyzed conditions. These reactions have been of some value in rearranging ring systems, especially in the area of terpene synthesis, as illustrated by entries 4 and 5 in Scheme 9.6.

Aminomethylcarbinols yield ketones when treated with nitrous acid. This reaction has been used synthetically to form ring-expanded cyclic ketones, a procedure known as the *Tiffeneau–Demjanov reaction*.[97] The diazotization procedure generates the same type of β-hydroxycarbonium ion that is formed in the





Ref. 98

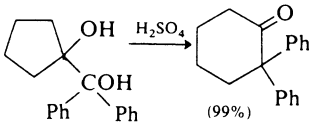
pinacol rearrangement. One method for obtaining the required aminomethylcarbinols involves cyanohydrin formation, followed by reduction:

97. P. A. S. Smith and D. R. Baer, *Org. React.* **11**, 157 (1960).
98. F. F. Blicke, J. Azuara, N. J. Dorrenbos, and E. B. Hotelling, *J. Am. Chem. Soc.* **75**, 5418 (1953).

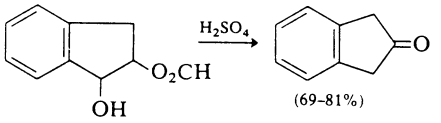
Scheme 9.6. Rearrangements Promoted by Adjacent Heteroatoms

A. Pinacol-Type Rearrangements

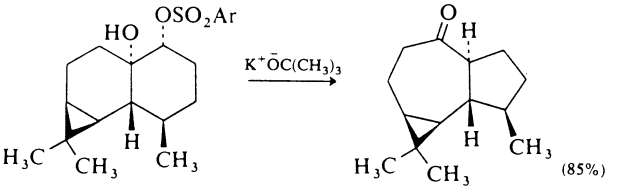
1[a]



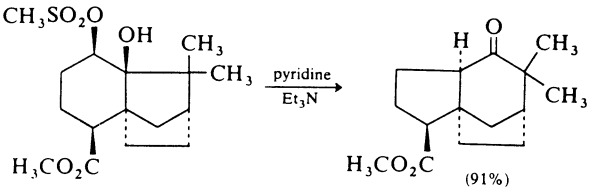
2[b]



3[c]

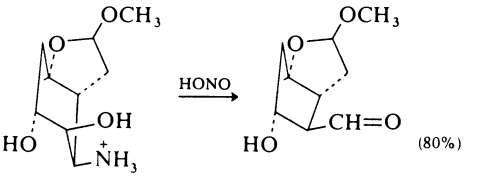


4[d]

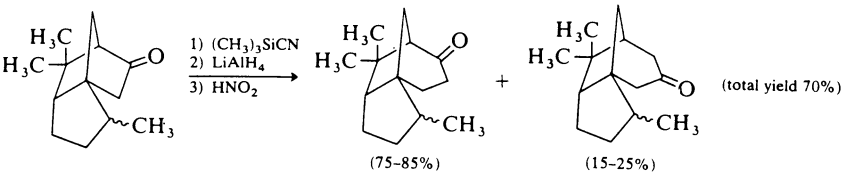


B. Rearrangement of β-Aminoalcohols by Diazotization

5[e]

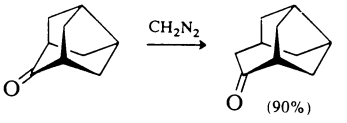


6[f]



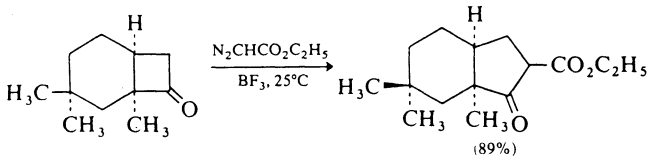
C. Ring Expansion of Cyclic Ketones with Diazo Compounds

7[g]

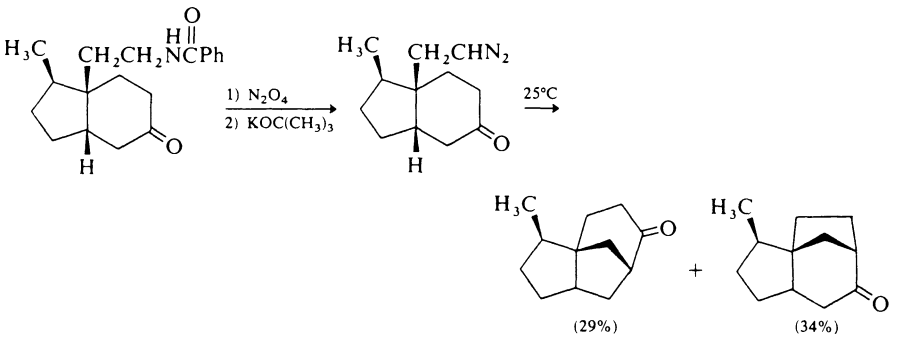


Scheme 9.6.—*continued*

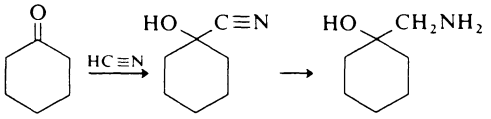
8[h]



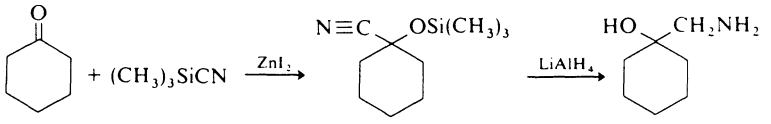
9[i]



a. H. E. Zaugg, M. Freifelder, and B. W. Horrom, *J. Org. Chem.* **15**, 1191 (1950).
b. J. E. Horan and R. W. Schiessler, *Org. Synth.* **41**, 53 (1961).
c. G. Büchi, W. Hofheinz, and J. V. Paukstelis, *J. Am. Chem. Soc.* **88**, 4113 (1966).
d. D. F. MacSweeney and R. Ramage, *Tetrahedron* **27**, 1481 (1971).
e. R. B. Woodward, J. Gosteli, I. Ernest, R. J. Friary, G. Nestler, H. Raman, R. Sitrin, C. Suter, and J. K. Whitesell, *J. Am. Chem. Soc.* **95**, 6853 (1973).
f. E. G. Breitholle and A. G. Fallis, *J. Org. Chem.* **43**, 1964 (1978).
g. Z. Majerski, S. Djigas, and V. Vinkovic, *J. Org. Chem.* **44**, 4064 (1979).
h. H. J. Liu and T. Ogino, *Tetrahedron Lett.*, 4937 (1973).
i. P. R. Vettel and R. M. Coates, *J. Org. Chem.* **45**, 5430 (1980).



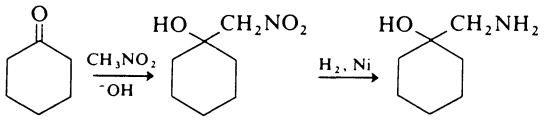
More recently, it has been found that trimethylsilyl cyanide reacts with ketones to give trimethylsilyl ethers of cyanohydrins. These compounds can be directly reduced to the aminomethylcarbinol by lithium aluminum hydride.[99] Another method for



Ref. 99

99. D. A. Evans, G. L. Carroll, and L. K. Truesdale, *J. Org. Chem.* **39**, 914 (1974).

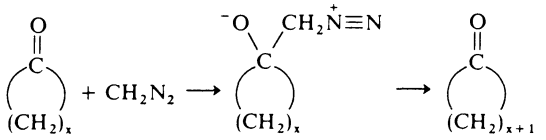
the synthesis of aminomethylcycloalkanols involves reduction of the adducts of nitromethane and cyclic ketones.[100]



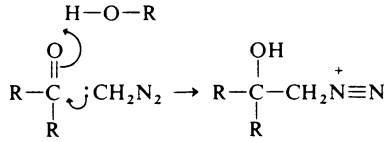
Ref. 100

Diazotization of aminomethylcycloalkanes can also lead to ring expansion, but due to the absence of participation by a hydroxyl group in the rearrangement, this is a much less specific reaction and mixtures of alkenes and alcohols, both rearranged and unrearranged, are usually obtained. The reaction is seldom synthetically attractive.

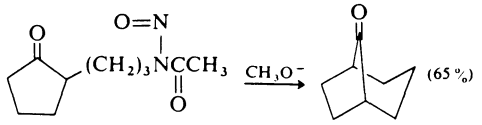
The reactions of ketones with diazoalkanes sometimes lead to a ring-expanded ketone in synthetically useful yields.[101] The reaction occurs by addition of diazoalkane, followed by elimination of nitrogen and migration:



In protic solvents, at least, the reaction proceeds via essentially the same intermediate that is involved in the Tiffeneau–Demjanov reaction. Since the product is also a ketone, subsequent addition of diazomethane can lead to higher homologs. The best yields are obtained when the starting ketone is more reactive than the product. For this reason, strained ketones often work well in this reaction. Higher diazoalkanes can also be employed.[102] The reaction has been found to be accelerated by alcoholic solvents. This effect probably involves the hydroxyl group acting as a proton donor and thus facilitating the addition step.[103]



Intramolecular reactions between diazo groups and carbonyl centers can be used to construct bicyclic ring systems:

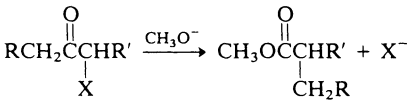


Ref. 104

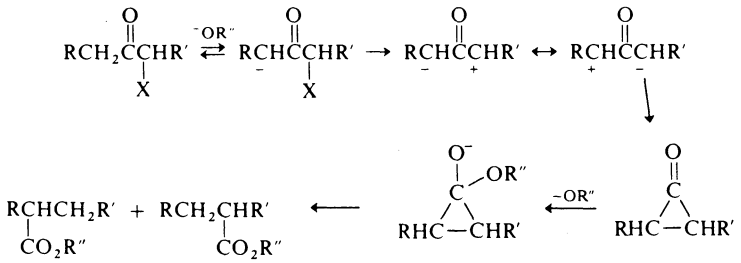
100. W. E. Noland, J. F. Kneller, and D. E. Rice, *J. Org. Chem.* **22**, 695 (1957).
101. C. D. Gutsche, *Org. React.* **8**, 364 (1954).
102. J. A. Marshall and J. J. Partridge, *J. Org. Chem.* **33**, 4090 (1968).
103. J. N. Bradley, G. W. Cowell, and A. Ledwith, *J. Chem. Soc.*, 4334 (1964).
104. C. D. Gutsche and D. M. Bailey, *J. Org. Chem.* **28**, 607 (1963).

9.5. Other Rearrangements

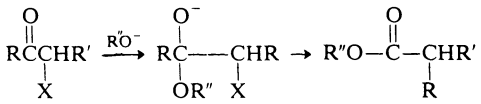
α-Haloketones undergo a skeletal change when treated with base. The mechanism is somewhat different from those of the rearrangement processes discussed earlier. The overall structural change that is effected is similar, however, to that caused by rearrangement of α-diazoketones; the reaction can therefore be conveniently discussed at this point. The most commonly used bases are alkoxide ions, which lead to esters as the reaction products. If the ketone is cyclic, a ring contraction



occurs. This base-catalyzed conversion of α-haloketones to carboxylic acid derivatives is known as the *Favorskii reaction.*[105] The reaction has been subjected to extensive mechanistic studies. There is strong evidence that the rearrangement involves the open 1,3-dipolar form of a cyclopropanone and/or the cyclopropanone as a reaction intermediate.[106] There is also a related mechanism that can operate



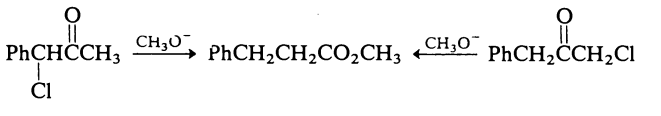
in the absence of an acidic α-hydrogen; it is known as the "semibenzilic" rearrangement:



The net structural change is the same for both mechanisms. The energy requirements of the cyclopropanone and semibenzilic mechanisms may be fairly closely balanced, as instances of the operation of the semibenzilic mechanism have been reported even for compounds with hydrogen available for enolization.[107] Included in the evidence that the cyclopropanone mechanisms usually operates, in preference to the semibenzilic mechanism, is the demonstration, in several instances, that a

105. A. S. Kende, *Org. React.* **11**, 261 (1960); A. A. Akhrem, T. K. Ustynyuk, and Y. A. Titov, *Russ. Chem. Rev.* (English trans.) **39**, 732 (1970).
106. F. G. Bordwell, T. G. Scamehorn, and W. R. Springer, *J. Am. Chem. Soc.* **91**, 2087 (1969); F. G. Bordwell and J. G. Strong, *J. Org. Chem.* **38**, 579 (1973).
107. E. W. Warnhoff, C. M. Wong, and W. T. Tai, *J. Am. Chem. Soc.* **90**, 514 (1968).

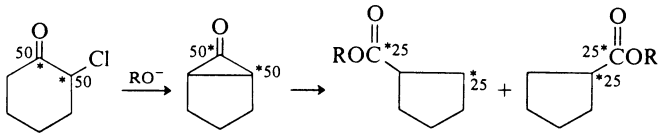
symmetrical intermediate is involved. The isomeric chloroketones **2** and **3**, for example, lead to the same ester, while it has been shown that the two ketones are



Ref. 106

2 **3** **4**

not interconverted under the conditions of the rearrangement. A common intermediate, such as the cyclopropanone, can explain this observation. The occurrence of a symmetrical intermediate has also been demonstrated by ^{14}C labeling in the case of α-chlorocyclohexanone.[108]

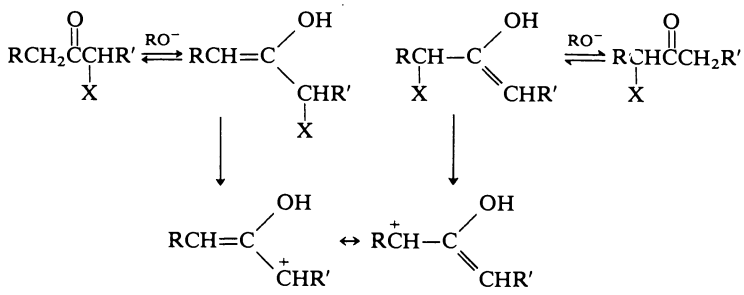


* = ^{14}C label

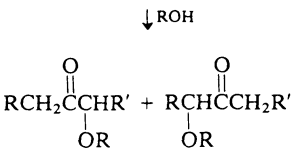
Numbers refer to percentage of label at each carbon.

Because of the operation of the cyclopropanone mechanism, the structure of the ester product cannot be predicted directly from the structure of the reacting haloketone. Instead, the identity of the product is governed by the direction of ring opening of the cyclopropanone intermediate. The dominant mode of ring opening would be expected to be that which forms the more stable of the two possible ester enolates. For this reason, a phenyl substituent favors breaking the bond to the substituted carbon, but an alkyl substituent directs the cleavage to a less substituted carbon.[109] That both **2** and **3** above give the same ester, **4**, is illustrative of directing effect the phenyl group can have on the ring-opening step.

α-Alkoxyketones are common by-products of Favorskii rearrangements catalyzed by alkoxide ions. Generally, these by-products are not formed by a direct S_N2 displacement, since a symmetrical intermediate appears to be involved. The most satisfactory general mechanism suggests that the enol form of the chloroketone is the precursor of the alkoxyketones.[110]

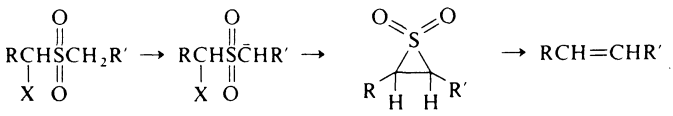


108. R. B. Loftfield, *J. Am. Chem. Soc.* **73**, 4707 (1951).
109. C. Rappe, L. Knutsson, N. J. Turro, and R. B. Gagosian, *J. Am. Chem. Soc.* **92**, 2032 (1970).
110. F. G. Bordwell and M. W. Carlson, *J. Am. Chem. Soc.* **92**, 3377 (1970).

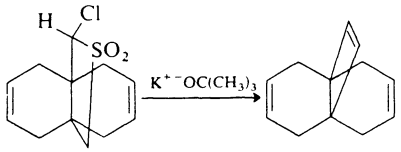


The Favorskii reaction has been used to effect ring contraction in the course of synthesis of strained ring systems. Entry 4 in Scheme 9.7 illustrates this application of the reaction. With α,α'-dihaloketones, the rearrangement is accompanied by dehydrohalogenation to yield an α,β-unsaturated ester, as illustrated by entry 3 in Scheme 9.7.

α-Halosulfones undergo a related rearrangement. The carbanion formed by deprotonation forms an unstable thiirane dioxide.[111] The thiirane dioxides decom-



pose with elimination of sulfur dioxide. The reaction is useful for the synthesis of certain types of olefins.



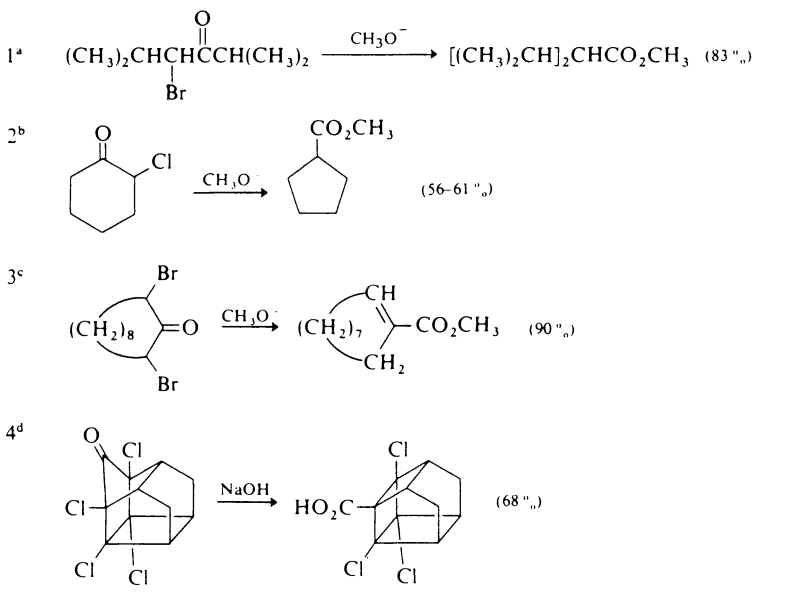
Ref. 112

9.6. Carbon–Carbon Bond Formation Involving Carbonium Ions

The formation of carbon–carbon bonds in aromatic systems often takes place by an electrophilic attack on the ring by a carbonium ion or a species with carbonium ion character. The large family of reactions related to Friedel–Crafts reaction are of this type. In aliphatic chemistry carbon electrophiles are more likely to be encountered as carbonyl groups or as such compounds as halides and tosylates, which are subject to nucleophilic displacement. Many examples of these types of reactions have been discussed, particularly in Chapters 1, 2, and 6. There are also some valuable synthetic procedures in which carbon–carbon bond formation results from electrophilic attack by a carbonium ion on an alkene. It is this group of reactions that we will now consider.

111. L. A. Paquette, *Acc. Chem. Res.* **1**, 209 (1968); L. A. Paquette, in *Mechanisms of Molecular Migrations*, Vol. 1, B. S. Thyagarajan (ed.), Wiley-Interscience, New York (1968), Chap. 3.
112. L. A. Paquette, J. C. Philips, and R. E. Wingard, Jr., *J. Am. Chem. Soc.* **93**, 4516 (1971).

Scheme 9.7. Base-Catalyzed Rearrangements of α-Haloketones



a. S. Sarel and M. S. Newman, *J. Am. Chem. Soc.* **78**, 416 (1956).
b. D. W. Goheen and W. R. Vaughan, *Org. Synth.* **IV**, 594 (1963).
c. E. W. Garbisch, Jr., and J. Wohllebe, *J. Org. Chem.* **33**, 2157 (1968).
d. R. J. Stedman, L. S. Miller, L. D. Davis, and J. R. E. Hoover, *J. Org. Chem.* **35**, 4169 (1970).

Consideration of the energetics of the attack of a carbonium ion on an alkene reveals that such reactions are not likely to be efficient unless the intermediate which is formed, which is itself some type of carbonium ion, is more stable than the attacking reagent. In fact, most of the reactions which have attained synthetic importance involve alkenes which are capable of specific subsequent stabilization of the intermediate carbonium ion.

One group of alkenes which react efficiently with electrophilic carbon species are the allylsilanes. The carbon–silicon bond is broken as the reaction proceeds, thus providing a low-energy product.[113] Among the electrophilic carbon species

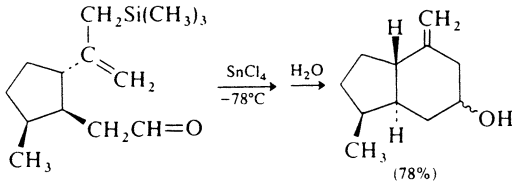
$$(CH_3)_3Si\overset{\frown}{-CH_2}-CH=\overset{\frown}{CH_2}\ \overset{+}{C}R_3 \rightarrow X-Si(CH_3)_3 + CH_2=CHCH_2CR_3$$

which react to give efficient bond formation are aldehydes,[114a] ketones,[114a] α,β-

113. T. H. Chan and I. Fleming, *Synthesis* 761 (1979); P. Magnus, *Aldrichimica Acta* **13**, 43 (1980).
114a. A. Hosomi and H. Sakurai, *Tetrahedron Lett.*, 1295 (1976).

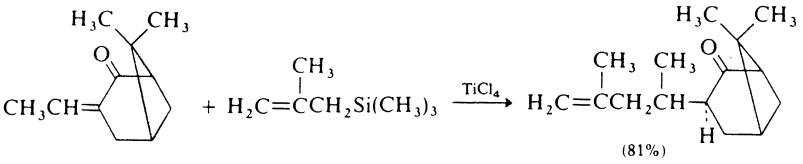
Scheme 9.8. Electrophilic Substitution of Allylsilanes

1[a] $CH_2{=}CHCH_2Si(CH_3)_3 + PhCH_2CH_2CH{=}O \xrightarrow{TiCl_4} CH_2{=}CHCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_2Ph$ (96%)

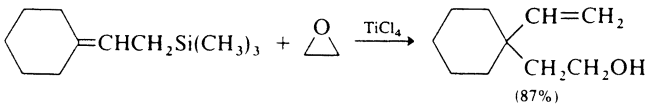
2[b] 

(78%)

3[c] $CH_2{=}CHCH{=}CHCH_2Si(CH_3)_3 + PhCH{=}O \xrightarrow{TiCl_4} CH_2{=}CHCH{=}CHCH_2\underset{\displaystyle OH}{\underset{|}{C}}HPh$ (51%)

4[d] 

(81%)

5[e] 

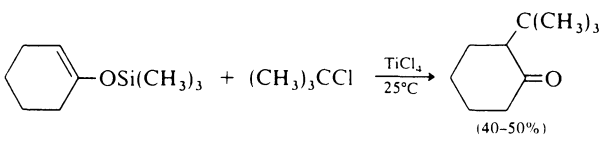
(87%)

a. A. Hosomi and H. Sakurai, *Tetrahedron Lett.*, 1295 (1976).
b. T. K. Sarkar and N. H. Andersen, *Tetrahedron Lett.*, 3513 (1978).
c. D. Seyferth and J. Pornet, *J. Org. Chem.* **45**, 1721 (1980).
d. T. Yanami, M. Miyashita, and A. Yoshikoshi, *J. Org. Chem.* **45**, 607 (1980).
e. I. Fleming and I. Paterson, *Synthesis*, 446 (1979).

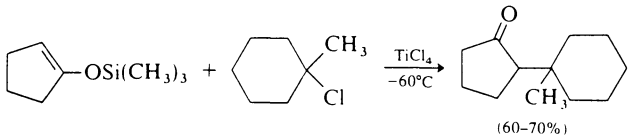
unsaturated ketones,[114b] acid chlorides,[114c] *t*-alkyl halides,[114d] and ethylene oxide.[114d] The silyl group facilitates this reaction, both by stabilizing the initial buildup of positive charge and by permitting the concerted bond cleavage which makes the reaction energetically favorable. Some examples of these reactions are given in Scheme 9.8.

Silyl enol ethers also readily undergo electrophilic attack with desilylation to give α-substituted carbonyl compounds. This reaction has been developed into a method for introducing tertiary alkyl groups α to a carbonyl. This, of course, cannot be achieved under the standard conditions of base-catalyzed enolate alkylation because of the strong tendency for tertiary halides to undergo elimination. Slightly

114b. A. Hosomi and H. Sakurai, *J. Am. Chem. Soc.* **99**, 1673 (1977); T. Yanami, M. Myashita, and A. Yoshikoshi, *J. Org. Chem.* **45**, 607 (1980).
c. J.-P. Pillot, J. Dunogues, and R. Calas, *Tetrahedron Lett.*, 1871 (1976); J.-P. Pillot, G. Deleris, J. Dunogues, and R. Calas, *J. Org. Chem.* **44**, 3397 (1979).
d. I. Fleming and I. Paterson, *Synthesis* 446 (1979).



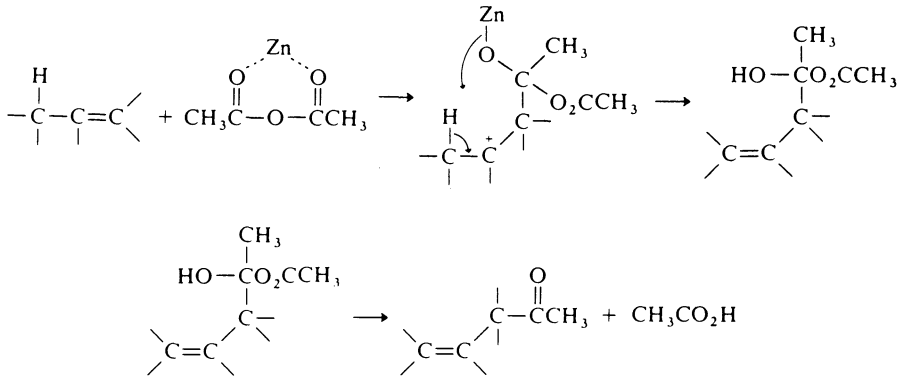
Ref. 115



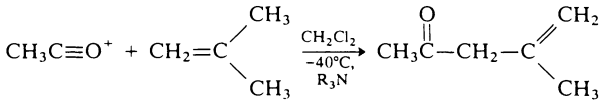
Ref. 116

less reactive halides such as secondary benzyl bromides, allyl bromides, and α-chloro ethers undergo analogous reactions with $ZnBr_2$ as the catalyst.[117]

Alkenes react with acyl halides or acid anhydrides in the presence of Lewis acid catalysts. The reaction works better with cyclic alkenes than for acyclic ones. A mechanistically significant feature of this reaction is the kinetic preference for formation of β,γ-unsaturated ketones. Mechanistic studies using acetic anhydride and zinc chloride as the reagent system are consistent with a two-step mechanism in which the location of the double bond in the product is determined by ease of deprotonation of the initial adduct.[118] A related reaction occurs when alkenes react

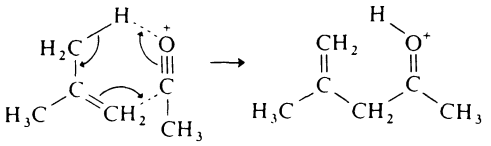


with acylium ions in inert solvent; the reaction of isobutylene and acetylium ion is illustrative.[119] This reaction again leads specifically to β,γ-enones. A concerted

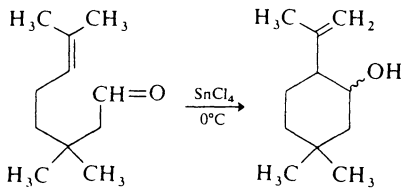


115. T. H. Chan, I. Paterson, and J. Pinsonnault, *Tetrahedron Lett.*, 4183 (1977).
116. M. T. Reetz, I. Chatzuosifidis, U. Löwe, and W. F. Maier, *Tetrahedron Lett.*, 1427 (1979).
117. I. Paterson, *Tetrahedron Lett.*, 1519 (1979).
118. P. Beak and K. R. Berger, *J. Am. Chem. Soc.* **102**, 3848 (1980).
119. H. M. R. Hoffmann and T. Tsushima, *J. Am. Chem. Soc.* **99**, 6008 (1977).

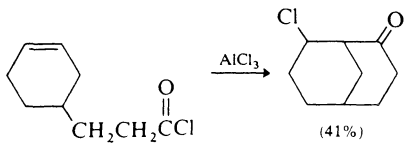
"ene reaction" transition state has been suggested. A variety of other reaction conditions have been examined for acylation of alkenes, with acid chlorides in



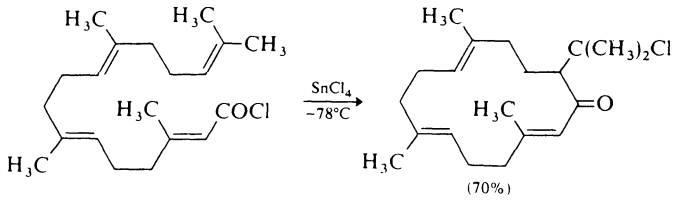
particular. Using typical Lewis acid catalysts, product mixtures including both conjugated and unconjugated enones, α-chloroketones and rearrangement products are frequently observed.[120] Cyclizations by intramolecular acylation of olefinic bonds have been more useful in general than the intermolecular reactions. The cation generated by the cyclization can either capture a nucleophile or lose a proton. The following examples are illustrative of intramolecular cyclizations:



Ref. 121



Ref. 122



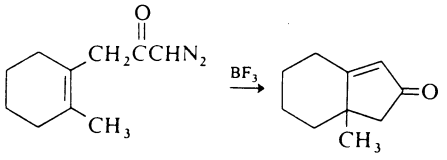
Ref. 123

In those cases where the geometry of the transition state makes it possible, the deprotonation again seems to be an integral part of the cyclization process.[121]

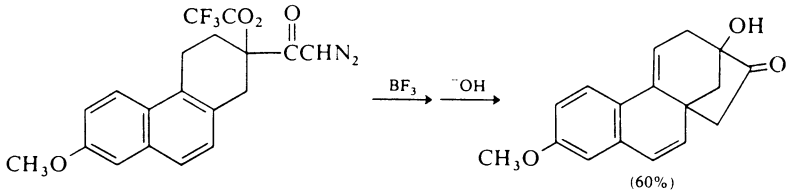
Treatment of diazomethyl ketones with boron trifluoride generates an electrophilic reagent which undergoes cyclization when there is an appropriately located

120. For example, T. S. Cantrell, J. M. Harless, and B. L. Strasser, *J. Org. Chem.* **36**, 1191 (1971); L. Rand and R. J. Dolinski, *J. Org. Chem.* **31**, 3063 (1966).
121. N. H. Andersen and D. W. Ladner, *Synth. Commun.*, 449 (1978).
122. E. N. Marvell, R. S. Knutson, T. McEwen, D. Sturmer, W. Federici, and K. Salisbury, *J. Org. Chem.* **35**, 391 (1970).
123. T. Kato, M. Suzuki, T. Kobayashi, and B. P. Moore, *J. Org. Chem.* **45**, 1126 (1980).

point of unsaturation.[124,125] The reactive electrophilic species in this process might

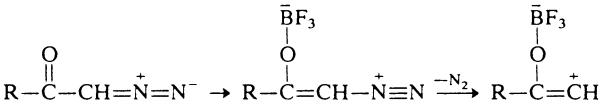


Ref. 124

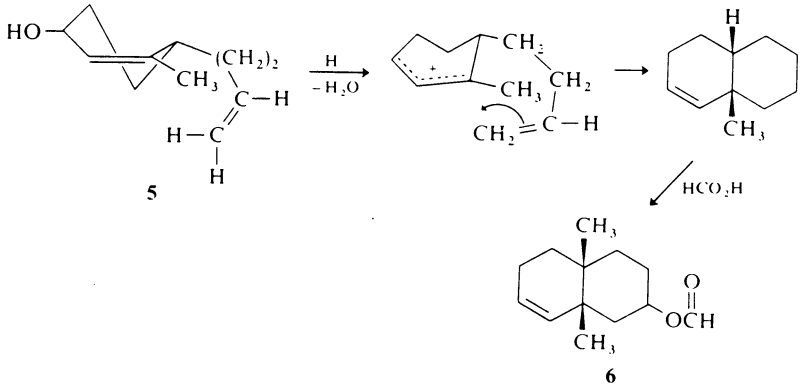


Ref. 125

be formulated as a complexed β-oxyvinyl cation. In any case, it is sufficiently reactive to form new carbon–carbon bonds with olefinic or aromatic π bonds in the β-γ, γ-δ, or δ-ε position.



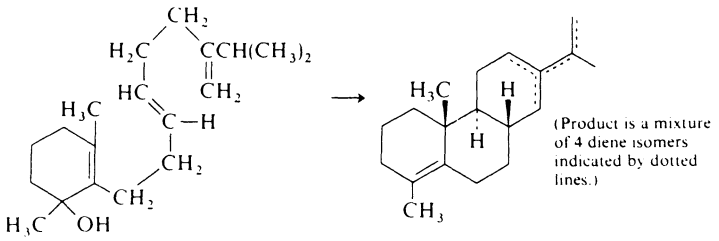
Generation of a cationic site in appropriately constructed polyolefins can be a very efficient means of cyclization. The reaction proceeds through an electrophilic attack, and requires that the olefin units that are to participate in the cyclization be properly juxtaposed. For example, compound **5** is converted quantitatively to **6** on treatment with formic acid. The reaction is initiated by protonation and ionization of the allylic alcohol.



Ref. 126

124. A. B. Smith, III, B. H. Toder, S. J. Branca, and R. K. Dieter, *J. Am. Chem. Soc.* **103**, 1996 (1981).
125. T. R. Klose and L. M. Mander, *Aust. J. Chem.* **27**, 1287 (1974).
126. W. S. Johnson, P. J. Neustaedter, and K. K. Schmiegel, *J. Am. Chem. Soc.* **87**, 5148 (1965).

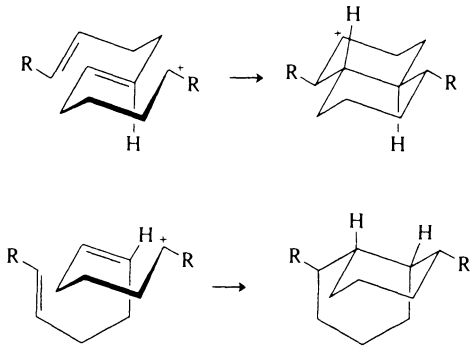
More extended polyolefins can cyclize to polycyclic systems:



Ref. 127

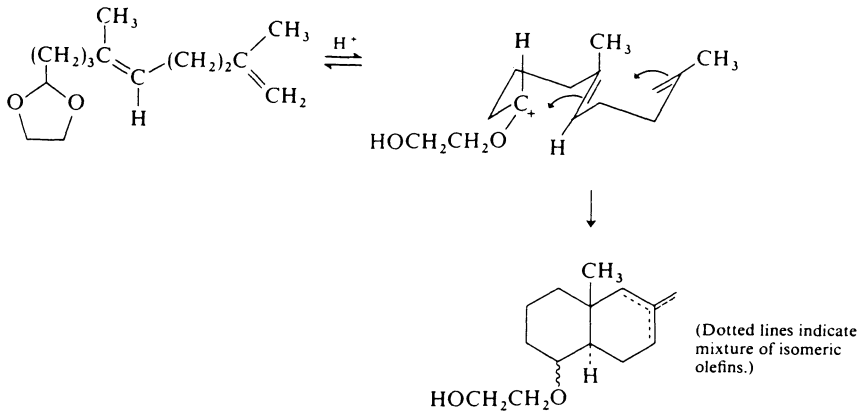
The reactions are usually highly stereoselective, with the stereochemical outcome being predictable on the basis of reactant conformation.[128] The stereochemistry of cyclization products of the decalin family can be predicted by assuming chair conformations for the developing cyclohexane rings.

The stereochemistry at ring junctures is that expected from *anti* attack at the participating double bond(s):



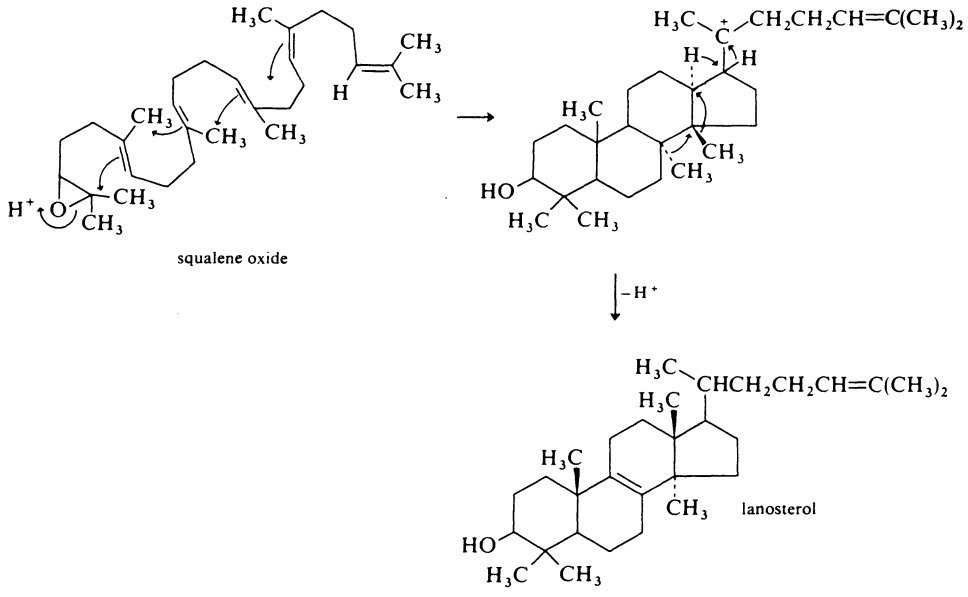
To be of maximum synthetic value, the generation of the cationic site that initiates cyclization of polyolefins must involve mild reaction conditions. The most versatile systems to date have been allylic alcohols, which are readily cyclized in acidic media. Formic acid and Lewis acids such as stannic chloride have proved to be effective reagents for cyclizing polyolefinic allylic alcohols. Acetals generate α-alkoxy carbonium ions in acidic solutions and can initiate the cyclization of appropriate polyolefinic systems.[129] Another significant method of generating the requisite electrophilic site is acid-catalyzed epoxide ring opening.[130]

127. W. S. Johnson, N. P. Jensen, J. Hooz, and E. J. Leopold, *J. Am. Chem. Soc.* **90**, 5872 (1968).
128. W. S. Johnson, *Acc. Chem. Res.* **1**, 1 (1968).
129. A. van der Gen, K. Wiedhaup, J. J. Swoboda, H. C. Dunathan, and W. S. Johnson, *J. Am. Chem. Soc.* **95**, 2656 (1973).
130. E. E. van Tamelen and R. G. Nadeau, *J. Am. Chem. Soc.* **89**, 176 (1967).



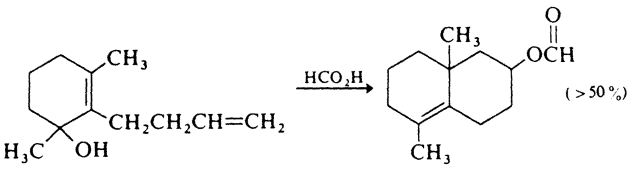
Since the immediate product of the cyclization step is a carbonium ion, it is often found that the product consists of a mixture of closely related compounds, all resulting from the same carbonium ion. These usually include products from the capture of the carbonium ion by nucleophilic solvent and a mixture of the various alkenes resulting from loss of a proton.

Polyolefin cyclizations have been of substantial value in the systhesis of polycyclic natural products of the terpene type. To a large extent, these syntheses probably resemble the processes by which polycyclic compounds are assembled in nature from linear polyolefins. The most dramatic example of biological synthesis of a polycyclic skeleton from an acyclic intermediate is the conversion of squalene oxide to the steroid lanosterol and then to other steroids. Scheme 9.9 gives some representative example of laboratory syntheses involving polyolefin cyclizations.

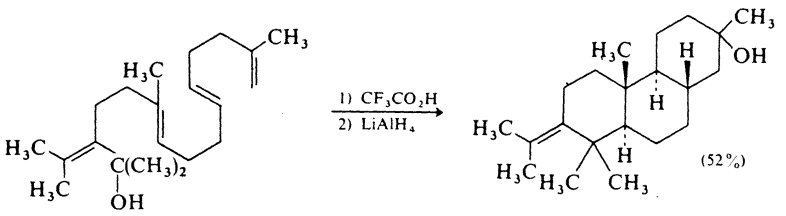


Scheme 9.9. Polyolefin Cyclizations

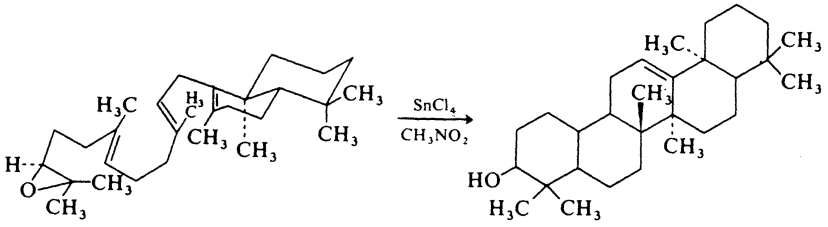
1[a]



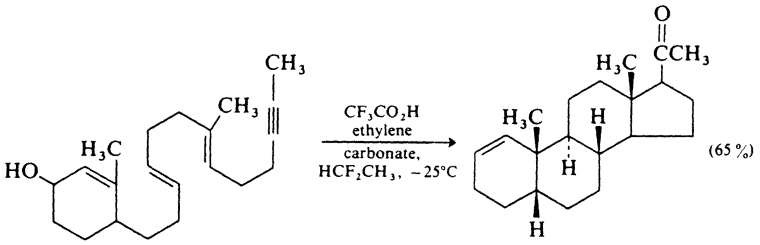
2[b]



3[c]



4[d]

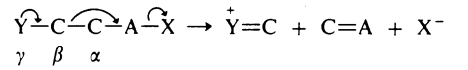


a. J. A. Marshall, N. Cohen, and A. R. Hochstetler, *J. Am. Chem. Soc.* **88**, 3408 (1966).
b. W. S. Johnson and T. K. Schaaf, *Chem. Commun.* 611 (1969).
c. E. E. van Tamelen, R. A. Holton, R. E. Hopla, and W. E. Konz, *J. Am. Chem. Soc.* **94**, 8228 (1972).
d. B. E. McCarry, R. L. Markezich, and W. S. Johnson, *J. Am. Chem. Soc.* **95**, 4416 (1973).

9.7. Fragmentation Reactions

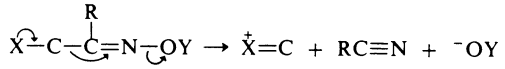
The name "fragmentation" applies to reactions in which a carbon–carbon bond is broken when an electron deficiency develops. A structural feature that permits fragmentation to occur readily is the presence of a carbon *beta* to the developing electron deficiency that can readily accept carbonium ion character. This type of reaction occurs particularly readily when the γ-atom is a heteroatom, such as

nitrogen or oxygen, having unshared electron pairs available for stabilization of

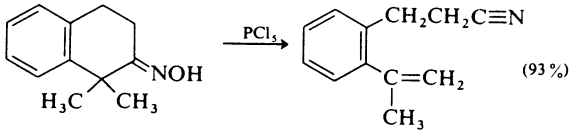


the new carbonium ion center.[131] The fragmentation can occur as a concerted process or stepwise. The concerted mechanism is characterized by accelerated reaction rates and is restricted to molecular geometry that is appropriate for continuous overlap of the participating orbitals. An example is the solvolysis of 4-chloropiperidine, which is more rapid than solvolysis of chlorocyclohexane and occurs with ring opening by fragmentation of the C-2–C-3 bond.[132]

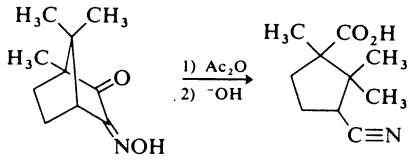
The Beckmann rearrangement reaction provides a number of examples of fragmentation. The products that result from fragmentation are a carbonium ion and a nitrile. Fragmentation is very likely to occur if X is a nitrogen, oxygen, or



sulfur atom. It is also likely to occur when one of the oxime substituents is a tertiary alkyl group.



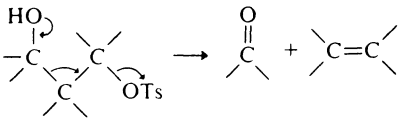
Ref. 133



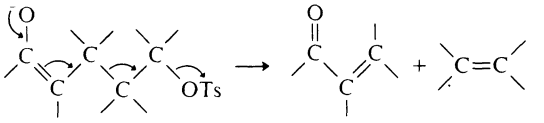
Ref. 134

A particularly useful type of substrate for fragmentation are diols or hydroxy ethers in which the two oxygen functionalities are in a 1,3-relationship. If the diol or hydroxy ether is then converted to a monotosylate, the remaining oxygen function serves to promote fragmentation. Similarly, a carbonyl group at the fifth carbon

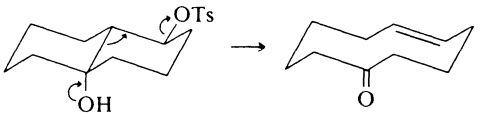
131. C. A. Grob, *Angew. Chem. Int. Ed. Engl.* **8**, 535 (1969).
132. R. D'Arcy, C. A. Grob, T. Kaffenberger, and V. Krasnobajew, *Helv. Chim. Acta.* **49**, 185 (1966).
133. R. T. Conley and R. J. Lange, *J. Org. Chem.* **28**, 210 (1963).
134. A. Hassner, W. A. Wentworth, and I. H. Pomerantz, *J. Org. Chem.* **28**, 304 (1963).



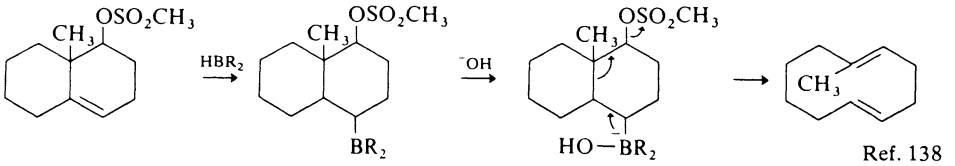
from a leaving group, reacting via the enolate, promotes fragmentation with formation of an enone.[135]



The usual synthetic objective of a fragmentation reaction is the construction of a medium-size ring, 8–13 atoms, from a fused ring system. Furthermore, because the fragmentation reactions of the type being discussed are usually concerted processes, the stereochemistry of the reactions is predictable. In 3-hydroxyalkyltosylates, the fragmentation is favorable only for geometry in which the carbon–carbon bond being broken can be in an *anti*-periplanar relationship to the leaving group.[136] Other stereochemical relationships in the molecule are retained during the concerted fragmentation so the newly formed double bond has the *E*-configuration.



Organoboranes have been shown to undergo fragmentation if a good leaving group is present on the δ-carbon.[137] The reactive intermediate is the tetrahedral intermediate formed by addition of hydroxide ion at boron.



Ref. 138

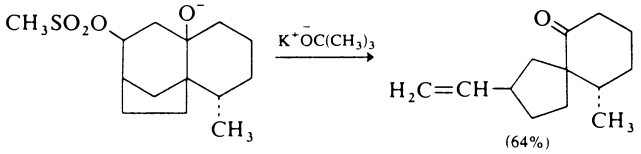
Scheme 9.10 provides some additional examples of fragmentation reactions which have been employed in a synthetic context.

135. J. M. Brown, T. M. Cresp, and L. N. Mander, *J. Org. Chem.* **42**, 3984 (1977); D. A. Clark and P. L. Fuchs, *J. Am. Chem. Soc.* **101**, 3567 (1979).
136. P. S. Wharton and G. A. Hiegel, *J. Org. Chem.* **30**, 3254 (1965); C. H. Heathcock and R. A. Badger, *J. Org. Chem.* **37**, 234 (1972).
137. J. A. Marshall, *Synthesis*, 229 (1971); J. A. Marshall and G. L. Bundy, *Chem. Commun.* 854 (1967); P. S. Wharton, C. E. Sundin, D. W. Johnson, and H. C. Kluender, *J. Org. Chem.* **37**, 34 (1972).
138. J. A. Marshall and G. L. Bundy, *J. Am. Chem. Soc.* **88**, 4291 (1966).

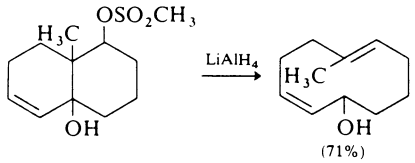
Scheme 9.10. Fragmentation Reactions

A. Heteroatom-Promoted Fragmentation

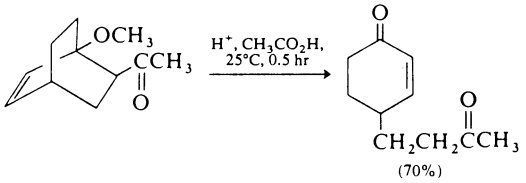
1[a]



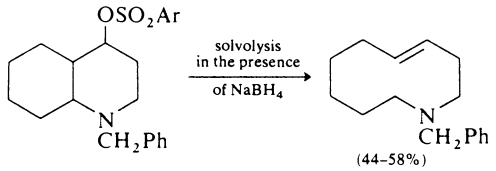
2[b]



3[c]

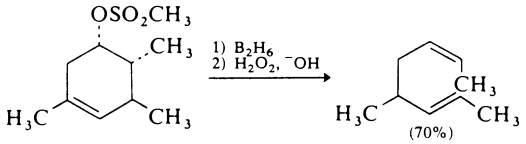


4[d]



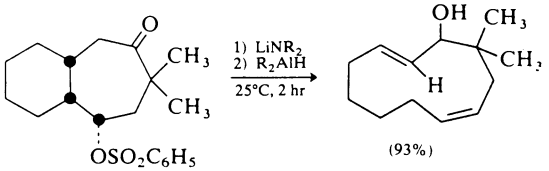
B. Boronate Fragmentations

5[e]



C. δ-Tosyloxy Enolate Fragmentation

6[f]



a. J. A. Marshall and S. F. Brady, *J. Org. Chem.* **35**, 4068 (1970).
b. J. A. Marshall, W. F. Huffman, and J. A. Ruth, *J. Chem. Soc.* **94**, 4691 (1972).
c. A. J. Birch and J. S. Hill, *J. Chem. Soc. C*, 419 (1966).
d. J. A. Marshall and J. H. Babler, *J. Org. Chem.* **34**, 4186 (1969).
e. J. A. Marshall and J. H. Babler, *Tetrahedron Lett.*, 3861 (1970).
f. D. A. Clark and P. L. Fuchs, *J. Am. Chem. Soc.* **101**, 3567 (1979).

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Carbenes

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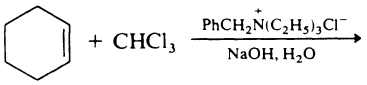
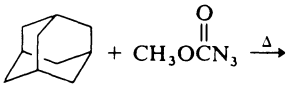
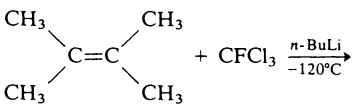
Problems

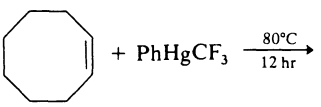
(*References for these problems will be found on page 628.*)

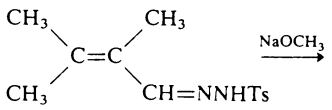
1. Indicate the major product to be expected in the following reactions:

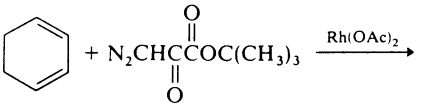
(a) 

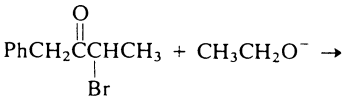
(b) 

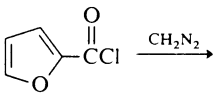
(c) 

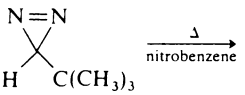
(d) 

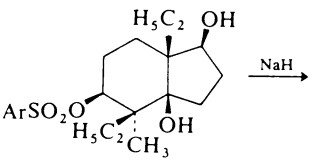
(e) 

(f) 

(g) 

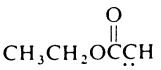
(h) 

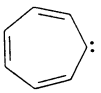
(i) 

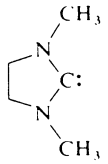
(j) 

2. Each of the following carbenes has been predicted to have a singlet ground state, either as the result of qualitative structural considerations or on the basis of theoretical calculations. Indicate what structural feature in each case might lead to stabilization of the singlet state.

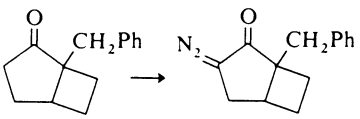
(a) 

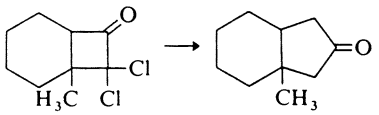
(b) 

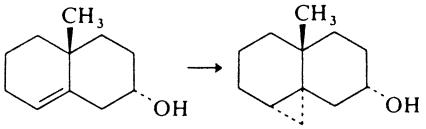
(c) 

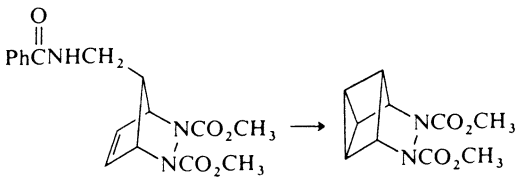
(d) 

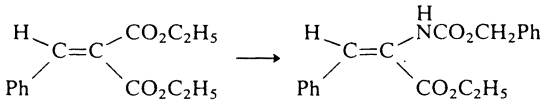
3. Indicate appropriate reagents and conditions or a short reaction sequence which could be expected to effect the following transformations:

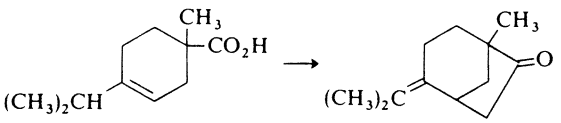
(a) 

(b) 

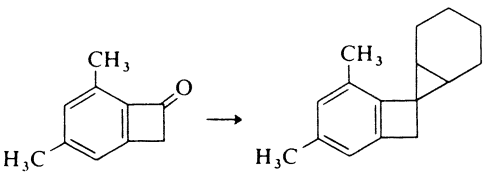
(c) 

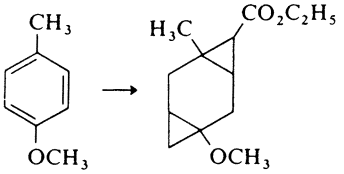
(d) 

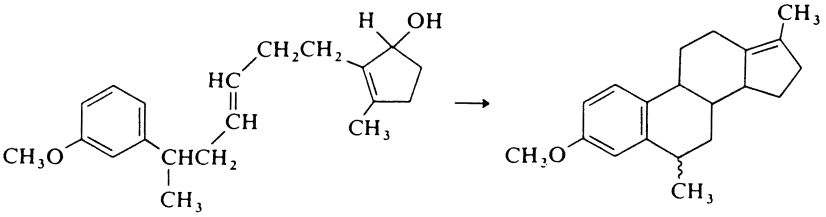
(e) 

(f) 

(g) $CH_2{=}CHCH{=}CHCO_2H \rightarrow CH_2{=}CHCH{=}CH\overset{H}{N}CO_2CH_2Ph$

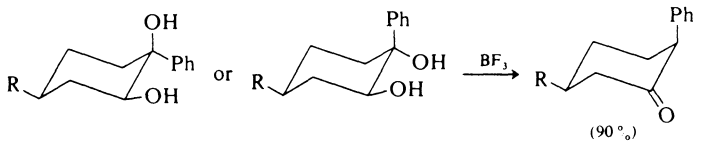
(h) 

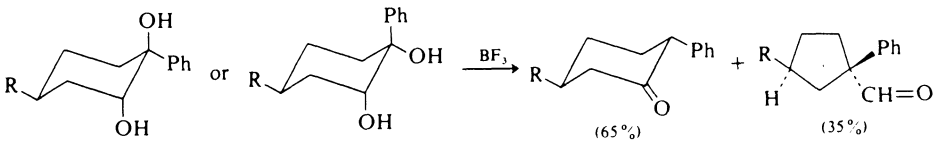
(i) 

(j) 

4. The hydroxyl group in *trans*-cycloocten-3-ol determines the stereochemistry of reaction of this compound with the Simmons–Smith reagent. By examining a model, predict the stereochemistry of the resulting product.

5. Discuss the significance of the relationships between substrate stereochemistry and product composition exhibited by the reactions shown below:

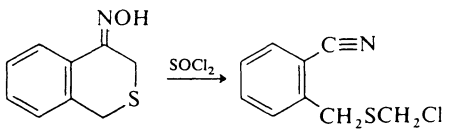




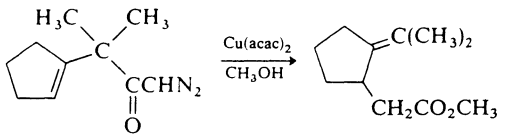
R = *t*-butyl

6. Suggest a mechanistic rationalization for the following reactions. Point out the structural features which contribute to the unusual or abnormal course of the reaction. What product might have been expected if the reaction followed a "normal" course?

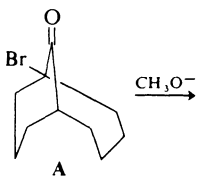
(a)



(b)



7. Give the structure of the expected Favorskii rearrangement product of compound **A**:

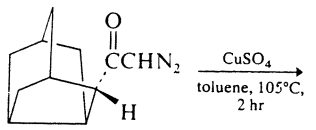


A

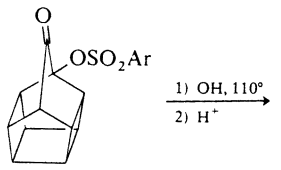
Experimentally, it has been found that the above ketone can rearrange by either the cyclopropanone or the semibenzilic mechanism, depending on the reaction conditions. Devise two experiments that would permit you to determine which mechanism was operating under a given set of circumstances.

8. Predict the major product of the following reactions:

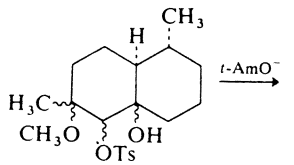
(a)



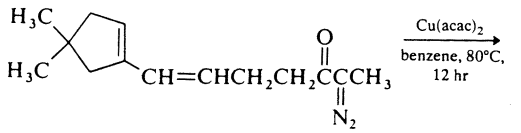
(b)



(c)



(d)



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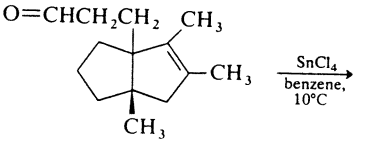

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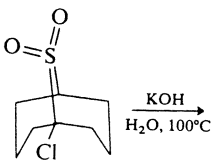
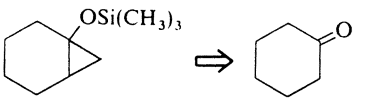


9. Short reaction series can effect formation of the desired material on the left from the starting material on the right. Devise an appropriate reaction sequence.

(a)



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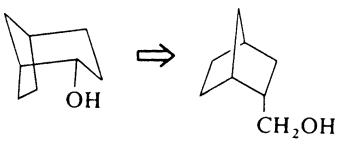
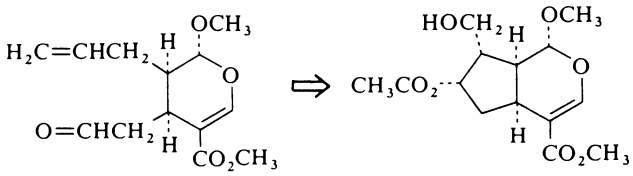
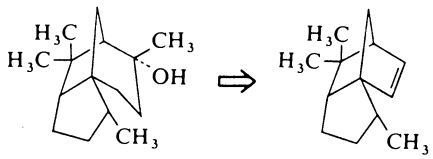


(c)

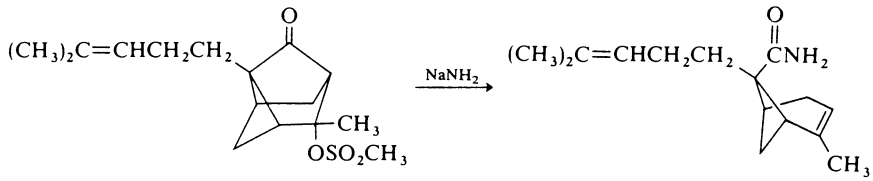


(d)

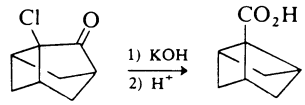


10. Formulate mechanisms for the following reactions:

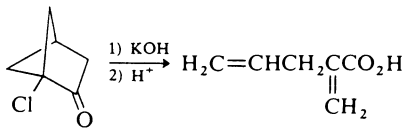
(a)



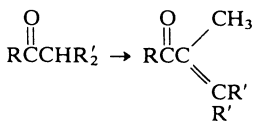
(b)



(c)



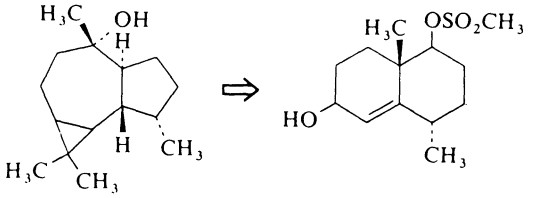
11. A sequence of reactions for converting acyclic and cyclic ketones to α,β-unsaturated ketones with an additional $=CCH_3$ unit has been developed.



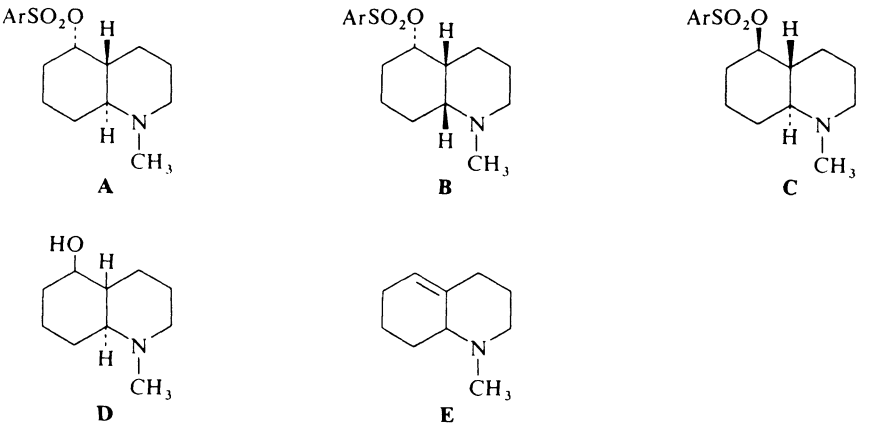
The method utilizes a carbenoid reagent, 1-lithio-1,1-dichloroethane, as a key reagent. The overall sequence involves three steps, one of them before and one of them after the carbenoid reaction. Attempt, by analysis of the bond changes and your knowledge of carbene chemistry, to devise such a reaction sequence.

12. The synthesis of globulol from the octalin derivative shown proceeds in four stages. These include, not necessarily in sequence, addition of a carbene, fragmentation, and an acid-catalyzed cyclization of a cyclodeca-2,7-dienol. The

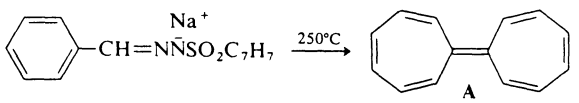
final stage of the process converts a dibromocyclopropane to a dimethylcyclopropane using dimethylcuprate. Working back from globulol, attempt to discover the appropriate sequence of reactions and suggest appropriate reagents for each step.



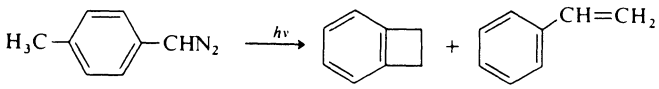
13. The three decahydroquinolines shown below each gives a different product composition on solvolysis. One gives 9-methylamino-*trans*-5-nonenal, one gives 9-methylamino-*cis*-nonenal, and the third gives a mixture of the two quinoline derivatives **D** and **E**. Deduce which compound gives rise to which product. Explain your reasoning.



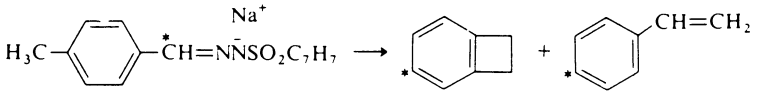
14. Pyrolysis of the sodium salt of benzaldehyde *p*-toluenesulfonylhydrazone gives heptafulvalene **A**:



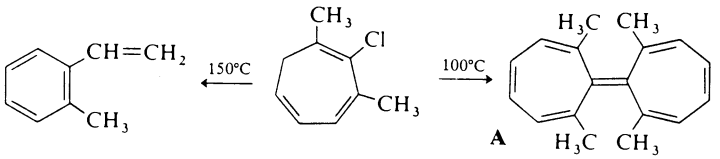
Photolysis of *m*-tolyldiazomethane or *p*-tolyldiazomethane gives product mixtures that include styrene and benzocyclobutene:



The same products are formed by pyrolysis of the *o*-, *m*-, or *p*-methylbenzaldehyde *p*-toluenesulfonylhydrazones. When the *p*-tolualdehyde was labeled at the aldehyde carbon, the label appeared in the product as shown.

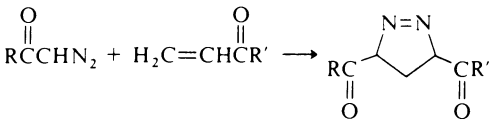


On treatment with potassium *t*-butoxide 2-chloro-1,3-dimethyl-1,3,5-cycloheptatriene gives either tetramethylfulvalene (A) or *o*-methylstyrene, depending on the temperature.

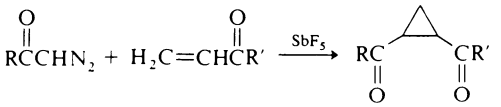


Suggest how these various reactions are related. What intermediate or intermediates could account for the various reactions. Which of these intermediates are consistent with the isotopic labeling results?

15. Normally the dominant reaction between acyldiazo compounds and simple α,β-unsaturated carbonyl compounds is a cycloaddition.



If, however, the reaction is run in the presence of a Lewis acid, particularly antimony pentafluoride, the reaction takes a different course giving a diacyl cyclopropane.



Formulate a mechanism to account for the altered course of the reaction in the presence of SbF_5.

10

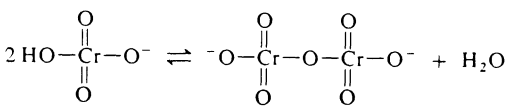
Oxidations

This chapter will be concerned with reactions which transform a functional group to a more highly oxidized derivative. There are a very large number of such processes and the reactions have been chosen for discussion on the basis of their general utility in organic synthesis. As the mechanisms of the reactions are considered, it will become evident that the material in this chapter scans a wider variety of mechanistic patterns than is true for most of the earlier chapters. Because of this variety in mechanistic patterns, the chapter has been organized along the lines of the functional-group transformation that is accomplished. This organization facilitates comparison of the methods available for effecting a given synthetic transformation, but has the less desirable result of scattering the reactions of a given oxidant, such as the permanganate ion, into several sections. In general, oxidants have been grouped into three classes: transition metal derivatives; oxygen, ozone and peroxides, and other oxidizing agents.

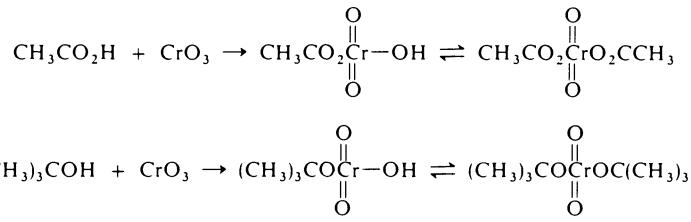
10.1. Oxidation of Alcohols to Aldehydes, Ketones, or Carboxylic Acids

10.1.1. Transition Metal Oxidants

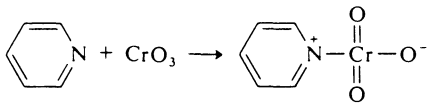
The most widely employed of the oxidants based on transition metals are the Cr(VI) oxidants. The dominant form of Cr(VI) in aqueous solution depends upon concentration and pH. In dilute solution, the monomeric acid chromate ion is present; as concentration increases, however, the dichromate ion dominates. The



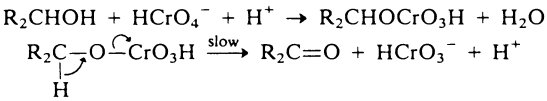
extent of protonation of these ionic species varies with pH. In solutions prepared from CrO_3 and hydroxylic organic solvents, chromium is present in species that



are essentially esters of chromic acid.[1] In pyridine, chromium is present as a complex involving Cr–N bonding:



The oxidation state of Cr in each of these species is (VI), and they are powerful oxidants. The precise reactivity, however, depends on the solvent and the form of Cr present, so that substantial selectivity can be achieved by choice of the particular reagent and conditions. The transformation most often effected with CrO_3-based oxidants is the conversion of alcohols to the corresponding ketone or aldehyde. The mechanism that is believed to be operative in alcohol oxidations is outlined below:

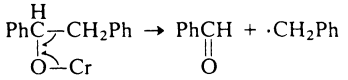


The kinetics of the reaction also indicate a contribution from a variation including an additional proton in the rate-determining transition state. An important piece of evidence pertinent to identification of the rate-determining step is the fact that a large isotope effect is observed when the α-H is replaced by deuterium.[2] The Cr(IV) that is produced in the initial step is not stable, and this species is capable of contributing further to the oxidation. Although other schemes have received consideration and the matter is still a subject of active research, it is believed that a part of the substrate is oxidized via a free-radical intermediate resulting from oxidation by Cr(IV).[3–6] This scheme also includes Cr(V) as a participant in the mechanism.

1. K. B. Wiberg, *Oxidation in Organic Chemistry*, Part A, Academic Press, New York (1965), pp. 69–72.
2. F. H. Westheimer and N. Nicolaides, *J. Am. Chem. Soc.* **71**, 25 (1949).
3. M. Rahman and J. Rocek, *J. Am. Chem. Soc.* **93**, 5462 (1971).
4. P. M. Nave and W. S. Trahanovsky, *J. Am. Chem. Soc.* **92**, 1120 (1970).
5. K. B. Wiberg and S. K. Mukherjee, *J. Am. Chem. Soc.* **96**, 1884 (1974).
6. M. Doyle, R. J. Swedo, and J. Rocek, *J. Am. Chem. Soc.* **95**, 8352 (1973).

$$R_2CHOH + Cr(IV) \rightarrow R_2COH + Cr(III) + H^+$$
$$R_2COH + Cr(VI) \rightarrow R_2C{=}O + Cr(V) + H^+$$
$$R_2CHOH + Cr(V) \rightarrow R_2C{=}O + Cr(III) + 2H^+$$

Because of the participation of this free-radical process, a competing fragmentation is often observed with molecules that can generate a relatively stable radical by homolytic fragmentation. This process can be formulated as involving an alkoxy radical formed by one-electron oxidation. (See Chapter 11, Part A for other examples of this type of bond cleavage.)



A variety of experimental conditions have been used for oxidation of alcohols by Cr(VI) on a synthetic scale. For simple unfunctionalized alcohols the generally preferred method involves addition of an acidic aqueous solution containing chromic acid (known as *Jones' reagent*) to an acetone solution of the alcohol. Oxidation normally occurs quite rapidly, and overoxidation is minimal. Often, the reduced chromium salts precipitate, and the acetone solution can be decanted, thus facilitating workup. Entries 2 and 4 in Scheme 10.1 are examples of this technique.

The complex formed by chromium trioxide and pyridine has been found useful in situations where other functional groups in the molecule, especially carbon–carbon double bonds, might be susceptible to oxidation by Cr(VI),[7] or when the molecule is sensitive to acid. A procedure for utilizing the CrO_3–pyridine complex originated by Collins[8] has become quite widely accepted. The CrO_3–pyridine complex is isolated and dissolved in dichloromethane. With an excess of reagent, oxidation of simple primary and secondary alcohols proceeds to completion in a few minutes, giving aldehydes and ketones, respectively, in high yields. A procedure that avoids isolation of the complex can further simplify the experimental operations.[9] Chromium trioxide is added to pyridine in dichloromethane. Subsequent addition of the alcohol to this solution results in rapid oxidation in high yields. Entries 5–8 in Scheme 10.1 demonstrate the excellent results that have been reported using the CrO_3–pyridine complex in dichloromethane.

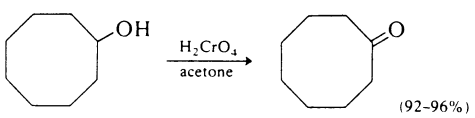
Use of the CrO_3–pyridine reagent seems to circumvent a side reaction leading to esters that can be a competing process in the oxidation of primary alcohols. Esters are formed when aldehyde and unreacted alcohol form a hemiacetal.[10] The

7. G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.* **75**, 422 (1953); W. S. Johnson, W. A. Vredenburgh, and J. E. Pike, *J. Am. Chem. Soc.* **82**, 3409 (1960); W. S. Allen, S. Bernstein, and R. Littell, *J. Am. Chem. Soc.* **76**, 6116 (1954).
8. J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.* 3363 (1968).
9. R. Ratcliffe and R. Rodehorst, *J. Org. Chem.* **35**, 4000 (1970).
10. W. A. Mosher and D. M. Preiss, *J. Am. Chem. Soc.* **75**, 5605 (1953).

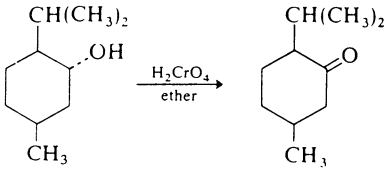
Scheme 10.1. Oxidations

A. Chromic Acid Solutions

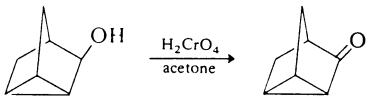
1[a] $CH_3CH_2CH_2OH \xrightarrow[H_2O]{H_2CrO_4} CH_3CH_2CH{=}O$ (45–49%)

2[b] 

(92–96%)

3[c] 

(84%)

4[d] 

(79–88%)

B. Chromium Trioxide–Pyridine

5[e] $CH_3(CH_2)_5CH_2OH \xrightarrow[CH_2Cl_2]{CrO_3\text{-pyridine}} CH_3(CH_2)_5CH{=}O$ (70–84%)

6[f] $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}H(CH_2)_4CH_2OH \xrightarrow[CH_2Cl_2]{CrO_3\text{-pyridine}} CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}H(CH_2)_4CH{=}O$ (69%)

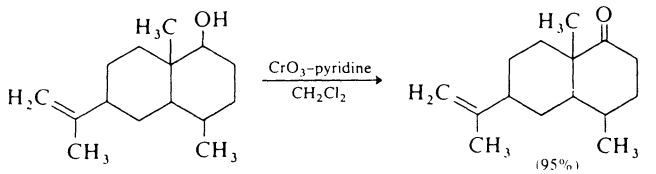
mechanism of the oxidation of the hemiacetal is presumably analogous to that of oxidation of simple alcohols.

$$RCH_2OH + RCH{=}O \rightleftharpoons RCH_2O-\underset{\displaystyle H}{\underset{|}{\overset{\displaystyle R}{\overset{|}{C}}}}-OH \xrightarrow{Cr(VI)} RCH_2O\overset{\displaystyle O}{\overset{\|}{C}}R$$

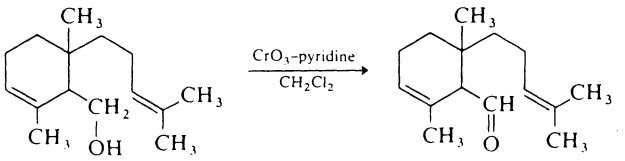
Another very useful Cr(VI) reagent is pyridinium chlorochromate (PCC), which is prepared by dissolving CrO_3 in hydrochloric acid and adding pyridine to obtain a solid reagent having the composition $CrO_3Cl \cdot$ pyridine.[11] This reagent can be used in close to the stoichiometric ratio. Entries 9 and 10 in Scheme 10.1 are examples of the use of this reagent. Reaction of pyridine with CrO_3 in a small amount of water gives pyridinium dichromate, which is also a useful oxidant.[12] As

11. E. J. Corey and J. W. Suggs, *Tetrahedron Lett.* 2647 (1975).
12. E. J. Corey and G. Schmidt, *Tetrahedron Lett.* 399 (1979).

7[g]



8[h]



C. Pyridinium Chlorochromate

9[i] $(CH_3)_2C{=}CHCH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2OH \xrightarrow{PCC} (CH_3)_2C{=}CHCH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH{=}O$ (82%)

10[j] $HOCH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}H_2CH{=}CHCO_2CH_3 \xrightarrow{PCC} O{=}CHCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}H_2CH{=}CHCO_2CH_3$ (83%)

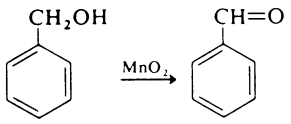
a. C. D. Hurd and R. N. Meinert, *Org. Synth.* **II**, 541 (1943).
b. E. J. Eisenbraun, *Org. Synth.* **IV**, 310 (1973).
c. H. C. Brown, C. P. Garg, and K.-T. Liu, *J. Org. Chem.* **36**, 387 (1971).
d. J. Meinwald, J. Crandall, and W. E. Hymans, *Org. Synth.* **45**, 77 (1965).
e. J. C. Collins and W. W. Hess, *Org. Synth.* **52**, 5 (1972).
f. J. I. DeGraw and J. O. Rodin, *J. Org. Chem.* **36**, 2902 (1971).
g. R. Ratcliffe and R. Rodehorst, *J. Org. Chem.* **35**, 4000 (1970).
h. M. A. Schwartz, J. D. Crowell, and J. H. Musser, *J. Am. Chem. Soc.* **94**, 4361 (1972).
i. E. J. Corey and J. W. Suggs, *Tetrahedron Lett.* 2647 (1975).
j. R. D. Little and G. W. Muller, *J. Am. Chem. Soc.* **103**, 2744 (1981).

a solution in dimethylformamide or a suspension in methylene chloride, this reagent oxidizes secondary alcohols to ketones. Allylic primary alcohols give the corresponding aldehydes. Depending upon the conditions saturated primary alcohols give either the aldehyde or the corresponding carboxylic acid.

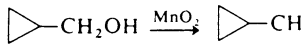
Potassium permanganate has found little application in the oxidation of alcohols to ketones and aldehydes. The reagent is less selective than Cr(VI), and overoxidation is a problem. On the other hand, manganese(IV) dioxide has found appreciable use.[13] This reagent preferentially attacks allylic and benzylic hydroxyl groups, and therefore possesses a useful degree of selectivity. Manganese dioxide is precipitated by reaction of $Mn(II)SO_4$ with $KMnO_4$ and sodium hydroxide. The precise reactivity

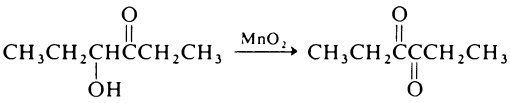
13. D. G. Lee, in *Oxidation*, Vol. 1, R. L. Augustine (ed.), Marcel Dekker, New York (1969), pp. 66–70; A. J. Fatiadi, *Synthesis* 65 (1976).

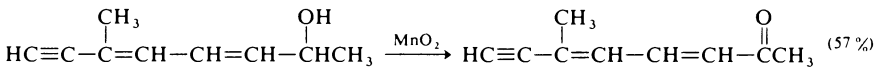
Scheme 10.2. Oxidations of Alcohols with Manganese Dioxide

1[a] 

2[b] $PhCH{=}CHCH_2OH \xrightarrow{MnO_2} PhCH{=}CHCH{=}O$ (70%)

3[c]  (61%)

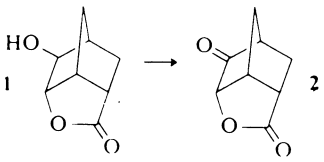
4[d] 

5[e]  (57%)

a. E. F. Pratt and J. F. Van De Castle, *J. Org. Chem.* **26**, 2973 (1961).
b. I. M. Goldman, *J. Org. Chem.* **34**, 1979 (1969).
c. L. Crombie and J. Crossley, *J. Chem. Soc.* 4983 (1963).
d. E. P. Papadopoulos, A. Jarrar, and C. H. Issidorides, *J. Org. Chem.* **31**, 615 (1966).
e. J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.* 1094 (1952).

of MnO_2 depends on its mode of preparation and the extent of drying.[14] Scheme 10.2 illustrates the various classes of alcohols that are most susceptible to MnO_2 oxidation.

Another reagent that has applicability for oxidation of alcohols to ketones is ruthenium tetroxide. For example, the oxidation of **1** to **2** was successfully achieved with this reagent after a number of other methods failed.



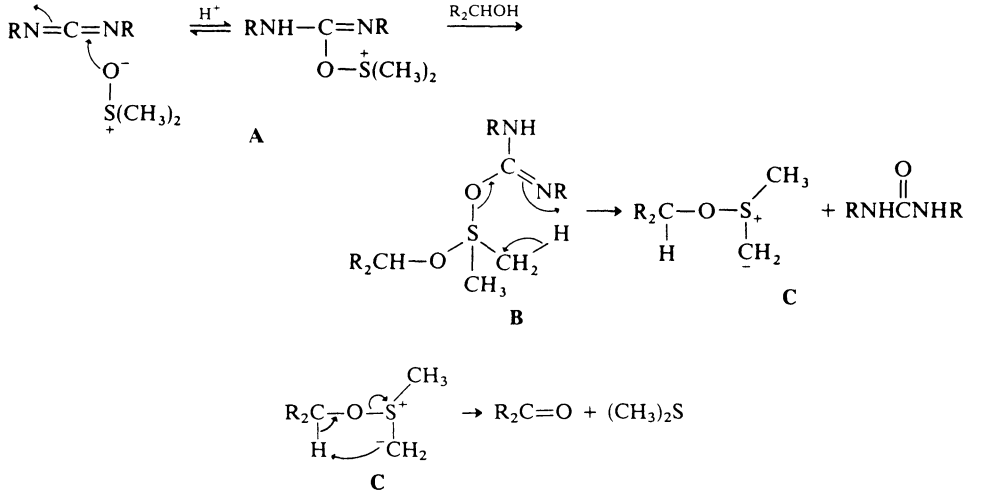
Ref. 15

This is a potent oxidant, however, and it readily attacks carbon–carbon double bonds.[16]

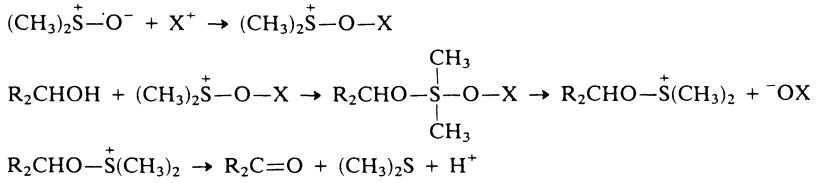
14. J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.* 1094 (1952); I. M. Goldman, *J. Org. Chem.* **34**, 1979 (1969).
15. R. M. Moriarty, H. Gopal, and T. Adams, *Tetrahedron Lett.* 4003 (1970).
16. J. L. Courtney and K. F. Swansborough, *Rev. Pure Appl. Chem.* **22**, 47 (1972); D. G. Lee and M. van den Engh, in *Oxidation*, Part B, W. S. Trahanovsky (ed.), Academic Press, New York (1973), Chap. IV.

10.1.2. Other Oxidants

A very useful group of procedures for oxidation of alcohols to ketones have been developed that involve dimethyl sulfoxide (DMSO) and any one of a number of electrophilic molecules, particularly dicyclohexylcarbodiimide, acetic anhydride, trifluoroacetic anhydride, oxalyl chloride, and sulfur trioxide. The initial work involved the DMSO–dicyclohexylcarbodiimide system.[17] The utility of the method has been greatest in the oxidation of molecules that are highly sensitive to more powerful oxidants and therefore cannot tolerate alternative methods. The mechanism of the oxidation involves formation of intermediate **A** by nucleophilic attack of DMSO on the carbodiimide, followed by reaction of this species with the alcohol. A major part of the driving force for the reaction is derived from the conversion of the carbodiimide to a urea, with formation of an amide carbonyl.[18]

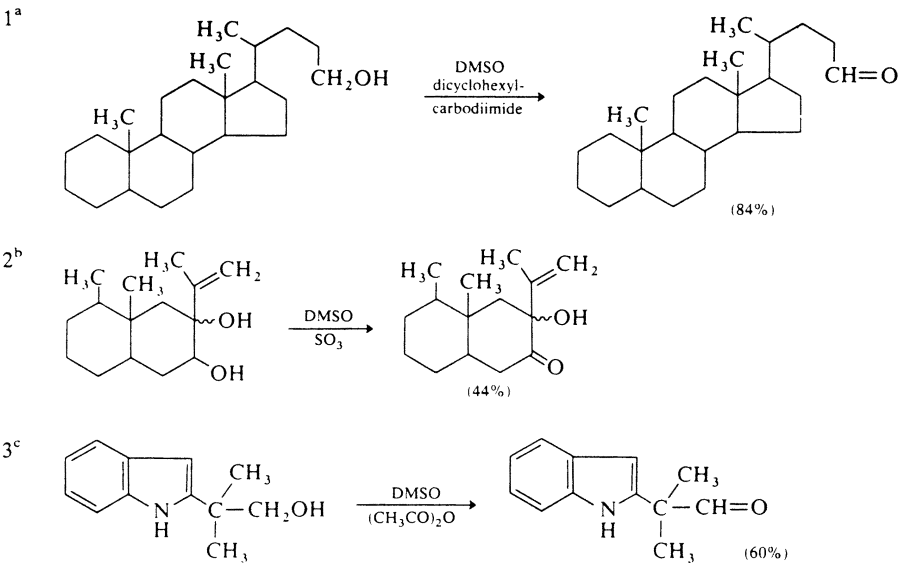


The role of activating DMSO toward the nucleophilic addition step can be accomplished by other electrophilic species. All of these reagents are believed to form a sulfoxonium species by electrophilic attack at the sulfoxide oxygen. The introduction of the alcohol being oxidized as a nucleophile and the departure of the sulfoxide oxygen as part of a leaving group generates an intermediate comparable to **C** in the above mechanism.



17. K. E. Pfitzner and J. G. Moffatt, *J. Am..Chem. Soc.* **87**, 5661, 5670 (1965).
18. J. G. Moffatt, *J. Org. Chem.* **36**, 1909 (1971).

Scheme 10.3. Oxidation of



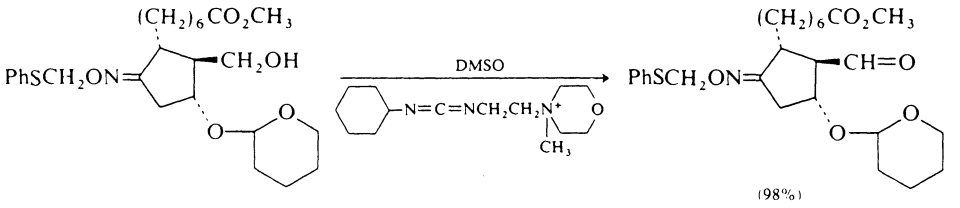
a. J. G. Moffatt, *Org. Synth.* **47**, 25 (1967).
b. J. A. Marshall and G. M. Cohen, *J. Org. Chem.* **36**, 877 (1971).
c. E. Houghton and J. E. Saxton, *J. Chem. Soc. C*, 595 (1969).

Acid anhydrides and chlorides are reactive as the electrophile for activation of dimethyl sulfoxide. Preparatively useful procedures based on acetic anhydride,[19] trifluoroacetic anhydride,[20] and oxalyl chloride[21] have come into general use. The pyridine–SO_3 complex is also useful.[22] Scheme 10.3 gives some representative examples. Entry 4 is an example of the use of a water-soluble carbodiimide as the activating reagent. The modified carbodiimide facilitates product purification by providing for easy removal of the by-product urea formed from the carbodiimide.

Oxidation of alcohols under extremely mild conditions can be achieved by a procedure that is mechanistically related to the DMSO method. Dimethyl sulfide is converted to a sulfonium derivative by reaction with *N*-chlorosuccinimide. This sulfur species reacts readily with alcohols, generating the same kind of alkoxysulfonium salt that is involved in the DMSO procedures. In the presence of mild base, elimination of dimethyl sulfide completes the oxidation.[23] Similarly, reaction of

19. J. D. Albright and L. Goldman, *J. Am. Chem. Soc.* **89**, 2416 (1967).
20. J. Yoshimura, K. Sato, and H. Hashimoto, *Chem. Lett.* 1327 (1977); K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.* **41**, 957 (1976); S. L. Huang, K. Omura, and D. Swern, *J. Org. Chem.* **41**, 3329 (1976).
21. A. J. Mancuso, S.-L. Huang, and D. Swern, *J. Org. Chem.* **43**, 2480 (1978).
22. J. R. Parikh and W. von E. Doering, *J. Am. Chem. Soc.* **89**, 5505 (1967).
23. E. J. Corey and C. U. Kim, *J. Am. Chem. Soc.* **94**, 7586 (1972).

4[d]

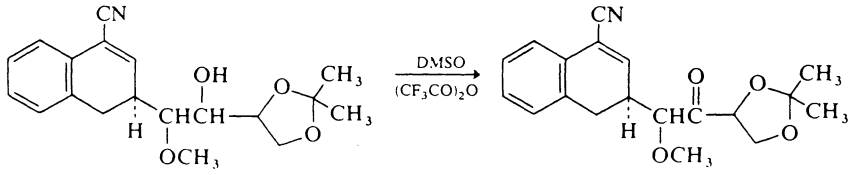


(98%)

5[e] $(CH_3)_2CHCH{=}CHCH{=}CHCH_2OH \xrightarrow[ClCOCOCl]{DMSO} (CH_3)_2CHCH{=}CHCH{=}CHCH{=}O$

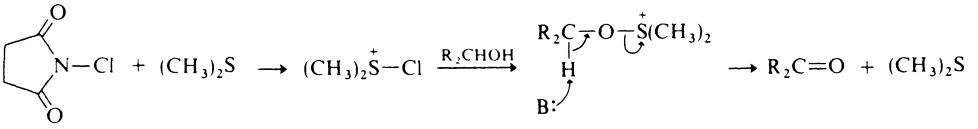
(93%)

6[f]

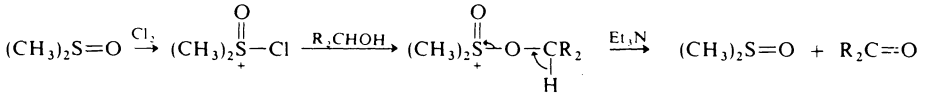


(90%)

d. N. Finch, L. D. Vecchia, J. J. Fitt, R. Stephani, and I. Vlattas, *J. Org. Chem.* **38**, 4412 (1973).
e. W. R. Roush, *J. Am. Chem. Soc.* **102**, 1390 (1980).
f. R. W. Franck and T. V. John, *J. Org. Chem.* **45**, 1170 (1980).



chlorine and DMSO at low temperature gives an adduct that reacts with alcohols, presumably by displacement of chloride from sulfur, to give the ketone and DMSO[24]:



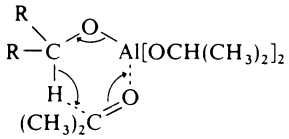
The development of the CrO_3–pyridine complex and the DMSO-based systems has decreased the number of instances in which older oxidation techniques are used. One such method, the *Oppenauer oxidation*,[25] is the reverse of the Meerwein–Pondorff–Verley reduction (Chapter 5). It involves heating the alcohol to be

24. E. J. Corey and C. U. Kim, *Tetrahedron Lett.* 919 (1973).
25. C. Djerassi, *Org. React.* **6**, 207 (1951).

oxidized with an aluminium alkoxide in the presence of a carbonyl compound, which acts as the hydrogen acceptor. The reaction is an equilibrium process and proceeds through a cyclic transition state. It can be driven in the desired direction

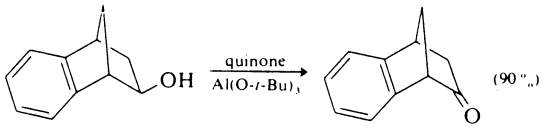
$$R_2CHOH + Al[OCH(CH_3)_2]_3 \rightleftarrows R_2CHOAl[OCH(CH_3)_2]_2 + (CH_3)_2CHOH$$

$$R_2CHOAl[OCH(CH_3)_2]_2 + (CH_3)_2C{=}O \longrightarrow$$



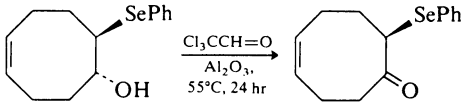
$$\longrightarrow R_2C{=}O + Al[OCH(CH_3)_2]_3$$

by including a carbonyl compound that is a strong hydrogen acceptor in the reaction system. Quinone and fluorenone have been utilized for this purpose. Alternatively, use of an excess of the hydride acceptor will favor complete oxidation of the reactant. Since the reaction conditions are nonacidic, this method can be valuable for substances that would not tolerate acidic conditions or the presence of transition metal oxidants.



Ref. 26

Probably related mechanistically to the Oppenauer oxidations are several techniques for oxidation which involve transfer of hydrogen to trichloroacetaldehyde. These reactions are mediated by alumina and the reaction is carried out by simply mixing the alcohol to be oxidized, the hydrogen acceptor, and alumina in an inert solvent.[27] The reaction is suitable for selective oxidation of secondary alcohols in the presence of primary alcohols (which do not react) and also for the preparation of compounds containing other easily oxidized functional groups such as sulfides or selenides.

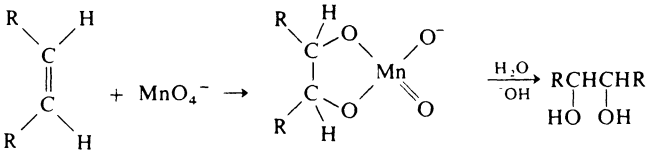


Ref. 28

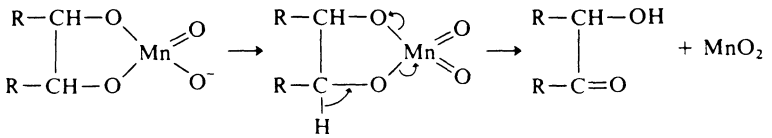
26. P. D. Bartlett and W. P. Giddings, *J. Am. Chem. Soc.* **82**, 1240 (1960).
27. G. H. Posner, *Angew. Chem. Int. Ed. Engl.* **17**, 487 (1978); G. H. Posner, R. B. Perfetti, and A. W. Runquist, *Tetrahedron Lett.* 3499 (1976).
28. G. H. Posner and M. J. Chapdelaine, *Tetrahedron Lett.* 3227 (1977).

10.2.1. Transition Metal Oxidants

The high oxidation states of certain transition metals, particularly the permanganate ion and osmium tetroxide, are effective reagents for addition of oxygen atoms at a double bond. Mild reaction conditions with potassium permanganate can permit relatively high-yield conversion of olefins to glycols. This oxidant is, however, capable of further oxidizing the glycol and cleaving the olefin with formation of carboxylic acids, so that careful control of reaction conditions is essential for efficient oxidation. A cyclic manganese ester is an intermediate in these oxidations. In view of the cyclic nature of this intermediate, it would be expected that glycols would be formed from cyclic alkenes with *cis* stereochemistry, and this is indeed the case. In cases where careful product studies have been carried

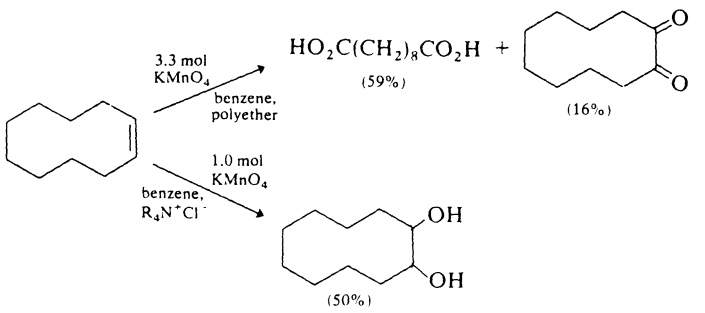


out, it is found that ketols are formed along with glycols. The ratio between the two products is pH dependent, shifting in favor of the glycol at alkaline pH. The ketols are believed to arise by an oxidation of an intermediate cyclic hypermanganate ester.[29] The ketols do not arise from the glycols.

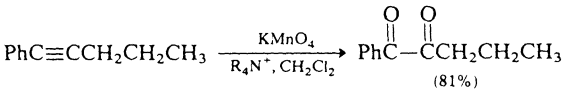


It is also possible to carry out permanganate oxidations in organic solvents by using crown ethers or phase transfer agents to effect solubilization of permanganate salts. Studies using 5-decene and cyclododecene as typical alkenes revealed that mixtures of carboxylic acids, diones, ketols, and diols were obtained, but that the ratio of the various products could be controlled, within limits, by the amount of

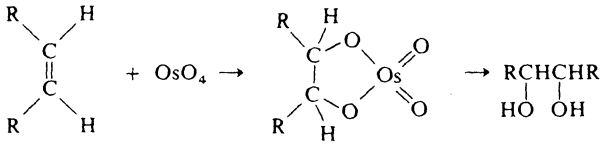
29. S. Wolfe, C. F. Ingold, and R. U. Lemieux, *J. Am. Chem. Soc.* **103**, 938 (1981).



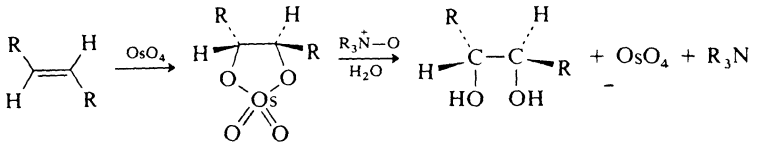
oxidant used.[30] Use of phase transfer catalysts to effect reaction between nonterminal acetylenes and solid potassium permanganate gives diones in 50–80% yield.[32]



Osmium tetroxide is a highly selective oxidant which gives glycols by stereospecific *syn*-addition.[33] The reaction occurs through a cyclic osmate ester. The



reagent is quite expensive and very toxic but these disadvantages have been minimized by development of procedures which require only a catalytic amount of osmium tetroxide. A very useful procedure involves an amine oxide such as morpholine-*N*-oxide as the stoichiometric oxidant.[34] Use of *t*-butyl hydroperoxide[35]



or barium chlorate[36] as the oxidant also gives good yields of diols using a catalytic amount of OsO_4. In all of these procedures the added oxidant reoxidizes the osmium

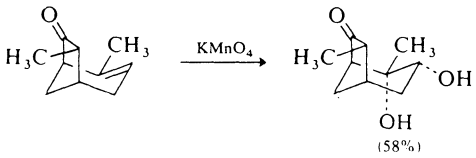
30. D. G. Lee and V. S. Chang, *J. Org. Chem.* **43**, 1532 (1978).
31. W. P. Weber and J. P. Shepherd, *Tetrahedron Lett.* 4907 (1972).
32. D. G. Lee and V. S. Chang, *J. Org. Chem.* **44**, 2726 (1979).
33. M. Schröder, *Chem. Rev.* **80**, 187 (1980).
34. V. Van Rheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett.* 1973 (1976).
35. K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc.* **98**, 1986 (1976); K. Akashi, R. E. Palermo, and K. B. Sharpless, *J. Org. Chem.* **43**, 2063 (1978).
36. L. Plaha, J. Weichet, J. Zvacek, S. Smolik, and B. Kakac, *Collect. Czech. Chem. Commun.* **25**, 237 (1960); A. S. Kende, T. V. Bentley, R. A. Mader, and D. Ridge, *J. Am. Chem. Soc.* **96**, 4332 (1974).

Scheme 10.4. Hydroxylation of Alkenes

A. Potassium Permanganate

1[a] $CH_2{=}CHCH(OC_2H_5)_2 + KMnO_4 \rightarrow HOCH_2CHCH(OC_2H_5)_2$ (67%)

2[b]



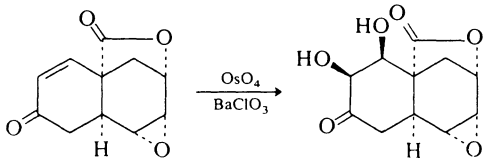
(58%)

B. Osmium Tetroxide

3[c] $CH_3CH_2CH{=}CHC{\equiv}CCH_3 \xrightarrow[OsO_4]{} CH_3CH_2CHCHC{\equiv}CCH_3$ (65%)

4[d] $CH_3CH{=}CHCO_2C_2H_5 \xrightarrow[t\text{-BuOOH}]{OsO_4} CH_3CHCHCO_2C_2H_5$ (72%)

5[e]



(84%)

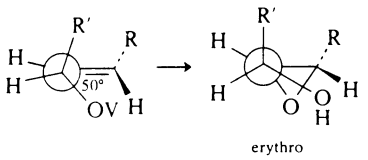
a. E. J. Witzeman, W. L. Evans, H. Haas, and E. F. Schroeder, *Org. Synth.* **II**, 307 (1943).
b. S. D. Larsen and S. A. Monti, *J. Am. Chem. Soc.* **99**, 8015 (1977).
c. E. J. Corey, P. B. Hopkins, S. Kim, S. Yoo, K. P. Nambiar, and J. R. Falck, *J. Am. Chem. Soc.* **101**, 7131 (1979).
d. K. Akashi, R. E. Palermo, and K. B. Sharpless, *J. Org. Chem.* **43**, 2063 (1978).
e. S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, *J. Am. Chem. Soc.* **99**, 6066 (1977).

to OsO_4 during the reaction so that only a small amount is required. Scheme 10.4 includes some specific examples of these catalytic hydroxylations.

In addition to glycols, certain epoxides can be synthesized by oxidation of alkenes with transition metal oxidants. The most useful procedures involve *t*-butyl hydroperoxide as the oxidant and vanadium, molybdenum, or titanium as the metal species. Allylic alcohols react with a catalytic amount of VO(acac) and *t*-butyl hydroperoxide to give epoxides in good yield. The hydroxyl groups of the alcohol plays both an activating and stereodirecting role in this reaction. In cyclic systems, oxidation occurs *cis* to adjacent hydroxyl groups.[37] This effect probably is the result

37. K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.* **95**, 6136 (1973).

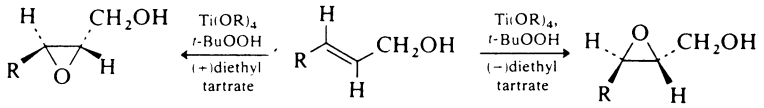
of the catalytic metal species becoming coordinated at the hydroxyl group. In the case of acyclic alkenes a dihedral angle of about 50° between the C–O and double bond is considered optimum in the transition state. The minimization of eclipsing



erythro

interactions of R^1 leads to a preference for the formation *erythro*-epoxy alcohols from relatively unhindered allylic alcohols.

With optically active tartrate esters present in the reaction system, titanium alkoxides catalyze a very stereoselective oxidation of allylic alcohols. This method must depend on specific interactions in the transition state by which the hydroxyl group controls the relationship between the double bond and approaching reagent and the tartrate establishes a chiral environment at the metal atom. The (+) and (−) enantiomers of diethyl tartrate give enantiomeric epoxides, each in >90% yield.[38,39]

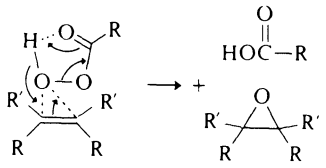


10.2.2. Epoxides from Olefins and Peroxide Reagents

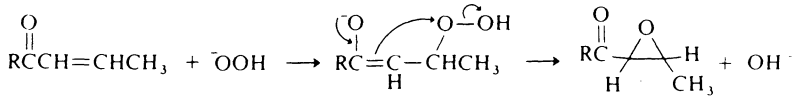
The most widely used method for conversion of olefins to epoxides is reaction with any of several peroxycarboxylic acids.[40] *m*-Chloroperoxybenzoic acid, which is commercially available or readily prepared,[41] is a particularly convenient laboratory reagent. Peroxyacetic acid, peroxybenzoic acid, peroxytrifluoroacetic acid, and others have also been used frequently.

It has been demonstrated that ionic intermediates are not involved in the epoxidation process. The reaction rates are not directly related to solvent polarity.[42] *Syn*-addition with retention of the stereochemistry of the olefin substituents is consistently observed. The reaction is therefore believed to be a concerted process. A representation of the transition state for the reaction is illustrated below:

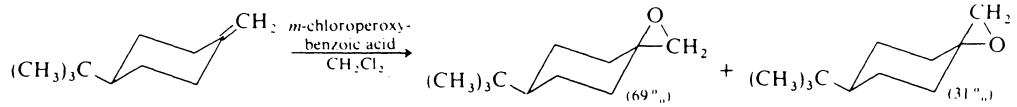
38. B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *J. Am. Chem. Soc.* **103**, 464 (1981).
39. T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.* **102**, 5974 (1980).
40. D. Swern, *Organic Peroxides*, Vol. II, Wiley-Interscience, New York (1971), pp. 355–533; B. Plesnicar, in *Oxidation in Organic Chemistry*, Part C, W. Trahanovsky (ed.), Academic Press, New York (1978), pp. 211–253.
41. R. N. McDonald, R. N. Steppel, and J. E. Dorsey, *Org. Synth.* **50**, 15 (1970).
42. N. N. Schwartz and J. N. Blumbergs, *J. Org. Chem.* **29**, 1976 (1964).



The salient structure–reactivity relationships that have been established include the fact that olefin reactivity is increased by electron-donating alkyl substituents and that peroxyacids with electron-attracting substituents are more reactive than alkyl peroxyacids. This order of reactivity demonstrates that the peroxyacids act as electrophilic species in the oxidation. The transition state cannot be highly polar, however, as the reaction shows fairly low sensitivity to substituent effects. The ρ value for oxidation of *trans*-stilbene by a series of substituted peroxybenzoic acids is about -0.8.[43] Very low reactivity is encountered with olefins conjugated with carbonyl or other strongly electron-attracting substituents, and more strongly oxidizing peroxyacids, such as trifluoroperoxyacetic acid, are required for successful oxidation.[44] Such compounds are also epoxidized by alkaline solutions of hydrogen peroxide or *t*-butyl hydroperoxide. A quite different mechanism, initiated by conjugate nucleophilic addition by the hydroperoxide anion, operates in this case.[45]

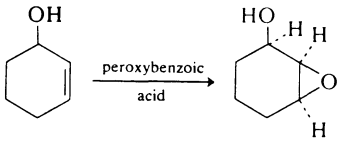


The stereochemistry of epoxidation with peroxycarboxylic acids has been well studied. Attack and addition of oxygen occurs preferentially from the less hindered side of the molecule. Norbornene, for example, gives a 96:4 *exo*:*endo* ratio.[46] In molecules where two potential modes of approach are not greatly different, a mixture of products is to be expected. For example, unhindered double bonds exocyclic to six-membered rings yield the epoxides resulting from both the equatorial and axial directions of attack[47]:



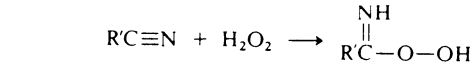
Exceptions to the preference for addition from the less hindered side are noted when polar substituents, particularly hydroxyl groups, are present in the molecule. Hydroxyl groups apparently complex with the attacking reagent, so that the addition occurs from the side of the molecule occupied by the polar substituent.[48] This is a

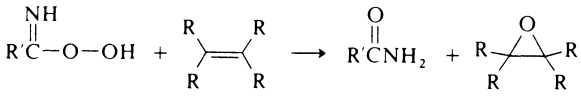
43. B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.* 1525 (1955).
44. W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.* **77**, 89 (1955).
45. C. A. Bunton and G. J. Minkoff, *J. Chem. Soc.* 665 (1949).
46. H. Kwart and T. Takeshita, *J. Org. Chem.* **28**, 670 (1963).
47. R. G. Carlson and N. S. Behn, *J. Org. Chem.* **32**, 1363 (1967).
48. H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.* 1958 (1957).



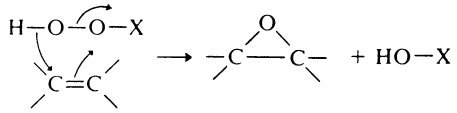
strong directive effect and can usually be relied on for stereochemical control even when steric effects are opposed. Several examples of epoxidation reactions are given in Scheme 10.5. Entries 4 and 5 illustrate the hydroxyl directing effect.

A process that is effective for epoxidation that completely avoids acidic reaction conditions involves reaction of an alkene, a nitrile, and hydrogen peroxide.[49] The nitrile and hydrogen peroxide react, forming a peroxyimidic acid which epoxidizes alkenes, presumably by a mechanism similar to that proposed for peroxyacids. An important contribution to the reactivity of the peroxyimidic acids comes from the formation of the stable amide carbonyl group.

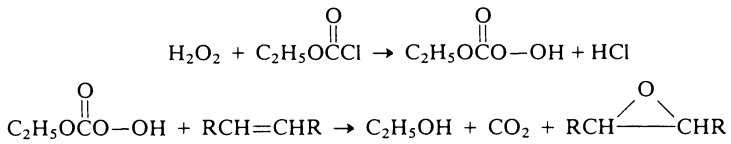




A variety of other reagents have been examined with the objective of activating H_2O_2 to become a good epoxidizing agent. In principal, any species which can convert one of the hydroxyl groups in hydrogen peroxide to a good leaving group might function as an epoxidizing reagent. In practice, promising results have been



obtained for several systems. Fair to good yields of epoxides are obtained when a two-phase system consisting of alkene and ethyl chloroformate is stirred with a buffered basic aqueous solution of hydrogen peroxide. The active epoxidant is assumed to be *O*-ethylperoxycarbonic acid.[50] Similarly, the adduct of hydrogen



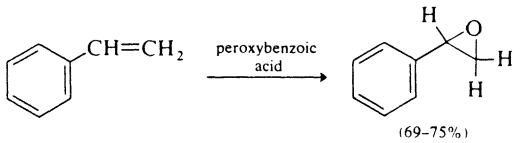
peroxide and hexafluoroacetone is an active epoxidizing agent.[51] Although neither

49. G. B. Payne, *Tetrahedron* **18**, 763 (1962).
50. R. D. Bach, M. W. Klein, R. A. Ryntz, and J. W. Holubka, *J. Org. Chem.* **44**, 2569 (1979).
51. R. P. Heggs and B. Ganem, *J. Am. Chem. Soc.* **101**, 2484 (1979).

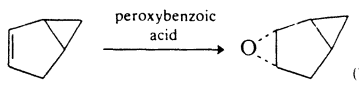
Scheme 10.5. Synthesis of Epoxides from Alkenes

A. Oxidation of Alkenes with Peroxyacids

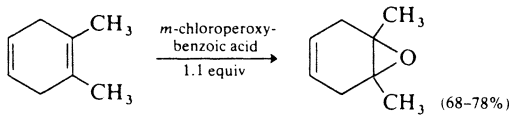
1[a]



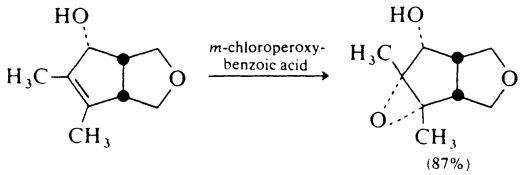
2[b]



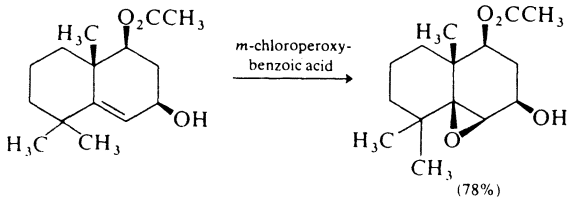
3[c]



4[d]

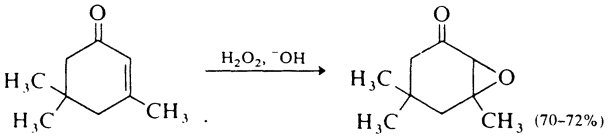


5[e]

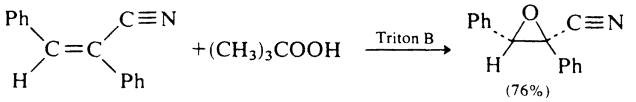


B. Epoxidation of Electrophilic Alkenes

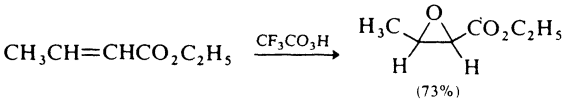
6[f]



7[g]

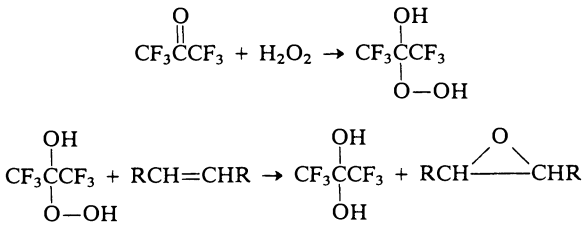


8[h]



a. H. Hibbert and P. Burt, *Org. Synth.* **I**, 481 (1932).
b. E. J. Corey and R. L. Dawson, *J. Am. Chem. Soc.* **85**, 1782 (1963).
c. L. A. Paquette and J. H. Barrett, *Org. Synth.* **49**, 62 (1969).
d. R. M. Scarborough, Jr., B. H. Toder, and A. B. Smith, III, *J. Am. Chem. Soc.* **102**, 3904 (1980).
e. M. Miyashita and A. Yoshikoshi, *J. Am. Chem. Soc.* **96**, 1917 (1974).
f. R. L. Wasson and H. O. House, *Org. Synth.* **IV**, 552 (1963).
g. G. B. Payne and P. H. Williams, *J. Org. Chem.* **26**, 651 (1961).
h. W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.* **77**, 89 (1955).

of these reagents, nor similar combinations, are as generally useful as the more

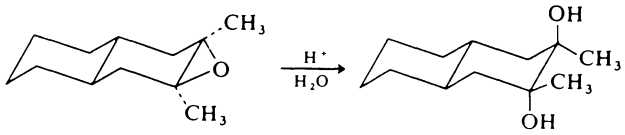


accessible peroxycarboxylic acids, they do serve to illustrate the point that epoxidizing activity is not unique to the "peracids."

10.2.3. Subsequent Transformations of Epoxides

Epoxides are useful synthetic intermediates and the conversion of an alkene to an epoxide is often a part of a more extensive molecular transformation. In many instances the molecule remains at the oxidation level of the epoxide, but advantage is taken of the high reactivity of the epoxide ring to attain new functionality. These two- or three-step operations can accomplish a specific oxidative transformation of the alkene which would be impossible or more difficult to accomplish by a single-step oxidation. We will consider some of these transformations at this point. Scheme 10.6 provides a preview of the type of reactivity to be discussed.

Epoxidation may be preliminary to solvolytic or nucleophilic ring opening in synthetic sequences. In acidic aqueous media, epoxides are opened to give diols by an *anti* addition process. In cyclic systems, ring opening occurs to give the diaxial diol. Base-catalyzed epoxide ring openings, in which the nucleophile provides the



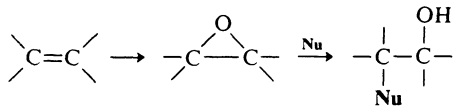
Ref. 52

driving force for ring opening, usually involve breaking the bond to the less substituted carbon, since this is the position most open to nucleophilic attack.[53] The situation in acid-catalyzed reactions is more complex. The bonding of a proton to the oxygen weakens the C–O bond, facilitating its rupture by weak nucleophiles. If the C–O bond is largely intact at the transition state, the nucleophile will become attached to the less substituted position for the same steric reasons that were cited in the case of nucleophilic ring opening. If, on the other hand, C–O rupture is nearly complete when the transition state is reached, the opposite orientation will

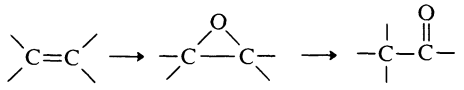
52. B. Rickborn and D. K. Murphy, *J. Org. Chem.* **34**, 3209 (1969).
53. R. E. Parker and N. S. Isaacs, *Chem. Rev.* **59**, 737 (1959).

Scheme 10.6. Multistep Synthetic Transformations via Epoxides

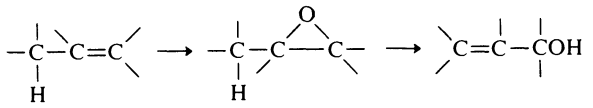
A. Epoxidation Followed by Nucleophilic Ring Opening



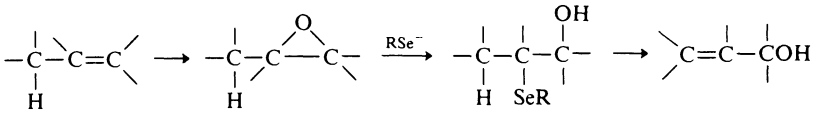
B. Epoxidation Followed by Rearrangement to a Carbonyl Compound



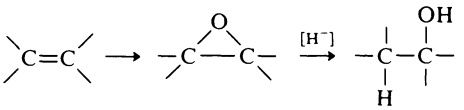
C. Epoxidation Followed by Ring Opening to an Allyl Alcohol



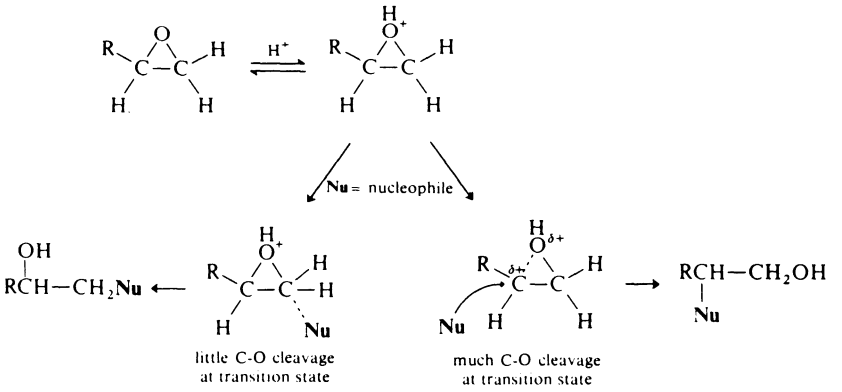
D. Epoxidation Followed by Ring Opening and Elimination



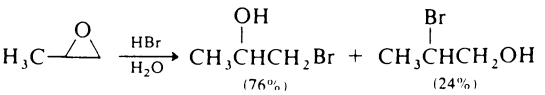
E. Epoxidation Followed by Reductive Ring Opening



be observed because of the greater ability of the more substituted carbon to bear the developing positive charge. When simple aliphatic epoxides such as propylene

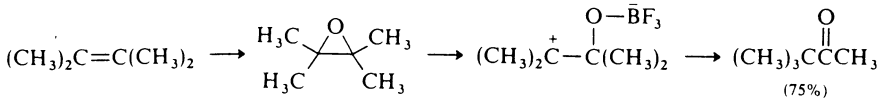


oxide react with hydrogen halides, the dominant mode of reaction introduces halide at the less substituted primary carbon.[54] Substituents that would further stabilize a carbonium ion intermediate lead to reversal of the mode of addition.[55] Some examples of both acid-catalyzed and nucleophilic ring opening are shown in Scheme 10.7.

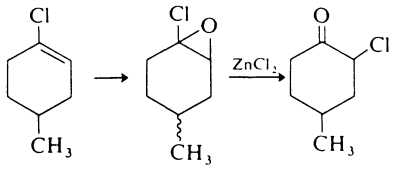


Alumina has been found to be a useful catalyst for nucleophilic ring opening of epoxides by amines, alcohols, carboxylic acids, and thiols.[56] These reactions are believed to be concerted processes in which both the alumina and nucleophile participate with the alumina acting as a Lewis acid. In unsymmetrical epoxides, the reactions show a modest (1:2–1:10) selectivity for attack by the nucleophile at the less hindered carbon of the epoxide.

Epoxides can be isomerized to carbonyl compounds by Lewis acids.[57] Boron trifluoride has been used most frequently. Carbonium ions appear to be involved, and the structure and stereochemistry of the product are determined by the factors governing the substituent migration that follows carbonium ion formation. Clean, high-yield reactions can be expected only where structural or conformational factors promote a very selective rearrangement. Lithium perchlorate also catalyzes ring opening and rearrangement to carbonyl compounds via carbonium ions.[58] Olefins can be oxidized directly to carbonyl compounds by using a reaction medium containing both peroxytrifluoroacetic acid and boron trifluoride.[59] Epoxides are presumably intermediates. High yields of a single product are anticipated only when the olefin is highly symmetrical, as in the case of 2,3-dimethyl-2-butene.



Double bonds having oxygen and halogen substituents are susceptible to epoxidation, and the reactive epoxides that are thereby generated serve as intermediates in some useful synthetic transformations. Vinyl chlorides furnish haloepoxides, which can rearrange to α-haloketones:



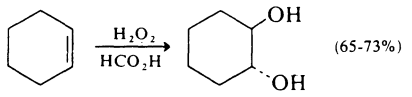
Ref. 60

54. C. A. Stewart and C. A. VanderWerf, *J. Am. Chem. Soc.* **76**, 1259 (1954).
55. S. Winstein and L. L. Ingraham, *J. Am. Chem. Soc.* **74**, 1160 (1952).
56. G. H. Posner and D. Z. Rogers, *J. Am. Chem. Soc.* **99**, 8208 (1977).
57. J. N. Coxon, M. P. Hartshorn, and W. J. Rae, *Tetrahedron* **26**, 1091 (1970).
58. B. Rickborn and R. M. Gerkin, *J. Am. Chem. Soc.* **93**, 1693 (1971).
59. H. Hart and L. R. Lerner, *J. Org. Chem.* **32**, 2669 (1967).
60. R. N. McDonald and T. E. Tabor, *J. Am. Chem. Soc.* **89**, 6573 (1967).

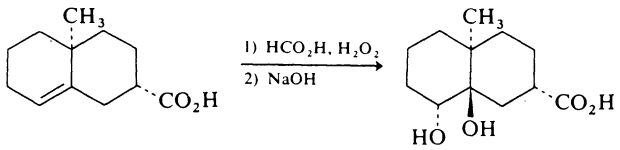
Scheme 10.7. Nucleophilic and Solvolytic Ring Opening of Epoxides

A. Oxidation with Solvolysis of the Intermediate Epoxide

1[a]

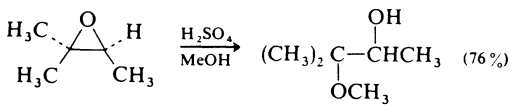


2[b]

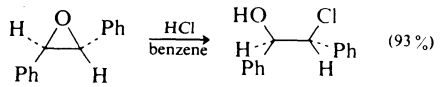


B. Acid-Catalyzed Solvolytic Ring Opening

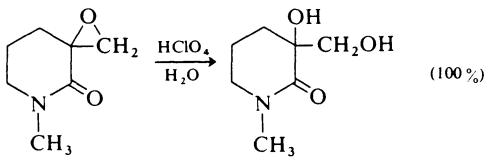
3[c]



4[d]

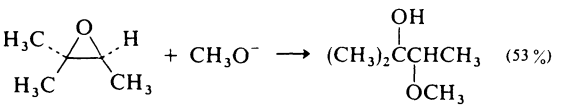


5[e]

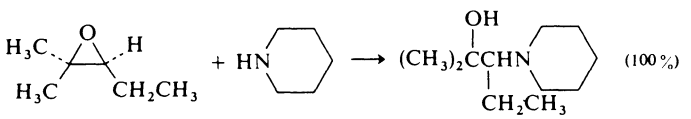


C. Nucleophilic Ring-Opening Reactions

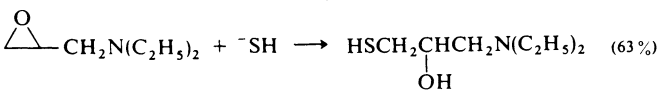
6[c]



7[f]

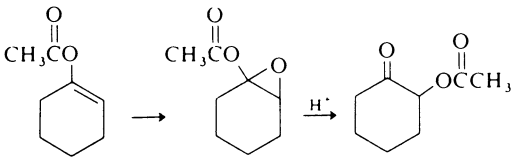


8[g]

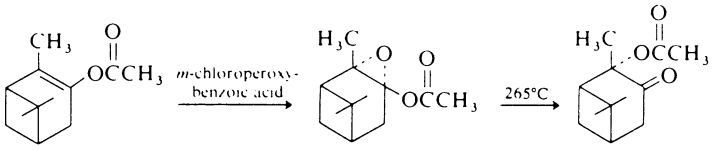


a. A. Roebuck and H. Adkins, *Org. Synth.* **III**, 217 (1955).
b. T. R. Kelly, *J. Org. Chem.* **37**, 3393 (1972).
c. S. Winstein and L. L. Ingrahm, *J. Am. Chem. Soc.* **74**, 1160 (1952).
d. G. Berti, F. Bottari, P. L. Ferrarini, and B. Macchia, *J. Org. Chem.* **30**, 4091 (1965).
e. M. L. Rueppel and H. Rapoport, *J. Am. Chem. Soc.* **94**, 3877 (1972).
f. T. Colclough, J. I. Cunneen, and C. G. Moore, *Tetrahedron* **15**, 187 (1961).
g. D. M. Burness and H. O. Bayer, *J. Org. Chem.* **28**, 2283 (1963).

Enol acetates form epoxides which can rearrange to α-acetoxy ketones:

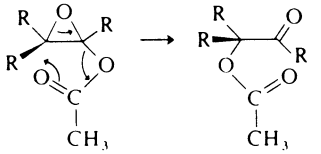


Ref. 61

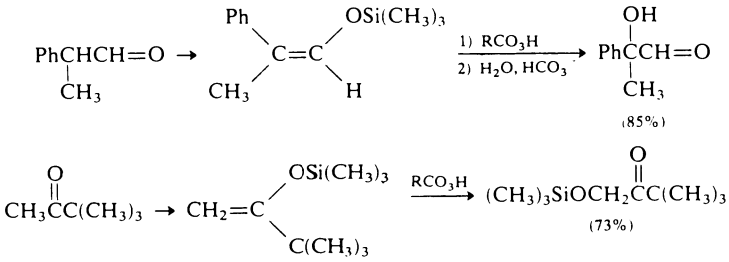


Ref. 62

The stereochemistry of the rearrangement of the acetoxy epoxides involves inversion at the carbon to which the acetoxy group migrates.[63] The reaction probably proceeds through a cyclic transition state.



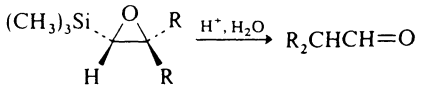
A more synthetically useful version of this reaction involves epoxidation of enol trimethylsilyl ethers of ketones. The methods for synthesis of these compounds were discussed in Section 1.2. Epoxidation of the silyl enol ethers followed by aqueous workup gives α-hydroxy ketones and α-hydroxy aldehydes.[64] The oxidation



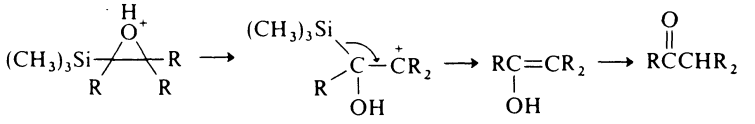
of silyl enol ethers with the osmium tetroxide–amine oxide combination also leads to α-hydroxy ketones in generally good yields.[65]

61. K. L. Williamson, J. I. Coburn, and M. F. Herr, *J. Org. Chem.* **32**, 3934 (1967).
62. R. G. Carlson and J. K. Pierce, *J. Org. Chem.* **36**, 2319 (1971).
63. K. L. Williamson and W. S. Johnson, *J. Org. Chem.* **26**, 4563 (1961).
64. A. Hassner, R. H. Reuss, and H. W. Pinnick, *J. Org. Chem.* **40**, 3427 (1975).
65. J. P. McCormick, W. Tomasik, and M. W. Johnson, *Tetrahedron Lett.* 607 (1981).

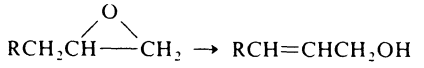
Epoxides derived from vinylsilanes are converted by mildly acidic conditions into ketones or aldehydes.[66] The ring opening is facilitated by the stabilizing effect



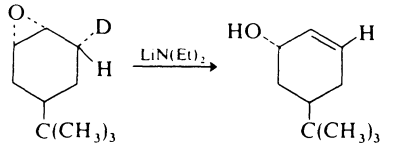
that silicon has on a positive charge in the β-position. The reaction proceeds through the enol of the carbonyl compound. This facile transformation permits vinylsilanes to serve as masked carbonyl groups in certain multistep transformations.[67]



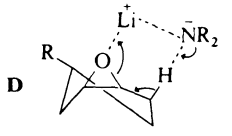
Base-catalyzed ring opening of epoxides constitutes a route to allylic alcohols:



Strongly basic reagents, such as the lithium salt of dialkylamines, are required to promote the reaction, which probably involves concerted proton abstraction and ring opening. The stereochemistry of the ring opening has been investigated by deuterium labeling. The proton *cis* to the epoxide ring is selectively removed.[68] A



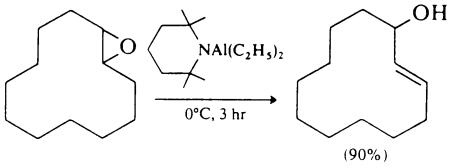
transition state geometry that could account for this stereochemistry is shown as **D**. Such an arrangement could be favored by ion pairing, which requires the close



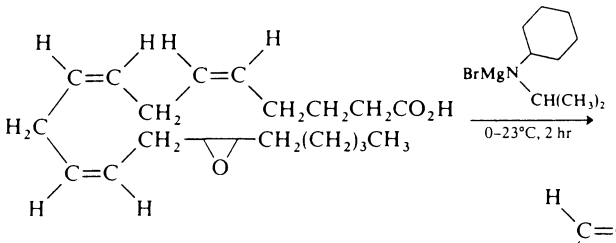
association of the amide anion and a lithium cation. If lithium is also coordinated with the epoxide oxygen, a *syn* elimination would result. Among the other reagents

66. G. Stork and E. Colvin, *J. Am. Chem. Soc.* **93**, 2080 (1971).
67. G. Stork and M. E. Jung, *J. Am. Chem. Soc.* **96**, 3682 (1974).
68. R. P. Thummel and B. Rickborn, *J. Am. Chem. Soc.* **92**, 2064 (1970).

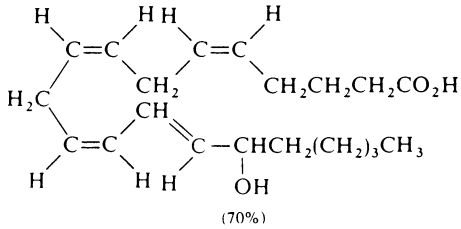
which effect this transformation are diethylaluminum 2,2,6,6-tetramethylpiperidide[69] and magnesium *N*-cyclohexyl-2-propylamide.[70] These latter reagents



Ref. 69

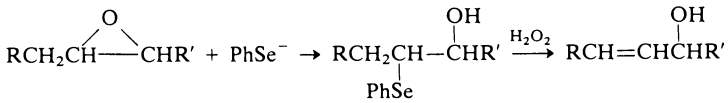


Ref. 70



are appropriate for very sensitive molecules. Their efficacy is presumably due to the strong Lewis acid effect of the aluminum and magnesium ions in these reagents. The highly hindered nature of the amides minimizes competition from nucleophilic ring opening.

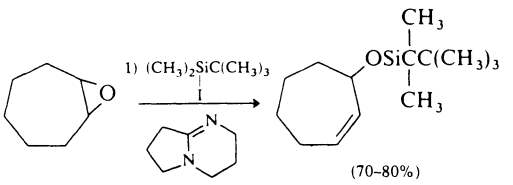
Allylic alcohols can also be obtained from epoxides by ring opening with a selenide anion followed by elimination via the selenoxide as discussed in Section 7.6.3.



The elimination occurs regiospecifically away from the hydroxyl group and the reaction occurs under mild conditions.[71]

Epoxides can also be converted to allylic alcohols using electrophilic reagents. The treatment of epoxides with trisubstituted silyl iodides such as dimethyl-*t*-butylsilyl iodide and an organic base give the silyl ethers of the allylic alcohols.[72]

69. A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.* **96**, 6513 (1974).
70. E. J. Corey, A. Marfat, J. R. Falck, and J. O. Albright, *J. Am. Chem. Soc.* **102**, 1433 (1980).
71. K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.* **95**, 2697 (1973).
72. M. R. Detty, *J. Org. Chem.* **45**, 924 (1980); M. R. Detty and M. D. Seidler, *J. Org. Chem.* **46**, 1283 (1981).



In most instances, iodohydrins are probably formed as intermediates which then undergo elimination of HI.

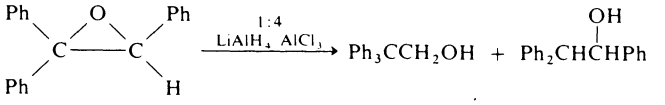
Each of these procedures for epoxidation and ring opening is the equivalent of the oxidation of an alkene with migration of the double bond.

$$R_2CHCH{=}CHR' \rightarrow R_2C{=}CH{-}\underset{\displaystyle OH}{\underset{|}{C}}HR'$$

In Section 10.2.4 alternative means of effecting this transformation will be described.

Epoxides can be reduced to alcohols. Lithium aluminum hydride is a nucleophilic reducing agent and the hydride is therefore added at the less substituted carbon atom. Lithium triethylborohydride is more reactive than $LiAlH_4$ and is superior for epoxides that are resistant to reduction.[73] Reduction by metals, particularly lithium in ethylenediamine,[74] also gives good yields.

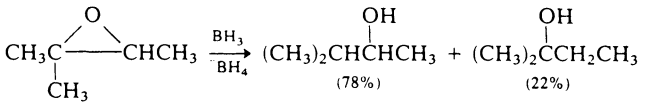
A good deal of work has been done on the reduction of epoxides with species generated from reaction of aluminum chloride and lithium aluminum hydride.[75] The active reagents in these reactions are alane (AlH_3) and chloroalanes. These species have considerable Lewis acid character, and hydride is often added at the more substituted carbon of the epoxide. In some cases, migration of substituents occurs, presumably via carbonium ions generated by electrophilic opening of the epoxide rings.



Diborane in tetrahydrofuran reduces epoxides, but the yields are low, and other products are formed by pathways that result from the electrophilic character of diborane.[76] Diborane reduction occurs in better yield in the presence of BH_4^-, but the electrophilic role played by diborane is still evident because the

73. S. Krishnamurthy, R. M. Schubert, and H. C. Brown, *J. Am. Chem. Soc.* **95**, 8486 (1973).
74. H. C. Brown, S. Ikegami, and J. H. Kawakami, *J. Org. Chem.* **35**, 3243 (1970).
75a. M. N. Rerick and E. L. Eliel, *J. Am. Chem. Soc.* **84**, 2356 (1962).
b. E. C. Ashby and J. Prather, *J. Am. Chem. Soc.* **88**, 729 (1966).
c. P. T. Lansbury, D. J. Scharf, and V. A. Pattison, *J. Org. Chem.* **32**, 1748 (1967).
d. B. Rickborn and W. E. Lamke, II, *J. Org. Chem.* **32**, 537 (1967).
e. D. K. Murphy, R. L. Alumbaugh, and B. Rickborn, *J. Am. Chem. Soc.* **91**, 2649 (1969).
76. D. J. Pasto, C. C. Cumbo, and J. Hickman, *J. Am. Chem. Soc.* **88**, 2201 (1966).

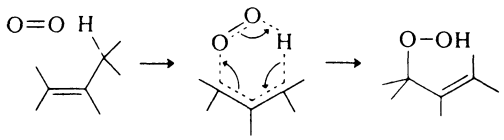
dominant product is that resulting from addition of hydride at the more substituted carbon.[77]



The overall transformation of alkenes to alcohols which is accomplished by epoxidation and reduction corresponds to alkene hydration. The hydration methods discussed in Chapter 4, therefore, constitute alternatives for this overall transformation.

10.2.4. Reactions of Alkenes with Singlet Oxygen

Also among the oxidative reactions that add oxygen at a carbon–carbon double bond is the reaction with singlet oxygen. For most alkenes this reaction proceeds with the specific removal of an allylic hydrogen so that the initial product is an allylic hydroperoxide. This result, along with other detailed mechanistic studies,



points to a concerted ene-type reaction mechanism.[78] Singlet oxygen is usually generated from oxygen by dye-sensitized photochemical excitation, although, as shown in Scheme 10.8, there are some alternative methods.

The excited oxygen molecule will decay to the ground state triplet if it does not encounter a suitable alkene and react chemically. The rate of this decay process has been shown to depend strongly on the identity of the solvent.[79] Measured lifetimes range from roughly 700 μsec in carbon tetrachloride to 2 μsec in water. It is evident that the solvent can then have a pronounced effect on the efficiency of oxidation; the longer the excited state lifetime, the more likely it is that a productive encounter with an alkene will occur.

The reactivity order of alkenes is that expected for attack by an electrophillic reagent. Reactivity increases with the number of alkyl substituents on the alkene.[80,81] Terminal alkenes are relatively inert and are usually not converted to product in significant amount. The reaction is also prevented when the double bond is severely sterically hindered.[82] Steric effects govern the direction of approach of

77. H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc.* **90**, 2686 (1968).
78. L. M. Stephenson, M. J. Grdina, and M. Orfanopoulos, *Acc. Chem. Res.* **13**, 419 (1980).
79. P. B. Merkel and D. R. Kearns, *J. Am. Chem. Soc.* **94**, 1029, 7244 (1972).
80. K. R. Kopecky and H. J. Reich, *Can. J. Chem.* **43**, 2265 (1965).
81. C. S. Foote and R. W. Denny, *J. Am. Chem. Soc.* **93**, 5162 (1971).
82. A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.* **83**, 1498 (1961).

Scheme 10.8. Generation of Singlet Oxygen

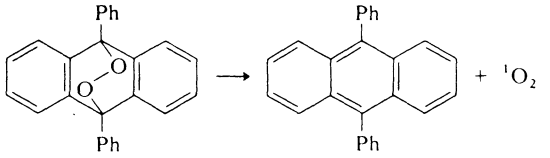
1[a] Photosensitizer + $h\nu$ → ^{1}[Photosensitizer]*

^{1}[Photosensitizer]* → ^{3}[Photosensitizer]*

^{3}[Photosensitizer]* + $^3O_2$ → $^1O_2$ + Photosensitizer

2[b] $H_2O_2 + {}^-OCl \rightarrow {}^1O_2 + H_2O + Cl^-$

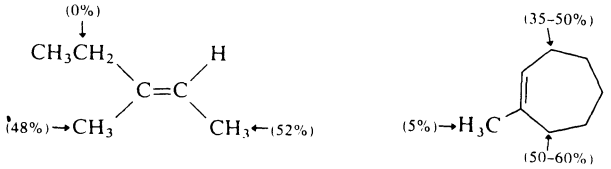
3[c] $(RO)_3P + O_3 \rightarrow (RO)_3P(O_2) \rightarrow (RO)_3P{=}O + {}^1O_2$

4[d] 

a. C. S. Foote and S. Wexler, *J. Am. Chem. Soc.* **86**, 3880 (1964).
b. C. S. Foote and S. Wexler, *J. Am. Chem. Soc.* **86**, 3879 (1964).
c. R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.* **90**, 537 (1964).
d. H. H. Wasserman, J. R. Scheffer, and J. L. Cooper, *J. Am. Chem. Soc.* **94**, 4991 (1972).

the oxygen, and the dominant mode of attack of the oxygen is from the less hindered side of the molecule. Alkenes, such as norbornene, that cannot accommodate the concerted reaction for stereoelectronic reasons are unreactive toward singlet oxygen.[83]

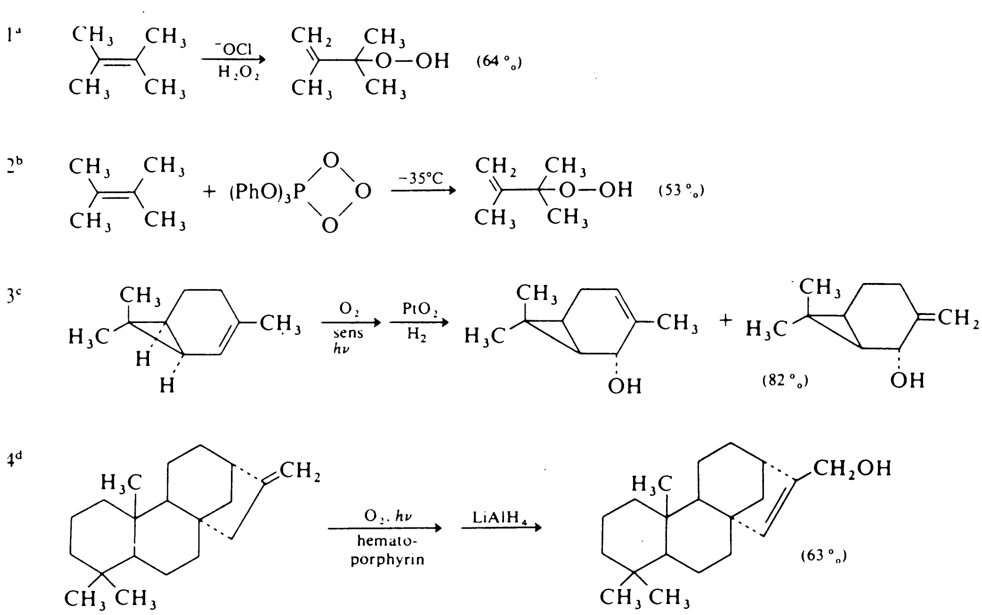
Many alkenes present several different allylic hydrogens and in this type of situation it is important to be able to predict the degree of selectivity. A useful generalization of this aspect is that *there is a preference for abstraction of hydrogen from the more congested side of the double bond.*[84] Exactly how this selectivity relates to the details of the reaction mechanism remains to be clarified.



The allyl hydroperoxides generated by singlet oxygen oxidation are normally reduced to the corresponding allyl alcohol. The net synthetic transformation is then

83. F. A. Litt and A. Nickon, *Oxidation of Organic Compounds—III*, Advances in Chemistry Series, No. 77, American Chemical Society, Washington, D.C. (1968), pp. 118–132.
84. M. Orfanopoulos, M. B. Grdina, and L. M. Stephenson, *J. Am. Chem. Soc.* **101**, 275 (1979); K. H. Schulte-Elte, B. L. Muller and V. Rautenstrauch, *Helv. Chim. Acta.* **61**, 2777 (1978); K. H. Schulte-Elte and V. Rautenstrauch, *J. Am. Chem. Soc.* **102**, 1738 (1980).

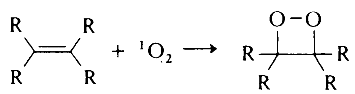
Scheme 10.9. Oxidation of Alkenes with Singlet Oxygen



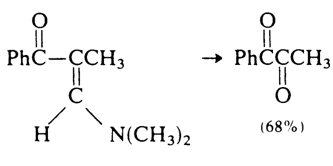
a. C. S. Foote, S. Wexler, W. Ando, and R. Higgins, *J. Am. Chem. Soc.* **90**, 975 (1968).
b. R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.* **91**, 5358 (1968).
c. K. Gollnick and G. Schade, *Tetrahedron Lett.* 2335 (1966).
d. R. A. Bell, R. E. Ireland, and L. N. Mander, *J. Org. Chem.* **31**, 2536 (1966).

formation of an allylic alcohol with a transposition of the double bond. Scheme 10.9 gives some examples of syntheses involving singlet oxygen.

Certain compounds react with singlet oxygen in a different manner, giving cyclic dioxetane adducts[85]:

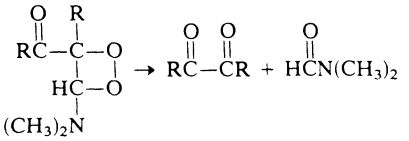


This reaction is not usually a major factor with alkenes bearing only alkyl substituents, but becomes important with vinyl ethers. Enamino ketones undergo a clean oxidation to an α-diketone[86]:

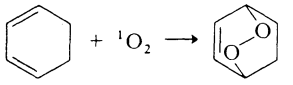


85. W. Fenical, D. R. Kearns, and P. Radlick, *J. Am. Chem. Soc.* **91**, 3396 (1969); S. Mazur and C. S. Foote, *J. Am. Chem. Soc.* **92**, 3225 (1970); P. D. Bartlett and A. P. Schaap, *J. Am. Chem. Soc.* **92**, 3223 (1970).
86. H. H. Wasserman and J. L. Ives, *J. Am. Chem. Soc.* **98**, 7868 (1976).

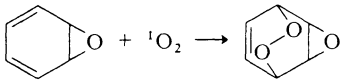
Unstable dioxetanes may be intermediates in this reaction:



Singlet oxygen undergoes 4 + 2 cycloaddition reactions with dienes, generating peroxides:



Ref. 87

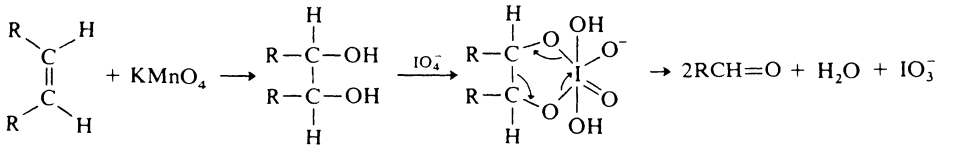


Ref. 88

10.3. Cleavage of Carbon–Carbon Double Bonds

10.3.1. Transition Metal Oxidants

The most selective methods for cleaving organic molecules at carbon–carbon double bonds are based on procedures in which glycols are intermediates. Oxidation of alkenes to glycols was discussed in Section 10.2. Cleavage of alkenes can be carried out in one operation under mild conditions by using solutions containing periodate ion and a catalytic amount of permanganate ion.[89] The permanganate effects the hydroxylation, and the glycol is then cleaved by reaction with periodate. A cyclic intermediate is believed to be involved in the periodate oxidation. Permanganate is continuously regenerated by the oxidizing action of periodate.



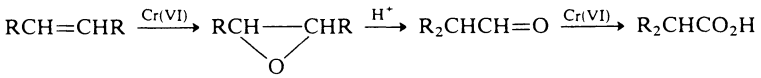
Osmium tetroxide used in combination with sodium periodate can also effect alkene cleavage cleanly.[90,91] Successful oxidative cleavage of double bonds using ruthenium

87. C. S. Foote, S. Wexler, W. Ando, and R. Higgins, *J. Am. Chem. Soc.* **90**, 975 (1968).
88. C. H. Foster and G. A. Berchtold, *J. Am. Chem. Soc.* **94**, 7939 (1972).
89. R. U. Lemieux and E. von Rudloff, *Can. J. Chem.* **33**, 1701, 1710 (1955); E. von Rudloff, *Can. J. Chem.* **33**, 1714 (1955).
90. R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.* **21**, 478 (1956).
91. H. Vorbrueggen and C. Djerassi, *J. Am. Chem. Soc.* **84**, 2990 (1962).

tetroxide and sodium periodate has also been reported.[92] In these procedures the osmium or ruthenium can be used in substoichiometric amounts because the periodate reoxidizes the metal to the tetroxides which are necessary for the initial reaction with the double bond. Entries 1–4 in Scheme 10.10 are examples of these procedures.

The strong oxidants Cr(VI) and MnO_4^- can also be used for oxidative cleavage of double bonds, provided there are no other sensitive groups in the molecule. The permanganate oxidation proceeds first to the diols and ketols as described earlier and these are further oxidized to the carboxylic acid. Good yields can be obtained, provided care is taken to prevent subsequent further oxidative degradation of the product. Entries 4 and 5 in Scheme 10.10 are illustrative.

The oxidation of cyclic alkenes by Cr(VI) reagents can be a useful method for formation of dicarboxylic acids. The initial oxidation step appears to yield an epoxide, which then undergoes solvolytic ring opening to glycols or glycol esters. These are then oxidatively cleaved.[93] Two possible complications which can be encountered are competing allylic attack and skeletal rearrangement of the epoxide. Allylic attack can lead to the eventual formation of a dicarboxylic acid which has lost one carbon atom. Pinacol-type rearrangement of the epoxide or glycol intermediate can give rise to rearranged products.



10.3.2. Ozonolysis

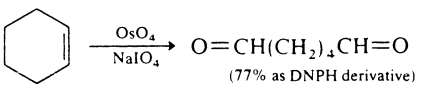
The reaction of olefins with ozone constitutes an important method of cleaving carbon–carbon double bonds.[94] This reaction is a useful degradative tool and also finds some use in synthesis. Recent years have seen the application of detailed low-temperature spectroscopic techniques to the study of the rather unstable species that are intermediates in the ozonolysis process. These studies, along with isotope labeling results, have put early mechanistic ideas on a firmer basis and have elaborated many additional details of the reaction mechanism.[95]

The two key intermediates in ozonolysis appear to be the 1,2,3-trioxolane, or initial ozonide, and the 1,2,4-trioxolane, or ozonide. The main course of the reaction involves an initial cycloaddition to give the 1,2,3-trioxolane followed by a rearrangement to the 1,2,4-trioxolane by fragmentation–recombination. The initial step fits

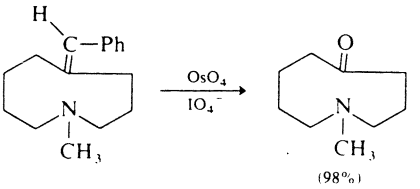
92. W. G. Dauben and L. E. Friedrich, *J. Org. Chem.* **37**, 241 (1972).
93. J. Rocek and J. C. Drozd, *J. Am. Chem. Soc.* **92**, 6668 (1970); A. K. Awasthy and J. Rocek, *J. Am. Chem. Soc.* **91**, 991 (1969).
94. P. S. Bailey, *Ozonation in Organic Chemistry*, Vol. 1, Academic Press, New York (1978).
95. C. W. Gillies, R. P. Lattimer, and R. L. Kuczkowski, *J. Am. Chem. Soc.* **96**, 1536 (1974); G. Klopman and C. M. Joiner, *J. Am. Chem. Soc.* **97**, 5287 (1975); I. C. Hisatsune, K. Shinoda, and J. Heicklen, *J. Am. Chem. Soc.* **101**, 2524 (1979).

Scheme 10.10. Oxidative Cleavage of Carbon–Carbon Double Bonds with Transition Metal Oxidants

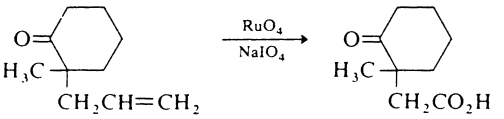
1[a]



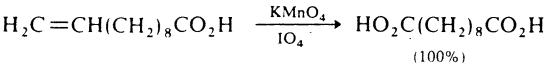
2[b]



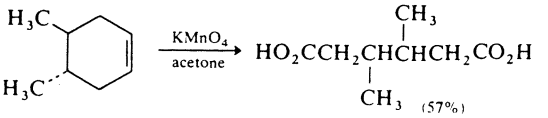
3[c]



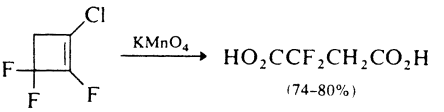
4[d]



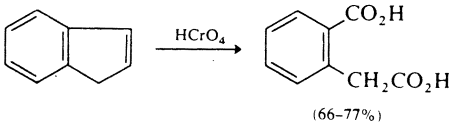
5[e]



6[f]

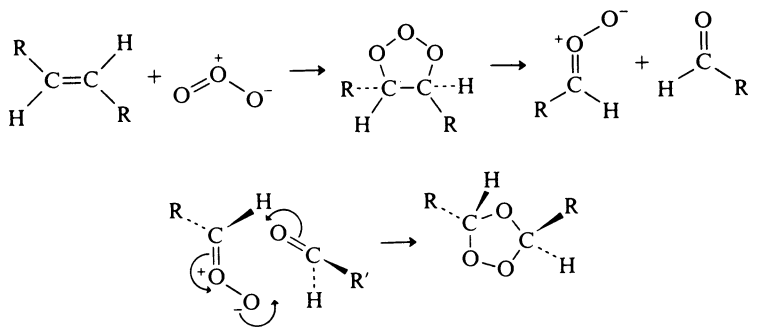


7[g]



a. R. U. Lemieux and E. von Rudloff, *Can. J. Chem.* **33**, 1701 (1955).
b. M. G. Reinecke, L. R. Kray, and R. F. Francis, *J. Org. Chem.* **37**, 3489 (1972).
c. A. A. Asselin, L. G. Humber, T. A. Dobson, J. Komlossy, and R. R. Martel, *J. Med. Chem.* **19**, 787 (1976).
d. R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.* **21**, 478 (1956).
e. W. C. M. C. Kokke and F. A. Varkvisser, *J. Org. Chem.*, **39**, 1535 (1974).
f. N. S. Raasch and J. E. Castle, *Org. Synth.* **42**, 44 (1962).
g. O. Grummitt, R. Egan, and A. Buck, *Org. Synth.* **III**, 449 (1955).

the mechanistic pattern of a concerted 1,3-dipolar cycloaddition reaction. Ozone is expected to be a very electrophilic 1,3-dipole because of the accumulation of electronegative oxygen atoms in the ozone molecule. The cycloaddition and the subsequent fragmentation and recombination reactions are all predicted to be



exothermic on the basis of thermochemical considerations.[96] To rationalize the observation that the stereochemistry of the ozonide depends upon the configuration of the initial alkene, it is necessary that both the fragmentation and recombination steps be somewhat stereoselective.[97]

The actual products isolated after ozonolysis depend upon the conditions of work-up. The carbons in the ozonide are at the carbonyl oxidation level, but simple hydrolysis also liberates hydrogen peroxide, which can give rise to secondary oxidations. Thus it is usually preferable that a mild reducing agent capable of reducing peroxide bonds be included in the workup. The current practice is to use dimethyl sulfide, though numerous other reducing agents have been used, including zinc,[98a] trivalent phosphorus compounds,[98b] and sodium sulfite.[98c]

When ozonolysis is effected in alcoholic solvents, the zwitterionic cleavage intermediates are trapped as α-hydroperoxy ethers.[99] Recombination is then prevented, and the carbonyl compound formed in the cleavage step can also be isolated under these conditions. If the reaction mixture is then treated with dimethyl sulfide,

$$R_2C{=}\overset{+}{O}{-}O^- + CH_3OH \rightarrow R_2\underset{\displaystyle OCH_3}{\underset{|}{C}}OOH$$

$$PhCH{=}CH_2 \xrightarrow[CH_3OH]{O_3} \underset{(31\,\%)}{PhCH(OCH_3)OOH} + \underset{(23\,\%)}{CH_2(OCH_3)OOH} + \underset{(26\,\%)}{PhCH{=}O} + \underset{(27\,\%)}{CH_2{=}O}$$

which reduces the hydroperoxide, isolation of the carbonyl compounds in good yield is possible.[100] This procedure prevents oxidation of the carbonyl products,

96. P. S. Nangia and S. W. Benson, *J. Am. Chem. Soc.* **102**, 3105 (1980).
97. N. L. Bauld, J. A. Thompson, C. E. Hudson, and P. S. Bailey, *J. Am. Chem. Soc.* **90**, 1822 (1968); R. P. Lattimer, R. L. Kuczkowski and C. W. Gillies, *J. Am. Chem. Soc.* **96**, 348 (1974).
98. J. J. Pappas, E. P. Keaveney, M. Berger, and R. V. Rush, *J. Org. Chem.* **33**, 787 (1968); W. S. Knowles and Q. E. Thompson, *J. Org. Chem.* **25**, 1031 (1960); A. Furlenmeier, A. Fürst, A. Langemann, G. Waldvogel, P. Hocks, U. Kerb, and R. Wiechert, *Helv. Chim. Acta.* **50**, 2387 (1967); R. H. Callighan and M. H. Wilt, *J. Org. Chem.* **26**, 4912 (1961).
99. W. P. Keaveney, M. G. Berger, and J. J. Pappas, *J. Org. Chem.* **32**, 1537 (1967).
100. J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.* 4273 (1966).

especially aldehydes, by the peroxidic compounds present at the conclusion of ozonolysis.

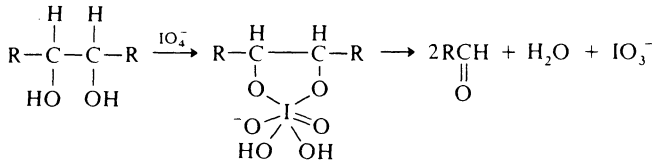
If the alcohol corresponding to the reduction of the carbonyl cleavage product is desired, the reaction mixture can be reduced with hydride reducing agents.[101] Carboxylic acids are formed in good yields from aldehydes when the ozonolysis reaction mixture is worked up in the presence of excess hydrogen peroxide to ensure complete oxidation of aldehyde groups.[102]

Scheme 10.11 illustrates some cases where ozonolysis has been used in synthetic procedures.

10.4. Selective Oxidative Cleavages at Other Functional Groups

10.4.1. Cleavage of Glycols

As indicated in connection with cleavage reactions that originate by oxidative attack on carbon–carbon double bonds, the glycol unit is susceptible to mild oxidative cleavage. The most commonly used reagent for oxidative cleavage of glycols is the periodate anion.[103] Mechanistic work has indicated that the key intermediate is a cyclic adduct of the glycol and oxidant. Investigations of the



relationship between glycol stereochemistry and rate of oxidation have established that structural features that would retard formation of a cyclic intermediate decrease the oxidation rate. For example, *cis*-1,2-dihydroxycyclohexane is substantially more reactive than the *trans* isomer.[104] The rate retardation can be attributed to increased strain in the cyclic ester derived from the *trans*-diol. Glycols in which the geometry of the molecule precludes the possibility of a cyclic intermediate are essentially inert to periodate.

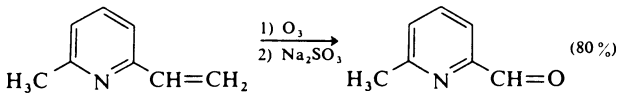
Certain other systems containing adjacent functional groups that are capable of forming a cyclic intermediate are also cleaved by periodate. Diketones are cleaved to carboxylic acids, and it has been proposed that a reactive cyclic intermediate is formed by nucleophilic attack on the diketone.[105] α-Hydroxy ketones and

101. F. L. Greenwood, *J. Org. Chem.* **20**, 803 (1955).
102. A. L. Henne and P. Hill, *J. Am. Chem. Soc.* **65**, 752 (1943).
103. C. A. Bunton, in *Oxidation in Organic Chemistry*, Part A, K. B. Wiberg (ed.), Academic Press, New York (1965), pp. 367–388; A. S. Perlin, in *Oxidation*, Vol. 1, R. L. Augustine (ed.), Marcel Dekker, New York (1969), pp. 189–204.
104. C. C. Price and M. Knell, *J. Am. Chem. Soc.* **64**, 552 (1942).
105. C. A. Bunton and V. J. Shiner, Jr., *J. Chem. Soc.* 1593 (1960).

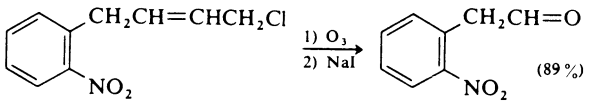
Scheme 10.11. Ozonolysis Reactions

A. Reductive Workup

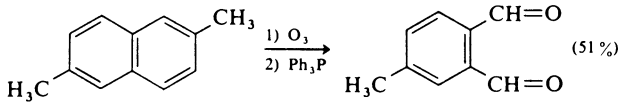
1[a]



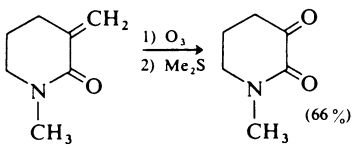
2[b]



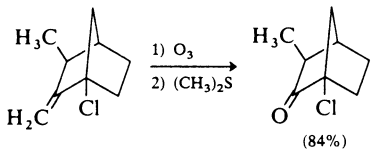
3[c]



4[d]

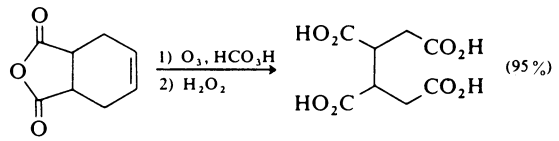


5[e]

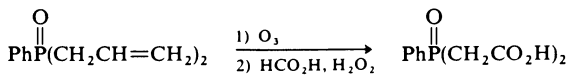


B. Oxidative Workup

6[f]

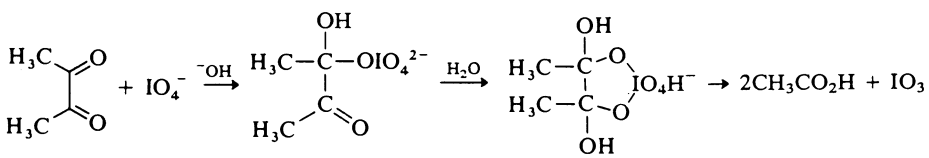


7[g]



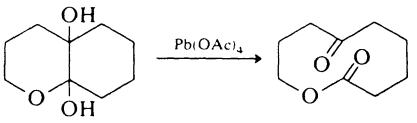
a. R. H. Callighan and M. H. Wilt, *J. Org. Chem.* **26**, 4912 (1961).
b. W. E. Noland and J. H. Sellstedt, *J. Org. Chem.* **31**, 345 (1966).
c. J. J. Pappas, W. P. Keaveney, M. Berger, and R. V. Rush, *J. Org. Chem.* **33**, 787 (1968).
d. M. L. Rueppel and H. Rapoport, *J. Am. Chem. Soc.* **94**, 3877 (1972).
e. J. V. Paukstelis and B. W. Macharia, *J. Org. Chem.* **38**, 646 (1973).
f. J. E. Franz, W. S. Knowles, and C. Osuch, *J. Org. Chem.* **30**, 4328 (1965).
g. J. L. Eichelberger and J. K. Stille, *J. Org. Chem.* **36**, 1840 (1971).

α-amino alcohols are subject to similar oxidative cleavage.



Lead tetraacetate is an alternative reagent to periodate for glycol cleavage. It is particularly useful for glycols that have low solubility in the aqueous media used for periodate reactions. A cyclic intermediate is indicated by the same kind of stereochemistry–reactivity relationships discussed for periodate.[106] Unlike periodate, however, glycols that cannot form cyclic intermediates are eventually oxidized. For example, *trans*-9,10-dihydroxydecalin is oxidized, although the rate for the *cis* isomer is 100 times greater.[107] Thus, while a cyclic transition state appears to provide the lowest energy pathway for this oxidative cleavage, it cannot be the only viable mechanism.

Both the periodate cleavage and lead tetraacetate oxidation can be applied synthetically to the generation of medium-sized rings when the glycol is at the junction of two rings.



Ref. 108

10.4.2. Oxidative Decarboxylation

Carboxylic acids are oxidized by lead tetraacetate. Decarboxylation occurs, and the product may be an alkene, alkane, acetate ester, or, under modified conditions, an alkyl halide. A free-radical mechanism operates, and the product

$$Pb(OAc)_4 + RCO_2H \rightleftharpoons RCO_2Pb(OAc)_3 + CH_3CO_2H$$

$$RCO_2Pb(OAc)_3 \rightarrow R\cdot + CO_2 + Pb(OAc)_3$$

$$R\cdot + Pb(OAc)_4 \rightarrow R^+ + Pb(OAc)_3 + CH_3CO_2^-$$

and

$$R\cdot + Pb(OAc)_3 \rightarrow R^+ + Pb(OAc)_2 + CH_3CO_2^-$$

composition depends on the fate of the radical intermediate.[109] The reaction is catalyzed by cupric salts, which function by oxidizing the intermediate radical to the carbonium ion (step 3). Cu(II) is much more reactive than $Pb(OAc)_4$ in this step.

Alkanes are formed when the intermediate radical abstracts hydrogen from solvent faster than it is oxidized to the carbonium ion. This reductive process is

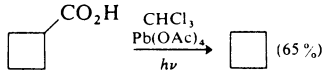
106. C. A. Bunton, in *Oxidation in Organic Chemistry*, K. Wiberg (ed.), Academic Press, New York (1965), pp. 398–405; W. S. Trahanovsky, J. R. Gilmore, and P. C. Heaton, *J. Org. Chem.* **38**, 760 (1973).

107. R. Criegee, E. Höger, G. Huber, P. Kruck, F. Marktscheffel, and H. Schellenberger, *Justus Liebig's Ann. Chem.* **599**, 81 (1956).

108. T. Wakamatsu, K. Akasaka, and Y. Ban, *Tetrahedron Lett.* 2751, 2755 (1977).

109. R. A. Sheldon and J. K. Kochi, *Org. React.* **19**, 279 (1972).

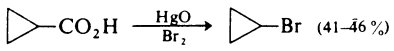
promoted by good hydrogen donor solvents. It is also most favorable for primary alkyl radicals because of the higher activation energy associated with formation of primary carbonium ions. The most favorable conditions for alkane formation involve photochemical decomposition of the carboxylic acid in chloroform, which is a relatively good hydrogen donor. Normally, the dominant products are the alkene



Ref. 110

and ester. These arise from the carbonium ion intermediate by, respectively, elimination of a proton, and capture of an acetate ion. The presence of copper acetate increases the alkene : ester ratio.[111]

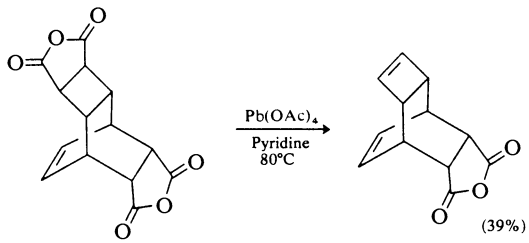
A related method for conversion of carboxylic acids to bromides with decarboxylation is the *Hansdiecker reaction.*[112] The most convenient method for carrying out this transformation involves heating the carboxylic acid with mercuric oxide and bromine:



Ref. 113

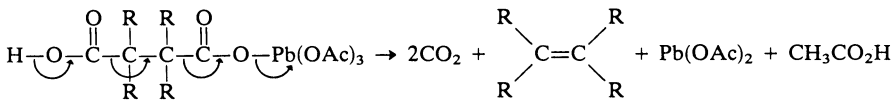
The overall transformation can also be accomplished by reaction of thallium(I) carboxylate with bromine.[114]

1,2-Dicarboxylic acids undergo bis-decarboxylation on reaction with lead tetraacetate to give alkenes. This reaction has found occasional synthetic use, when the required dicarboxylic acid is available, for the synthesis of strained alkenes.



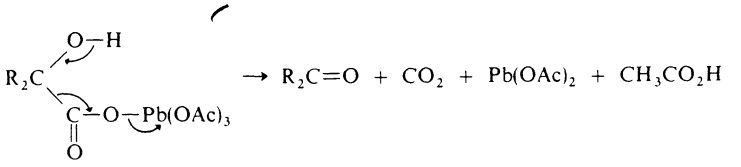
Ref. 115

The reaction can be formulated as occurring via a concerted process initiated by a two-electron oxidation:

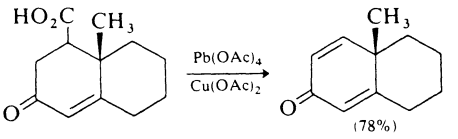


110. J. K. Kochi and J. D. Bacha, *J. Org. Chem.* **33**, 2746 (1968).
111. J. D. Bacha and J. K. Kochi, *Tetrahedron* **24**, 2215 (1968).
112. C. V. Wilson, *Org. React.* **9**, 332 (1957).
113. J. S. Meek and D. T. Osuga, *Org. Synth.* **V**, 126 (1973).
114. A. McKillop, D. Bromley, and E. C. Taylor, *J. Org. Chem.* **34**, 1172 (1969).
115. E. Grovenstein, Jr., D. V. Rao, and J. W. Taylor, *J. Am. Chem. Soc.* **83**, 1705 (1961).

A concerted mechanism is also possible for α-hydroxycarboxylic acids, and these compounds readily undergo oxidative decarboxylation to ketones.[116]



γ-Ketocarboxylic acids are oxidatively decarboxylated to enones.[117] This reaction is presumed to proceed through the usual oxidative decarboxylation, with the carbonium ion intermediate being especially efficiently deprotonated because of the developing conjugation.

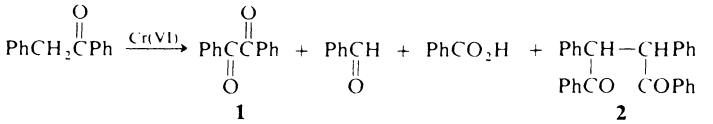


Ref. 117

10.5. Oxidations of Ketones and Aldehydes

10.5.1. Transition Metal Oxidants

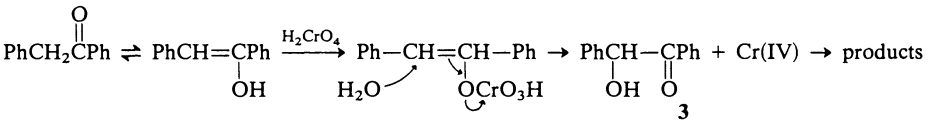
Ketones are cleaved oxidatively by Cr(VI) or Mn(VII) reagents. The reaction is sometimes of utility in the synthesis of difunctional molecules by ring cleavage. The mechanism for both reagents is believed to involve cleavage of an enolic intermediate,[118] although in neither case have all the details been established. A study involving both kinetic data and quantitative product studies has permitted a fairly complete description of the Cr(VI) oxidation of benzyl phenyl ketone (desoxybenzoin).[119] The products include both oxidative-cleavage products and benzil **1**, resulting from oxidation alpha to the carbonyl. In addition, the dimeric product **2**, which is suggestive of radical intermediates, was formed under some conditions:



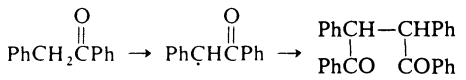
1 **2**

116. R. Criegee and E. Büchner, *Chem. Ber.* **73**, 563 (1940).
117. J. E. McMurry and L. C. Blaszczak, *J. Org. Chem.* **39**, 2217 (1974).
118. K. B. Wiberg and R. D. Geer, *J. Am. Chem. Soc.* **87**, 5202 (1965); J. Rocek and A. Riehl, *J. Am. Chem. Soc.* **89**, 6691 (1967).
119. K. B. Wiberg, O. Aniline, and A. Gatzke, *J. Org. Chem.* **37**, 3229 (1972).

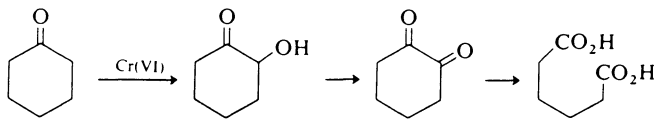
Both the diketone and cleavage products were shown to be formed from benzoin, **3**. Benzoin arises from oxidation of the enol of the starting ketone. The coupling



product is considered to involve an intermediate formed by one-electron oxidation, probably effected by Cr(IV):

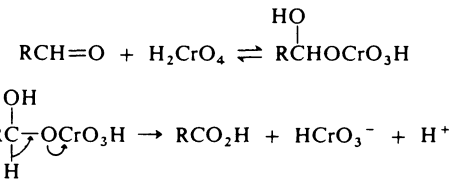


Studies in the case of cyclohexanone have indicated the intermediacy of 2-hydroxycyclohexanone, which is further oxidized to cyclohexanedione and cleaved to adipic acid.[120] Because of the efficient oxidation of alcohols to ketones, the alcohols can

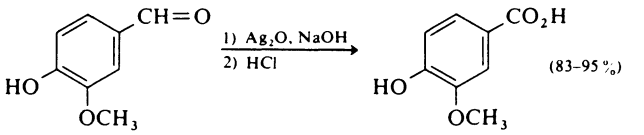


be used as the actual starting materials in oxidative cleavages. The oxidation to the carboxylic acid oxidation level requires more vigorous conditions than the alcohol-to-ketone transformation.

Aldehydes can be oxidized to carboxylic acids by both Mn(VII) and Cr(VI). Fairly detailed mechanistic studies have been completed in the case of Cr(VI). A chromate ester of the aldehyde hydrate is believed to be formed, and this species decomposes in the rate-determining step by a mechanism similar to that which is



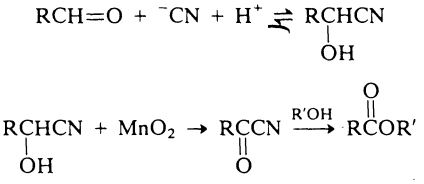
operative in alcohol oxidations.[121] An alternative reagent for carrying out the aldehyde-to-carboxylic acid oxidation synthetically is silver oxide:



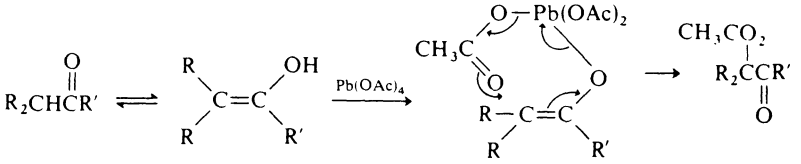
Ref. 122

120. J. Rocek and A. Riehl, *J. Org. Chem.* **32**, 3569 (1967).
121. K. B. Wiberg, *Oxidation in Organic Chemistry*, Part A, Academic Press, New York (1965), pp. 172–178.
122. I. A. Pearl, *Org. Synth.* **IV**, 972 (1963).

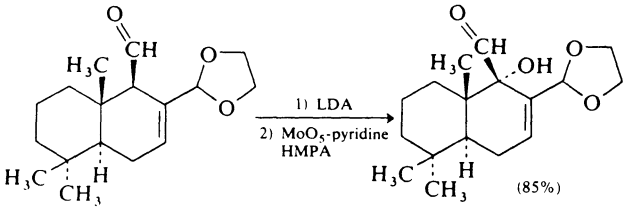
The reaction of aldehydes with MnO_2 in the presence of cyanide ion in an alcoholic solvent is a convenient method of converting aldehydes directly to esters.[123] This reaction involves the cyanohydrin as an intermediate. The initial product is an acyl cyanide which is solvolyzed under the conditions.



Lead tetraacetate can effect oxidation of carbonyl groups, leading to the formation of α-acetoxy ketones.[124] Reported yields are seldom high, however. Boron trifluoride can be used to catalyze these oxidations. It is presumed to function by catalysis of enolization, and it is assumed that the enol is the reactive species.[125] With unsymmetrical ketones product from oxidation of both α-methylene groups are found.[126]



Other procedures for α oxidation of ketones are based on prior generation of the enolate. The most useful oxidant in these procedures is a molybdenum compound, MoO_5·pyridine–HMPA, which is prepared by dissolving MoO_3 in hydrogen peroxide, followed by addition of HMPA (hexamethylphosphoric triamide). This reagent oxidizes the enolates of aldehydes, ketones, esters, and lactones to the corresponding α-hydroxy compound.[127] Another method for enolate



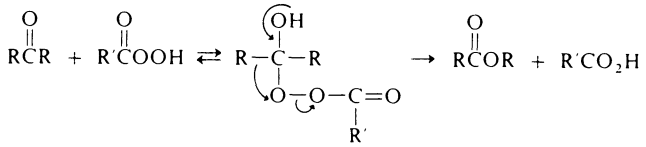
Ref. 128

oxidation which uses molecular oxygen as the oxidant will be discussed in the next section.

123. E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Am. Chem. Soc.* **90**, 5616 (1968).
124. R. Criegee, in *Oxidation in Organic Chemistry*, Part A, K. B. Wiberg (ed.), Academic Press, New York (1965), pp. 305–312.
125. J. D. Cocker, H. B. Henbest, G. H. Phillipps, G. P. Slater, and D. A. Thomas, *J. Chem. Soc.* 6 (1965).
126. S. Moon and H. Bohm, *J. Org. Chem.* **37**, 4338 (1972).
127. E. Vedejs, *J. Am. Chem. Soc.* **96**, 5945 (1974); E. Vedejs, D. A. Engler, and J. E. Telschow, *J. Org. Chem.* **43**, 188 (1978).
128. S. P. Tanis and K. Nakanishi, *J. Am. Chem. Soc.* **101**, 4398 (1979).

10.5.2. Oxidation of Ketones and Aldehydes by Peroxidic Compounds and Oxygen

In the presence of acid catalysts, peroxy compounds are capable of oxidizing carbonyl compounds in a manner involving formal insertion of an oxygen atom into one of the carbon–carbon bonds at the carbonyl group. This insertion is accomplished by a sequence of steps involving addition of the carbonyl group and migration to oxygen, as outlined in the mechanism below:



The concerted O–O heterolysis–migration is usually the rate-determining step.[129] The reaction is known as the *Baeyer–Villiger oxidation*.[130]

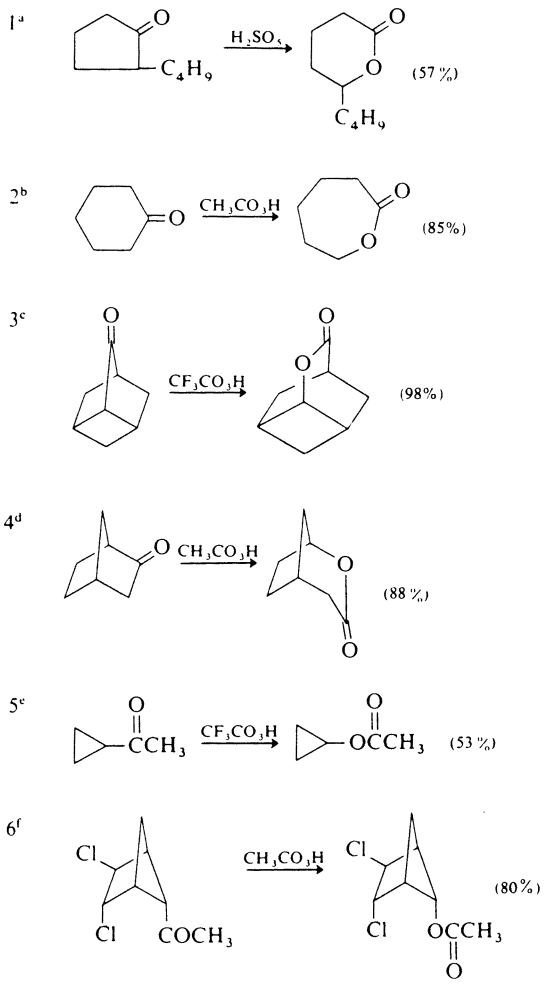
When the reaction involves an unsymmetric ketone, the structure of the product depends on which group migrates. A number of studies have been directed at ascertaining the basis of migratory aptitude in the Baeyer–Villiger oxidation. From these studies, a general order of likelihood of migration, or "migratory aptitude," has been established: *tert*-alkyl, *sec*-alkyl > benzyl, phenyl > *pri*-alkyl > cyclopropyl > methyl.[131] Thus, methyl ketones are uniformly found to give acetate esters resulting from migration of the larger group.[132] As is generally true of migration to an electron-deficient center, the configuration of the migrating group is retained in Baeyer–Villiger oxidations.

The precise factors that govern migratory aptitude are not completely clear. The electronic nature of the substituents surely contributes; in benzophenones, for example, the relative migratory aptitude as a function of *para* substituents decreases in the order $CH_3O > CH_3 > H > Cl > NO_2$.[133] It is believed that steric and conformational factors also come into play.[134] The selectivity in the migration also seems to depend on the identity of the peroxyacid, with trifluoroperoxyacetic acid showing somewhat less selectivity than weaker oxidants.

At the present time, trifluoroperoxyacetic acid and *m*-chloroperoxybenzoic acid are most often used to accomplish Baeyer–Villiger oxidation of ketones for synthetic purposes. Some typical examples are shown in Scheme 10.12. A tabulation of work prior to the mid-1950s provides many examples of the use of peroxyacetic

129. Y. Ogata and Y. Sawaki, *J. Org. Chem.* **37**, 2953 (1972).
130. C. H. Hassall, *Org. React.* **9**, 73 (1957).
131. H. O. House, *Modern Synthetic Reactions*, second edition, W. A. Benjamin, Menlo Park, California (1972), p. 325.
132. P. A. S. Smith, in *Molecular Rearrangements*, P. de Mayo (ed.), Interscience, New York (1963), pp. 584–587.
133. W. E. Doering and L. Speers, *J. Am. Chem. Soc.* **72**, 5515 (1950).
134. M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *J. Am. Chem. Soc.* **80**, 6393 (1958); J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.* **82**, 5235 (1960).

Scheme 10.12. Baeyer–Villiger Oxidations

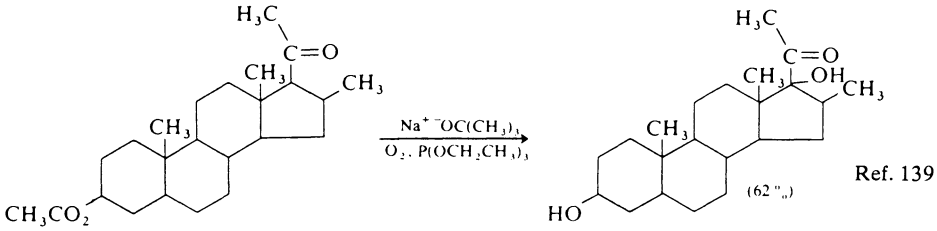


a. T. H. Parliment, M. W. Parliment, and I. S. Fagerson, *Chem. Ind.* 1845 (1966).
b. P. S. Starcher and B. Phillips, *J. Am. Chem. Soc.* **80**, 4079 (1958).
c. S. A. Monti and S.-S. Yuan, *J. Org. Chem.* **36**, 3350 (1971).
d. J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.* **82**, 5235 (1960).
e. W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.* **77**, 2287 (1955).
f. K. B. Wiberg and R. W. Ubersax, *J. Org. Chem.* **37**, 3827 (1972).

acid, peroxybenzoic acid, and hydrogen peroxide with strong acids.[135] Peroxysulfuric acid is also an effective reagent, at least for simple ketones.[136] Monoperoxyphosphoric acid, which is prepared from P_2O_5 and 90% H_2O_2 in acetonitrile, is also an effective reagent.[137]

135. C. H. Hassall, *Org. React.* **9**, 73 (1957).
136. N. C. Deno, W. E. Billups, K. E. Kramer, and R. R. Lastomirsky, *J. Org. Chem.* **35**, 3080 (1970).
137. Y. Ogata, K. Tomizawa, and T. J. Ikeda, *J. Org. Chem.* **43**, 2417 (1978).

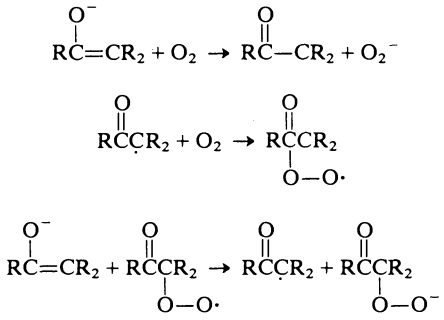
Although ketones are essentially inert to molecular oxygen, enolate anions are susceptible to oxidation. The combination of oxygen and a base has found synthetic utility in permitting introduction of an oxygen function at a potential carbanion site.[138] Hydroperoxides are the initial products of such oxidations, but when DMSO or some other substance capable of reducing the hydroperoxide is present, the corresponding alcohol is isolated. A procedure that has met with considerable success involves oxidation in the presence of a trialkyl phosphite.[139] The intermediate hydroperoxide is efficiently reduced by the phosphite ester. This



Ref. 139

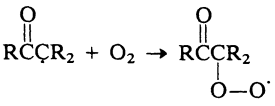
oxidative process has also been successful with enolates of esters[140] and lactones.[141] Hydrogen peroxide can also be used as the oxidant, in which case the alcohol is formed directly.[142]

There are two general mechanisms for this oxidation which have been considered. One is radical chain autoxidation in which the propagation step involves



electron transfer from the carbanion to a hydroperoxy radical.[143] Arguments for a non-chain-reaction between the enolate and oxygen to give hydroperoxide anion directly have also been advanced.[144] It does not appear that enough compounds

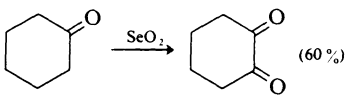
138. J. N. Gardner, T. L. Popper, F. E. Carlon, O. Gnoj, and H. L. Herzog, *J. Org. Chem.* **33**, 3695 (1968).
139. J. N. Gardner, F. E. Carlon, and O. Gnoj, *J. Org. Chem.* **33**, 3294 (1968).
140. E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.* **97**, 6908 (1975).
141. J. J. Plattner, R. D. Gless, and H. Rapoport, *J. Am. Chem. Soc.* **94**, 8613 (1972); R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *J. Am. Chem. Soc.* **93**, 5576 (1971).
142. G. Büchi, K. E. Matsumoto, and H. Nishimura, *J. Am. Chem. Soc.* **93**, 3299 (1971).
143. G. A. Russell and A. G. Bemis, *J. Am. Chem. Soc.* **88**, 5491 (1966).
144. H. R. Gersmann and A. F. Bickel, *J. Chem. Soc.* **B**, 2230 (1971).



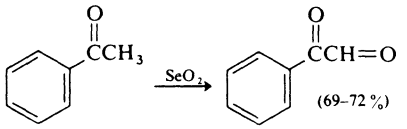
have been carefully investigated from a mechanistic point of view to make a reliable generalization as to when each mechanism operates.

10.5.3. Oxidation with Other Reagents

Selenium dioxide can be used to oxidize ketones and aldehydes to α-dicarbonyl compounds. The reaction often gives high yields of products when there is a single type of CH_2 group adjacent to the carbonyl group. In unsymmetrical ketones, oxidation usually occurs at the CH_2 that is most readily enolized.[145] The oxidation

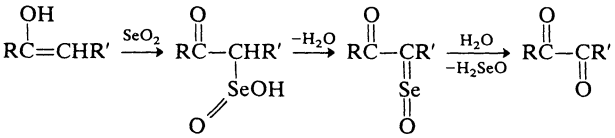


(60 %) Ref. 146

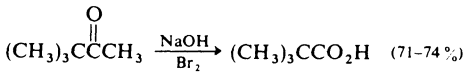


(69–72 %) Ref. 147

is regarded as taking place by an electrophilic attack of selenium dioxide (or selenous acid, H_2SeO_3, the hydrate) on the enol of the ketone or aldehyde. This is followed by hydrolytic elimination of selenium.[148]



Methyl ketones are degraded to the next lower carboxylic acid by reaction with hypochlorite or hypobromite ions. The initial step in these reactions involves base-catalyzed halogenation. The haloketones are more reactive than their precursors, and rapid halogenation to the trihalo compound results. Trihalomethyl ketones

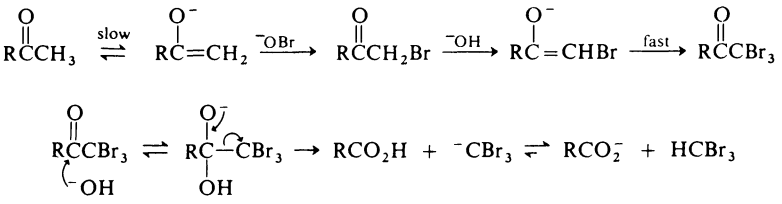


(71–74 %) Ref. 149

145. E. N. Trachtenberg, in *Oxidation*, Vol. 1, R. L. Augustine (ed.), Marcel Dekker, New York (1969), Chap. 3.
146. C. C. Hach, C. V. Banks, and H. Diehl, *Org. Synth.* **IV**, 229 (1963).
147. H. A. Riley and A. R. Gray, *Org. Synth.* **II**, 509 (1943).
148. K. B. Sharpless and K. M. Gordon, *J. Am. Chem. Soc.* **98**, 300 (1976).
149. L. T. Sandborn and E. W. Bousquet, *Org. Synth.* **I**, 512 (1932).

$$(CH_3)_2C{=}CHCOCH_3 \xrightarrow{KOCl} \xrightarrow{H^+} (CH_3)_2C{=}CHCO_2H \quad (49\text{–}53\,\%) \qquad \text{Ref. 150}$$

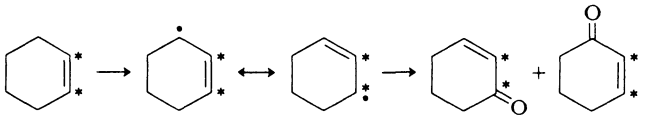
are susceptible to alkaline cleavage. This lability toward alkaline cleavage is the result of the inductive stabilization provided by the halogen atoms.



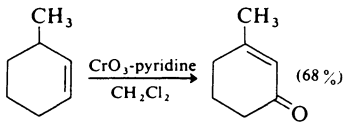
10.6. Allylic Oxidation

10.6.1. Transition Metal Oxidants

Carbon–carbon double bonds, besides being susceptible to direct oxidative transformations, also activate the allylic position toward oxidation. Synthetic utility, of course, requires that there be a good order of selectivity between reaction at the double bond and at the allylic position. Among transition metal oxidants, the CrO_3–pyridine reagent in methylene chloride appears to be the most satisfactory for allylic oxidation.[151] Several pieces of mechanistic information indicate that allylic radicals or cations are intermediates in these oxidations. Thus, ^{14}C in cyclohexene is distributed in the product cyclohexenone in a manner indicating that a symmetrical allylic intermediate is involved at some stage.[152] In many allylic



oxidations, the double bond is found in a position indicating that an "allylic shift" occurs in the course of the oxidation. When more than one allylic methylene group



Ref. 151

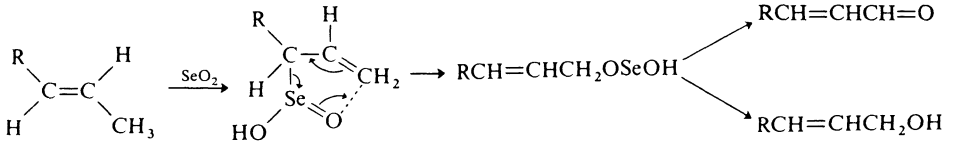
is present in an alkene, a mixture of products usually results. Oxidation at allylic

150. L. I. Smith, W. W. Prichard, and L. J. Spillane, *Org. Synth.* **III**, 302 (1955).
151. W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.* **34**, 3587 (1969).
152. K. B. Wiberg and S. D. Nielsen, *J. Org. Chem.* **29**, 3353 (1964).

methyl groups appears to be much slower than at more substituted positions, and has been observed only rarely. Detailed mechanistic understanding of the allylic oxidation has not been developed. One possibility is that an intermediate oxidation state of Cr, specifically Cr(IV), acts as the agent for allylic oxidation by abstracting hydrogen.[153]

10.6.2. Other Oxidants

Selenium dioxide is a very useful reagent for allylic oxidation of alkenes. The products are either carbonyl compounds or allyl alcohols or esters, depending upon reaction conditions. The basic mechanism consists of three essential steps: (a) an electrophilic "ene" reaction with SeO_2, (b) a sigmatropic rearrangement which restores the original location of the double bond, and (c) breakdown of the resulting selenium ester.[154] Under some circumstances, ionic processes can also intervene.[155]

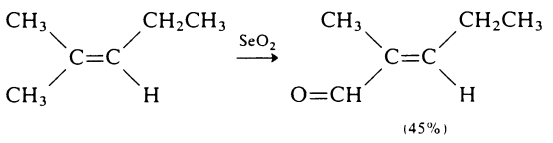


The alcohols that are the initial oxidation products are susceptible to further oxidation by SeO_2 to give the corresponding carbonyl compound. This further oxidation occurs under the normal reaction conditions so it is usually the carbonyl compound that is isolated. If the alcohol is the desired product the oxidation can be run in acetic acid as solvent, in which case acetate esters are formed.

Although the traditional conditions for effecting SeO_2 oxidations involve use of a stoichiometric or excess amount of SeO_2 it is also possible to carry out the reaction, with 1.5–2 mol % SeO_2, using *t*-butyl hydroperoxide to maintain the selenium in the reactive Se(IV) oxidation state. Under these conditions the allylic alcohol becomes the principal reaction product. The use of a stoichiometric amount of SeO_2 and excess *t*-butyl hydroperoxide permits good yields of allylic alcohols, even from alkenes which are poorly reactive toward the traditional reaction conditions.[156]

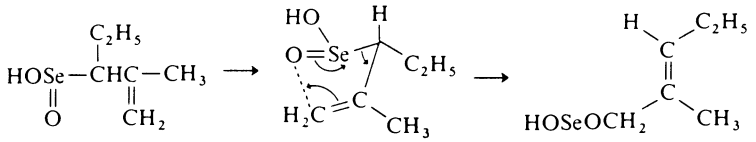
Selenium dioxide oxidation reveals a very high and useful selectivity when applied to trisubstituted *gem*-dimethyl olefins. The products are always predominantly the *E*-allylic alcohol or unsaturated aldehyde.[157] This stereoselectivity

153. P. Müller and J. Rocek, *J. Am. Chem. Soc.* **96**, 2836 (1974).
154. K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.* **94**, 7154 (1972).
155. L. M. Stephenson and D. R. Speth, *J. Org. Chem.* **44**, 4683 (1979).
156. M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.* **99**, 5526 (1977).
157. U. T. Bhalerao and H. Rapoport, *J. Am. Chem. Soc.* **93**, 4835 (1971); G. Büchi and H. Wüest, *Helv. Chim. Acta* **50**, 2440 (1967).

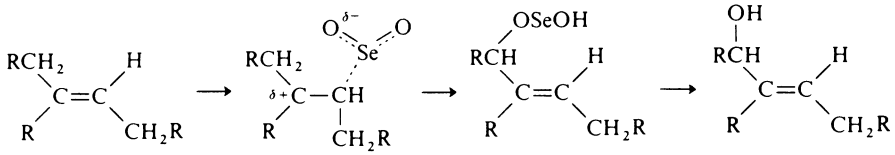


Ref. 157

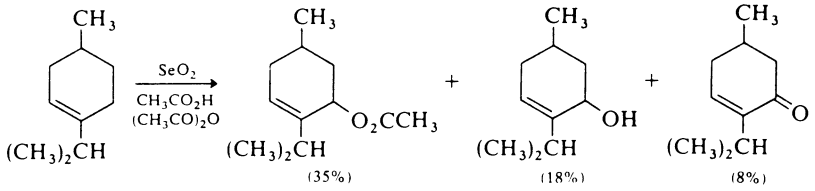
can be explained by the sigmatropic rearrangement step where a cyclic transition state in which the alkyl substituent adopts a pseudoequatorial conformation.



Trisubstituted alkenes are oxidized selectively at the more substituted end of the carbon–carbon double bond, indicating that ene reaction is electrophilic in

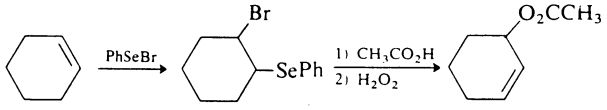


character. Thus, trisubstituted alkenes are oxidized at one of the allylic groups at the disubstituted carbon.



Ref. 158

The equivalent to allylic oxidation of alkenes, but with allylic transposition of the carbon–carbon double bond can be carried out by an indirect oxidative process involving addition of an electrophilic arylselenenyl reagent, followed by oxidative elimination of selenium. In one procedure, addition of an arylselenyl halide is followed by solvolysis and oxidation.[159] This reaction depends upon the facile



solvolysis of β-haloselenides and the oxidative selenoxide elimination which was discussed in Section 7.6.3. An alternative, which is experimentally simpler, involves

158. T. Suga, M. Sugimoto, and T. Matsuura, *Bull. Chem. Soc. Japan* **36**, 1363 (1963).
159. K. B. Sharpless and R. F. Lauer, *J. Org. Chem.* **39**, 429 (1974); D. L. J. Clive, *J. Chem. Soc. Chem. Commun.* 100 (1974).

reaction of alkenes with a mixture of diphenyl diselenide and phenylseleninic acid.[160] The two selenium reagents generate an electrophilic selenium species, phenylselenenic acid, PhSeOH.

$$RCH_2CH{=}CHR' \xrightarrow{PhSeOH} RCH_2\underset{PhSe}{\overset{}{C}}\overset{OH}{\overset{|}{C}}HR' \xrightarrow{t\text{-}BuOOH} RCH{=}\underset{OH}{\overset{}{C}}HR'$$

The elimination is promoted by oxidation to the selenoxide by *t*-butyl hydroperoxide. The regioselectivity in this reaction is such that the hydroxyl group will become bound at the more substituted end of the carbon–carbon double bond. The origin of this orientation is that the addition follows Markownikoff's rule with "$PhSe^+$" acting as the electrophile. The elimination step specifically proceeds away from the oxygen functionality.

10.7. Oxidations at Unfunctionalized Carbon

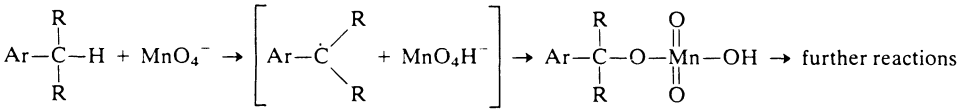
Attempts to achieve selective oxidations of hydrocarbons or other compounds when the desired site of attack is remote from an activating functional group are faced with difficulties. With the powerful transition-metal oxidants, the initial oxidation products are almost always more susceptible to oxidation than the starting material. Once a hydrocarbon is attacked, it is likely to be oxidized to a carboxylic acid, with chain cleavage by successive rapid oxidation of alcohol and carbonyl intermediates. There are a few circumstances under which oxidations of hydrocarbons can be synthetically useful processes. One group involves catalytic industrial processes. Much work has been expended on the development of selective catalytic oxidation processes and several have attained economic importance. Since the mechanisms are often obscured by limited understanding of heterogeneous catalysis, however, we will not devote additional attention to these reactions.

Perhaps the most familiar and useful hydrocarbon oxidation is the oxidation of aromatic side chains. Two factors enter into making this a high-yield procedure, despite the use of powerful oxidants: First, the benzylic site is activated to oxidation. Either radical or carbonium intermediates can be especially easily formed because of the potential resonance stabilization. Second, the aromatic ring is resistant to attack by the Mn(VII) and Cr(VI) oxidants that attack the alkyl side chain. Scheme 10.3 provides some examples of the familiar oxidation of aromatic alkyl substituents to carboxylic acid groups.

It has been difficult to formulate detailed reaction mechanisms for these oxidations, since several metal oxidation states are undoubtedly involved during the course of the reaction. In the case of permanganate, it is considered likely that

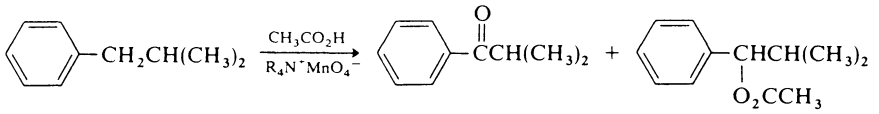
160. T. Hori and K. B. Sharpless, *J. Org. Chem.* **43**, 1689 (1978).

the initial attack involves hydrogen atom abstraction, probably followed by collapse to an ester of Mn(V).[161]



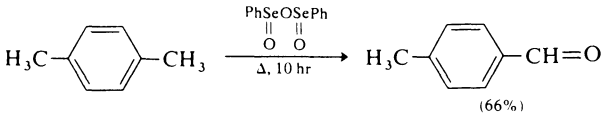
Under certain conditions oxidations by Cr(VI) reagents can be controlled to provide partial oxidation, usually to the carbonyl oxidation level. Entries 4 and 5 in Scheme 10.13 are examples.

Partial oxidations of side chains on aromatic compounds have also been achieved using tetraalkylammonium permanganates in organic solvents.[162]



These reagents, however, must be used with caution because of a potential danger of explosion.

Benzeneseleninic anhydride is an effective reagent for oxidizing methyl groups on aromatic hydrocarbons and certain substituted aromatics to aldehydes.[163]

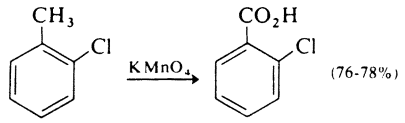


A second class of hydrocarbon substrates in which circumstances permit selective oxidations are the bicyclic hydrocarbons.[164] Here, the bridgehead position is the preferred site of initial attack because of the order of reactivity of C–H bonds, which is 3° > 2° > 1°. The tertiary alcohols which are the initial oxidation products, however, are not further oxidized with ease. The geometry of the bicyclic rings (Bredt's rule) prevents dehydration of the alcohol. Tertiary bridgehead hydroxyls, having no hydrogen, cannot be converted to ketones; oxidation that begins at a bridgehead position therefore stops at the alcohol stage. Since the competing methylene groups tend to be less reactive than the bridgehead positions, selective oxidation is possible. Chromic acid oxidation has been the most useful reagent for functionalizing unstrained bicyclic hydrocarbons. The reaction fails for strained bicyclics such as norbornane because the reactivity of the bridgehead position is

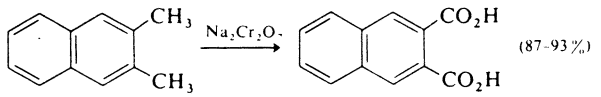
161. R. Stewart, in *Oxidation in Organic Chemistry*, Part A, K. B. Wiberg (ed.), Academic Press, New York (1965), pp. 36–41; J. I. Brauman and A. J. Pandell, *J. Am. Chem. Soc.* **92**, 329 (1970).
162. H. Jäger, J. Lütolf, and M. W. Meyer, *Angew. Chem. Int. Ed. Engl.* **18**, 756 (1979); H. J. Schmidt and H. J. Schäfer, *Angew. Chem. Int. Ed. Engl.* **18**, 787 (1979); H. J. Schmidt and H. J. Schäfer, *Angew. Chem. Int. Ed. Engl.* **18**, 68 (1979).
163. D. H. R. Barton, R. A. H. F. Hus, D. J. Lester, and S. V. Ley, *Tetrahedron Lett.* 3331 (1979).
164. R. C. Bingham and P. v. R. Schleyer, *J. Org. Chem.* **36**, 1198 (1971).

Scheme 10.13. Side-Chain Oxidation of Aromatic Compounds

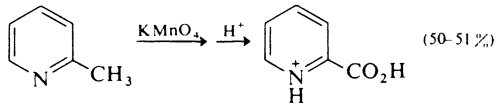
1[a]



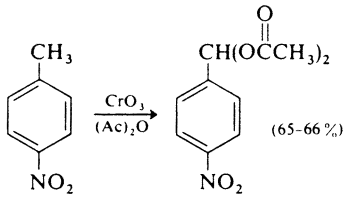
2[b]



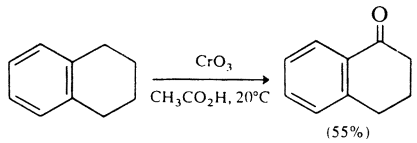
3[c]



4[d]

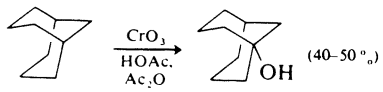


5[e]

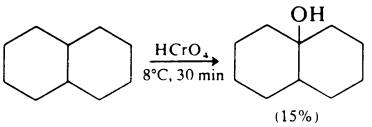


a. H. T. Clarke and E. R. Taylor, *Org. Synth.* **II**, 135 (1943).
b. L. Friedman, *Org. Synth.* **43**, 80 (1963); L. Friedman, D. L. Fishel, and H. Shechter, *J. Org. Chem.* **30**, 1453 (1965).
c. A. W. Singer and S. M. McElvain, *Org. Synth.* **III**, 740 (1955).
d. T. Nishimura, *Org. Synth.* **IV**, 713 (1963).
e. J. W. Burnham, W. P. Duncan, E. J. Eisenbraun, G. W. Keen, and M. C. Hamming, *J. Org. Chem.* **39**, 1416 (1974).

lowered by the unfavorable energy of either radical or carbonium ion intermediates.

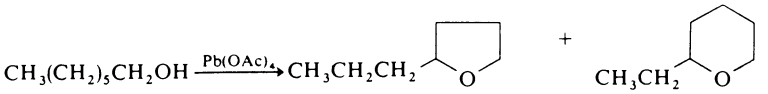


Other successful selective oxidations of hydrocarbons by Cr(VI) reagents have been reported—for example, the oxidation of *cis*-decalin to the corresponding alcohol—but careful attention to reaction conditions is required, and even then there are few hydrocarbons that have been reported to give high yields of oxidation products.

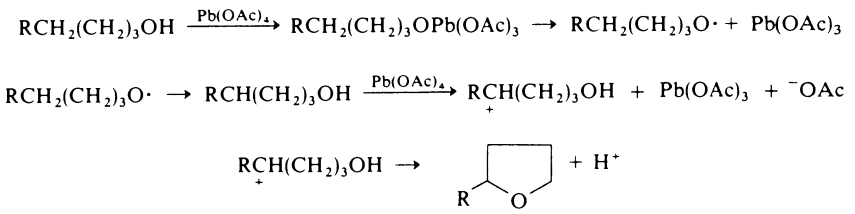


Ref. 165

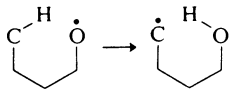
Lead tetraacetate effects oxidations at unfunctionalized C–H bonds, but the process intimately involves a functional group (hydroxyl) elsewhere in the molecule.[166] This reaction is believed to involve an alkoxylead intermediate.[167]



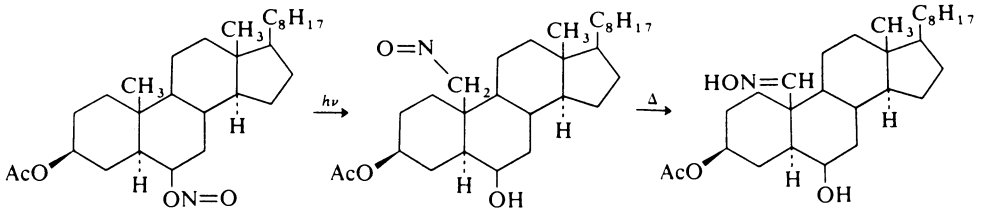
The crucial step for functionalization of the saturated chain involves an intramolecular hydrogen atom abstraction by an alkoxy radical:



The preferred transition state for this type of abstraction is six centered, so the major products are tetrahydrofuran derivatives. Smaller amounts of six-membered ring ethers are also often encountered.



Section 12.5 in Part A describes some additional reactions that are of synthetic value and involve intramolecular hydrogen abstraction at unactivated groups. Of particular note is a method, known as the *Barton reaction*, in which nitrite esters of alcohols are photolyzed. Nearby hydrocarbon groups, including methyl groups, can be functionalized by this method,[168] and the reaction has been applied to remote functionalization in steroids.



165. K. B. Wiberg and G. Foster, *J. Am. Chem. Soc.* **83**, 423 (1961).
166. V. M. Micovic, R. I. Mamuzic, D. Jeremic, and M. L. Mihailovic, *Tetrahedron* **20**, 2279 (1964).
167. K. Heusler and J. Kalvoda, *Angew. Chem.* **76**, 518 (1964).
168. D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.* **83**, 4076 (1961).

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W. S. Trahanovsky (ed.), *Oxidation in Organic Chemistry*, Part C, Academic Press, New York (1978).
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L. J. Chinn, *Selection of Oxidants in Synthesis*, Marcel Dekker, New York (1971).
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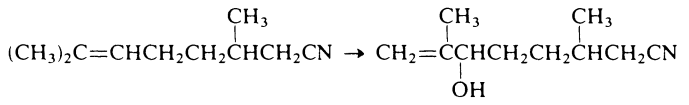
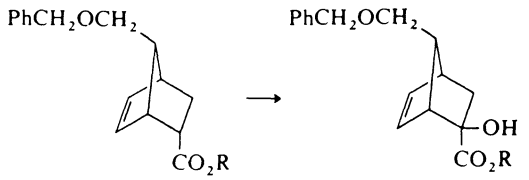
H. H. Wasserman and R. W. Murray, ed., *Singlet Oxygen*, Academic Press, New York (1979).

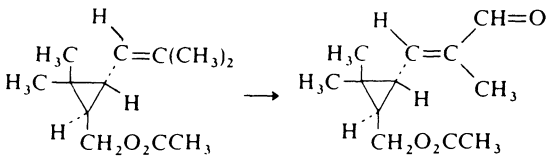
Problems

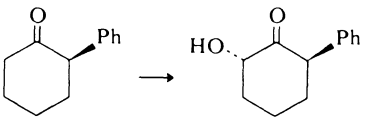
(*References for these problems will be found on page 629.*)

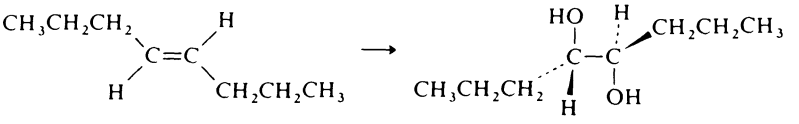
1. Indicate an appropriate oxidant for carrying out the following transformations:

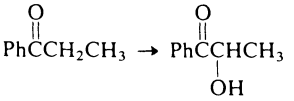
(a) 

(b) 

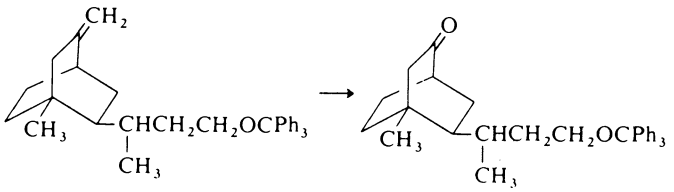
(c) 

(d) 

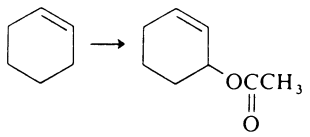
(e) 

(f) 

(g)

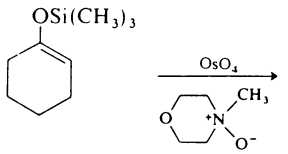


(h)

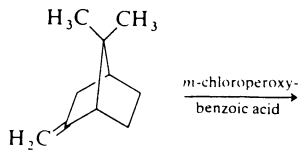


2. In chromic acid oxidation of isomeric cyclohexanols it is usually found that axial hydroxyl groups react more rapidly than equatorial groups. For example, *trans*-4-*t*-butylcyclohexanol is less reactive (by a factor of 3·2) than the *cis* isomer. An even larger difference is noted with *cis*- and *trans*-3,3,5-trimethylcyclohexanol. The *trans* alcohol is more than 35 times more reactive than the *cis*. Are these data compatible with the mechanism given on page 482? What additional detail do these data provide about the reaction mechanism? Explain.
3. Predict the products of the following reactions. Be careful to consider all stereochemical aspects.

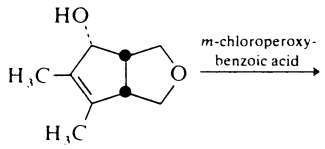
(a)



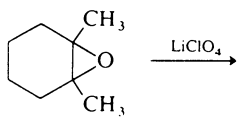
(b)



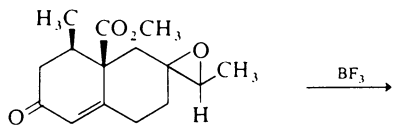
(c)

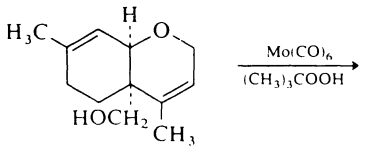


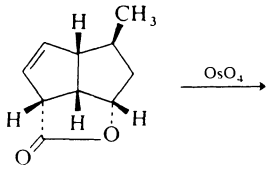
(d)

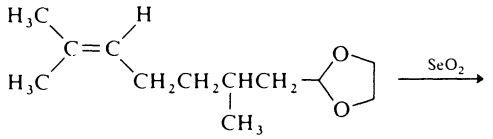


(e)

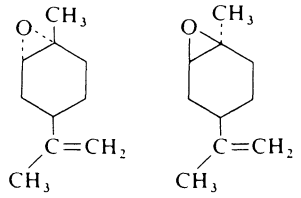


(f) 

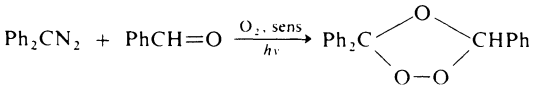
(g) 

(h) 

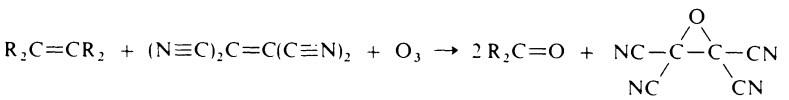
4. Predict the products from opening of the two stereoisomeric epoxides derived from limonene by reaction with (a) acetic acid, (b) dimethylamine, and (c) lithium aluminum hydride.



5. The direct oxidative conversion of primary halides or tosylates to aldehydes can be carried out by reaction with dimethyl sulfoxide under alkaline conditions. Formulate a mechanism for this general reaction.
6. A method for synthesis of ozonides that involves no ozone has been reported. It consists of photosensitized oxidation of solutions of diazo compounds and aldehydes. Suggest a mechanism.

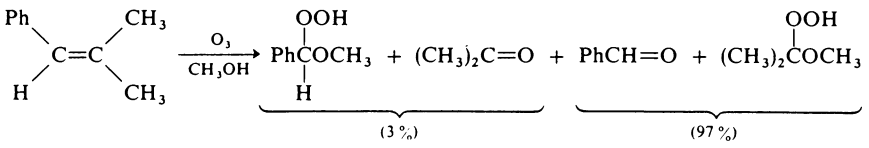


7. Overoxidation of carbonyl products during ozonolysis can be prevented by addition of tetracyanoethylene to the reaction mixture. The stoichiometry of the reaction is then



Propose a reasonable mechanism that would account for the effect of tetracyanoethylene. Does your mechanism suggest that tetracyanoethylene would be a particularly effective alkene for this purpose? Explain.

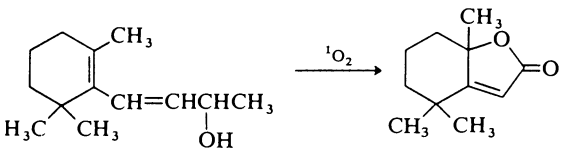
8. It has been noted that when unsymmetrical olefins are ozonized in methanol, there is often a large preference for one cleavage mode over the other. For example,



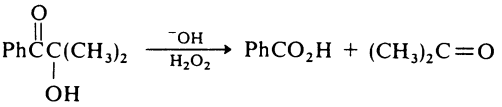
How would you explain this example of regioselective cleavage?

9. Suggest a mechanism by which the "abnormal" oxidations shown below might occur.

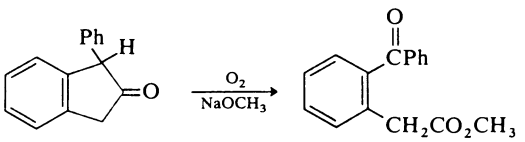
(a)



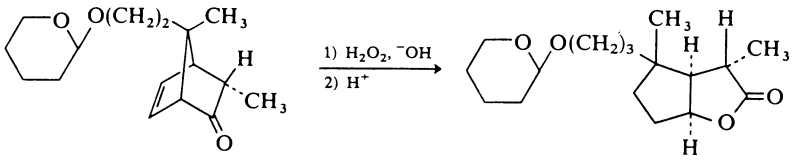
(b)



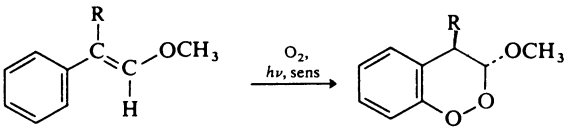
(c)



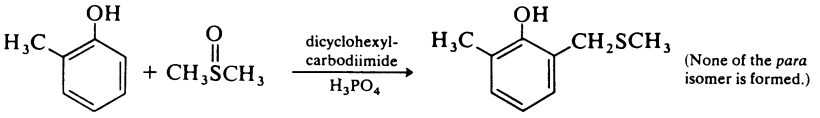
(d)



(e)



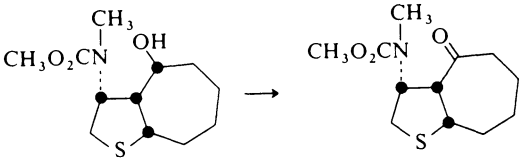
(f)



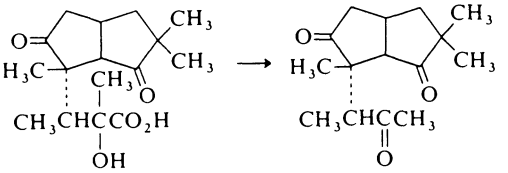
10. Indicate one or more satisfactory oxidants for effecting the following transformations. Each molecule poses problems of selectivity or the need to preserve a potentially sensitive functional group. In most cases a "single pot" process is possible and in no case is more than three steps required. Explain the basis

for your choice of reagent.

(a)



(b)



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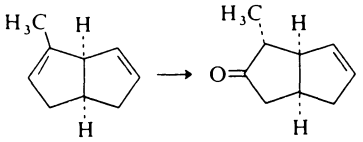
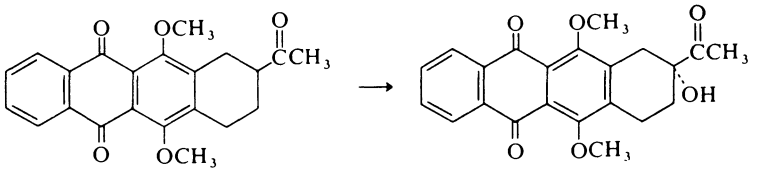


(d)



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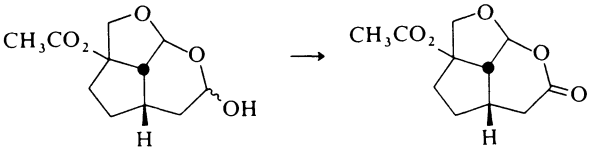

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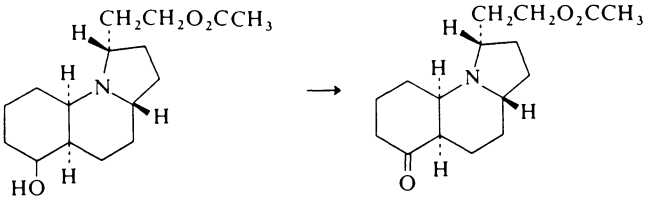
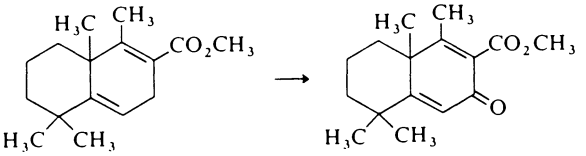
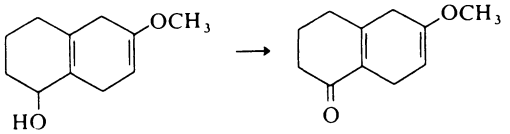


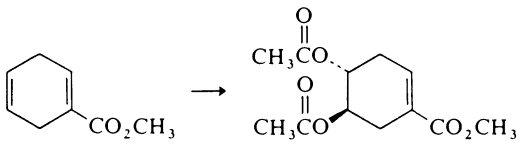
(g)



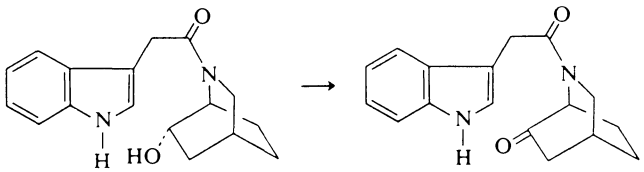
(h)



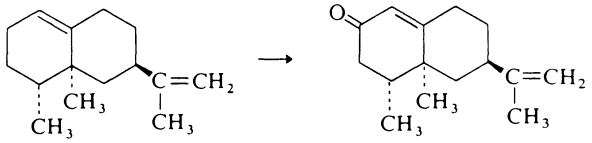
(i)



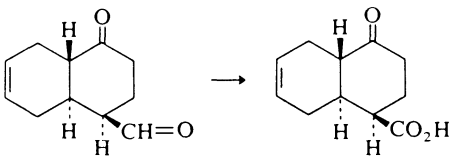
(j)



(k)

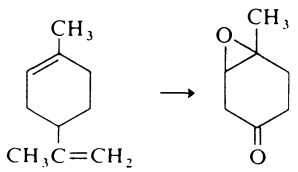


(l)

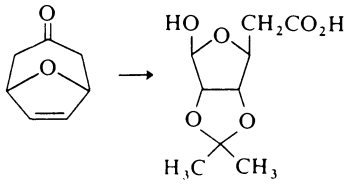


11. The two transformations shown below have been carried out by short reaction sequences involving several oxidative steps. Deduce a series of steps which could effect these transformations, and suggest reagents which might be suitable for each step.

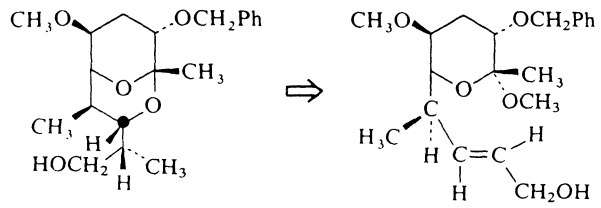
(a)

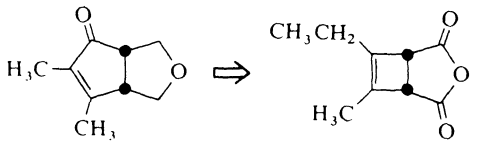


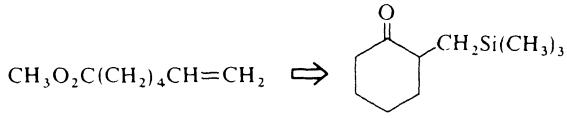
(b)

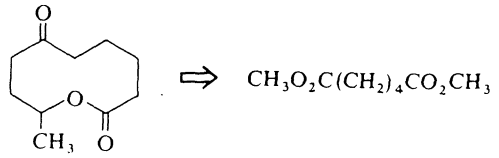


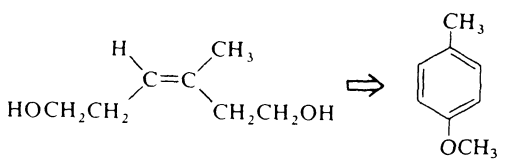
12. Devise a sequence of reactions which could accomplish the formation of the structure on the left from the potential precursor on the right. Pay close attention to stereochemical requirements.

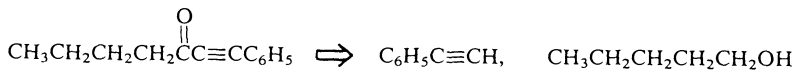
(a) 

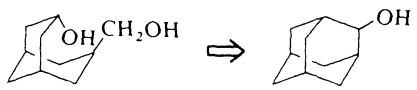
(b) 

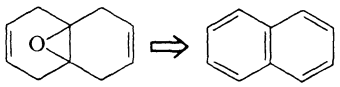
(c) 

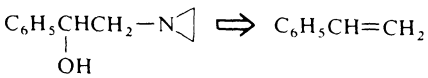
(d) 

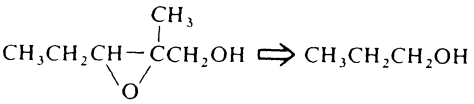
(e) 

(f) 

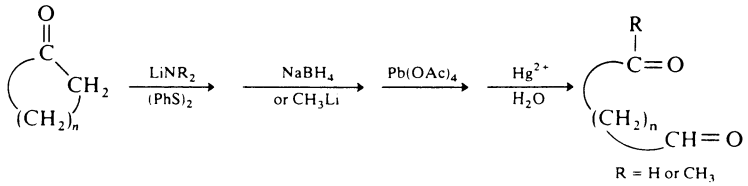
(g) 

(h) 

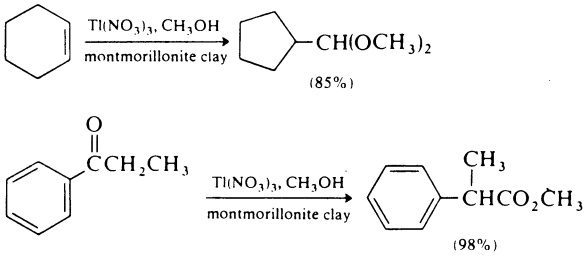
(i) 

(j) 

13. A method for oxidative cleavage of cyclic ketones involves a four-stage process. First, the ketone is converted to an α-phenylthio derivative (see Section 4.7). The ketone is then converted to an alcohol, either by reduction or addition of an organolithium reagent. This compound is then treated with lead tetraacetate to give an oxidation product in which the hydroxyl group has been acetylated and an additional oxygen added to the β-thioalcohol. Aqueous hydrolysis of this intermediate in the presence of Hg^{2+} gives a dicarbonyl compound. Formulate a likely structure for the product of each reaction step and an overall mechanism for this process.



14. Certain thallium salts, particularly $Tl(NO_3)_3$, effect oxidation with an accompanying rearrangement. Especially good yields are found when the thallium salt is supported on inert material. Two examples are given. Formulate a mechanistic rationalization.



11

Multistep Syntheses

The preceding chapters have discussed many of the reactions which are important tools for organic synthesis. Although some of the problems which accompany these chapters have dealt with synthesis, little has been said explicitly about the subject of multistep synthesis. In this chapter, the focus will be on multistep synthesis, using as essential background the knowledge of chemical reactions developed in the preceding chapters. The kinds of synthetic problems that are a challenge to organic synthetic techniques at present generally involve *multifunctional molecules.* Multistep synthesis therefore requires planning for the compatibility of proposed reactions with the various functional groups in the molecule. In Section 11.1, Protective Groups, we will consider ways of temporarily modifying functional groups that would otherwise interfere with reactions at other points in the molecule. In Section 11.2, Synthetic Equivalent Groups, the use of reactions which introduce or transform a functionality while in a "masked" form will be considered.

Most natural products and many other molecules which are the object of synthesis contain several chiral carbon atoms. The synthesis of such substances requires planning for control of stereochemistry in order to obtain the desired stereoisomer and to avoid the problems associated with separation and purification of mixtures of stereoisomers. Section 11.3, Asymmetric Synthesis, will consider this aspect of synthetic methodology and planning.

In Section 11.4, Synthetic Strategy, we will discuss some of the broad aspects of synthetic planning, and then in the final sections illustrate the execution of multistep syntheses, using some examples from the literature.

11.1. Protective Groups

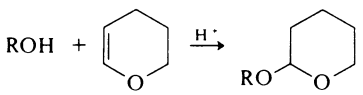
In the best of circumstances, each step in a synthetic sequence will affect only those sites in a molecule that are involved in the desired transformation. It often

happens, however, that a reagent which is required for a particular transformation will react not only with the target functional group, but also with some other site in the molecule. It then becomes necessary to temporarily modify the troublesome functional group in a way that makes it inert to the reagent, yet capable of being regenerated in a subsequent step.

Three considerations are important in choosing an appropriate protective group: (1) the nature of the group requiring protection; (2) the reaction conditions under which the protective group must exert its masking effect and, accordingly, to which it must be stable; and (3) the conditions that can be tolerated during removal of the protecting group. No universal protecting groups exist even for a single functionality. The state of the art has been developed to a high level, however, and the many mutually complementary protective groups provide a great deal of flexibility in the design of syntheses of complex molecules.[1]

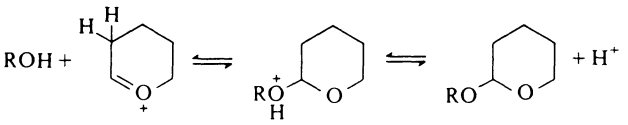
11.1.1. Hydroxyl-Protecting Groups

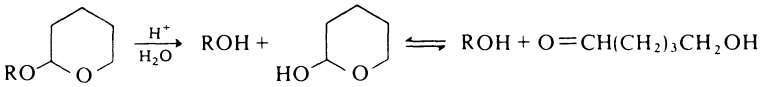
A common requirement in synthesis is that a hydroxyl group be masked as some derivative lacking an active hydrogen. An example of this requirement is in reactions involving a Grignard or other organometallic reagent. The acidic hydrogen of a hydroxyl group will destroy an equivalent of any strongly basic organometallic reagent, and possibly further adversely affect the reaction. The conversion of alcohols to alkyl or silyl ethers is the most common means of protecting hydroxyl groups. The choice of the most appropriate ether group is largely dictated by the conditions that can be tolerated in subsequent cleavage of the protecting group. An important method that is applicable when mildly acidic hydrolysis is an appropriate method for deprotection is to form the tetrahydropyranyl ether (THP group).[2]



This protective group is introduced by an acid-catalyzed addition to the vinyl ether moiety in dihydropyran. *p*-Toluenesulfonic acid or its pyridinium salt are recommended as catalysts,[3] though other acids are advantageous in special cases. The THP group can be removed by dilute aqueous acid. The chemistry involved in both the introduction and deprotection stages is the reversible acid-catalyzed formation and hydrolysis of an acetal (see Part A, Section 8.1).

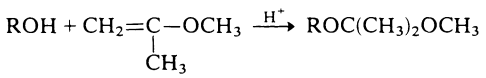
1. The book of T. W. Green, *Protective Groups in Organic Synthesis*, listed in the general references, provides a thorough and up-to-date survey of protective groups.
2. W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.* **70**, 4187 (1948).
3. J. H. van Boom and J. D. M. Herschied and C. B. Reese, *Synthesis*, 169 (1973).





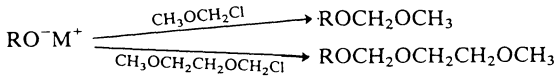
The tetrahydropyranyl group, like other acetals and ketals, is inert to nucleophilic reagents and is unchanged under such conditions as hydride reduction, organometallic reactions, or base-catalyzed reactions in aqueous solution. It also protects the hydroxyl group against oxidation reactions.

A disadvantage of the tetrahydropyranyl ether as a protecting group is the fact that a chiral center is produced at C-2 of the tetrahydropyran ring on reaction with the alcohol. This presents no difficulties if the alcohol is achiral, since a racemic mixture results, but if the alcohol is chiral the reaction gives a mixture of diastereomeric tetrahydropyranyl ethers, which may complicate purification and characterization. One way of surmounting this problem is to use methyl 2-propenyl ether, rather than dihydropyran. No new chiral center is introduced, and this acetal offers the further advantage of being hydrolyzed under milder conditions than those required for tetrahydropyranyl ethers.[4]



Ethyl vinyl ether is also useful as a hydroxyl-protecting group although it, like dihydropyran, also gives rise to diastereomers when a chiral alcohol is used.

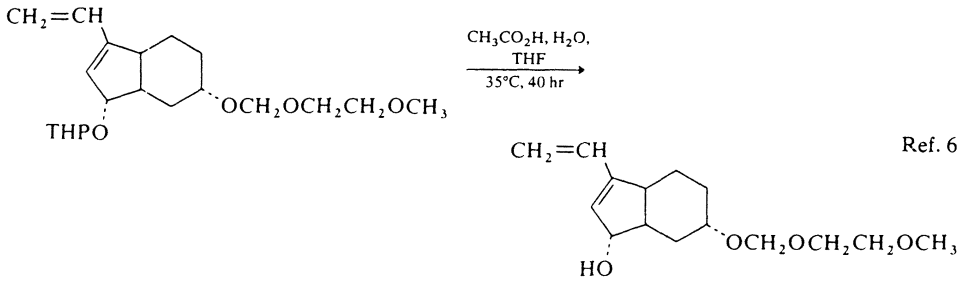
The methoxymethyl (MOM) and β-methoxyethoxymethyl (MEM) groups are used for protecting alcohols and phenols as formaldehyde acetals. These groups are introduced by reaction of an alkali metal salt of the alcohol with methoxymethyl chloride (chloromethyl methyl ether) or β-methoxyethoxymethyl chloride. An



attractive feature of the MEM group is the ease with which it can be removed under nonaqueous conditions. Lewis acids such as zinc bromide or titanium chloride permit its removal in halogenated solvents.[5] The MEM group is cleaved more rapidly than the MOM or THP group under these conditions. Conversely, the MEM group is more stable to acidic conditions than the THP group so it can be retained selectively by use of carefully controlled acidic cleavage conditions. These

4. A. F. Kluge, K. G. Untch and J. H. Fried, *J. Am. Chem. Soc.* **94**, 7827 (1972).
5. E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976).

relative reactivity relationships allow the THP and MEM groups to be used in a complementary fashion when two hydroxyl groups must be deprotected at different points in a synthetic sequence.



Ref. 6

The methylthiomethyl group is a related alcohol-protecting group. There are two alternative methods for introduction of the thiomethylmethyl group. Alkylation of an alcoholate by thiomethylmethyl chloride is efficient if catalyzed by iodide ion.[7a] Alcohols also react with dimethyl sulfoxide in the presence of acetic acid and acetic anhydride to give methylthiomethyl ethers.[7b]

$$RO^-M^+ + CH_3SCH_2Cl \xrightarrow{I^-} ROCH_2SCH_3$$

$$ROH + CH_3SOCH_3 \xrightarrow[(CH_3CO)_2O]{CH_3CO_2H} ROCH_2SCH_3$$

The thiomethylmethyl group is selectively removed under nonacidic conditions in aqueous solutions containing Ag^+ or Hg^{2+} salts.[7] The THP group is stable under these conditions. The group can also be removed by reaction with methyl iodide in moist acetone as a result of hydrolysis of the resulting sulfonium ion.[7b]

The simple alkyl groups are generally not very useful for protecting alcohol functions as ethers. Although they can be introduced readily enough by alkylation, subsequent cleavage requires strongly electrophilic reagents such as boron tribromide and boron trifluoride (see Section 3.3.1). The *t*-butyl group is an exception, and has found some use as a protecting group. Because of the stability of the *t*-butyl cation, *t*-butyl ethers can be cleaved under moderately acidic conditions.

The triphenylmethyl (trityl) group is removed under even milder conditions, and is an important hydroxyl-protecting group, especially in carbohydrate chemistry. This group is introduced by reaction of the alcohol with triphenylmethyl chloride via an S_N1 substitution. Hot aqueous acetic acid suffices to remove the trityl group. The ease of removal can be increased by addition of electron-releasing substituents. The *p*-methoxy derivatives have been employed for this purpose.[8]

6. E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.* **100**, 8031 (1978).
7a. E. J. Corey and M. G. Bock, *Tetrahedron Lett.*, 3269 (1975).
7b. P. M. Pojer and S. J. Angyal, *Tetrahedron Lett.*, 3067 (1976).
8. M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Am. Chem. Soc.* **84**, 430 (1962).

The triarylmethyl groups are sufficiently bulky that they can usually be introduced only at primary alcohol centers.

The benzyl group can serve as an alcohol-protecting group when acidic conditions for ether cleavage cannot be tolerated. The benzyl C–O bond is cleaved by catalytic hydrogenolysis,[9] or with sodium in liquid ammonia.[10] Benzyl ethers can also be cleaved using formic acid, cyclohexene, or cyclohexadiene as the source of hydrogen,[11] over a platinum black catalyst. A special method for removal of the benzyl group under non-reductive conditions has also been developed.[12] The

$$\mathrm{ROCH_2Ph} \xrightarrow{s\text{-BuLi}} \mathrm{ROCHPh}\,(\mathrm{Li}) \xrightarrow[2)\ H_2O_2]{1)\ B(OCH_3)_3} \mathrm{ROH}$$

mechanism for this cleavage can be understood as the oxidation reaction of an alkylborane like those discussed in Chapter 4.

$$\mathrm{ROCHPh}\,[(CH_3O)_2B] \xrightarrow{H_2O_2} \mathrm{ROCHPh}\,[OB(OCH_3)_2] \rightarrow \mathrm{ROH} + \mathrm{PhCH{=}O}$$

Allyl ethers may be removed by conversion to propenyl ethers, followed by acidic hydrolysis of the resulting enol ether. The isomerization of an allyl ether to

$$\mathrm{ROCH_2CH{=}CH_2} \rightarrow \mathrm{ROCH{=}CHCH_3} \xrightarrow{H_3O^+} \mathrm{ROH} + \mathrm{CH_3CH_2CH{=}O}$$

a propenyl ether can be achieved by treatment with potassium *tert*-butoxide in dimethyl sulfoxide[13] or by refluxing in ethanol with Wilkinson's catalyst, *tris*-triphenylphosphinechlororhodium.[14]

Silyl ethers play a very important role as hydroxyl-protecting groups. Alcohols can be easily converted to trimethylsilyl ethers by reaction with trimethylsilyl chloride in the presence of an amine or by heating with hexamethyldisilazane. *t*-Butyldimethylsilyl ethers are also of considerable use as alcohol-protecting groups.[15] The increased steric bulk of the *t*-butyldimethylsilyl group improves the

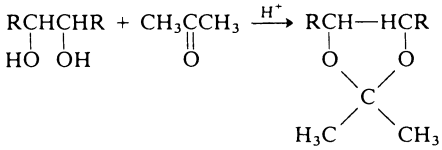
$$\mathrm{ROH} + (CH_3)_3SiCl \xrightarrow{R_3N} \mathrm{ROSi(CH_3)_3}$$

stability of the silyl group in such reactions as hydride reduction (diisobutylaluminum hydride) and Cr(VI) oxidation (chromic acid in acetone). This group is attached by

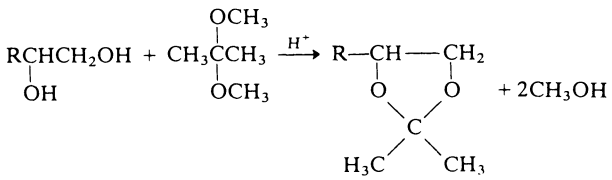
9. W. H. Hartung and R. Simonoff, *Org. React.* **7**, 263 (1953).
10. E. J. Reist, V. J. Bartuska, and L. Goodman, *J. Org. Chem.* **29**, 3725 (1964).
11. B. ElAmin, G. M. Anatharamaiah, G. P. Royer, and G. E. Means, *J. Org. Chem.* **44**, 3442 (1979); A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, and J. Meienhofer, *J. Org. Chem.* **43**, 4194 (1978); A. E. Jackson and R. A. W. Johnstone, *Synthesis*, 685 (1976); G. M. Anatharamaiah and K. M. Sivandaiah, *J. Chem. Soc. Perkin Trans. 1*, 490 (1977).
12. D. A. Evans, C. E. Sacks, W. A. Kleschick, and T. R. Taber, *J. Am. Chem. Soc.* **101**, 6789 (1979).
13. R. Giggs and C. D. Warren, *J. Chem. Soc. C*, 1903 (1968).
14. E. J. Corey and J. W. Suggs, *J. Org. Chem.* **38**, 3224 (1973).
15. J. F. Klebe, in *Advances in Organic Chemistry, Methods and Results*, Vol. 8, E. C. Taylor (ed.), Wiley-Interscience, New York (1972), pp. 97–178; A. E. Pierce, *Silylation of Organic Compounds*, Pierce Chemical Co., Rockford, Illinois (1968).

using imidazole as a catalyst for the reaction of the alcohol with *t*-butyldimethylsilyl chloride in dimethylformamide. Cleavage of the protecting group is slow under hydrolytic conditions, but fluoride ion (tetra-*n*-butylammonium fluoride in tetrahydrofuran),[16] aqueous HF,[17] or boron trifluoride[18] can be used to remove it.

Diols represent a special case in terms of applicable protecting groups. 1,2-Diols and 1,3-diols easily form cyclic acetals and ketals with aldehydes and ketones, unless cyclization is precluded by the geometry of the molecule. The isopropylidene derivatives (acetonides) formed by reaction with acetone are a good example. Being



a ketal, this protective group shares with tetrahydropyranyl derivatives the property of being resistant to basic and nucleophilic reagents, but is readily removed by aqueous acid. The isopropylidene group can also be introduced by acid-catalyzed exchange with 2,2-dimethoxypropane.[19] Formaldehyde, acetaldehyde, and benzal-

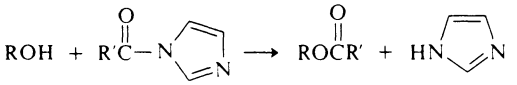


dehyde have all been used as the carbonyl component in formation of cyclic acetals. They function in the same manner as acetone, but usually offer no advantage relative to acetone. A disadvantage is present with acetaldehyde and benzaldehyde when the glycol contains a chiral center. The acetals formed from these aldehydes introduce a new chiral center, and thus can lead to a mixture of diastereomers.

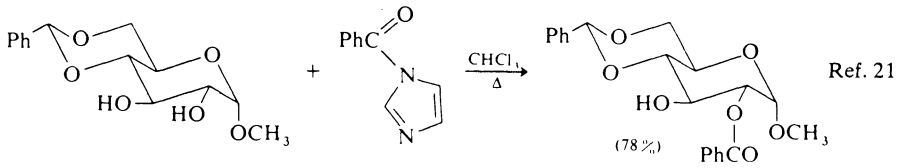
Protection of an alcohol function by esterification sometimes offers advantages over acetal-protecting groups such as the tetrahydropyranyl ethers. Generally, acetals are stable in base and labile in acid, while esters are more stable in acid than acetals and are readily hydrolyzed in base. Esters are especially useful in oxidations, but are not suitable in organometallic reactions. Acetates and benzoates are the most common ester-protecting groups; they can be conveniently prepared by reaction of unhindered alcohols with acetic anhydride or benzoyl chloride, respectively, in the presence of pyridine or other tertiary amines. The use of *N*-acylimidazoles (imidazolides) allows the reaction to be carried out in the absence

16. E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.* **94**, 6190 (1972).
17. R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, and S. M. Roberts, *Tetrahedron Lett.*, 3981 (1979).
18. D. R. Kelly, S. M. Roberts, and R. F. Newton, *Synth. Commun.* **9**, 295 (1979).
19. M. Tanabe and B. Bigley, *J. Am. Chem. Soc.* **83**, 756 (1961).

of added bases.[20] Imidazolides are less reactive than the corresponding acid

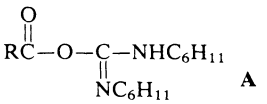


chlorides and can exhibit a high degree of selectivity in reactions with molecules possessing several hydroxyl groups:



Ref. 21

Hindered hydroxyl groups require special acylation procedures. One method is to increase the reactivity of the hydroxyl group by converting it to an alkoxide ion with strong base (e.g., *n*-BuLi, or KH). When this conversion is either not feasible or ineffective, more reactive acylating agents are used. Highly reactive acylating agents are generated *in situ* when carboxylic acids are mixed with trifluoroacetic anhydride. The mixed anhydrides exhibit increased reactivity because of the high reactivity of the trifluoroacetate as a leaving group.[22] Dicyclohexylcarbodiimide is another reagent that serves to activate carboxyl groups by forming the iminoanhydride **A** (see Section 3.4.1).



A

When base-catalyzed hydrolysis is inappropriate, alcohols can be protected as trichloroethyl carbonate esters. These are prepared by reaction of the alcohol with trichloroethyl chloroformate in the presence of pyridine. This protecting group is removed reductively by zinc.[23]

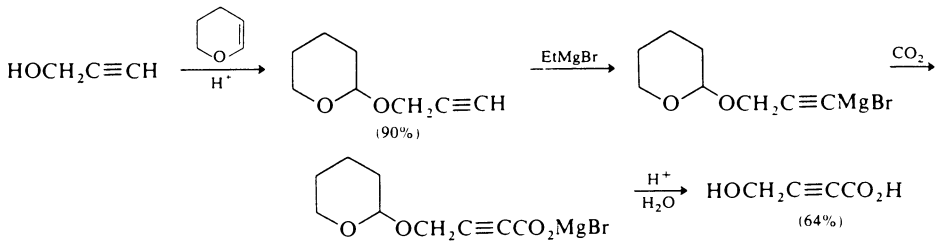
Cyclic carbonate esters are easily prepared from *vic*-diols and can be used in a fashion complementary to the cyclic acetals previously described. These esters are commonly prepared from *N,N'*-carbonyldiimidazole[24] or by transesterification using diethyl carbonate. These reagents are preferable to phosgene both in efficiency and convenience.

Scheme 11.1 depicts some short synthetic sequences that illustrate the use of several of the important hydroxyl-protecting groups.

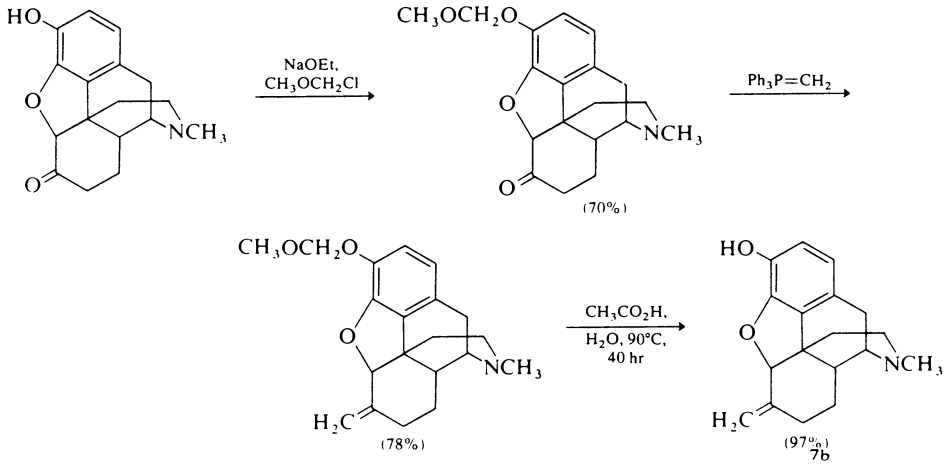
20. H. A. Staab, *Angew. Chem.* **74**, 407 (1962).
21. F. A. Carey and K. O. Hodgson, *Carbohyd. Res.* **12**, 463 (1970).
22. R. C. Parish and L. M. Stock, *J. Org. Chem.* **30**, 927 (1965); J. M. Tedder, *Chem. Rev.* **55**, 787 (1955).
23. T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).
24. J. P. Kutney and A. H. Ratchiffe, *Synth. Commun.*, 547 (1975).

Scheme 11.1. Protection

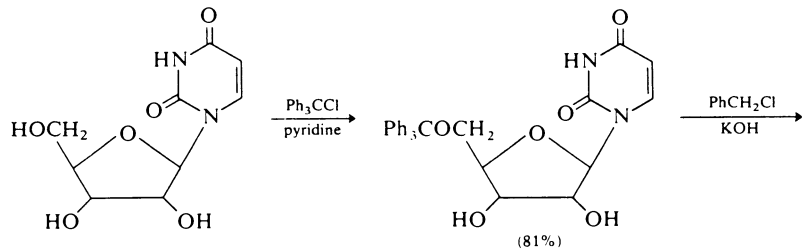
1. Tetrahydropyranyl ether[a]



2. Methoxymethyl ether[b]



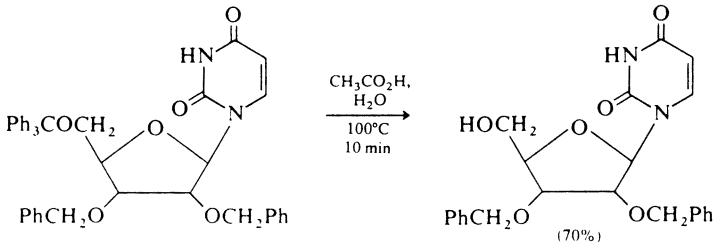
3. Triarylmethyl ether[c]



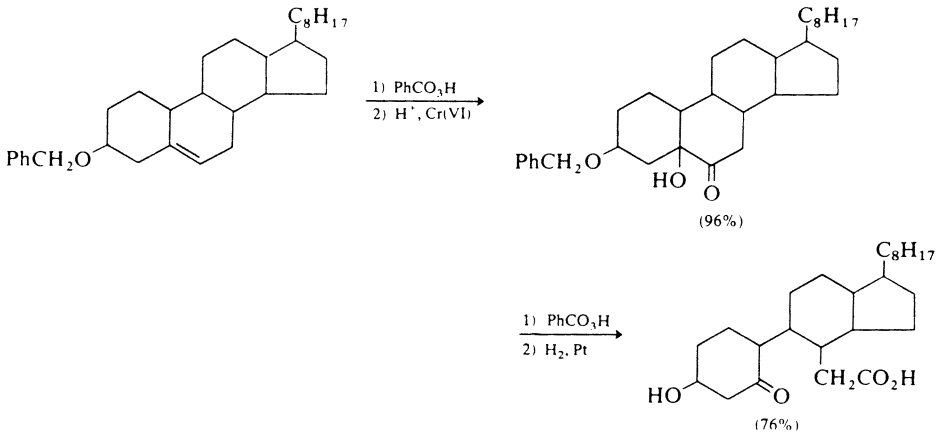
a. H. B. Henbest, E. R. H. Jones, and I. M. S. Walls, *J. Chem. Soc.*, 3646 (1950).
b. M. A. Abdel-Rahman, H. W. Elliott, R. Binks, W. Küng, and H. Rapoport, *J. Med. Chem.* **9**, 1 (1965).
c. A. M. Michelson and A. Todd, *J. Chem. Soc.*, 3459 (1956).

11.1.2. Amino-Protecting Groups

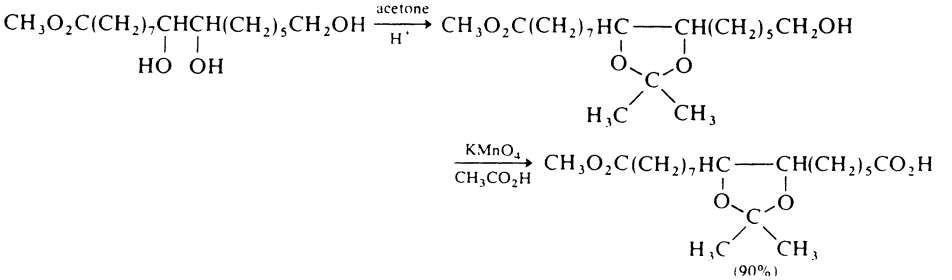
Primary and secondary amino groups are sites of both nucleophilicity and a weakly acidic hydrogen. If a given reaction cannot proceed in the presence of either



4. Benzyl ether[d]



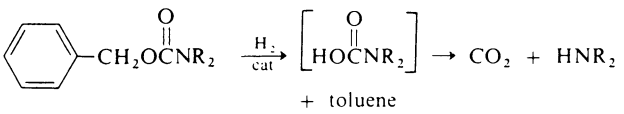
5. Glycol protection by isopropylidene derivative[e]



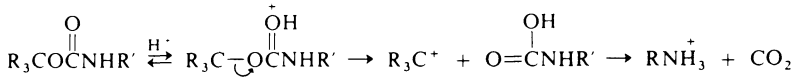
d. L. Knof, *Justus Liebigs Ann. Chem.* **656**, 183 (1962).
e. S. D. Sabnis, H. H. Mathur, and S. C. Bhattacharyya, *J. Chem. Soc.*, 2477 (1963).

of these types of reactivity, a protected derivative must be employed. The masking of nucleophilicity can be accomplished by acylation. A most useful protecting group for this purpose is the carbobenzyloxy group. The utility of this group lies in the ease with which it can be removed. Because of the lability of benzyl C–O bonds

toward hydrogenolysis, the amine can be regenerated from a carbobenzyloxy derivative by hydrogenation, which is accompanied by spontaneous decarboxylation:

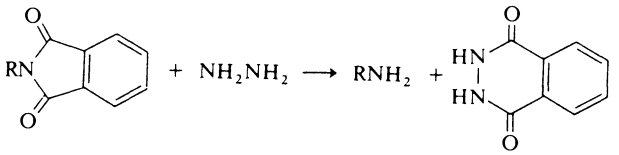


t-Butoxycarbonyl groups are also useful for protecting amines. The ease of removal in this case results from the stability of the tertiary carbonium ion. Acids such as

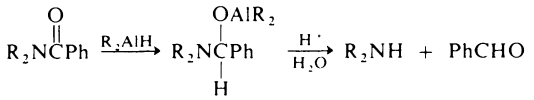


trifluoroacetic acid or *p*-toluenesulfonic acid bring about removal of *t*-butoxycarbonyl groups. The trichloroethoxycarbonyl group is also useful for protecting amines as carbamates. The group is reductively removed by zinc.[23]

Simple amides are satisfactory protecting groups only if the molecule as a whole can resist the vigorous acidic or alkaline conditions required for hydrolytic removal. Phthaloyl groups have been used to protect primary amine centers. The group can be removed hydrolytically or by treatment with hydrazine. The imide carbonyl groups are more reactive than simple amides and the deprotection is completed by an intramolecular cyclization.[25]



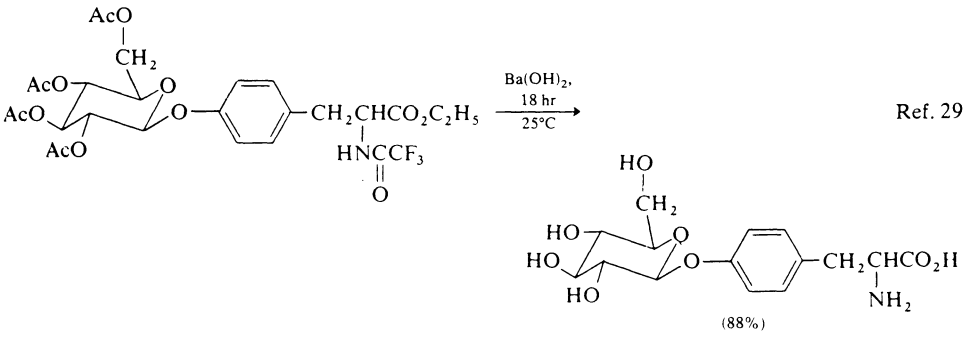
Under some circumstances, it is possible to effect removal of amide groups by selective hydride reduction. Trichloroacetamides are readily cleaved by sodium borohydride in alcohols.[26] Another reductive method that can be applied to benzamides, and probably to other simple amides, involves treatment with diisobutylaluminum hydride. At low temperatures, the reduction stops at the carbinolamine stage. Hydrolysis then yields the amine.[27]



The trifluoroacetyl group also finds some use as a protecting group. Because of the electron-withdrawing effect of the trifluoromethyl group, the

25. M. S. Gibson and R. N. Bradshaw, *Angew. Chem. Int. Ed. Engl.* **7**, 919 (1968).
26. F. Weygand and E. Frauendorfer, *Chem. Ber.* **103**, 2437 (1970).
27. J. Gutzwiller and M. Uskokovic, *J. Am. Chem. Soc.* **92**, 204 (1970).

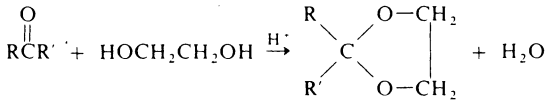
trifluoroacetamides are much more subject to alkaline hydrolysis than most amides, and can be removed under relatively mild conditions.[28]



Ref. 29

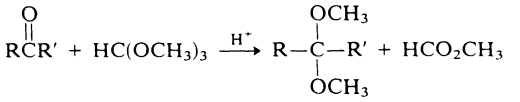
11.1.3. Carbonyl-Protecting Groups

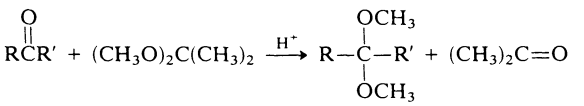
Conversion to acetals or ketals is a very general method for protecting aldehydes and ketones against addition by nucleophiles or reduction at the carboxyl group. Ethylene glycol, which gives a cyclic dioxolane derivative, is the most frequently employed reagent for this purpose. The derivative is usually prepared by heating the reagents in the presence of a trace of acid with provision for azeotropic



removal of water. The dioxolane ring is inert to powerful nucleophiles, including organometallic reagents and the hydride-reducing agents, but is readily removed in acidic solution containing water by the general hydrolysis mechanism for acetals and ketals (Part A, Section 8.1).

Acyclic acetals and ketals can also be prepared. A convenient route involves acid-catalyzed exchange with an orthoester[30] or an available ketal such as 2,2-dimethoxypropane. Ketals and acetals can also be prepared from the carbonyl

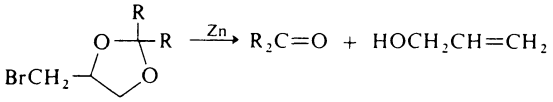




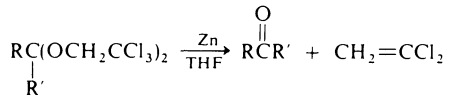
28. F. Weygand and E. Csendes, *Angew. Chem.* **64**, 136 (1952).
29. A. Taurog, S. Abraham, and I. L. Chaikoff, *J. Am. Chem. Soc.* **75**, 3473 (1953).
30. C. A. MacKenzie and J. H. Stocker, *J. Org. Chem.* **20**, 1695 (1955); E. C. Taylor and C. S. Chiang, *Synthesis*, 467 (1977).

compound and alcohol in the presence of an acidic catalyst. Provision of a means for removal of the water formed ensures that the reaction will go to completion.

If a carbonyl group must be regenerated under conditions other than acid-catalyzed hydrolysis, β-halo alcohols such as 3-bromo-1,2-dihydroxypropane or 2,2,2-trichloroethanol can be used. Reductive cleavage by zinc metal is then possible. Another variation is the use of mercaptoethanol in place of ethylene

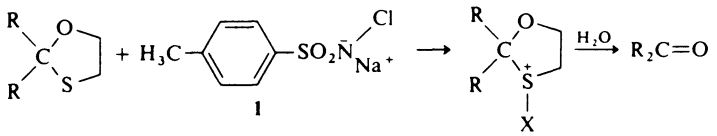


Ref. 31



Ref. 32

glycol. The 1,3-oxathiolane derivatives are readily formed from ketones and mercaptoethanol in the presence of BF_3,[33] or by heating in benzene with *p*-toluenesulfonic acid catalyst with azeotropic removal of water.[34] The 1,3-oxathiolanes have an advantage over the 1,3-dioxolanes for applications where nonacidic conditions are required for subsequent removal of the protecting group. The 1,3-oxathiolane group can be removed by treatment with Raney nickel in alcoholic solution, even under slightly alkaline conditions.[35] Removal can also be accomplished by treating with a mild halogenating agent such as chloramine-T which oxidizes the sulfur to a chlorosulfonium salt. This moiety is a more reactive leaving group, and removal of the protecting group then occurs by a hydrolytic process.[36]



The various derivatives of carbonyl compounds that involve formation of carbon–nitrogen double bonds at the carbonyl center are not very generally useful as protecting groups. This includes oximes, semicarbazones, and hydrazones. The compounds are usually formed easily enough, but mild conditions for removal are not available. An exception involves the removal of the oxime group by conversion to the acetate ester, followed by chromous ion reduction.[37]

31. E. J. Corey and R. A. Ruden, *J. Org. Chem.* **38**, 834 (1973).
32. J. L. Isidor and R. M. Carlson, *J. Org. Chem.* **38**, 554 (1973).
33. G. E. Wilson, Jr., M. G. Huang, and W. W. Scholman, Jr., *J. Org. Chem.* **33**, 2133 (1968).
34. C. Djerassi and M. Gorman, *J. Am. Chem. Soc.* **75**, 3704 (1953).
35. C. Djerassi, E. Batres, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.* **74**, 3634 (1952).
36. D. W. Emerson and H. Wynberg, *Tetrahedron Lett.*, 3445 (1971).
37. E. J. Corey and J. E. Richman, *J. Am. Chem. Soc.* **92**, 5276 (1970).

$$R_2C{=}NOH \xrightarrow{Ac_2O} R_2C{=}N{-}O{-}\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow{Cr(II)} R_2C{=}O$$

11.1.4. Carboxylic Acid-Protecting Groups

If only the O–H, as opposed to the carbonyl, group of a carboxyl function needs to be masked, this can be readily accomplished by the standard esterification techniques. Alkaline hydrolysis is the usual way for regenerating the acid. *t*-Butyl esters are readily cleaved by mildly acidic conditions because of the facile cleavage of the alkyl oxygen bond. 2,2,2-Trichloroethyl esters find some specialized use. This group can be removed with zinc dust in aqueous acetic acid.[38]

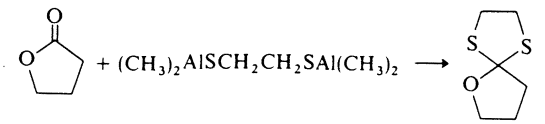
$$R\overset{\overset{O}{\|}}{C}OCH_2CCl_3 \xrightarrow{Zn} RCO_2H + CH_2{=}CCl_2$$

The more difficult problem of protecting the carbonyl group can be accomplished by conversion to a 2-oxazoline derivative. The most commonly used 2-oxazoline is the 4,4-dimethyl derivative, which can be prepared from the acid and 2-amino-2-methyl-1-propanol or from 2,2-dimethylaziridine.[39] The carboxyl function is successfully masked by the heterocyclic ring toward attack by Grignard reagents or hydride-reducing agents. The carboxyl group can be regenerated by acidic hydrolysis. Alternatively, treatment with acid in an alcohol returns the carboxylic ester.

$$RCO_2H + HOCH_2\underset{\displaystyle NH_2}{\overset{\displaystyle |}{C}}(CH_3)_2 \longrightarrow R{-}C\!\!<\!\!\begin{matrix}N{=}\\ O\end{matrix}\!\!-\!\!\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}$$

$$RCO_2H + HN\!<\!\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}} \longrightarrow RC(=O){-}N\!<\!\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}} \xrightarrow{H^+} \left[RC(OH){=}N{-}CH_2{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C^+}}\right] \longrightarrow R{-}\!<\!\begin{matrix}N\\ O\end{matrix}\!\!-\!\!\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}$$

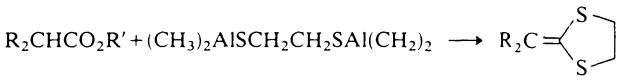
Lactones can be protected as dithioketals using a method which is analogous to ketone protection. The reagent required is prepared readily from trimethyl-



Ref. 40

38. R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, *J. Am. Chem. Soc.* **88**, 852 (1966).
39. A. I. Meyers, D. L. Temple, D. Haidukewych, and E. Mihelich, *J. Org. Chem.* **39**, 2787 (1974).
40. E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.* **95**, 5829 (1973).

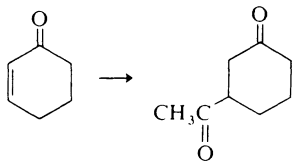
aluminum and ethanedithiol. Acyclic esters, however, react with this reagent to give ketenethioacetals. It is common to carry potential carboxylic acids through



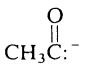
synthetic schemes as protected primary alcohols or protected aldehydes and then carry out an oxidation to the carboxylic acid at an appropriate stage. This strategy allows one to utilize the wider variety of alcohol- and aldehyde-protecting groups as indirect methods for carboxylate protection.

11.2. Synthetic Equivalent Groups

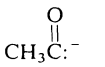
The protecting groups discussed in the previous section play only a passive role during a synthetic sequence. The groups are introduced and removed at appropriate stages but do not directly influence the reactivity of the molecule. It is often advantageous to combine the need for masking of a functional group with a desirable change in the reactivity of the functionality in question. As an example, suppose the transformation shown below was to be accomplished.



The electrophilic α,β-unsaturated ketone is reactive toward nucleophiles, but the nucleophile which is required,



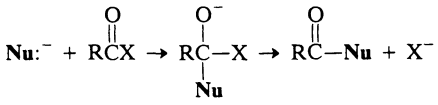
is not a chemically accessible entity. As will be demonstrated, however, there are several potential reactions which could introduce the hypothetical



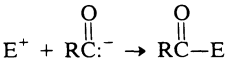
in a masked form. The concept of using a masked functionality in place of an inaccessible reactivity moiety is referred to as using a *synthetic equivalent* group. Sets of reagents and reaction sequences which accomplish identical overall transformations are said to be *synthetically equivalent.* Often the concept of "umpolung" is involved in devising or recognizing synthetic equivalents.[41] The term *umpolung*

41. For a general discussion and many examples of the use of the umpolung concept, see D. Seebach, *Angew. Chem. Int. Ed. Engl.* **18**, 239 (1979).

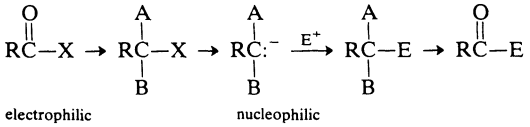
is applied to the formal reversal of the normal polarity of a functional group. Carbonyl groups are normally electrophilic.



Often, as in the example above, a synthetic operation may require transfer of an acyl group as if it were a nucleophilic acyl anion. While acyl anions are not commonly

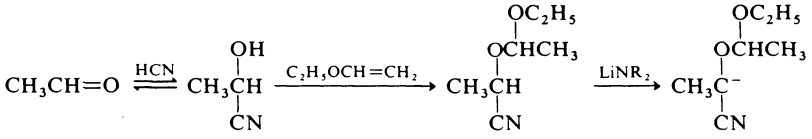


synthetically accessible, there are a variety of reagents which are synthetically equivalent to acyl anions, permitting the umpolung of carbonyl reactivity.



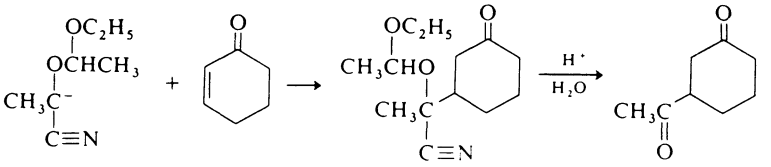
A third term which has become useful for the discussion of synthetic analysis and planning is *synthon*. This term refers to a structural unit which has the potential for some specific synthetic operation. Again using the example above, we are searching for a group which would serve as a nucleophilic acyl synthon; that is, some structural entity that would correspond to the addition of a nucleophilic acyl equivalent to an electrophilic carbon–carbon double bond.

The specific example discussed above is part of a more general synthetic question. There are very effective methods of accomplishing nucleophilic additions to carbonyl groups. How can one complement this family of reactions with processes which would allow the acyl group to act as the nucleophile? In other words, what *synthons* can serve as nucleophilic acyl equivalents? Because of the great importance of carbonyl groups in synthetic chemistry there has been substantial research effort devoted to this question. One successful sequence involves a three-step process in which an aldehyde is converted to the corresponding cyanohydrin which is then protected at the hydroxyl group and deprotonated.



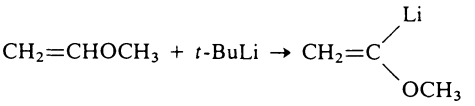
The resulting carbanion is an acyl anion equivalent since the carbonyl group can be regenerated by hydrolysis.[42] In fact, this sequence has been used to solve the problem of adding an acetyl group to an α,β-unsaturated ketone such as cyclohexenone.

42. G. Stork and L. Maldonado, *J. Am. Chem. Soc.* **93**, 5286 (1971); *J. Am. Chem. Soc.* **96**, 5272 (1974).

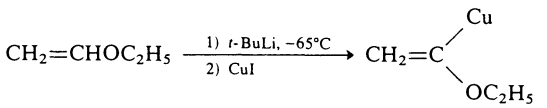


Ref. 42

Recent advances in methods of preparation of organometallic derivatives of vinyl ethers have provided another group of acyl anion equivalents.

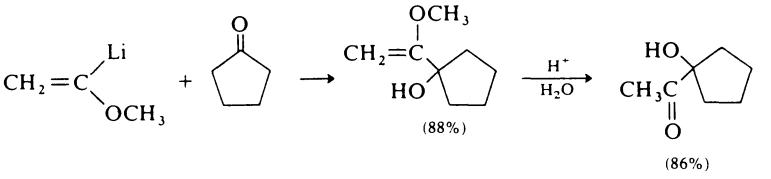


Ref. 43



Ref. 44

These reagents are capable of adding the α-alkoxyvinyl group at electrophilic centers. Subsequent hydrolysis can generate the carbonyl group and complete the overall transformation.



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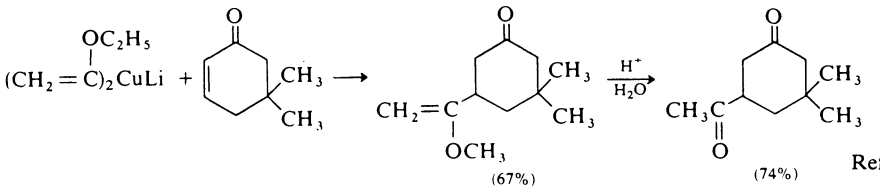
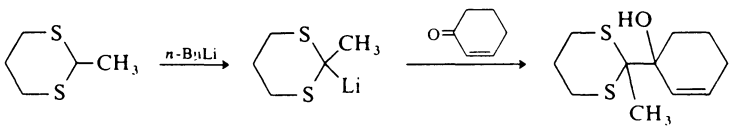
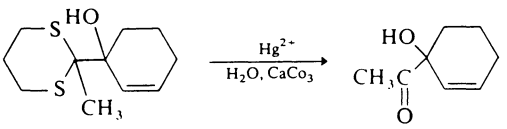


Ref. 44

Sulfur compounds have also proven useful as the basis for nucleophilic acyl equivalents. The first reagent to find general use was 1,3-dithiane, which on lithiation provides the nucleophilic acyl group masked as a thioketal. The lithium derivative is reactive toward alkyl halides and carbonyl compounds.[45] Closely

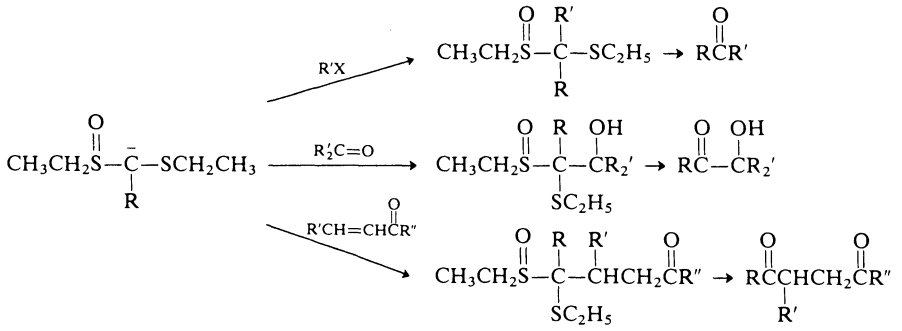


43. J. E. Baldwin, G. A. Höfle, and O. W. Lever, Jr., *J. Am. Chem. Soc.* **96**, 7125 (1974).
44. R. K. Boeckman, Jr. and K. J. Bruza, *J. Org. Chem.* **44**, 4781 (1979).
45. D. Seebach and E. J. Corey, *J. Org. Chem.* **40**, 231 (1975).



Ref. 46

related procedures are based on α-alkylthiosulfoxides, ethylthiomethyl ethyl sulfoxide derivatives being particularly convenient.[47]

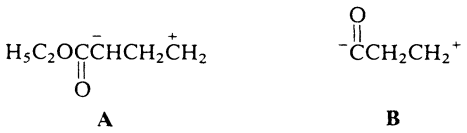


The α-ethylthiosulfoxides can be converted to the corresponding carbonyl compounds by hydrolysis catalyzed by mercuric ion. In both of these systems an umpolung is achieved as the result of the carbanion-stabilizing ability of the sulfur substituents. The same sulfur substituents provide access to the carbonyl group by the hydrolysis mechanism.

Another group of synthetic equivalents have been developed to correspond to the propionaldehyde "homoenolate" anion, $^{-}CH_2CH_2CH{=}O$. This will be recognized as equivalent to the umpolung of an important synthon, the *electrophilic* α,β-unsaturated aldehyde, acrolein. Scheme 11.2 lists some homoenolate equivalents. In general the compounds shown are reactive toward such electrophiles as alkyl halides and carbonyl compounds. Several general points can be made about the reagents in Scheme 11.2. First it should be noted that all deliver the product aldehyde in masked form, either as an acetal, enol ether, or thioenol ether. Thus a final hydrolytic step would be required. Except for entry 1, delocalized allylic anions are involved. Most electrophiles give some α attack as well as the dominant γ attack which is shown in the scheme. Entry 4, the thioacrolein dianion, is interesting in that this selectivity is reversed in favor of predominant α nucleophilicity if the metal is changed to magnesium.[48]

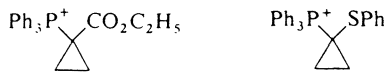
The concept of developing reagents which are synthetic equivalents of inaccessible species can be taken another step by considering some dipolar species; for example,

46. E. J. Corey and B. W. Erickson, *J. Org. Chem.* **36**, 3553 (1971).
47. J. E. Richman, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Lett.*, 3267 (1973); J. L. Herrmann, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 3267 (1973); J. L. Herrmann, J. E. Richman, P. J. Wepplo, and R. H. Schlessinger, *Tetrahedron Lett.*, 4707 (1973).
48. D. Seebach, K.-H. Geiss, and M. Pohmakotr, *Angew. Chem. Int. Ed.* **15**, 437 (1976).



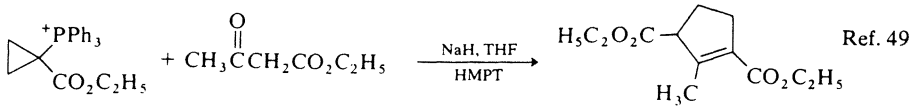
A **B**

Such reagents might, for example, be incorporated into annulation schemes since they have the ability of undergoing the formal equivalent of cycloaddition reactions. Among the real chemical species which have been developed along these lines are the cyclopropane derivatives **1** and **2**. The phosphonium salt **1** reacts with β-



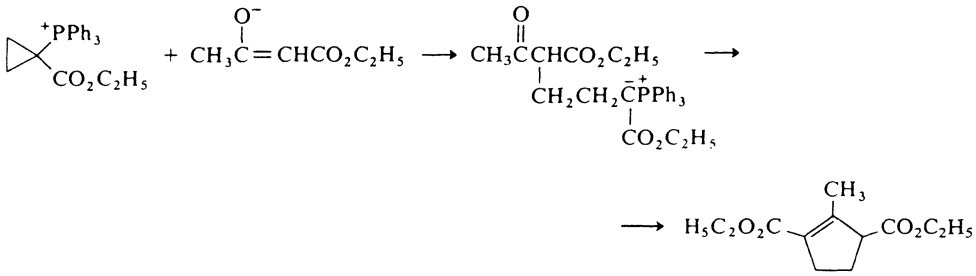
1 **2**

ketoesters and β-ketoaldehydes to give excellent yields of cyclopentenecarboxylate esters. Several steps are involved. First the enolate of the ketoester is formed and

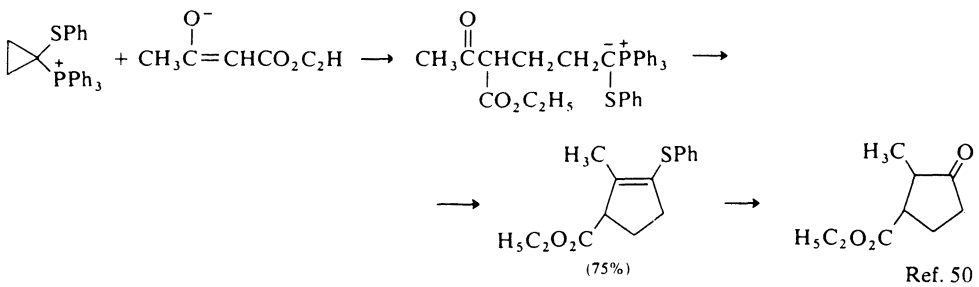


Ref. 49

opens the cyclopropane ring. The polarity of this process corresponds to that incorporated into the formal synthon **A**. The species which is generated by the ring opening is a stabilized Wittig ylide which goes on to react with the ketone carbonyl.



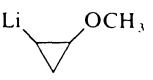
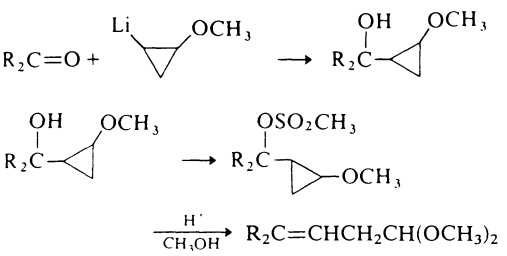
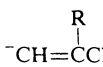
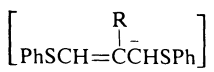
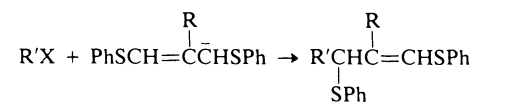
The second phosphonium salt **2** reacts very similarly to give vinyl sulfides. Because vinyl sulfides can be hydrolyzed to ketones, this is the synthetic equivalent of dipolar synthon **B**.



Ref. 50

49. P. L. Fuchs, *J. Am. Chem. Soc.* **96**, 1607 (1974); W. G. Dauben and D. J. Hart, *J. Am. Chem. Soc.* **99**, 7307 (1977).
50. J. P. Marino and R. C. Landick, *Tetrahedron Lett.*, 4531 (1975).

Scheme 11.2. Aldehyde Homoenolate Synthetic Equivalents

	Synthon	Reagent	Reaction Sequence
1[a]	$^{-}CH_2CH_2CH{=}O$		
2[b]	$^{-}CH_2CH_2CH{=}O$	$CH_2{=}CHCHOCH_3$ (Li)	$R_2C{=}O + CH_2{=}CHCHOCH_3$ (Li) → $R_2CCH_2CH{=}CHOCH_3$ (OH) → $R_2CCH_2CH_2CH{=}O$
3[c]	$^{-}CH_2CH_2CH{=}O$	$CH_2{=}CHCHOSi(CH_3)_3$ (Li)	$RX + CH_2{=}CHCHOSi(CH_3)_3$ (Li) → $RCH_2CH{=}CHOSi(CH_3)_3$ → $RCH_2CH_2CH{=}O$
4[d]	$^{-}CH_2CH_2CH{=}O$	$LiCH_2CH{=}CHS^{-}$	$R_2C{=}O + LiCH_2CH{=}CHS^{-}$ → $R_2C(OH)CH_2CH{=}CHS^{-}$ → $R_2CCH_2CH{=}CHSCH_3$
5[e]	$^{-}CH{=}CHCH{=}O$	$[CH_3SCH{=}C\bar{C}HSCH_3]$	$R'X + CH_3SCH{=}C\bar{C}HSCH_3$ → $R'CH(SCH_3)CH{=}CHSCH_3$
6[f]			

a. E. J. Corey and P. Ulrich, *Tetrahedron Lett.*, 3685 (1975).
b. D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Am. Chem. Soc.* **96**, 5560 (1974).
c. W. C. Still and T. L. Macdonald, *J. Am. Chem. Soc.* **96**, 5561 (1974).
d. K.-H. Geiss, B. Seuring, R. Pieter, and D. Seebach, *Angew. Chem. Int. Ed. Engl.* **13**, 479 (1974); K.-H. Geiss, D. Seebach, and B. Seuring, *Chem. Ber.* **110**, 1833 (1977).
e. E. J. Corey, B. W. Erickson, and R. Noyori, *J. Am. Chem. Soc.* **93**, 1724 (1971).
f. T. Cohen, D. A. Bennett, and A. J. Mura, Jr., *J. Org. Chem.* **41**, 2506 (1976).

Many additional examples of synthetic equivalent groups have been developed. For example, in Chapter 6 the use of dienes and dienophiles with masked functionality in Diels–Alder reactions was discussed. It should also be recognized that the difference between a "reagent" and a "synthetic equivalent group" is not an absolute one. For example, we think of potassium cyanide as a reagent, but the cyanide ion can be viewed as the synthetic equivalent of a nucleophilic carboxyl group, $^{-}CO_2H$, when employed as part of the classical scheme for making carboxylic acids from halides. The important point to recognize is that synthetic planning need not be

$$RX + KCN \rightarrow RCN \xrightarrow[H^+]{H_2O} RCO_2H$$

restricted to the specific functionalities which appear in the target molecule. Groups which are masked versions of these functionalities may provide an entry to important steps which would not be possible with the functionality itself.

11.3. Asymmetric Synthesis

The design of a multistep synthesis usually requires very careful consideration of elements of stereochemistry. In synthesis, the goal is to be able to control the formation of centers of chirality in the molecule. This topic is broadly covered by the term *asymmetric synthesis*,[51] which has been defined as "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts."[52] The required stereochemical control, in general, may be exercised by a structural element already present in the molecule or by a reagent or catalyst. Asymmetric synthesis can be further subdivided into diastereoselective processes and enantioselective processes. The relevant terminology was discussed in detail in Chapter 2, Part A, and we recall here that *enantiomers* are characterized by opposite configuration at *all* chiral centers in the molecule, whereas *diastereomers* differ in configuration at one or more, but not all, chiral centers. To be *enantioselective* a synthesis must provide an excess of one enantiomer over its mirror image and therefore must be controlled by an optically active reagent or catalyst. Optically inactive reagents can undergo an enantioselective synthesis only under the influence of optically active reagents or catalysts. *Diastereoselective* processes give rise to a preference for one possible diastereomer over the other possible diastereomers. Since the identity of any diastereoisomer is determined by the relative configuration of all chiral centers within the molecule, to be diastereoselective a reaction process

51. For wide-ranging discussions of asymmetric synthesis see the books listed in the general references.
52. J. D. Morrison and H. W. Mosher, *Asymmetric Organic Reactions*, Prentice-Hall, Englewood Cliffs, New Jersey (1971).

must control the relative stereochemical relationships among the chiral centers created in the reaction and their relationship to existing chiral centers in the molecule. A diastereoselective process may involve the conversion of achiral or racemic starting materials into racemic products, so there is no inherent need in a diastereoselective process that the starting materials, reagents, or catalysts be optically active.

Throughout the preceding chapters, as reactions were introduced, characteristic stereochemical features of the reactions were considered. This information provides the basis for achieving diastereoselectivity, that is controlling *relative stereochemistry*, in a given reaction process. Among the examples which have been encountered are the following: the stereochemical preferences for adjacent chiral centers generated in aldol condensations (Chapter 2, Section 2.2); the preference for addition of hydrogen from the less hindered side of double bonds which establishes the relative stereochemistry of the new sp^3 centers with respect to adjacent substituents; the control of addition of organometallics to carbonyl centers by adjacent chiral carbons (Section 6.1.2 in Chapter 6); the directive effect of nearby hydroxyl groups in both peracid and metal ion-catalyzed epoxidations (Chapter 10, Sections 10.2.1 and 10.2.2). Many other examples could be cited. The essential point to recognize is that if, for any reason, there is an energy difference between the transition states leading to diastereomeric products, the processes will be diastereoselective. Since there is always *some* energy difference between diastereomers, the corresponding transition states will also differ in energy. The goal of planning a diastereoselective synthesis is to *maximize* these energy differences and thereby achieve maximum selectivity. This analysis must take into account the mechanism of the synthetic step which is to be carried out and the degree of selectivity of the various reagents which are available for the particular transformation. Usually diastereoselectivity is achieved as a result of kinetic control, so that specific favorable interactions in the transition state, relative ease of approach (steric approach control) and geometric constraints on specific orbital interactions (stereoelectronic factors) are the types of issues which must be considered in addressing the need for diastereoselectivity.

Diastereoselectivity can be achieved as the result of thermodynamic as well as kinetic factors. If the desired diastereomer is the most stable of the series, then establishment of conditions for equilibration will permit a diastereoselective synthesis. As a general rule, better selectivity is achieved by kinetic methods because the greater sensitivity of the transition state to stabilizing and destabilizing interactions will be reflected in greater preference for one particular product.

The second broad type of asymmetric syntheses are *enantioselective* processes which give rise to one of the enantiomers of a pair in excess. Enantioselective syntheses can only be achieved by the participation of optically active starting materials, reagents, or catalysts in the reaction process. There are several ways in which an enantioselective synthesis can be achieved. In principle, the ideal method is to use a single enantiomer of an available chiral substance as a *catalyst*. The advantage is that, theoretically, an optically active catalyst can generate an unlimited amount of product. A second possible choice is the use of an optically active

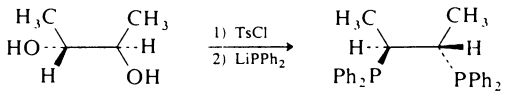
reagent, in stoichiometric or greater quantity, to generate the desired product. In this case the chiral reagent is consumed during the reaction but, depending on the particular system, it may subsequently be recovered. Finally, one may start with an available substance in optically active form and carry out a sequence of chemical steps in which the orginal chirality controls the stereochemistry at all the new chiral centers as they are created. The types of starting materials that are readily available include natural materials such as carbohydrates, amino acids, certain terpenoid materials, and a few synthetic reagents which are available in resolved form.

The basic requirement for an enantioselective synthesis is a significant energy difference between the transition states leading to the possible products. The greater the energy difference, of course, the greater the preference for one of the products. The extent of enantioselectivity is expressed in terms of the *percent enantiomeric excess*.

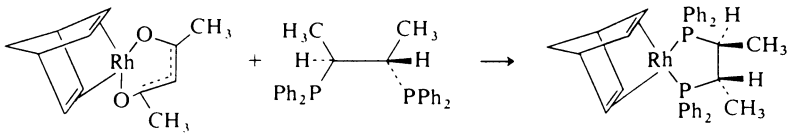
$$\%\ \text{enantiomeric excess} = \%\ \text{major enantiomer} - \%\ \text{minor enantiomer}$$

Thus 80% enantiomeric excess would correspond to formation of 90% one enantiomer and 10% of the other. The design of conditions for high enantioselectivity involve attempting to maximize differences in transition state energies. Conversely, analysis of the outcome of an enantioselective reaction involves analysis of the competing transition states for factors which would favor one over the other. Any or several of the usual structural features—steric interactions, hydrogen bonding, polar interactions, metal ion chelation—can control these energy differences.

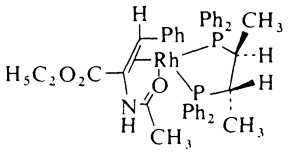
A good example of enantioselective synthesis using catalysts is the hydrogenation of various alkenes, employing soluble transition metal complexes derived from optically active phosphines. For example (+)-(2*R*,3*R*)-2,3-butanediol can be converted to a diphosphine ligand. A variety of other such *bis*-phosphines have been



synthesized in optically pure form. The diphosphines are then used to form chiral hydrogenation catalysts. Soluble complexes of rhodium(I) and dienes have been studied most thoroughly. In the homogeneous reaction solution, the diene



ligand is replaced by the substrate and hydrogen, while the phosphine ligand remains in place. The environment around the metal atom is therefore chiral and as a result there is a preferred approach of the alkene. Interestingly, it appears that reduction may take place through a *minor, particularly reactive*, complex, since X-ray structure determination of the structure of the major complex formed from α-

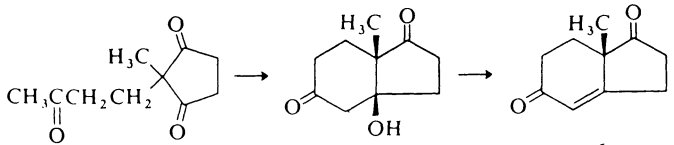


Structure of major complex between ethyl α-acetamidocinnamate and chiral Rh complex

acetamidocinnamate indicates it would give the enantiomer of the actual product.[53] Table 11.1. reports the results of some hydrogenations carried out with optically active complexes as catalysts.

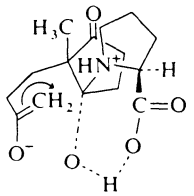
One important point to be made is that while these and numerous other data establish the *feasibility* of asymmetric hydrogenation with high enantiomeric excess, the most successful studies to date have been restricted to α-amidoacrylates. The range of other substrates which give high enantiomeric excesses with these catalysts is somewhat limited. It is believed that a chelated transition state is required for high stereoselectivity and when the requisite structural features are lacking, only low optical yields are noted. Thus, at the present time, it cannot be presumed that *every* catalytic hydrogenation can be performed to give products of high optical purity.

Another impressive example of a catalytic enantioselective synthesis is the conversion of the *prochiral* substance **4** into the cyclic products **5** and **6** in >90% optical yield.[54] Use of the amino acid *S*-proline as the catalyst for the cyclization



4 **5** **6**

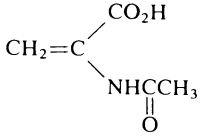
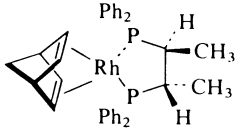
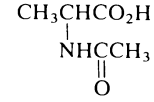
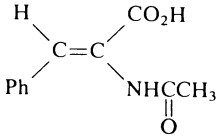
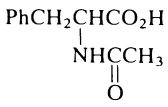
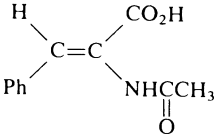
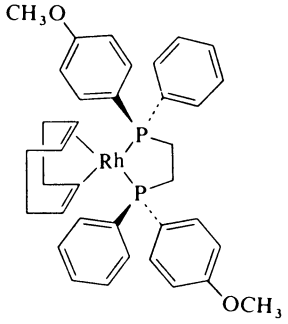
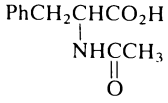
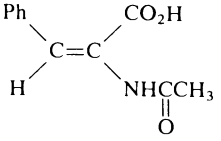
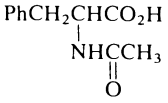
in solvents such as dimethylformamide or acetonitrile gives **5** in nearly quantitative yield. There have been several representations given for the transition state for this cyclization, one of which[55] is shown below.

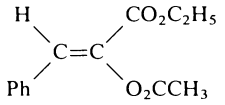
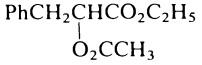
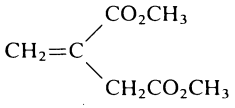
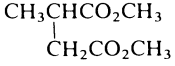
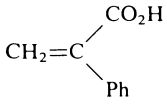
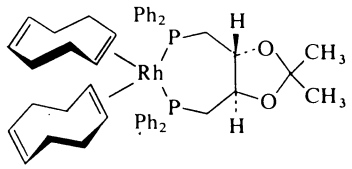
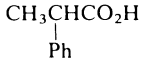
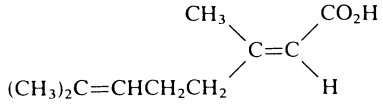
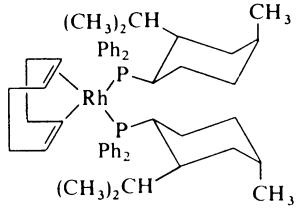
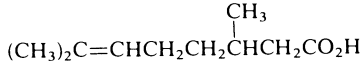


As in the case of asymmetric catalytic hydrogenation, it is believed that a fairly rigid transition state with multiple points of interaction between the chiral catalyst and the prochiral substrate must be involved to account for the high enantioselectivity of the reaction. The free carboxyl group is important to the mechanism,

53. A. S. C. Chan, J. J. Pluth, and J. Halpern, *J. Am. Chem. Soc.* **102**, 5952 (1980).
54. Z. G. Hajos and D. R. Parrish, *J. Org. Chem.* **39**, 1615 (1974); N. Cohen, *Acc. Chem. Res.* **9**, 412 (1976); U. Eder, G. Sauer, and R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **10**, 496 (1971).
55. M. E. Jung, *Tetrahedron* **32**, 3 (1976).

Table 11.1. Enantiomeric Excess (E.E.) for Asymmetric Catalytic Hydrogenation of Substituted Acrylic Acids

Substrate	Catalyst	Product	Configuration	% E.E.	Ref.
			R	90	a
	Same as above		R	95	a
			S	94	b
	Same as above		S	47	b

	Same as above		S	90	b
	Same as above		R	88	c
			S	64	d
			R	79	e

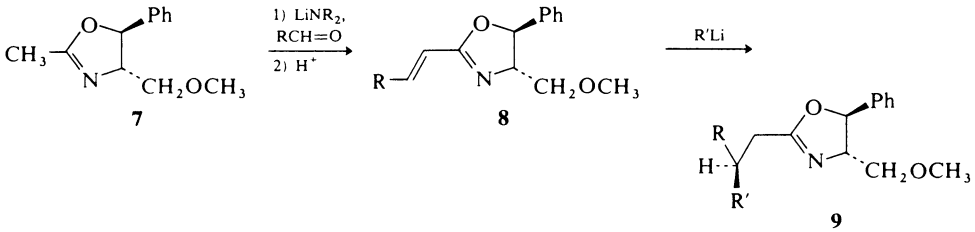
a. M. D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc.* **99**, 6262 (1977).
b. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, and D. J. Weinkauff, *J. Am. Chem. Soc.* **99**, 5946 (1977).
c. W. C. Christopfel and B. D. Vineyard, *J. Am. Chem. Soc.* **101**, 4406 (1979).
d. H. B. Kagan and T.-P. Dang, *J. Am. Chem. Soc.* **94**, 6429 (1972).
e. D. Valentine, Jr., K. K. Johnson, W. Priester, R. C. Sun, K. Toth, and G. Saucy, *J. Org. Chem.* **45**, 3698 (1980).

suggesting that hydrogen bonding or a proton-transfer step is involved. The cyclization can be carried out using as little as 3 mol% (*S*)-proline to catalyze the reaction.

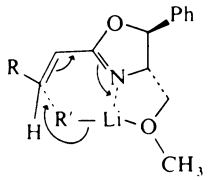
There are many more enantioselective processes in which optically active products are obtained by the use of an *optically active reagent*, which can subsequently be recovered. For example, ketones can be converted to enamines or imines using chiral amines. Alkylation gives optically active ketone and the amine can be recovered after the normal hydrolytic workup. Table 11.2 records some examples of amines which have been used and the level of enantiomeric excess which has been achieved. Section 1.9 can be consulted for a review of the mechanism of these alkylation reactions.

Entries 5 and 6 represent amines in which chelation of the metal ion is likely. The resulting rigidity of the transition state again is presumably important for achieving the high level of enantioselectivity. The level of enantioselectivity dropped, however, when very similar conditions were applied to an aliphatic aldehyde (entry 7). This may reflect a reduced steric sensitivity on the part of the more accessible carbonyl group of the aldehyde. At the present stage of development, it is clear that there are specific instances where ketone alkylation can be conducted with a high degree of enantioselectivity but no single reagent has yet been demonstrated to be generally superior for this purpose.

Closely related chemistry has permitted the development of an enantioselective synthesis of certain classes of carboxylic acids.[56] The key reagent is the oxazoline **7**, which is commercially available in optically active form. The oxazoline condenses with aldehydes to give the alkylidene derivatives **8**. The alkylidene intermediates can undergo conjugate addition of organolithium reagents in a highly stereoselective



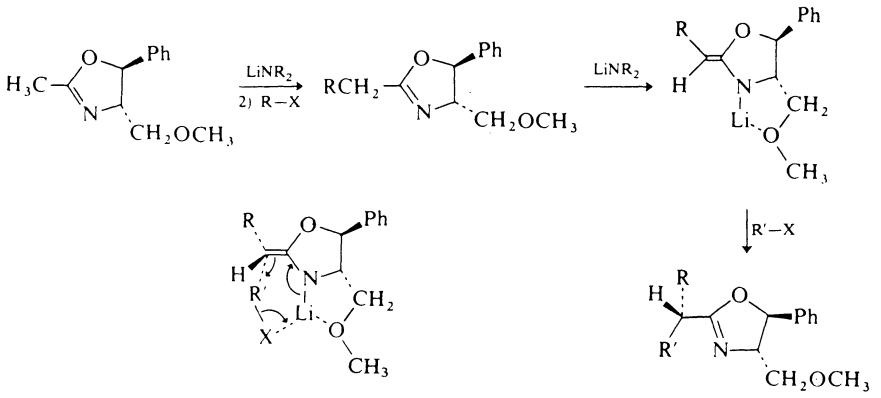
manner. Liberation of the optically active β,β-disubstituted acetic acid is accomplished by hydrolysis of the oxazoline ring. The degree of enantioselectivity is high and this is attributed to a transition state in which the alkyl group is transferred from a chelated lithium atom. It should be noted that the configuration of the asymmetric carbon is a function of which substituent is introduced via the aldehyde



56. A. I. Meyers, R. K. Smith, and C. E. Whitten, *J. Org. Chem.* **44**, 2250 (1979).

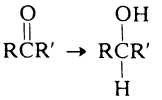
condensation and which via the conjugate addition. Reversal of the identity of the two groups reverses the configuration of the final product. A wide variety of disubstituted acids have been successfully synthesized in this way with enantiomeric excesses ranging from 91% to 99%.

Optically active α,α-disubstituted acetic acids have also been obtained using oxazoline intermediates. The oxazoline can be alkylated via the lithium derivative. Subsequent deprotonation gives a new enolate which is considered to have the chelated structure shown.



The transition state in this instance is envisioned as involving the chelated lithium ion, which acts as a Lewis acid toward the halide, facilitating a specific direction of approach. The range of enantiomeric excess observed for this procedure is 70%–90%.[57]

There have been many efforts made to develop conditions under which some of the most fundamental synthetic reactions can be carried out with high enantioselectivity. The reduction of an unsymmetrical ketone to an alcohol is one such process in which a chiral center is created. Most of the optically active hydrogenation



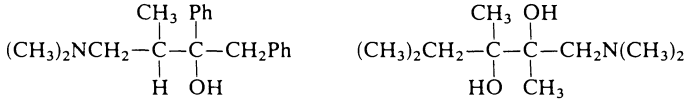
catalysts examined to date have resulted in only low enantioselectivity in this reaction. The situation is improved when the ketone contains additional functionality, probably because the additional interactions augment differences in transition state energy. A second approach involves the preparation of modified hydride-reducing agents containing chiral alcohols or amines. Several optically active amino alcohols have given appreciable selectivity; among them are 4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol and 1,4-bis(dimethylamino)butane-2,3-diol.

57. A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *J. Am. Chem. Soc.* **98**, 567 (1976).

Table 11.2. Enantioselectivity in Alkylation of Ketones and Aldehydes

Substrate	Amine	Alkylating agent	% E.E.	Ref.
1. Cyclohexanone	(−)Isobornylamine	CH_3I	72	a
2. Cyclohexanone	(*S*)-2-Amino-1-methoxy-3-phenylpropane	CH_3I	87	b
3. Cyclohexanone	(*S*)-β-Phenylethylamine (lithium salt of imine)	CH_3I	26	c
4. Cyclohexanone	(+)-*trans*-2,3-Dimethylpyrrolidine	CH_3I	93	d
5. Cyclohexanone	(*R*)-2-Aminobutyl butyl ether	CH_3I	81	e
6. Cyclohexanone	(*R*)-1-Methoxy-3-phenyl-2-propylamine (lithium salt of imine)	$(CH_3O)_2SO_2$	82	f
7. Octanal	(*R*)-2-Methoxy-1-phenylethylamine (lithium salt of imine)	CH_3I	33	g
8. Propionaldehyde	α-Phenylethylamine (lithium salt of imine)	$PhCH_2Br$	67	h
9. 3-Pentanone	(*S*)-2-Amino-1-methoxy-3-phenylpropane	C_2H_5I	77	i

a. D. Mea-Jacheet and A. Horeau, *Bull. Soc. Chim. France*, 4571 (1968).
b. A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, and M. Druelinger, *J. Am. Chem. Soc.* **103**, 3081 (1981).
c. M. Kitamoto, K. Hiroi, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* **22**, 459 (1974).
d. J. K. Whitesell and S. W. Felman, *J. Org. Chem.* **42**, 1663 (1977).
e. J. K. Whitesell and M. A. Whitesell, *J. Org. Chem.* **42**, 377 (1977).
f. A. I. Meyers, D. R. Williams, and M. Druelinger, *J. Am. Chem. Soc.* **98**, 3032 (1976).
g. A. I. Meyers, G. S. Poindexter, and Z. Brich, *J. Org. Chem.* **43**, 892 (1978).
h. R. R. Fraser, F. Akiyama, and J. Banville, *Tetrahedron Lett.*, 3939 (1979).
i. A. I. Meyers, D. R. Williams, S. White, and G. W. Erickson, *J. Am. Chem. Soc.* **103**, 3088 (1981).



Mixtures of $LiAlH_4$ with these compounds form mixed alkoxyaluminum hydride reagents, presumably with additional chelation by the amino group. The aluminum and remaining hydrides are then in a chiral environment. So far, none of the reagents of this type have given a uniformly high degree of enantioselectivity with a wide range of ketones, but certain types of ketones do give good results. Some representative data are shown in Table 11.3.[58]

There has also been considerable study of substituted borohydride-reducing agents prepared from optically active boranes by reaction with alkyllithiums.[59]

58. For a summary of available data, see D. Valentine, Jr. and J. W. Scott, *Synthesis*, 329 (1978).
59. E. J. Corey and R. K. Varma, *J. Am. Chem. Soc.* **93**, 7319 (1971); M. F. Grundon, W. A. Khan, D. R. Boyd, and W. R. Jackson, *J. Chem. Soc. C*, 2557 (1971); S. Krishnamurthy, F. Vogel, and H. C. Brown, *J. Org. Chem.* **42**, 2534 (1977); E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Am. Chem. Soc.* **93**, 1491 (1971).

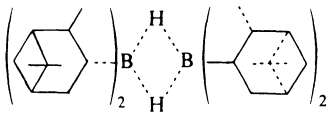
Table 11.3. Enantioselectivity in Reduction of Ketones by Hydride-Reducing Agents in the Presence of Chiral Ligands

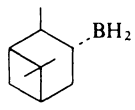
Ketone	Hydride	Chiral ligand	% E.E.	Ref.
$PhCCH_3$ (O)	$LiAlH_4$	4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol	68[a]	b
$PhCC(CH_3)_3$ (O)	$LiAlH_4$	4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol	30–35[a]	c
$PhCCH_2CH_3$ (O)	$LiAlH_4$	1,4-Bis(dimethylamino)butane-2,3-diol	44	d
$HC{\equiv}CCC_5H_{11}$ (O)	$LiAlH_4$	4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol	66	e
$PhCCH_3$ (O)	$LiAlH_4$	2-Anilinomethylpyrrolidine	89	f

a. These values are strikingly dependent on the time elapsed between preparation and use of the hydride–ligand mixture.
b. S. Yamaguchi, H. S. Mosher, and A. Pohland, *J. Am. Chem. Soc.* **94**, 9254 (1972).
c. S. Yamaguchi and H. S. Mosher, *J. Org. Chem.* **38**, 1870 (1973).
d. D. Seebach and H. Daum, *Chem. Ber.* **107**, 1748 (1974).
e. R. S. Brinkmeyer and V. M. Kapoor, *J. Am. Chem. Soc.* **99**, 8339 (1977).
f. M. Asami, H. Ohno, S. Kobayashi, and T. Mukaiyama, *Bull. Chem. Soc. Japan* **51**, 1869 (1978).

Though there are some examples of up to 50% enantiomeric excess being achieved with such reagents, the general result has been that reduction products of low optical purity are obtained. This is in marked contrast to the high diastereoselectivity (see Chapter 4) that these reagents exhibit. This result illustrates the more exacting requirements for achieving high enantioselectivity.

As a final example of a process in which enantioselective synthesis is achieved using an optically active reagent, let us consider some of the results of hydroboration with optically active boranes. The boranes are normally prepared by reaction of diborane with one of several available terpene-derived alkenes. One such reagent is "diisopinocampheylborane," which is prepared from diborane and α-pinene.[60]



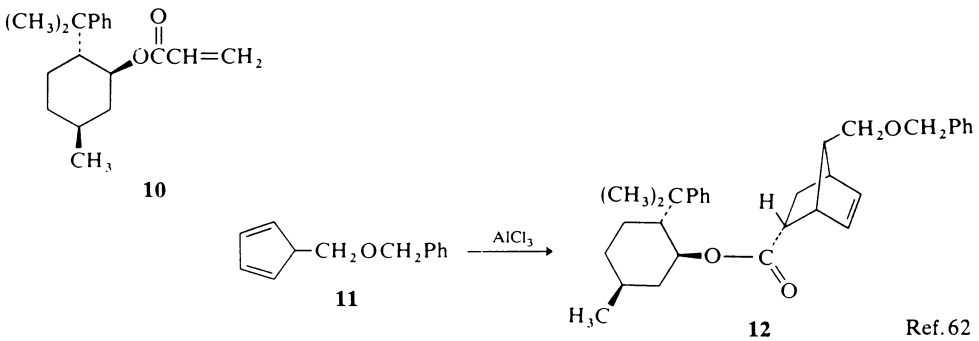


The corresponding monoalkylborane can also be prepared via an exchange reaction with "thexylborane."[61] These boranes react stereoselectively with alkenes to give boranes which can then be oxidized in the usual way to alcohols. Since this oxidation goes with retention of configuration at the new chiral center, the alcohols are

60. H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Am. Chem. Soc.* **86**, 397 (1964).
61. H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc.* **99**, 5514 (1977).

optically active. The disubstituted reagent gives good enantioselectivity with *cis*-disubstituted alkenes but poorer results are obtained with the *trans* isomers or with highly substituted systems. The monosubstituted reagent gives enantiomeric excess on the order of 50–70% with trisubstituted alkenes, however. It can be presumed that steric interactions in the diastereomeric transition states lead to the observed selectivity. It should be noted that the alkyl substituent on the borane is quite a bulky group. This may be important in accentuating the steric factors which differentiate between the diastereomeric transition states.

Diastereoselective processes can serve as the basis for synthesis of optically active material if one of the reagents is optically active. If a reaction involving an optically active reagent is diastereoselective with respect to creation of a new chiral center, the newly created chiral center will be predominantly of one configuration. A good example of this type of process involves Diels–Alder reactions of optically active esters of acrylic acid. The optically active acrylate **10**, derived from an available terpenoid ketone (*S*)-pulegone, gives an 89% yield of the adduct **12** on reaction with 5-benzyloxymethylcyclopentadiene in a catalyzed Diels–Alder reaction. The diastereoselectivity of the reaction is evidently very high although it was



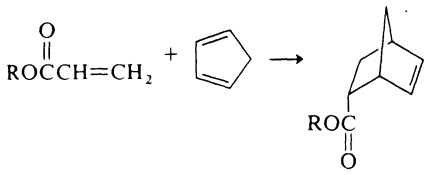
Ref. 62

not reported.[62] After hydrolysis of the ester and recovery of the original optically active alcohol, the carboxylic acid is available in optically active form for further use in the synthesis of prostaglandins. The alcohol, of course, can be reused after re-esterification.

Several studies have indicated that Diels–Alder reactions catalyzed by Lewis acids are much more likely to give high diastereoselectivity than are uncatalyzed reactions.[63,64] In one study, the results of which are shown in Table 11.4, several optically active acrylate esters were allowed to react with cyclopentadiene in the presence or absence of BF_3–OEt_2 catalyst. The product of the uncatalyzed reactions showed only about 10% optical purity after hydrolysis while the catalyzed reactions

62. E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.* **97**, 6908 (1975).
63. H. M. Walborsky, L. Barash, and T. C. Davis, *Tetrahedron* **19**, 2333 (1963); R. F. Farmer and J. Hamer, *J. Org. Chem.* **31**, 2418 (1966).
64. J. Sauer and J. Kredel, *Tetrahedron Lett.*, 6359 (1966).

Table 11.4. Diastereoselectivity of Some Diels–Alder Reactions of Chiral Acrylate Esters



R	% E.E. [b] BF_3–OEt_2, −70°C	% E.E. [b] uncatalyzed, 25–30°C
	66–85	7
$CH_3(CH_2)_5CHCH_3$ |	27	4
$(CH_3)_3CCHCH_3$ |	88	11

a. Data from J. Sauer and J. Kredel, *Tetrahedron Lett.*, 6359 (1966).
b. Enantiomeric excesses refer to norbornene carboxylic acid obtained by hydrolysis of the reaction product.

ranged as high as 88%, depending on the particular ester. Two factors probably contribute to the improved selectivity of the catalyzed reaction. The first is the fact that the temperature at which the catalyzed reaction proceeds is 100°C lower and, of course, at the lower temperature the energy differences in the competing transition states exert a relatively greater effect. The Lewis acid may also contribute to the bulk and rigidity of the transition state and thereby magnify the steric differences between the competing transition states.

11.4. Synthetic Strategy

The material covered to this point has been primarily a description of the tools at the disposal of the synthetic chemist. The most fundamental component is the extensive catalog of reactions available to organic chemists. The information on reaction conditions, stereochemistry, and efficiency that applies to a given reaction is basic to judging the applicability of the reaction to a given synthetic objective. General mechanistic insight is also an important tool. New synthetic procedures must often be developed to meet particular synthetic challenges, and the usual basis for proposing a new synthetic method is that the suggested reaction appears mechanistically sound. In this chapter, some special tactical tools of synthesis, such as protecting groups, synthetic equivalents, and methods for asymmetric synthesis

have been considered. All these tools of synthesis, however, must be coordinated by an adequate plan and strategy if they are to be applied successfully to a synthetic problem.

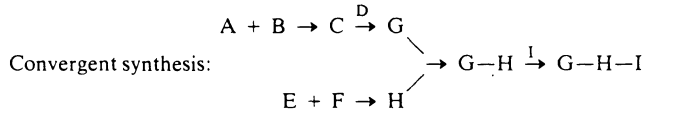
The key to planning the efficient synthesis of an organic compound lies in a critical comparative evaluation of alternative reaction sequences that could reasonably be expected to lead to the desired structure from available starting materials. In general, both the number of alternative sequences and the complexity of any single synthetic plan will increase with the size of the molecule and with increasing numbers of functional groups and chiral centers. The problem of analyzing synthetic possibilities with a view to choosing the most efficient of several routes is one of recognizing the possible pathways between the required goal and acceptable starting materials. A suitable pathway of synthetic steps must be laid out.

The restrictions applied to acceptable pathways will depend on the reasons for the synthesis. Control of stereochemistry is necessary if, for example, an optically active natural product with several chiral centers is the goal of the synthesis. A synthesis of a material to be prepared in substantial quantities may impose availability and cost of the starting material as the critical limiting factors. An industrial synthetic process would bear heavy restrictions as to acceptable by-products, a problem that is not as important in laboratory-scale syntheses.

The development of a satisfactory plan for the synthetic task at hand is the initial intellectual challenge to a synthetic chemist. This task puts a premium on creativity and imagination. There is no single correct answer, nor is there an established routine by which a synthetic plan can be formulated.

The initial step in the development of a synthetic plan should involve a *retrosynthetic* analysis. The structure of the molecule should be dissected step by step along reasonable pathways to successively simpler compounds until molecules acceptable as starting materials are reached. Several factors must enter into this process, and all are closely interrelated. There is the *molecular framework* that can be built up through a series of *key intermediates*. The initial stage in a retrosynthetic analysis is to recognize key fragments of the molecule that might be combined. At this stage of the analysis, the potential advantages of a *convergent synthesis* should be considered. If, for example, a molecule consists of two major fragments, G and H, and a side chain, I, it is more efficient to synthesize G and H separately and then combine them, rather than make G first and build H upon it, step by step. The overall yield in a synthetic sequence is the product of the yields of the individual steps so total yield tends to decrease with an increasing number of steps in a sequence. A linear sequence maximizes the number of steps to which the original starting materials must be subjected. A convergent synthesis, in contrast, allows one to build up separate fragments and then combine them; the number of steps to which each set of starting materials is subjected is thus decreased.[65]

65. A detailed formal analysis of the concept of convergency has been presented by J. B. Hendrickson, *J. Am. Chem. Soc.* **99**, 5439 (1977).



Linear synthesis: $A + B \rightarrow C \xrightarrow{D} G \xrightarrow{E} G{-}E \xrightarrow{F} G{-}H \xrightarrow{I} G{-}H{-}I$

The retrosynthetic analysis of a complex molecule to key intermediates will involve "antithetic transforms" or "bond disconnections." That is, the retrosynthetic analysis consists of the reverse of the synthetic process. These steps must be made in light of the *availability of synthetic methods to carry out the desired transformation in the forward synthetic direction.* Thus antithetic transforms must consider the functional groups which must be present to permit individual bond formations to take place.

Once candidates for key intermediates are recognized, the issues of *stereochemistry* must be faced. These take several forms: *cis–trans* isomerism at carbon–carbon double bonds, stereochemistry at ring junctions, and the relative and absolute configuration at chiral centers. Only those pathways that promise stereoselective formation of the desired compound are likely to be acceptable. For example, a structure with one possibility for *cis–trans* isomerism and two chiral centers allows for $1/2(2^3) = 4$ diastereomers. In a nonselective process the maximum yield for any one diastereomer is 25%. Furthermore, because diastereomers usually have rather similar physical properties, obtaining a single stereoisomer in pure form can be difficult.

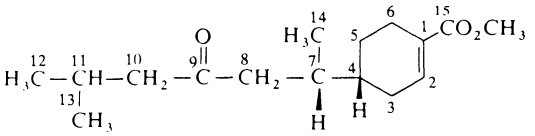
Finally, there is *functionality*. We have discussed in the sections on protecting groups and synthetic equivalents the idea of protected or masked functional groups. It is frequently necessary to interconvert related functional groups. A carbon atom that must be substituted by a hydroxyl group in the final product may be carried through a synthetic sequence as a carbonyl carbon, and then converted to the desired alcohol functionality rather late in the synthetic scheme. Similarly, a cyano group may eventually be converted to an ester group, and so on. There is, of course, a close relationship between functionality and bond disconnections. The placement and identity of functionality will determine which bond disconnections correspond to feasible synthetic operations. Achieving the final desired functionality is often somewhat less difficult than establishing the overall molecular skeleton and stereochemistry because of the large number of procedures for interconverting many of the common functional groups.

These ideas can be illustrated by considering some examples of successful multistep syntheses. In these examples, we have the benefit of hindsight, but let us attempt to recognize, in particular, the stages at which the matters of molecular skeleton, stereochemistry, and functionality were faced. The examples chosen are natural products, but the same ideas apply to any synthetic target.

11.5. Juvabione

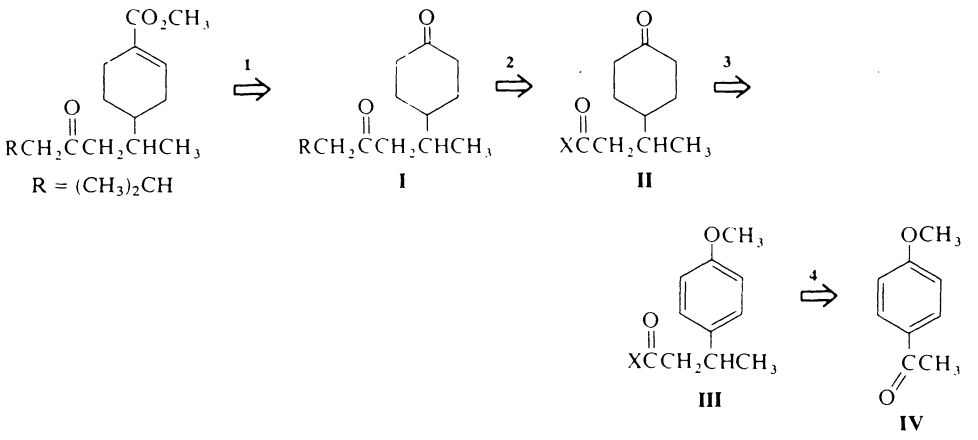
Let us look first at a molecule that has been synthesized in a number of alternative ways. Juvabione is a terpene-derived keto ester that has been isolated from certain plant species. It exhibits juvenile hormone activity; that is, it can modify the process of metamorphosis in certain insects. At least nine syntheses of this molecule have been completed.

In considering the retrosynthetic analysis of juvabione, two factors draw attention to the bond between C-4 and C-7 as numbered. First, this bond establishes



the single stereochemical feature of the molecule. The two carbons it connects are each chiral and therefore the relative configuration of these two centers determines whether the correct structure will be obtained. At some stage in a stereocontrolled synthesis of racemic material it will be necessary to establish the correct relative stereochemistry between carbon atoms 4 and 7. The second feature of the C-4–C-7 bond is that it joins the side chain to the ring. Because a compound with the ring already formed would be a desirable starting material, methods of connecting the side chain deserve attention. A second point of interest is the C-8–C-9–C-10 region. Because of the carbonyl group, a good deal of flexibility for synthetic operations exists at this point. The ester substituent is the final point of functionality. Again a good deal of flexibility is possible because the ester is remote from the other functionalities and no issues of stereochemistry are involved. Retrosynthetic analyses which correspond to most of the syntheses reported up to 1980 are shown in Schemes 11.3, 11.7, and 11.11 and the individual syntheses are also presented. The nine syntheses of juvabione fall into four groups on the basis of the type of starting material which was employed. Those in Schemes 11.4 and 11.5 lead back to a *para*-substituted aromatic ether. The key bond formations are made at C-9–C-10 and at C-4–C-7. The ester function is added late in the synthesis. The syntheses in Schemes 11.8, 11.9, and 11.10 begin with an accessible terpene intermediate. In 11.8 and 11.9 the terpene starts with C-15 as a methyl group. This requires an eventual oxidation, taking advantage of the allylic nature of the methyl group. With the C-4–C-7 bond already formed, these syntheses need only to construct the C_9–C_{13} array. The syntheses of Schemes 11.12 and 11.13 are related in starting with cyclohexenone and passing through an intermediate in which C-2 occurs as a carbonyl group. The final stages of both syntheses involve the introduction of the ester function and double bond by transformations of this carbonyl group. As will be mentioned shortly, only these two syntheses exercise complete stereocontrol. The final pathway is that of Scheme 11.14. Its unique feature is the construction of the carbon skeleton in a Diels–Alder reaction.

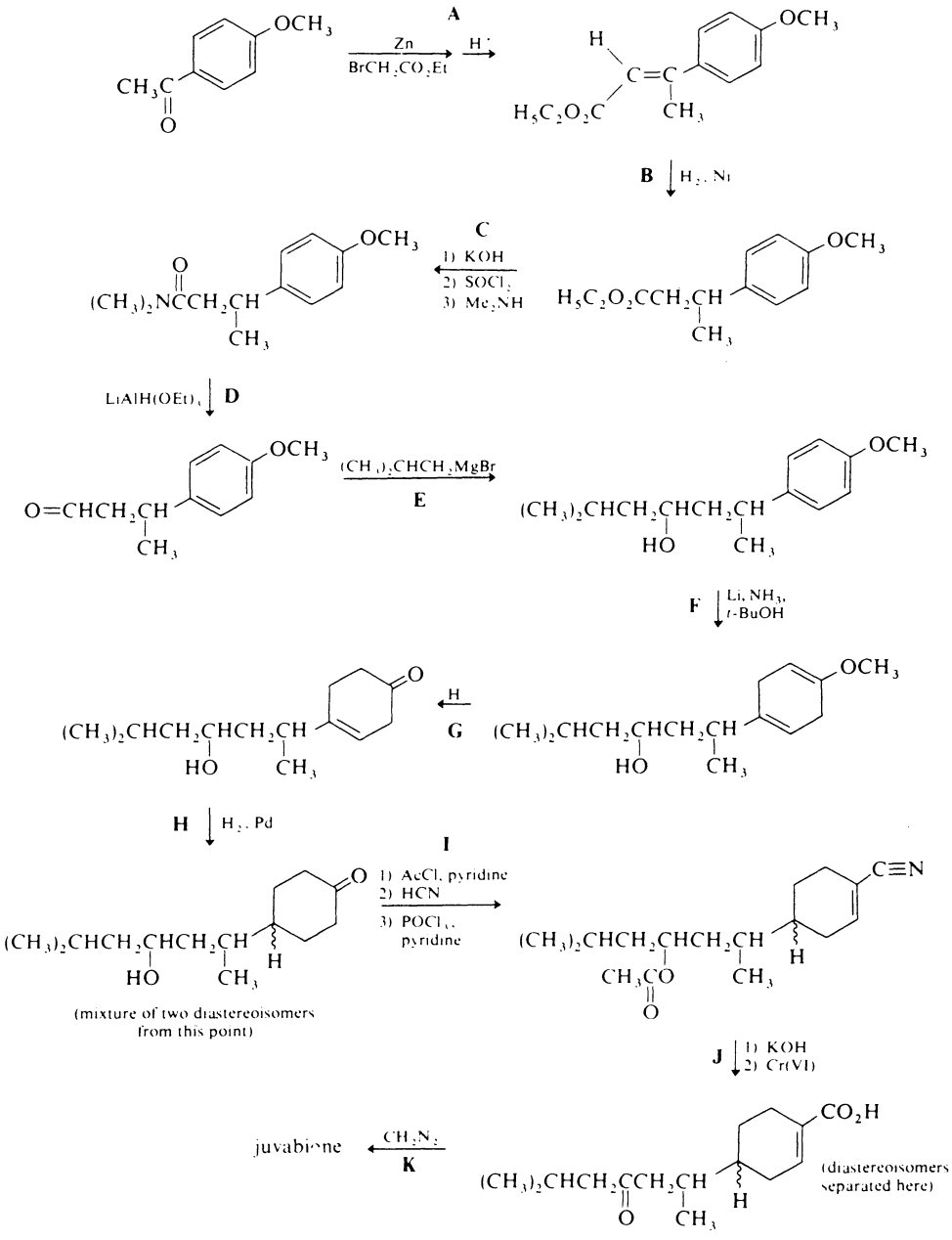
Scheme 11.3. Retrosynthetic Analysis of Juvabione with Disconnection to *p*-Methoxyacetophenone



Scheme 11.3 is a retrosynthetic analysis in terms of several key intermediates which corresponds to the synthetic concept employed in the syntheses shown in Schemes 11.4 and 11.5. The first reverse step corresponds to a decision that the ester function need not play a crucial role in the synthesis and therefore can be added as a last step. Attention then turns to the side chain. It is recognized that the isobutyl group can be added as a nucleophile at a carbonyl group, using an organometallic reaction for example, so the C-9–C-10 bond can be disconnected as in step 2. The third retrosynthetic step depends on recognizing that the cyclohexanone system might be advantageously obtained via an aromatic ring. There is a well-established synthetic method, based on the Birch reduction, for carrying out this change synthetically. The fourth retrosynthetic step recognizes the possible nucleophilicity of the carbon next to the carbonyl group. The C-7–C-8 bond then can be disconnected to some species in which C-7 is electrophilic. This final disconnection leads to the recognition of a very readily available aromatic compound as a possible precursor for intermediate III.

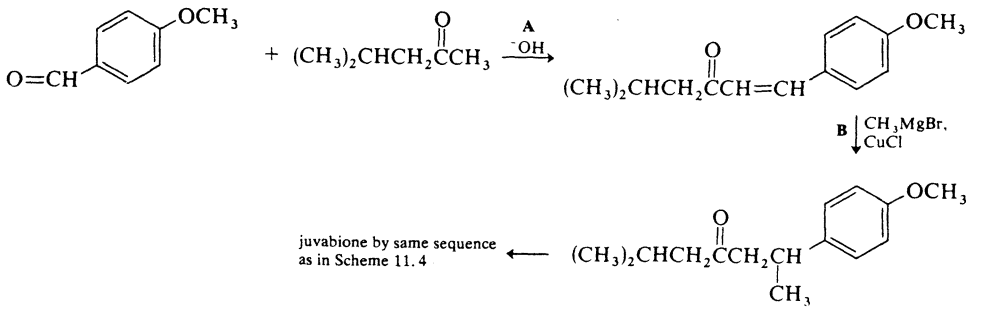
An actual synthesis corresponding to this pattern is shown in Scheme 11.4. It relies on well-known reaction types. Steps **I**, **J**, **K** correspond to the disconnection leading to intermediate **I**. The bond connection at C-9, C-10, corresponding to conversion of intermediate **II** to **I**, is done using a Grignard reagent in step **E**. This results in an alcohol oxidation level at C-9 which is adjusted to the required carbonyl much later in the synthesis (step **J**). The conversion of **IV** to **III** in the retrosynthetic scheme corresponds to step **A** in the synthesis. A Reformatsky reaction is employed. The overall synthesis is not stereocontrolled. The relative stereochemistry at C-4 and C-7 is established by the catalytic hydrogenation in step **H** of the synthesis. In principle, this reaction could be diastereoselective since the adjacent chiral center

Scheme 11.4. Juvabione Synthesis: K. Mori and M. Matsui[a]



a. K. Mori and M. Matsui, *Tetrahedron* **24**, 3127 (1968).

Scheme 11.5. Juvabione Synthesis: K. S. Ayyar and G. S. K. Rao[a]

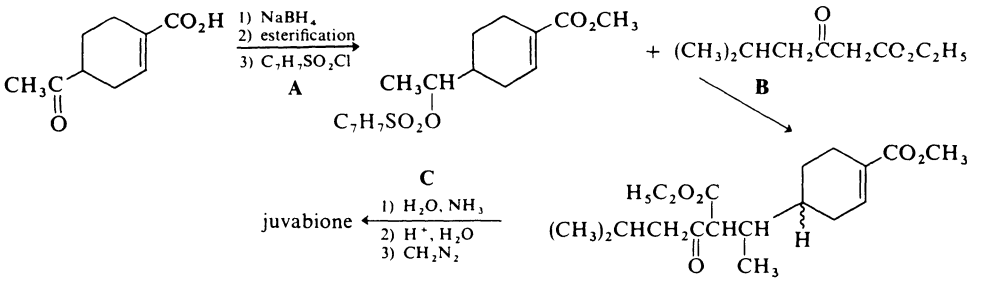


a. K. S. Ayyar and G. S. K. Rao, *Can. J. Chem.* **46**, 1467 (1968).

might control the approach to catalyst. In practice, such reductions are not very selective and a mixture of isomers was obtained. The other key feature of this synthesis is the use of a methoxybenzene ring as the synthon for the cyclohexanone structure. The fact that methoxyaromatics are subject to reduction to enol ethers, which are carbonyl equivalents, makes this possible.

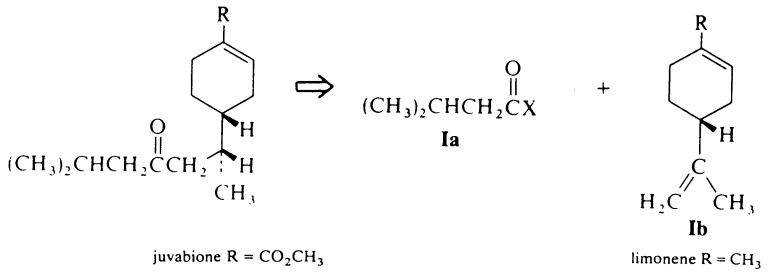
Scheme 11.5 also makes use of an aromatic starting material and is quite similar in general design to Scheme 11.4. A different method of introducing C-14 is employed. The starting material is *p*-methoxybenzaldehyde and the C-14 methyl is added by a copper-catalyzed conjugate addition in step **B**. This scheme also introduces the entire side chain, except for C-14, as a single unit. This approach is therefore more convergent than that in Scheme 11.4, where the side chain was added in two parts.

Scheme 11.6. Juvabione Synthesis: A. A. Drabkina and Y. S. Tsizin[a]

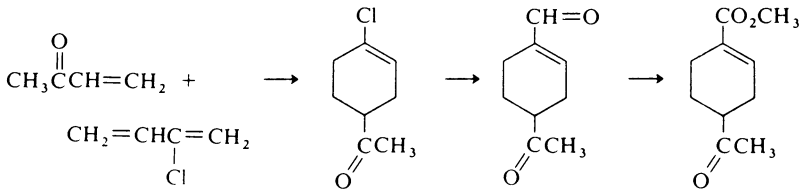


a. A. A. Drabkina and Y. S. Tsizin, *J. Gen. Chem. USSR* (Engl. translation) **43**, 422, 691 (1973).

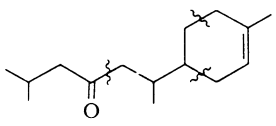
Scheme 11.7. Retrosynthetic Analysis of Juvabione with Disconnection to Limonene



The synthesis of Scheme 11.6 is similar to those of Schemes 11.4–11.5, but starts with the ring at the cyclohexenecarboxylic acid oxidation level. This compound was synthesized via several steps starting with a Diels–Alder adduct of methyl vinyl ketone and chloroprene.[66] This synthesis incorporates the ester group at C-1 into the desired starting material.



Scheme 11.7 is a retrosynthetic outline of the syntheses which are described in Schemes 11.8, 11.9, and 11.10. The common feature of these syntheses is the utilization of available, terpene-derived starting materials. The use of such a starting material is suggested by the structure of juvabione which can be recognized as having a terpenelike structure; that is, it may be divided into "isoprene units."

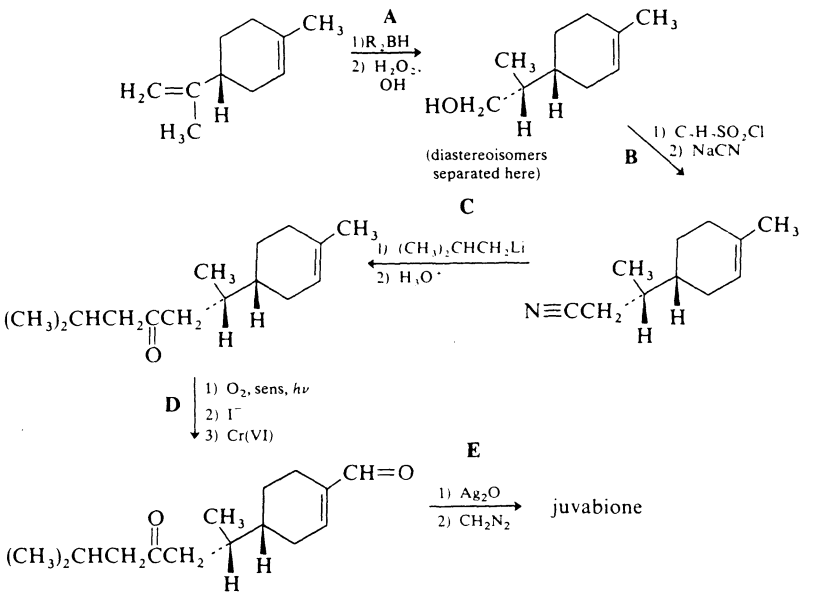


isoprene units in juvabione

The syntheses shown in Schemes 11.8 and 11.9 used limonene as the starting material ($R = CH_3$ in Scheme 11.7), whereas Scheme 11.10 uses an analog in which $R = CO_2CH_3$). The use of these starting materials focuses attention on attaching the side chain C-9–C-13. The synthesis of Scheme 11.10 does this in one step by a borane

66. A. A. Drabkina, O. V. Efimova, and Y. S. Tsizin, *J. Gen. Chem. USSR Engl. Transl.* **41**, 1421 (1971); **42**, 1129 (1972).

Scheme 11.8. Juvabione Synthesis: B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy[a]

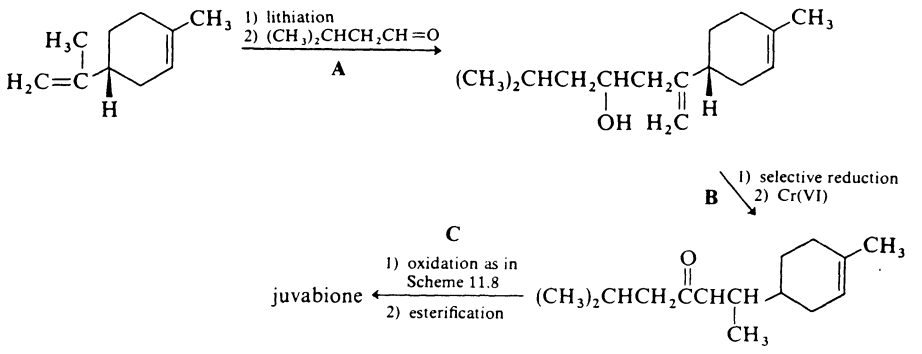


a. B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy, *J. Am. Chem. Soc.* **92**, 336 (1970).

carbonylation reaction. This synthesis is very short and the first four steps accomplish routine functional group transformations. The carbon–carbon bond formation is nonstereoselective, however, so the product is a 1 : 1 mixture of two diastereomers. In Schemes 11.8 and 11.9 well-established reactions are used to elaborate the side chain. Since the starting material is an optically active terpene, in principle, asymmetric syntheses controlled by the existing chirality at C-4 are feasible. Unfortunately, the hydroboration in step **A** of Scheme 11.8 showed only modest stereoselectivity so that a separation of diastereomers formed in a 3 : 2 ratio was required. Subsequent steps do not affect the chiral centers. The stereochemistry of Scheme 11.9 is not explicitly described in the reference given. It is unlikely high stereoselectivity was achieved, however, since the second chiral center is introduced by a catalytic hydrogenation not much different from step **H** of Scheme 11.4.

Both the syntheses in Schemes 11.8 and 11.9 use a two-step oxidation sequence to effect the required oxidation of the allylic methyl group. The first step is a singlet oxygen oxidation to a mixture of hydroperoxides with oxygen bound mainly at carbon atom 2. The mixture is reduced to the corresponding alcohols which were then subjected to oxidation with Cr(VI). The overall yield of this transformation is rather low.

Scheme 11.9. Juvabione Synthesis: R. J. Crawford[a]

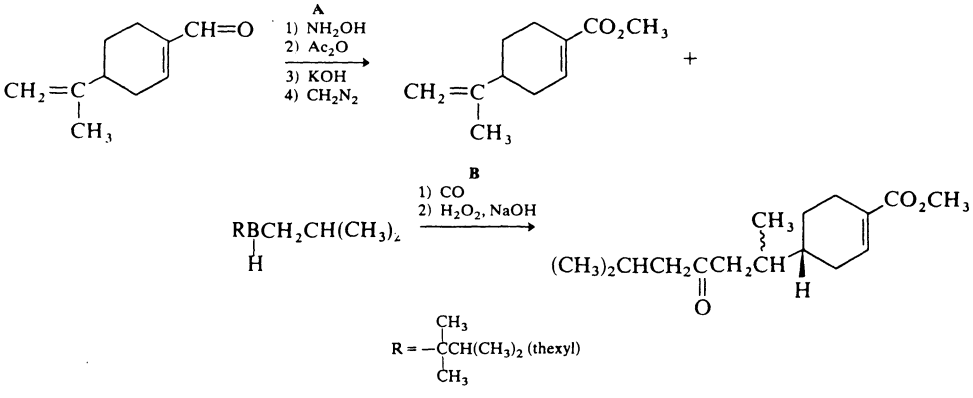


a. R. J. Crawford, U.S. Patent 3,676,506; *Chem. Abstr.* **77**, 113889e (1972).

The syntheses shown 11.12 and 11.13 have certain similarities. Both start ultimately from cyclohexenone, and both are stereoselective. The retrosyntheses shown in Scheme 11.11 correspond to the syntheses in Schemes 11.12 and 11.13. The retrosyntheses reveal a general similarity in the fragments which are utilized but the syntheses differ in the order of construction and the reagents employed.

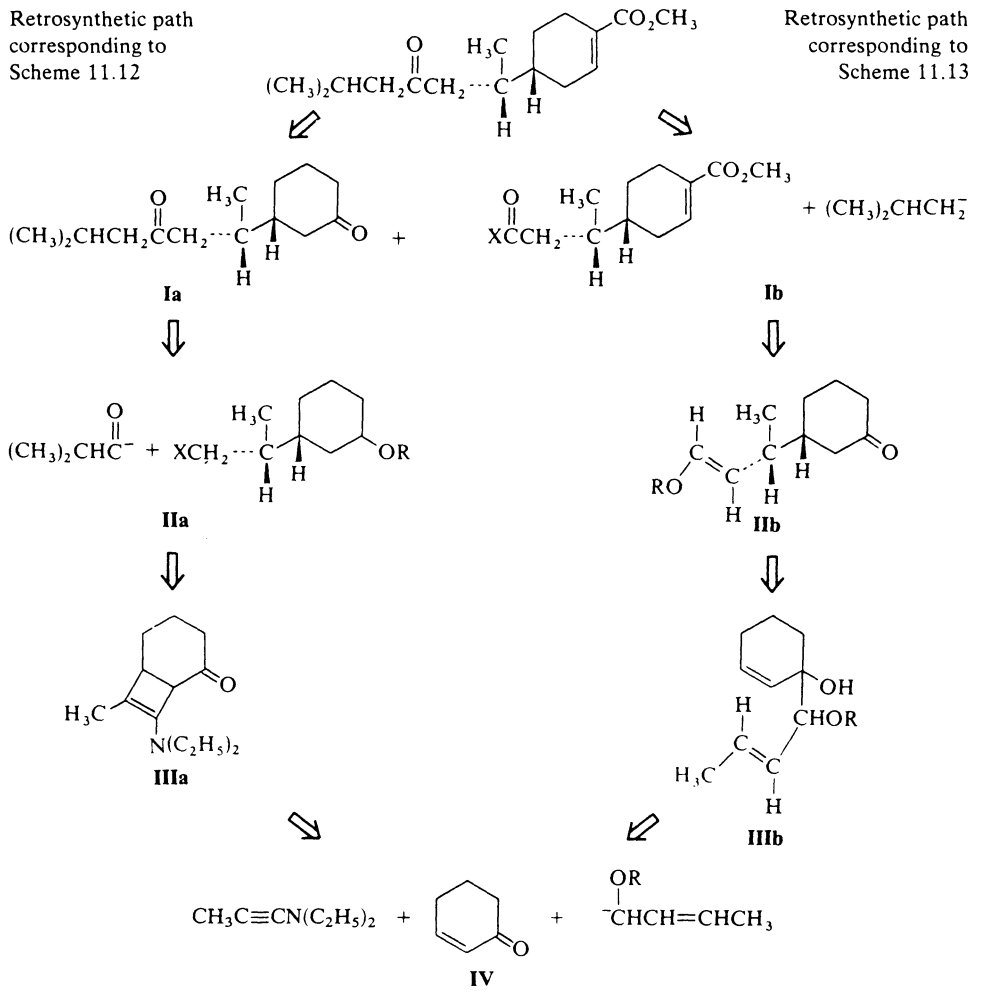
The final steps in the synthesis of Scheme 11.12 employ the C-2 carbonyl group to introduce the C-1 carboxy group and the C-1–C-2 double bond. Prior to

Scheme 11.10. Juvabione Synthesis: E. Negishi, M. Sabanski, J. J. Katz, and H. C. Brown[a]



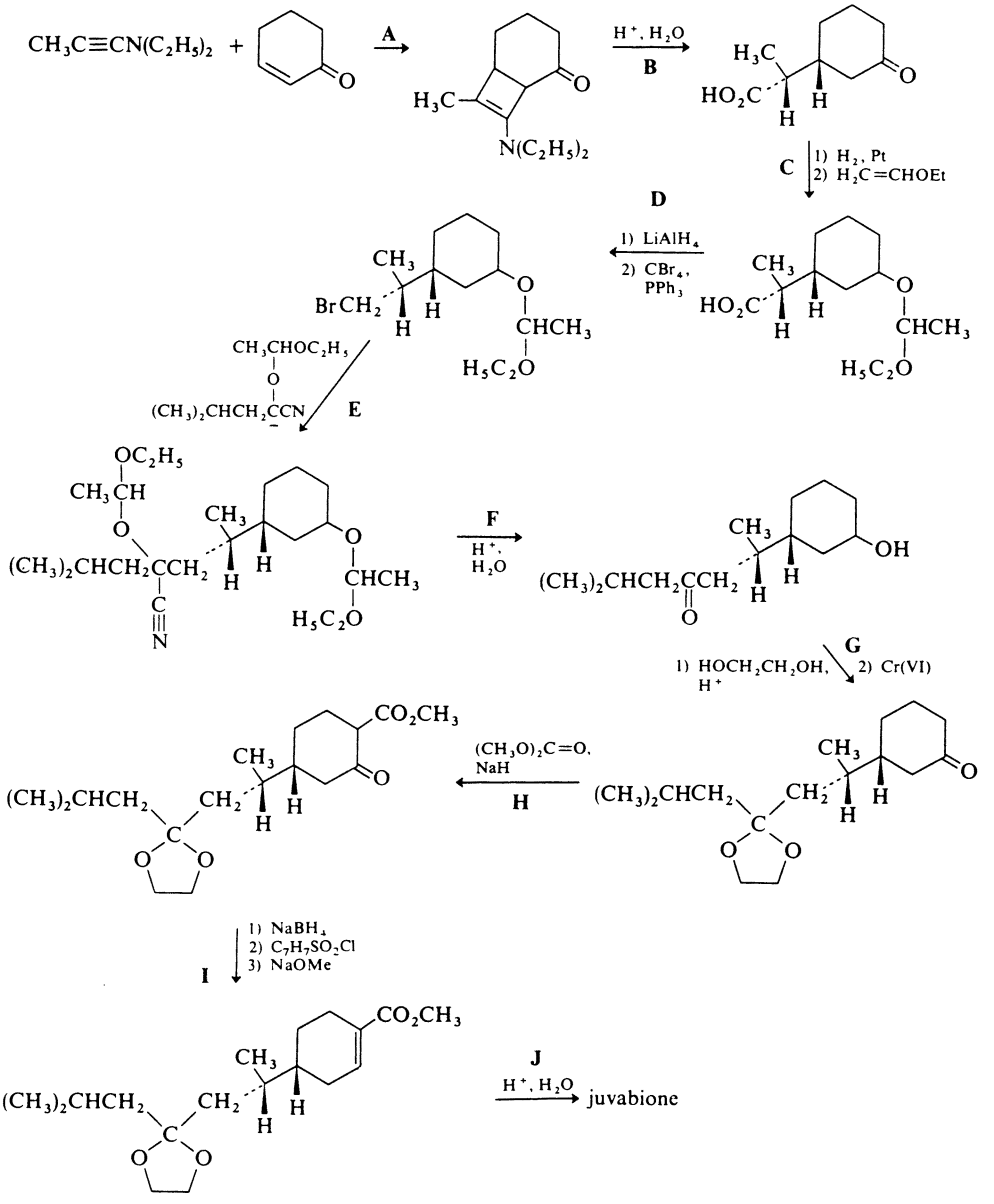
a. E. Negishi, M. Sabanski, J. J. Katz, and H. C. Brown, *Tetrahedron* **32**, 925 (1976).

Scheme 11.11. Retrosynthetic Analysis of Juvabione with Alternate Disconnections to Cyclohexenone



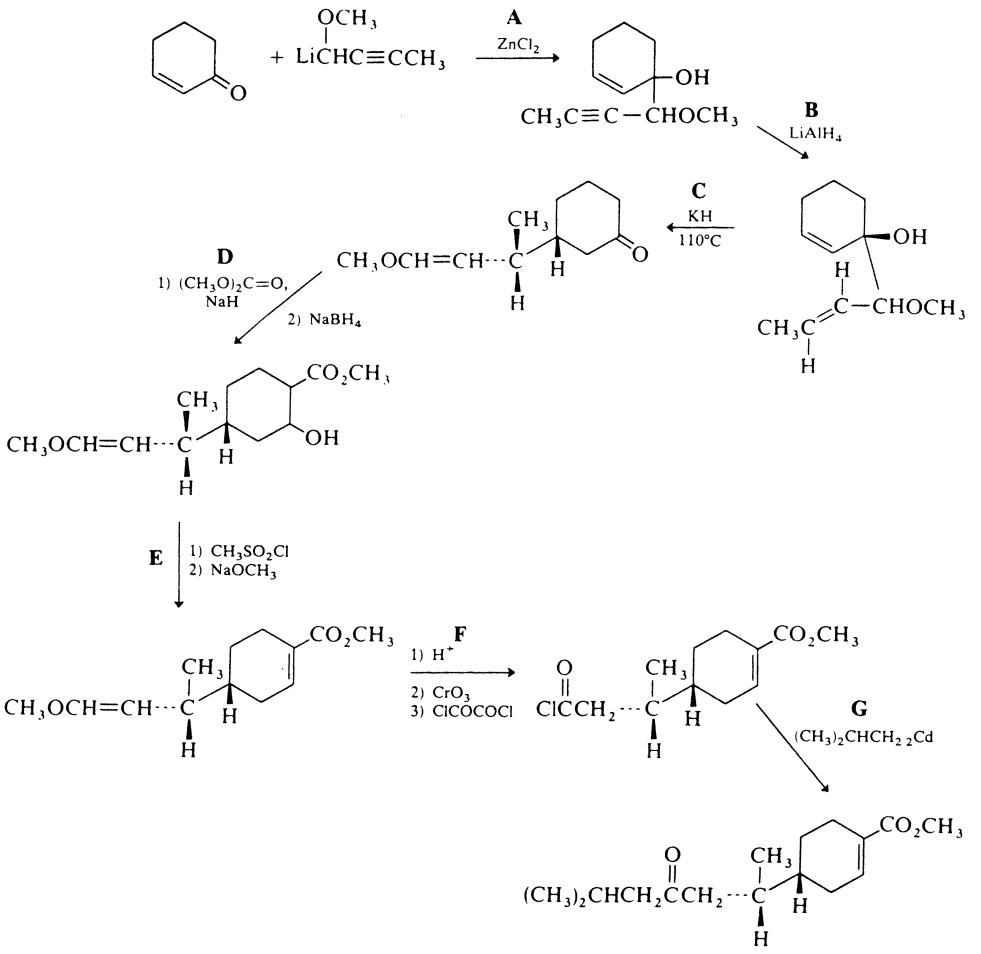
this the side chain is fully elaborated. The crucial step for controlling stereochemistry in this synthesis occurs at step **B**. The first intermediate is constructed by a 2 + 2 cycloaddition between reagents of complementary polarity, the electron-donating yneamine and the electron-accepting enone. The cyclobutene ring is then opened in a process which corresponds to retrosynthetic step **IIa** ⇒ **IIIa** shown in Scheme 11.11. The stereoselectivity of this step results from preferential protonation of

Scheme 11.12. Juvabione Synthesis: J. Ficini, J. D'Angelo, and J. Noiré[a]

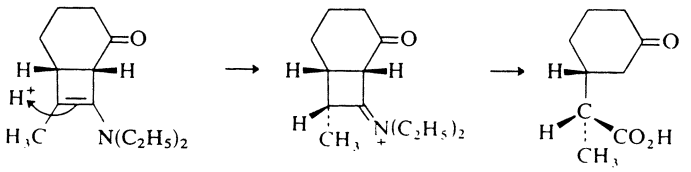


a. J. Ficini, J. D'Angelo, and J. Noiré, *J. Am. Chem. Soc.* **96**, 1213 (1974).

Scheme 11.13. Juvabione Synthesis: D. A. Evans and J. V. Nelson[a]

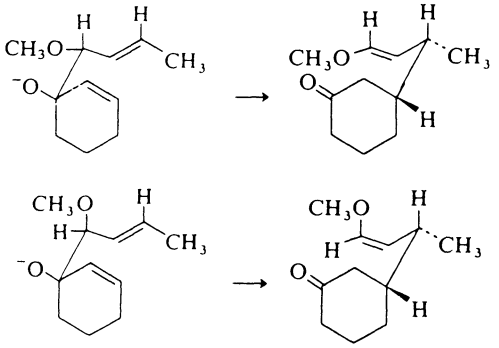


a. D. A. Evans and J. V. Nelson, *J. Am. Chem. Soc.* **102**, 774 (1980).



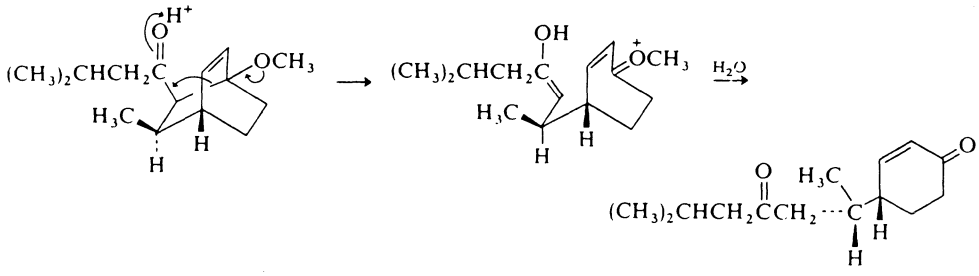
the enamine group from the less hindered side of the bicyclic intermediate. These chiral centers are unaffected by subsequent reactions steps so the overall sequence is stereoselective. Another key step in this synthesis is step **E**, which corresponds to the transformation **IIa** → **Ia** in the retrosynthesis. A protected cyanohydrin is used as a nucleophilic acyl anion equivalent.

The stereoselectivity of the synthesis in Scheme 11.13 is the result of a preferred conformation for the base-catalyzed oxy-Cope rearrangement in step **C** of the synthesis. Although the compound which is rearranged in step **C** is obtained as a mixture of stereoisomers, both give predominantly the desired relative stereochemistry at C-4 and C-7. Step **C** in the synthesis corresponds to the transfor-



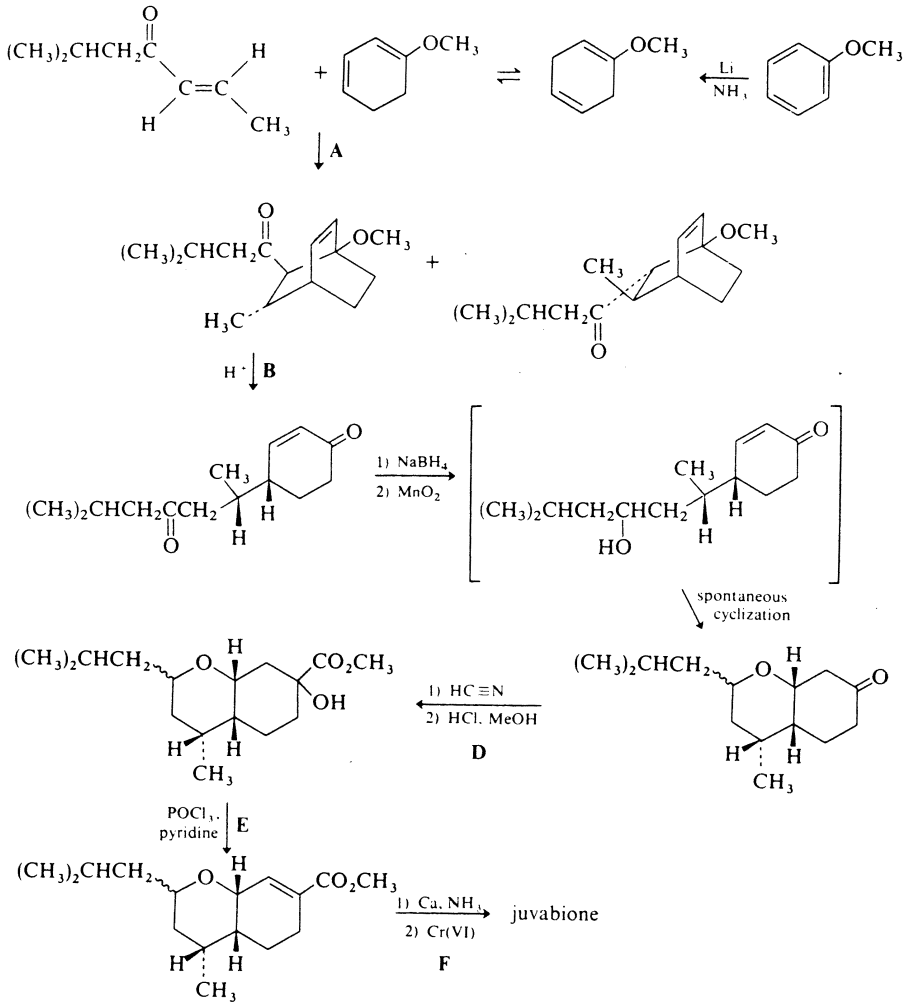
mation **IIb** ⇨ **IIIb** in the retrosynthesis. This is an important pattern for carbon–carbon bond formation with stereochemical control. The various sigmatropic processes related to the Claisen rearrangement are widely useful for γ-alkylation of allylic alcohols, and the stereochemical outcome can be predicted on the basis of the conformation of the cyclic transition state (see Section 7.3). The side-chain construction in this synthesis is done with "normal" polarity; that is, the carbonyl group in the side chain acts as an electrophile in the formation of the C-9–C-10 bond.

The synthesis of Scheme 11.14 is not highly stereoselective in a strict sense. The Diels–Alder reaction of step **A** gives a mixture of two adducts in approximately equal amounts. These are separated at this stage and only the adduct with the correct relative configurations at C-4 and C-7 is carried through the synthetic sequence. The most unique feature of this synthesis is step **B** in which the bicyclic ring is cleaved to generate the juvabione skeleton lacking only the ester function. This acid-catalyzed fragmentation proceeds via a carbonium ion intermediate which is stabilized both by the allylic conjugation and the methoxy substituent.



The sodium borohydride reduction in step **C** generates a mixture of diastereomers but this does not detract from the overall stereoselectivity beyond step **A** since this center is subsequently reoxidized. The fact that cyclization of this reduction product occurs is incidental to the overall strategy.

Scheme 11.14. Juvabione Synthesis: A. J. Birch, P. L. Macdonald, and V. H. Powell[a]

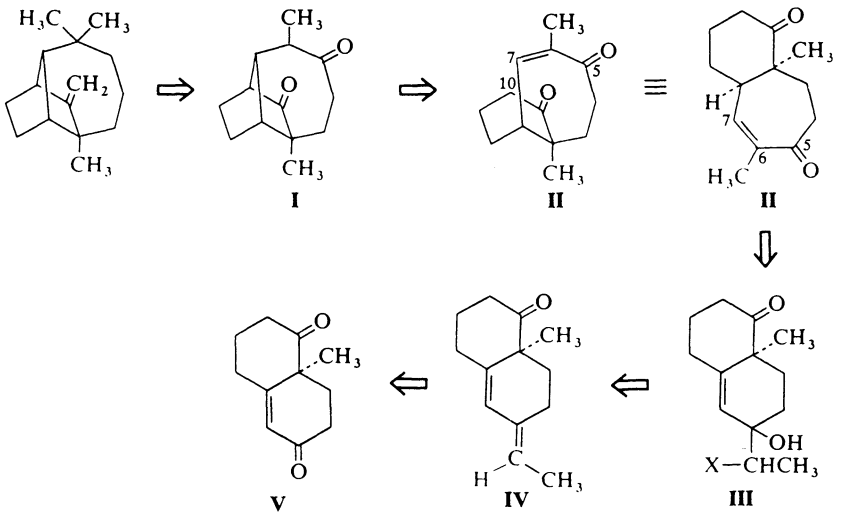


a. A. J. Birch, P. L. Macdonald, and V. H. Powell, *J. Chem. Soc. C*, 1469 (1970).

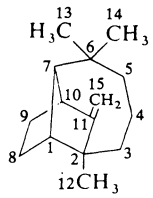
11.6. Longifolene

Longifolene is a tricyclic terpene. It is representative of the structural complexity that the terpenes can present. The terpenes have attracted much attention from organic chemists, first in determining structure and exploring reaction chemistry and more recently as objects of synthetic efforts. Schemes 11.15–11.20

Scheme 11.15. Retrosynthesis of Longifolene Corresponding to the Synthesis in Scheme 11.16



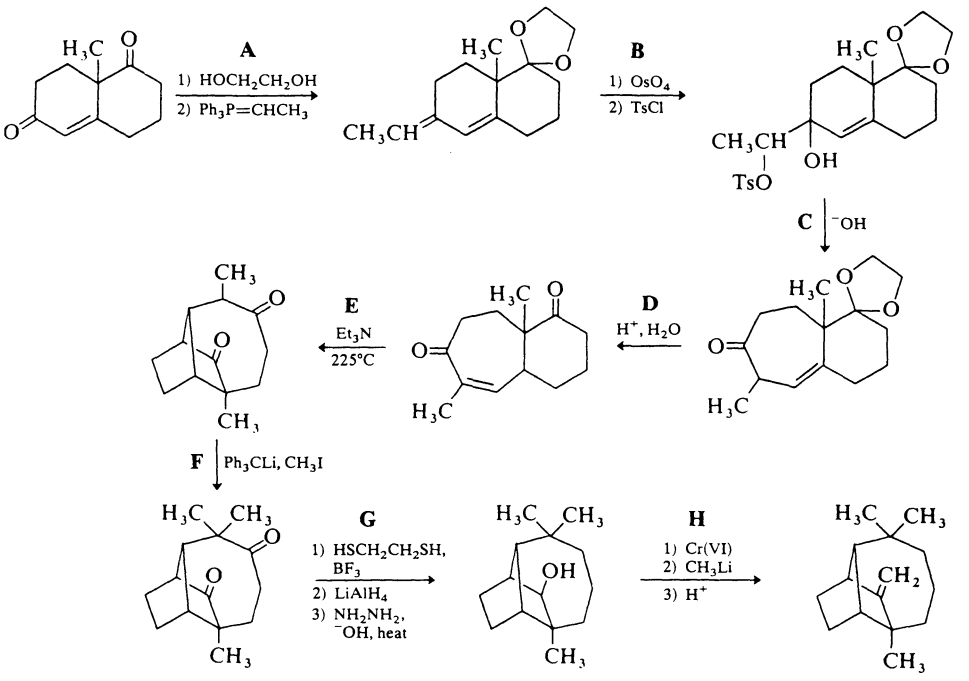
present four separate syntheses of longifolene. We wish to particularly emphasize the methods for formation of the carbon–carbon bonds in longifolene. There are



four chiral carbons in longifolene but they are not independent of one another, since the geometry of the ring system requires that they have a single relative relationship. That does not mean stereochemistry can be ignored, however, since the formation of the various rings will fail if the reactants are not of the appropriate stereochemical family.

The first successful synthesis of longifolene was described in detail by Corey and coworkers in 1964. Scheme 11.15 presents a retrosynthetic analysis corresponding to this route. A key disconnection is made on going from **I** → **II**. This simplifies the tricyclic skeleton to a bicyclic one. For this disconnection to correspond to a reasonable synthetic step, the functionality must engender mutual reactivity between carbon atoms 7 and 10. This is achieved in diketone **II** since the enolate of the C-11 carbonyl, which is nucleophilic at C-10 can undergo Michael addition to the C-7 carbon. Step **II** ⇒ **III** is retrosynthetically attractive since it gives a

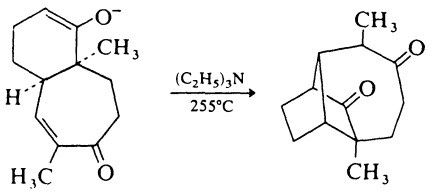
Scheme 11.16. Longifolene Synthesis: E. J. Corey, R. B. Mitra, and P. A. Vatakencherry[a]



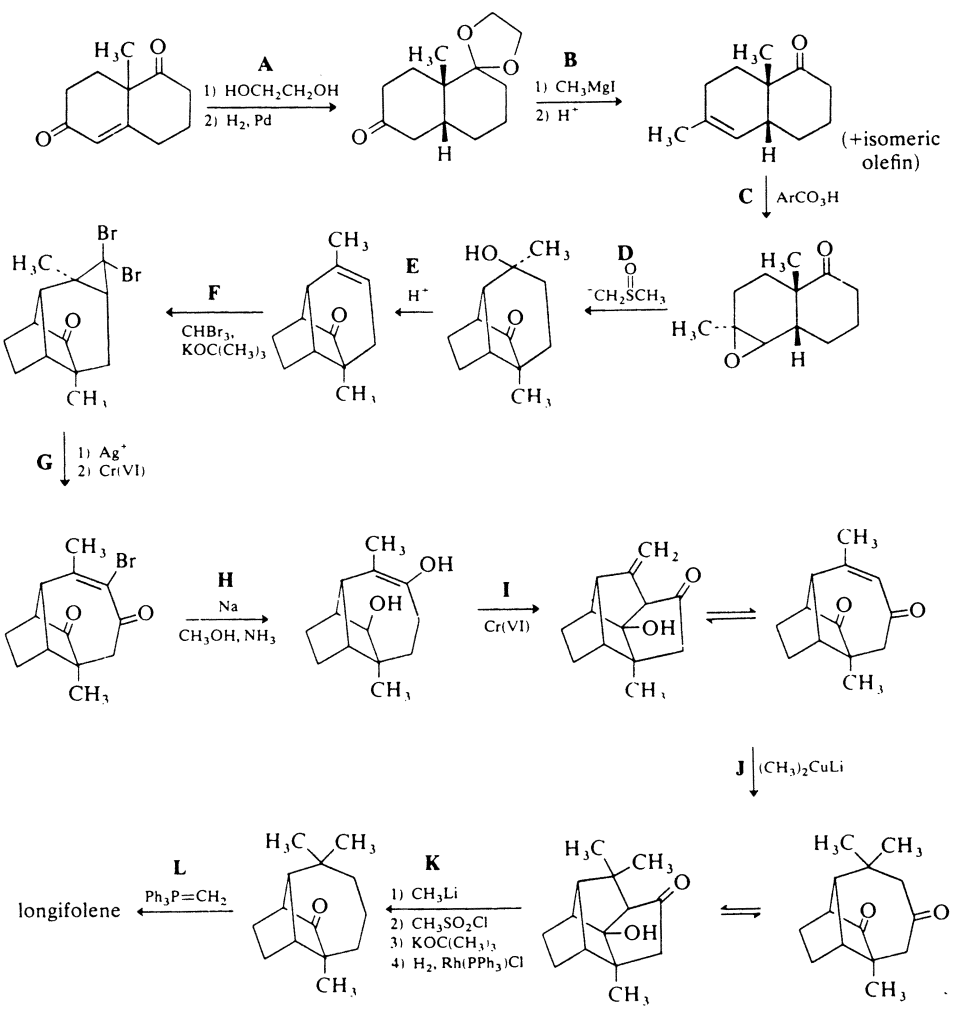
a. E. J. Corey, R. B. Mitra, and P. A. Vatakencherry, *J. Am. Chem. Soc.* **86**, 478 (1964).

decalin derivative. This type of structure has been well developed as a potential intermediate by studies on steroids and other terpenes. Can a chemical reaction be recognized which would permit **III** → **II** in the synthetic sense? The hydroxyl → carbonyl with carbon–carbon group migration corresponds to the pinacol-type rearrangement (Section 9.4). The carbonyl group at C-5 is a desired functionality. The retrosynthetic transform **II** ⇒ **III** corresponds to a viable synthetic step if **III** contains a leaving group X which could promote the rearrangement. The other two transformations **III** ⇒ **IV** ⇒ **V** are straightforward in concept, and correspond to recognition of an available starting material.

The synthesis, as it was actually carried out, is shown in Scheme 11.16. The key intramolecular Michael addition was accomplished using triethylamine and high-temperature conditions. The cyclization requires a *cis*-ring fusion. The



Scheme 11.17. Logifolene Synthesis: J. E. McMurry and S. J. Isser[a]

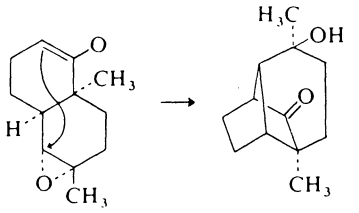


a. J. E. McMurry and S. J. Isser, *J. Am. Chem. Soc.* **94**, 7132 (1972).

stereochemistry is established when the double bond is moved into conjugation in step **D**. This product was not stereochemically characterized, and need not be, because the stereochemically important site can be epimerized under the basic conditions of the cyclization. Step **C** is the pinacol rearrangement corresponding to **II** ⇒ **III** in the retrosynthesis. A diol is formed and selectively tosylated at the secondary hydroxyl group (step **B**). Base then promotes the skeletal rearrangement (step **C**). The other transformations effect the addition of the remaining methyl and methylene groups by reactions which have been discussed in earlier sections of this text. Step **G**

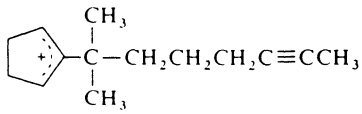
accomplishes a selective reduction of one of the two carbonyl groups to a methylene by taking advantage of the difference in the steric environment at the two carbonyls. Selective temporary protection of the C-5 carbonyl was done using a thioketal. The C-11 carbonyl was then reduced to give the alcohol and finally C-5 was reduced to a methylene group under Wolff–Kishner conditions.

The key bond closure in Scheme 11.17 is somewhat similar to that in Scheme 11.16 but is performed on a bicyclo[4.4.0] system. The ring juncture must again be *cis* to permit the intramolecular epoxide ring opening. The required *cis*-ring fusion is established by the catalytic hydrogenation in step **A**. The cyclization is



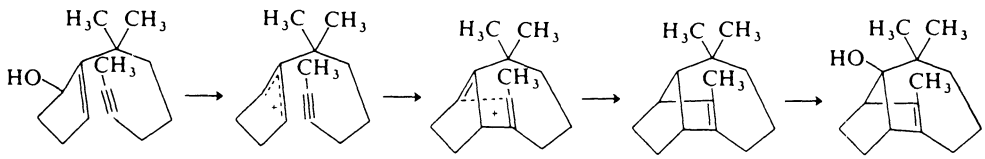
followed by a sequence of steps, **F–H**, which effect a ring expansion, via a carbene addition and cyclopropyl halide solvolysis. The products of steps **I** and **J** are interesting in that the tricyclic structures are largely converted to tetracyclic derivatives by intramolecular aldol reactions. The extraneous bond is broken in step **K**. First a diol is formed by $NaBH_4$ reduction and this is converted to a mesylate. The resulting β-hydroxy mesylate is capable of a concerted fragmentation which occurs on treatment with potassium *t*-butoxide. The double bond is removed by homogeneous catalytic hydrogenation.

A retrosynthetic analysis corresponding to the synthesis in Scheme 11.19 is shown in Scheme 11.18. The striking feature of this synthesis is the structural simplicity of the key intermediate **IV**. A synthesis according to this scheme would generate the tricyclic skeleton in a single step from a monocyclic intermediate. The disconnection **III** $\Rightarrow$ **IV** corresponds to a cationic cyclization of the highly symmetric cationic intermediate **IVa**. Thus no issues of stereochemistry arise until the carbon

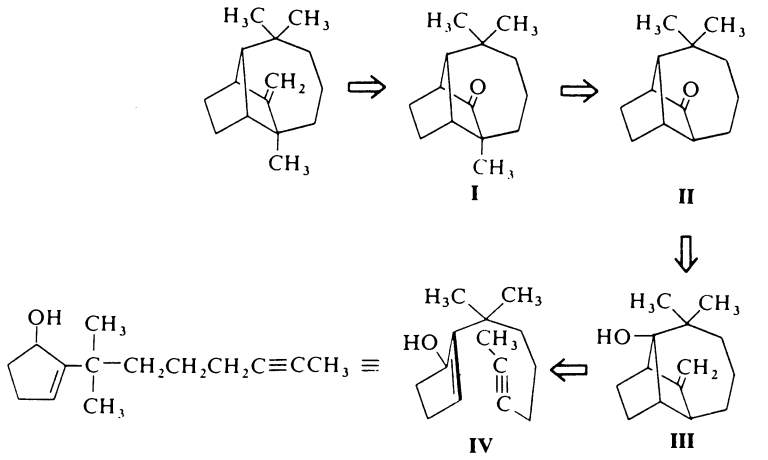


IVa

skeleton has been formed at which point all the chiral centers have been locked into the proper relationship. The molecular conformations of the successive cationic intermediates corresponding to the observed cyclization are shown below.

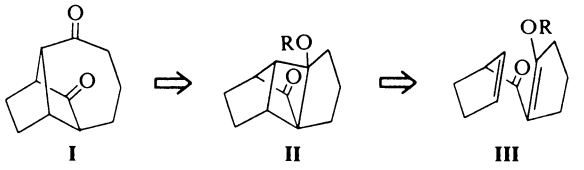


Scheme 11.18. Retrosynthetic Analysis Corresponding to Synthesis in Scheme 11.19



Evidently, this conformation is accessible and reactive since the synthesis was successfully achieved as shown in Scheme 11.19. Other than the key cyclization, step **D**, interesting transformations are carried out in step **E** where a bridgehead tertiary alcohol is reductively removed and at step **F** where a methylene group, which is eventually desired, must be removed to accommodate introduction of the C-12 methyl group.

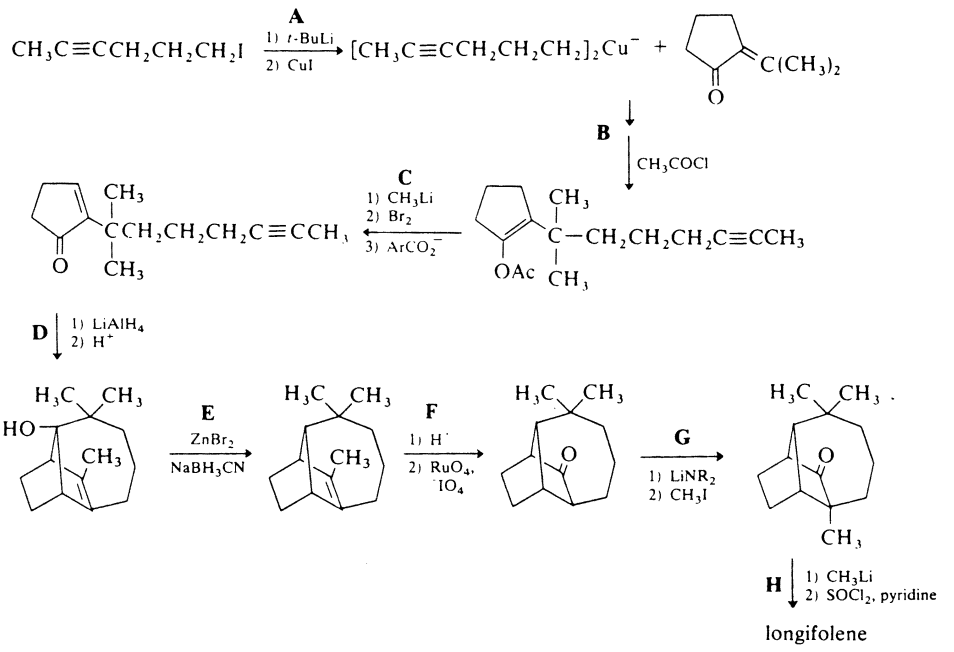
The synthesis of Scheme 11.20 also uses a remarkably simple starting material to achieve the synthesis of the tricyclic skeleton. A partial retrosynthesis is shown below:



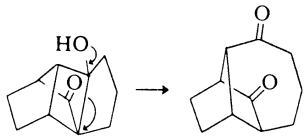
Intermediate **I** is the basic tricyclic skeleton of longifolene, shorn of all its substituent groups, but containing two carbonyl groups suitably placed that the C-2, and C-6 methyls as well as the C-11 methylene could be introduced. **I** ⇒ **II** corresponds to an intramolecular aldol condensation. However, **II** clearly is strained relative to **I**, so **II** (with OR=OH) should open to **I**. How might **II** be obtained? The four-membered ring suggests a 2 + 2 (photochemical) cycloaddition and this was in fact successful as shown in Scheme 11.20.

After liberation of the hydroxyl group by hydrogenolysis in step **C**, the extra carbon–carbon bond is spontaneously cleaved by the reverse aldol reaction. Step

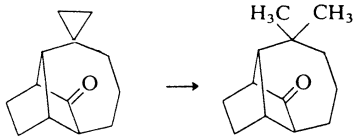
Scheme 11.19. Longifolene Synthesis: R. A. Volkmann, G. C. Andrews, and W. S. Johnson[a]



a. R. A. Volkmann, G. C. Andrews, and W. S. Johnson, *J. Am. Chem. Soc.* **97**, 4777 (1975).

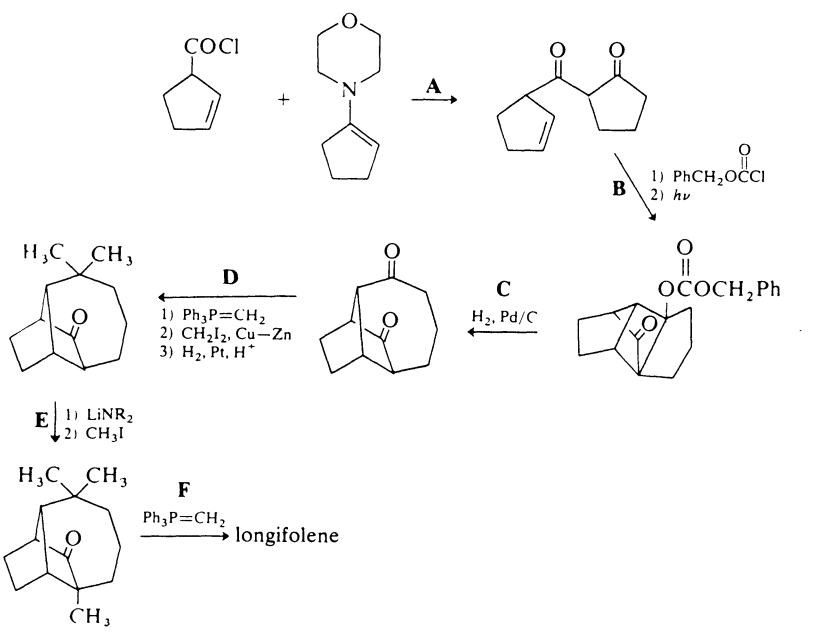


D in this synthesis is an interesting way of introducing the geminal dimethyl groups. It proceeds through a cyclopropane intermediate which is cleaved in the hydrogenation step.



These syntheses of longifolene are examples of the variety of approaches available for synthesis of ring compounds of this type. In each case a set of functionalities which have the potential for *intramolecular* reaction was assembled. After assembly of the carbon framework, the final functionality changes are effected. *It is the necessity for the formation of the skeleton which determined the functionalities which are present at the ring-closure stage.*

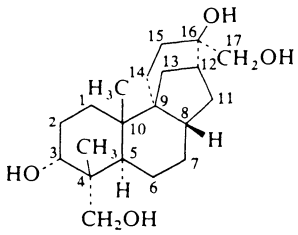
Scheme 11.20. Longifolene Synthesis: W. Oppolzer and T. Godel



a. W. Oppolzer and T. Godel, *J. Am. Chem. Soc.* **100**, 2583 (1978).

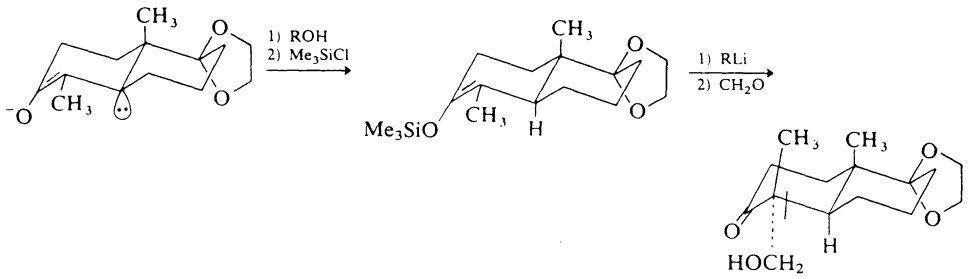
11.7. Aphidicolin

Aphidicolin is an antibiotic isolated from a fungus. It has antimitotic activity and inhibits the growth of *Herpes simplex* virus and thus is of considerable interest for evaluation as an antiviral agent. The molecule represents a somewhat more complicated synthetic target than juvabione or longifolene. It is, however, a good example of the sort of molecule which can be synthesized by present methodology and four different syntheses have been reported up to 1981. There are a total of

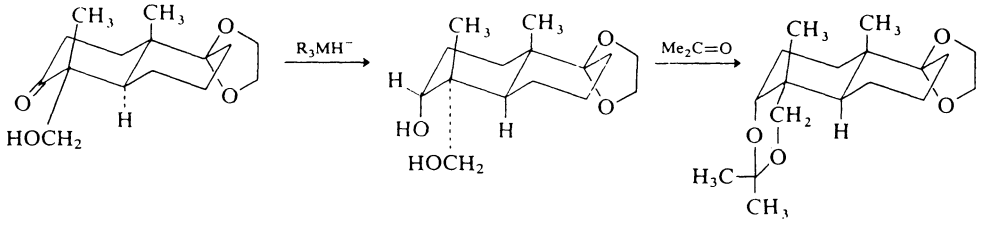


eight chiral centers. Excluding enantiomers, 128 stereoisomers are possible. Five stereocenters are associated with ring junctions so a major part of the planning of the synthesis of aphidicolin revolves around controlling the stereochemistry of ring formation. The syntheses which have been achieved are given in Schemes 11.21–11.24.

The syntheses of Schemes 11.21 and 11.22 employ the same starting material, an available[67] racemic decalin derivative. Both syntheses use rather similar methods to establish the required *trans* **A**,**B**-ring juncture and the stereochemistry at C-3 and C-4. The stereochemistry of the ring fusion is established by a dissolving metal reduction. The protonation generates the *trans* ring junction by approach *anti* to the axial methyl group at C-10. The enolate product is trapped as a silyl enol ether.

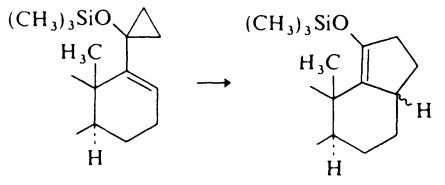


On regeneration of the enolate, reaction with formaldehyde again occurs on the side of the ring opposite the axial methyl group. The stereochemistry of the alcohol group at C-3 is then established by use of a bulky reducing agent which approaches from the equatorial direction. The two alcohol groups were then converted to an



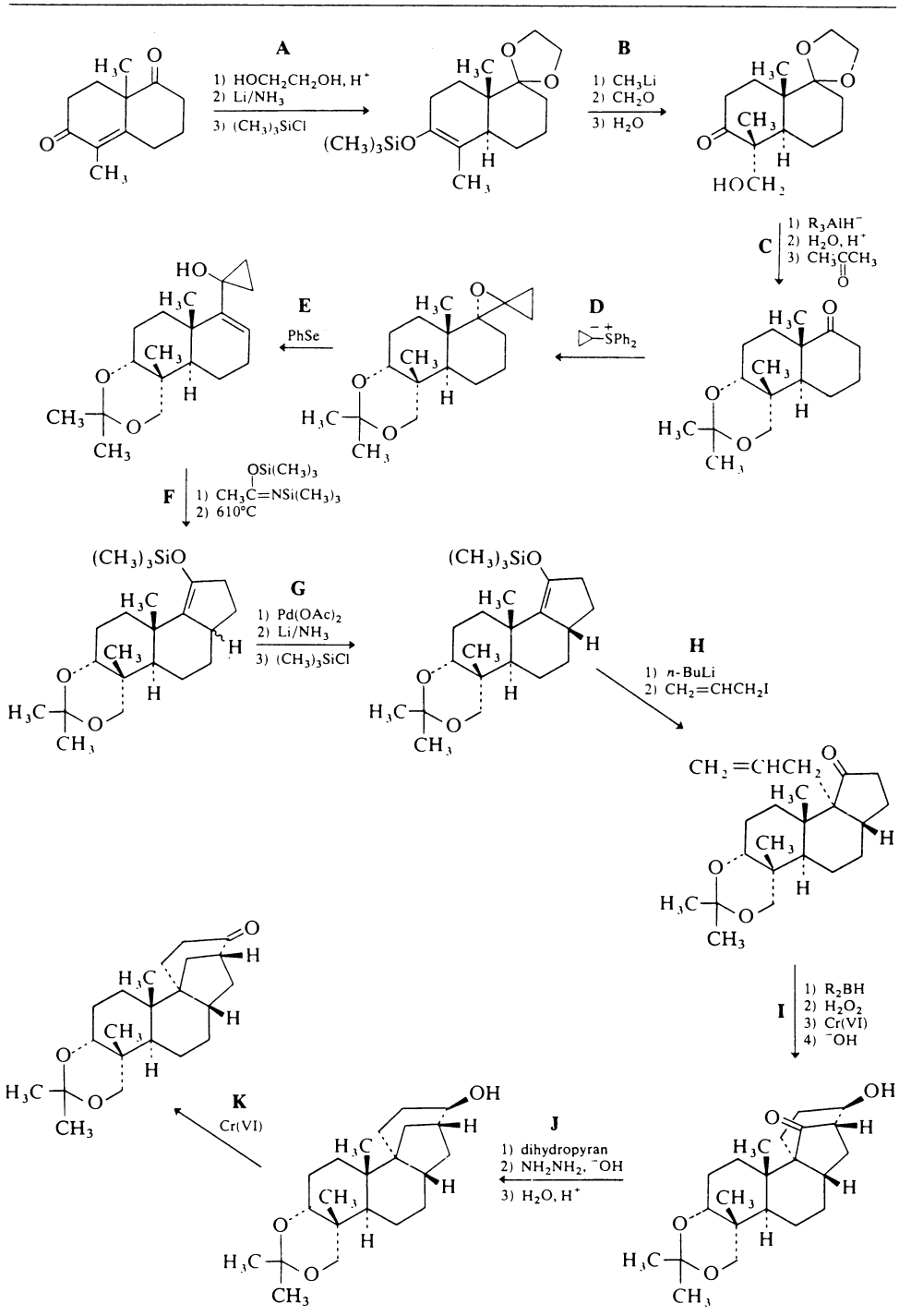
acetonide which serves to protect them throughout the course of the synthesis. This sequence of reactions established the relative configuration at carbons 3, 4, 5, and 10, one half of the total chiral centers in the molecule.

The methods for attachment of the third and fourth rings in these two syntheses diverge and will be considered separately. Scheme 11.21 uses an annulation sequence which had been developed and shown to be a reasonably general way of constructing a cyclopentanone ring onto an existing carbonyl system. The C-8–C-11 bond is established by a thermally-induced vinylcyclopropane rearrangement.



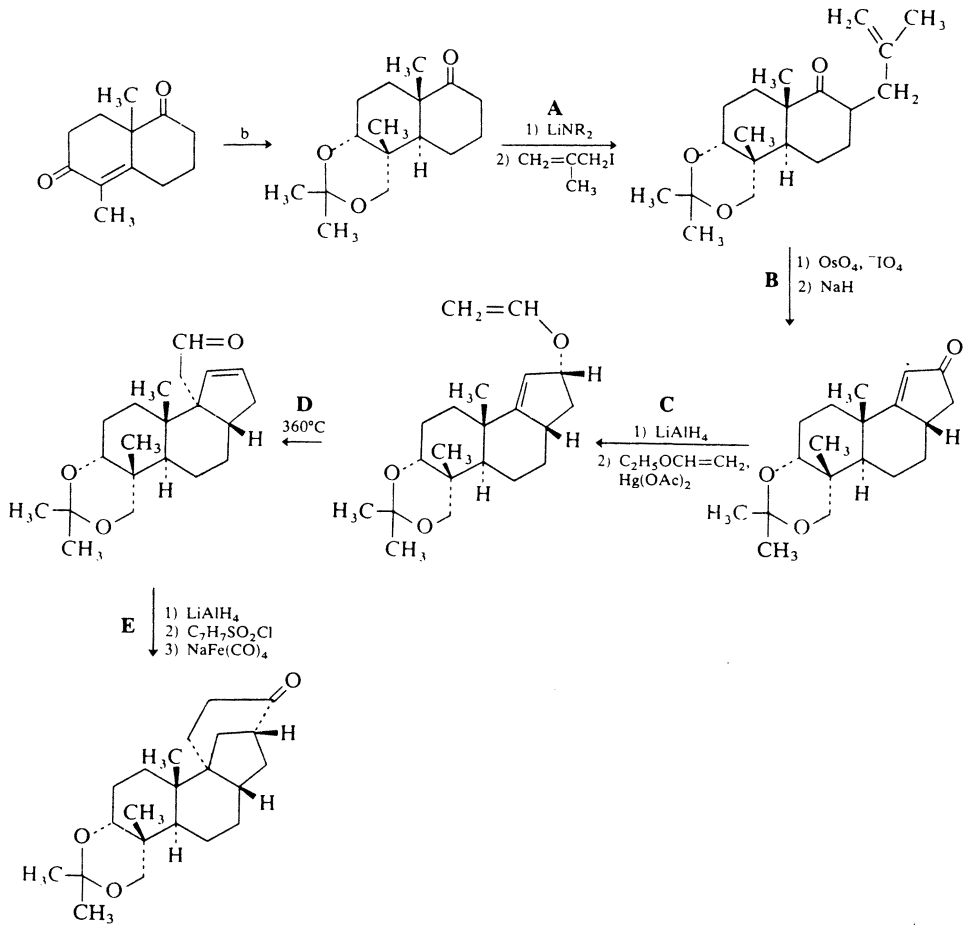
67. Y. Kitahara, A. Yoshikoshi, and S. Oida, *Tetrahedron Lett.*, 1763 (1964).

Scheme 11.21. Aphidicolin Synthesis: B. M. Trost, Y. Nishimura, and K. Yamamoto[a]



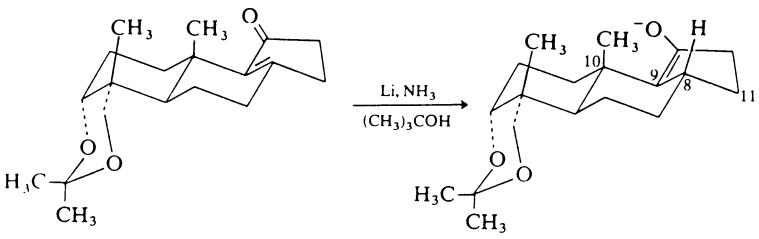
a. B. M. Trost, Y. Nishimura, and K. Yamamoto, *J. Am. Chem. Soc.* **101**, 1328 (1979).

Scheme 11.22. Aphidicolin Synthesis: J. E. McMurry, A. Andrus, G. M. Ksander, J. H. Musser, and M. A. Johnson[a]



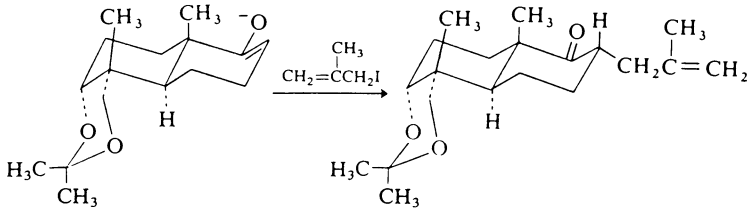
a. J. E. McMurry, A. Andrus, G. M. Ksander, J. H. Musser, and M. A. Johnson, *J. Am. Chem. Soc.* **101**, 1330 (1979).
b. This transformation is carried out by a sequence of reactions similar to that in Scheme 11.21.

This reaction proved not to be very stereoselective and an oxidation–reduction (step **G**) was necessary to establish the desired stereochemistry. The oxidation affords the α,β-unsaturated ketone which is reduced by Li/NH_3. The stereochemistry at C-8 is established by β protonation of the reduction intermediate (Section 5.5.1). Perhaps the dominant factor in controlling the stereochemistry is that it avoids forcing the C-8–C-11 bond into an axial conformation where a

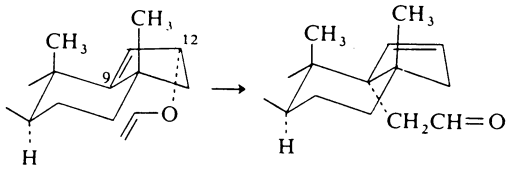


1,3-diaxial interaction with the C-10 methyl group would result. In step **H** the enolate is regenerated and attack by allyl iodide away from the axial methyl at C-10 generates the correct stereochemistry at C-9. Geometric constraints require that the final ring formation, which is carried out by an aldol condensation, proceed as shown in the Scheme.

In Scheme 11.22 the first configuration established after the common intermediate is at C-8, which is alkylated by methallyl iodide. The observed, and desired,



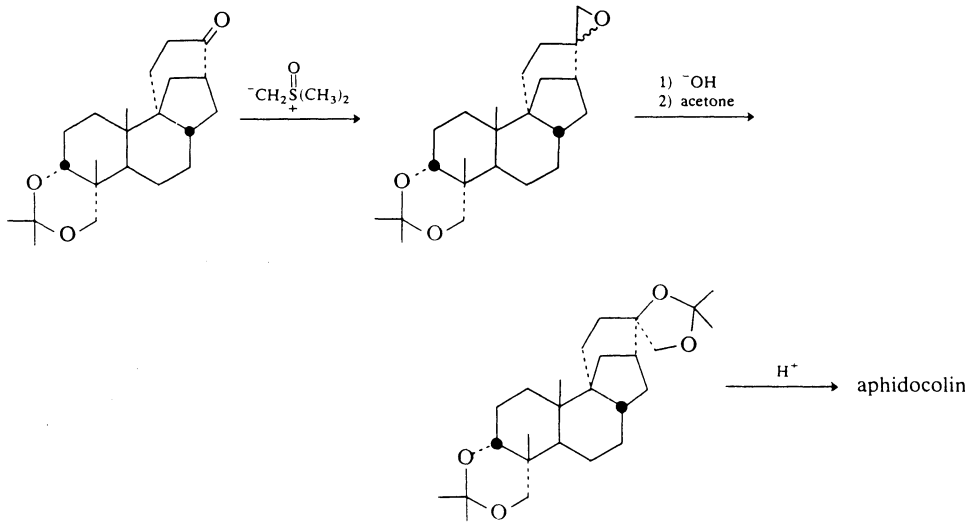
stereochemistry is presumably governed by the C-10 methyl group which blocks attack from the "top" side of the molecule. The reduction step (step **C**) establishes the configuration at C-13 and this chirality is transferred to C-9 by virtue of the intramolecular concerted transition state of the Claisen rearrangement. Again,



geometric constraints require the final C-12–C-16 bond formation give the proper stereochemistry. The final step in Scheme 11.22 is an interesting example of the use of the acylferrate chemistry discussed in Section 6.4.3.

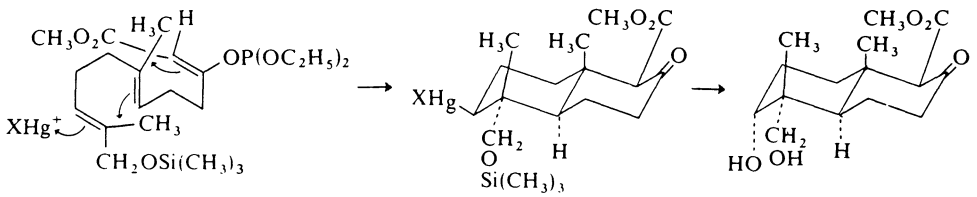
The final stage of the aphidicolin syntheses in Schemes 11.21 and 11.22 had already been developed during studies on structural proof of the material.[68] The sequence involves epoxide formation and hydrolysis of the epoxide to a diol.

68. W. Dalziel, B. Hesp, K. M. Stevenson, and J. A. J. Jarvis, *J. Chem. Soc. Perkin Trans. 1*, 2841 (1973).



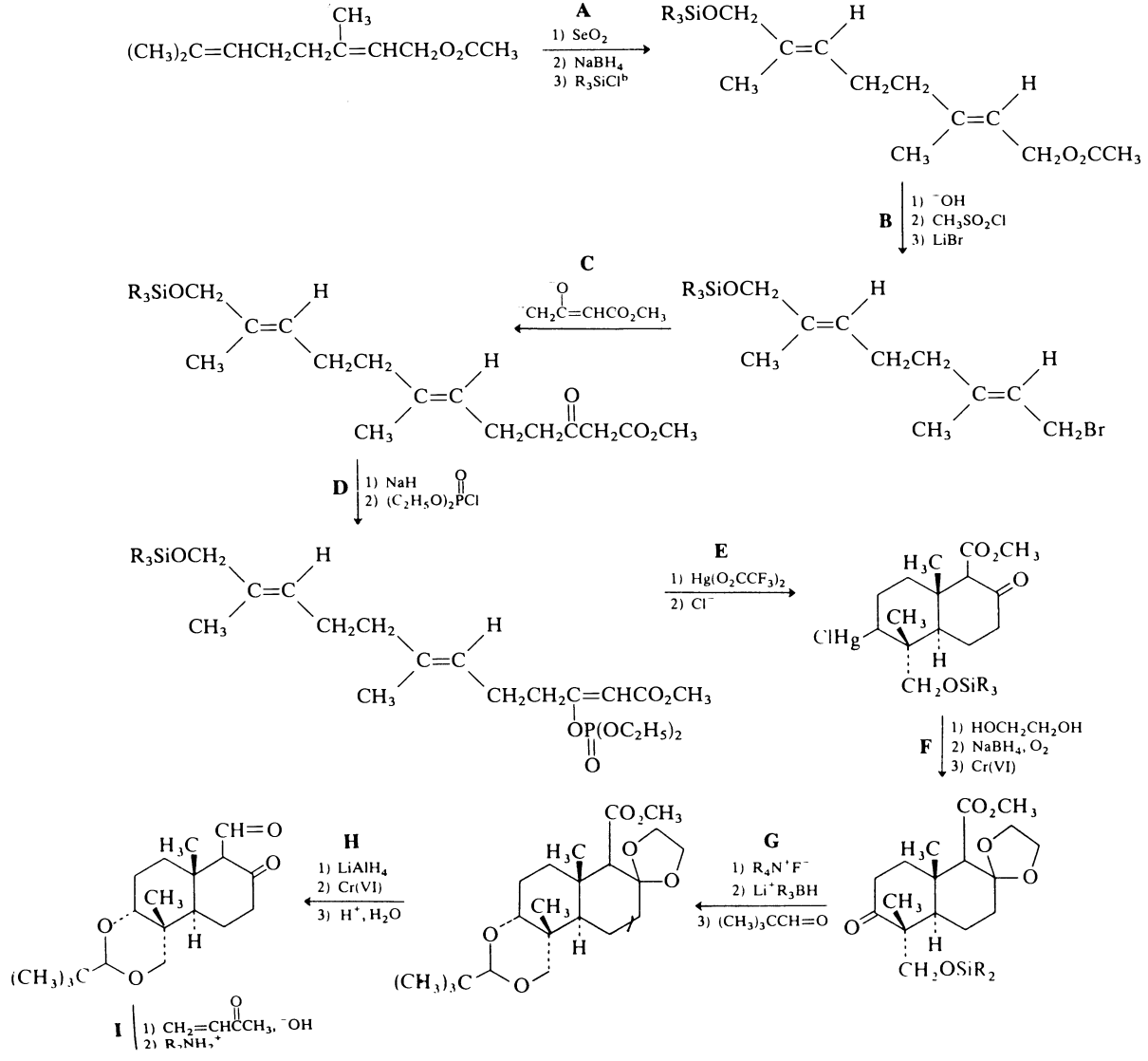
The syntheses in Schemes 11.21 and 11.22 were, therefore, not taken beyond the ketonic intermediate. The epoxide formation step in this sequence is not very stereoselective and gives a mixture of isomers which must be separated.

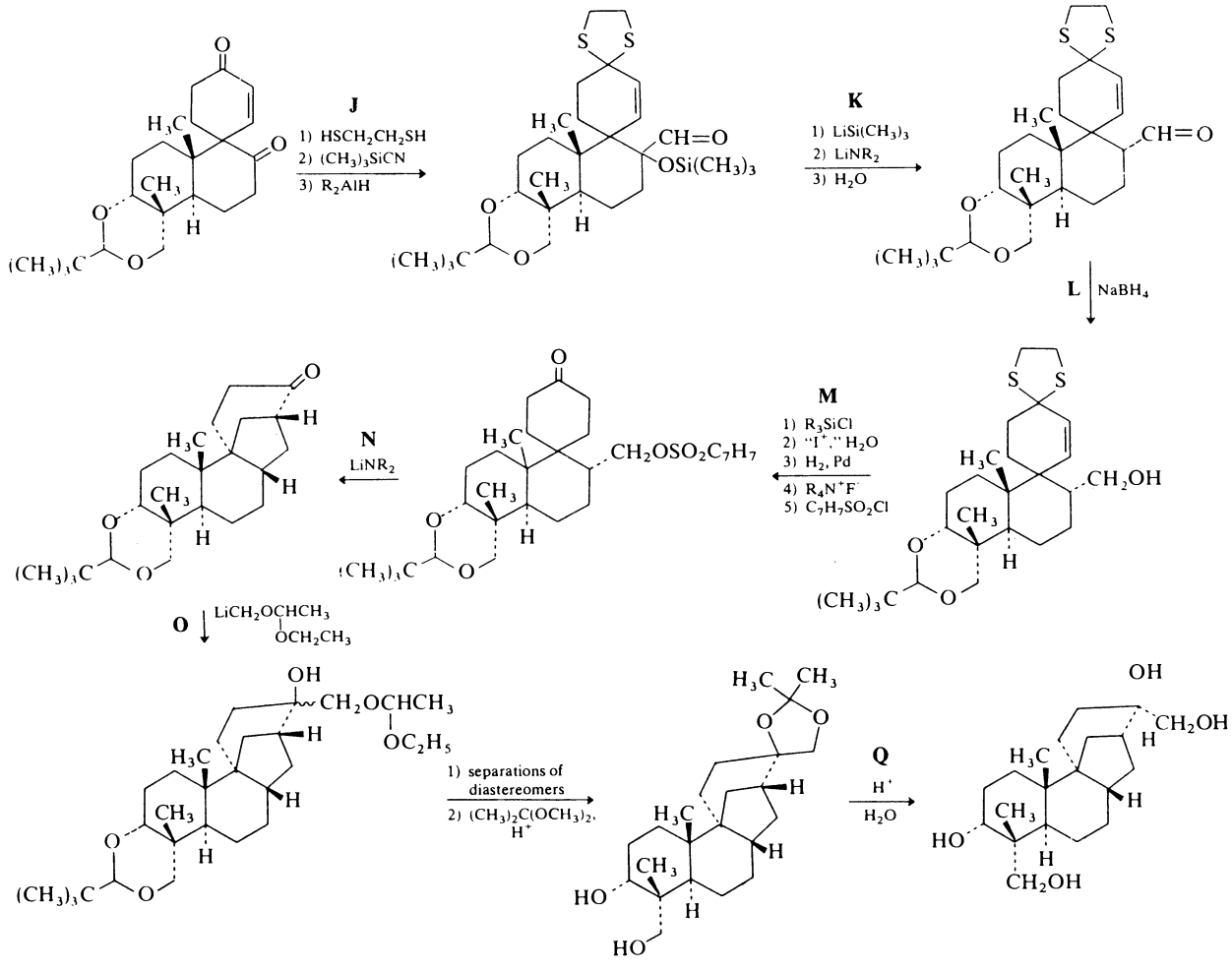
In the aphidicolin synthesis in Scheme 11.23, a key bicyclic intermediate is established by a mercuric ion-induced polyolefin cyclization. Steps **A–D** serve to construct the necessary polyene. As was discussed in Chapter 9, the stereochemistry of such cyclizations is predictable on the basis of the polyene conformation. The



configurations of three centers, C-4, C-5, and C-10, are established in the cyclization. The configuration at C-3 is established by converting it to a carbonyl group and then using a bulky reducing agent to introduce the axial hydroxyl. The six-membered ring encompassing C-13, 12, 16, 15, 14 is constructed by a Robinson type annulation in step **I**. This ring becomes symmetrical in step **M** so it does not present a stereochemical problem. The crucial element of stereochemistry is that at C-8 which is established via a novel series of steps invented to solve this particular problem. The ketone is first converted to a α-trimethylsilyoxynitrile. The initial cyanide attack probably occurs from the more open equatorial direction. The nitrile

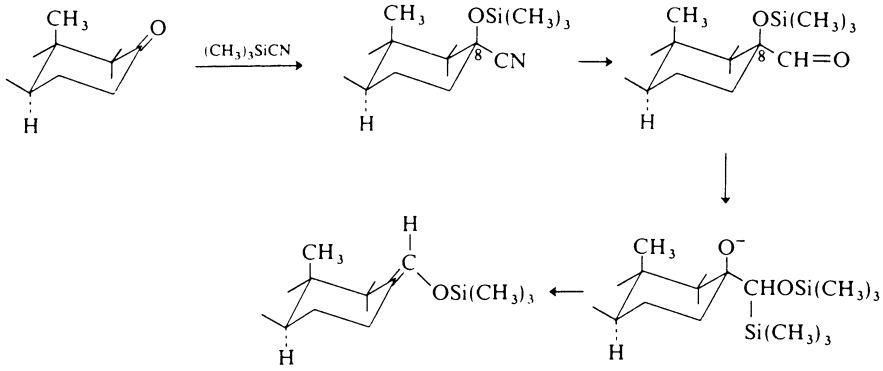
Scheme 11.23. Aphidocolin Synthesis: E. J. Corey, M. A. Tius, and J. Das[a]



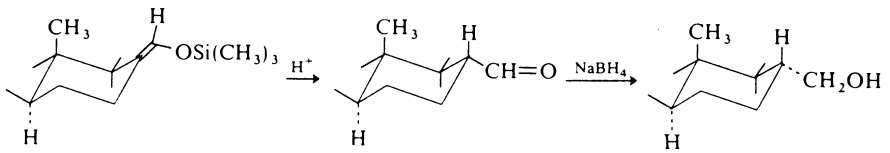


a. E. J. Corey, M. A. Tius, and J. Das, *J. Am. Chem. Soc.* **102,** 1742 (1980).
b. R_3Si = *t*-butyldimethylsilyl.

group is then reduced to an aldehyde and trimethylsilyllithium is added to the carbonyl group. This generates a β-hydroxysilane which undergoes elimination.



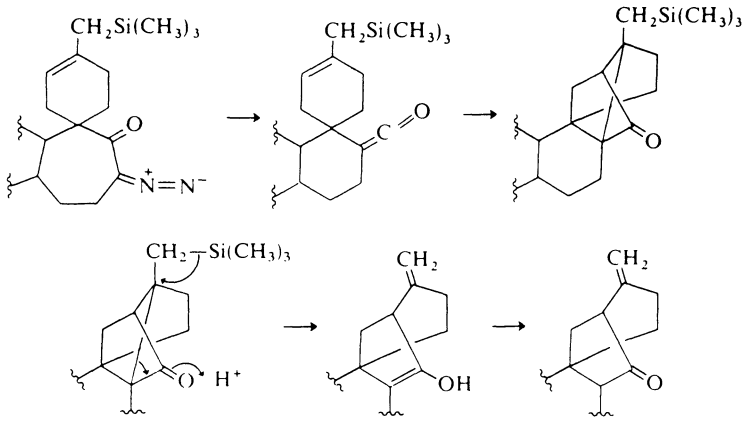
(See Section 2.6 for discussion of the mechanistic and stereochemical aspects of this elimination.) Because C-8 is reconverted to sp^2 hybridization, the stereochemistry up to this point is not crucial. The final stereochemistry at C-8 is established by protonation of the silyl enol ether. Evidently the C-10 methyl group again is the controlling factor. After the aldehyde group is in place it is reduced



to the alcohol (step **L**). The next series of reactions (step **M**) first removes the ketal-protecting group and then the carbon–carbon double bond. The primary hydroxyl group is protected as a silyl ether during this sequence. The alcohol group is then deprotected and converted to the tosylate. In step **N** the five-membered ring is constructed by intramolecular alkylation. Careful control of this reaction so as to generate the *kinetic enolate* by use of a hindered dialkylamide was crucial to obtaining the desired product. The synthesis in Scheme 11.23 was then carried on to aphidocolin by an independent method (steps **O–Q**), but this method, like that mentioned earlier, is not highly stereoselective.

The fourth published aphidicolin synthesis is given in Scheme 11.24. Steps **A** through **E** construct a key intermediate by a series of reactions, all of which have been discussed at earlier points in this text. Step **E** is a modified version of singlet oxygen oxidation which provides an enone as product as a result of decomposition of the intermediate allylic hydroperoxide. Steps **F–K** are the crucial ones for elaborating the **C** and **D** rings. A Diels–Alder reaction in which an α,β-unsaturated ketone functions as the diene gives a pyran in step **F**. After using the ester substituent to build up a vinyl group, a thermal Claisen rearrangement gives the spiro intermediate produced in step **H**. The ketone is then converted to a diazo ketone by a method which was considered in Section 9.1.2.

The key photolytic step is a Wolff rearrangement followed by an intermolecular 2 + 2 cycloaddition. The cyclobutanone formed in the cycloaddition is very acid sensitive and the silyl substituent controls the direction of the fragmentation. This

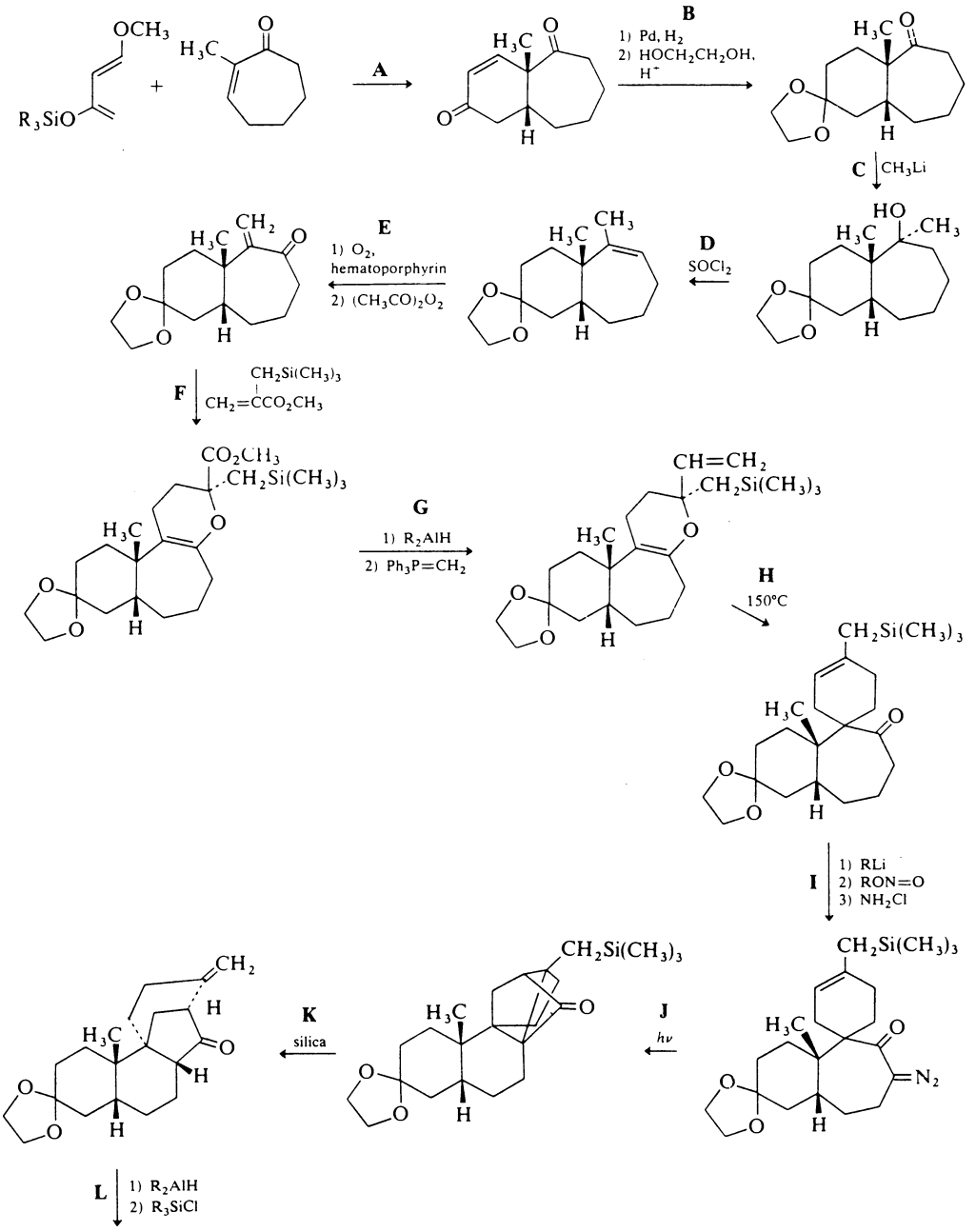


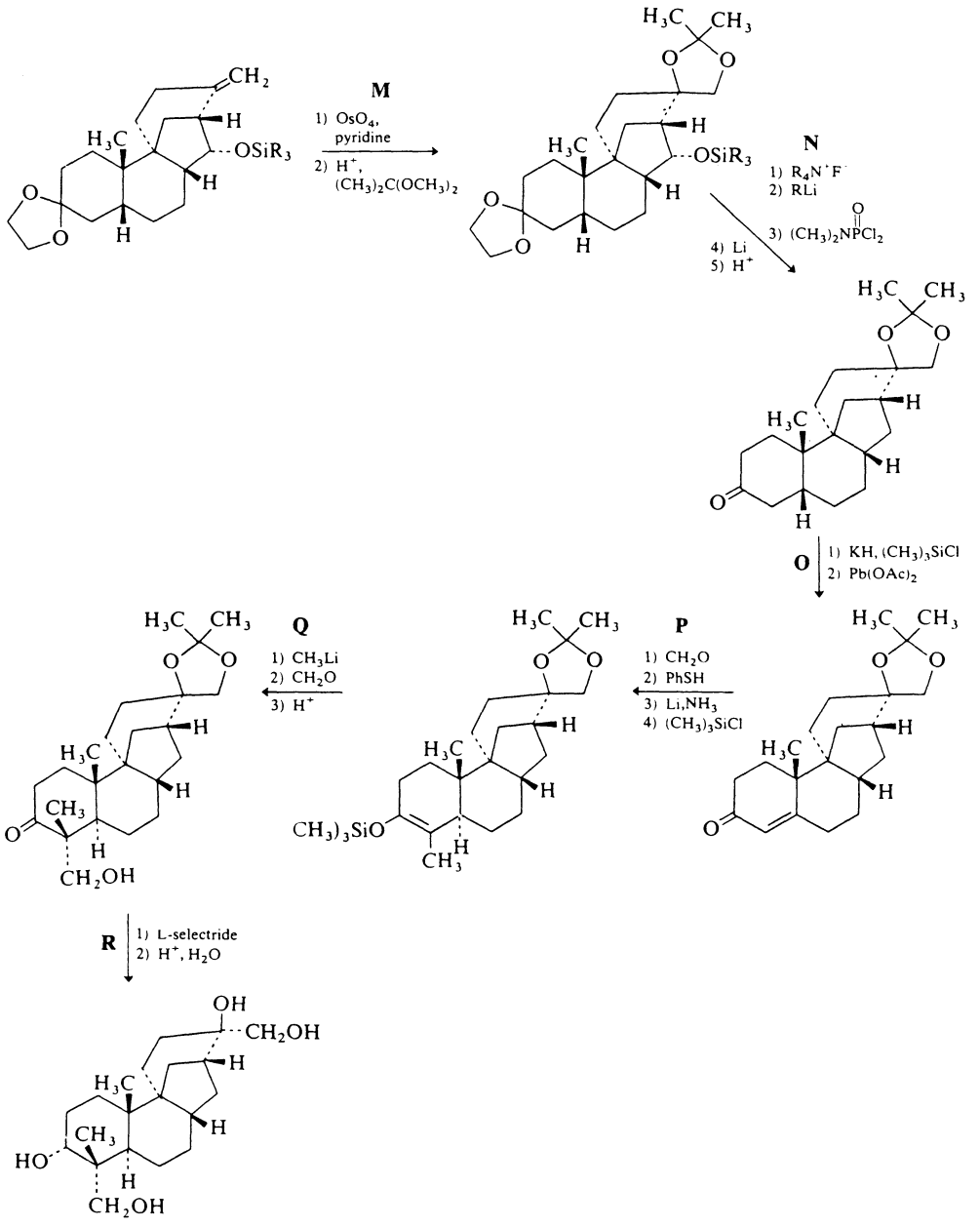
completes construction of the ring skeleton but there remains some functionalization, and in addition, a change in stereochemistry is required at C-5. The C-16 and C-17 hydroxylation is accomplished in step **M** and is stereoselective in the sense shown by virtue of using a large substituent (*t*-butyldimethylsilyl) as the alcohol-protecting group. Step **N** accomplishes reductive removal of the hydroxyl. The stereoinversion at C-5 is accomplished by an oxidation to the enone followed by lithium metal reduction. The stereochemistry is governed by preferred protonation of the enolate intermediate (Section 5.5.1). The final functionalization is similar to early steps in Schemes 11.21 and 11.22.

Each of these syntheses of aphidicolin provides an example of the utilization of stereochemistry established in an early intermediate to control subsequent stereochemistry as the synthesis is completed. This represents the control of *relative stereochemistry*, and the syntheses as a whole are *diastereoselective*. The final products are racemic materials. Most syntheses which have been completed to date have been of racemic materials, in which control of relative stereochemistry has been sufficient. As discussed in Section 11.3, the synthesis of a substance in optically pure form requires that either a catalyst, a reagent, or one of the starting materials be optically active. Diastereoselective syntheses, such as those discussed in Schemes 11.21–11.24, can be made enantioselective if an early intermediate can be obtained in optically active form by some enantioselective process. The advantage of establishing optical purity early in a multistep synthesis is that all the material subsequently formed by diastereospecific processes will possess the desired absolute stereochemistry. A resolution or other enantioselective process introduced late in a synthetic scheme can transform only one half of the material to the desired product.

A number of syntheses of natural products in optically active form have now been completed. One fruitful approach has been to start with carbohydrates which are readily available and optically pure. The synthesis of thromboxane B_2, which is discussed in the next section, is one example.

Scheme 11.24. Aphidicolin Synthesis: R. E. Ireland,

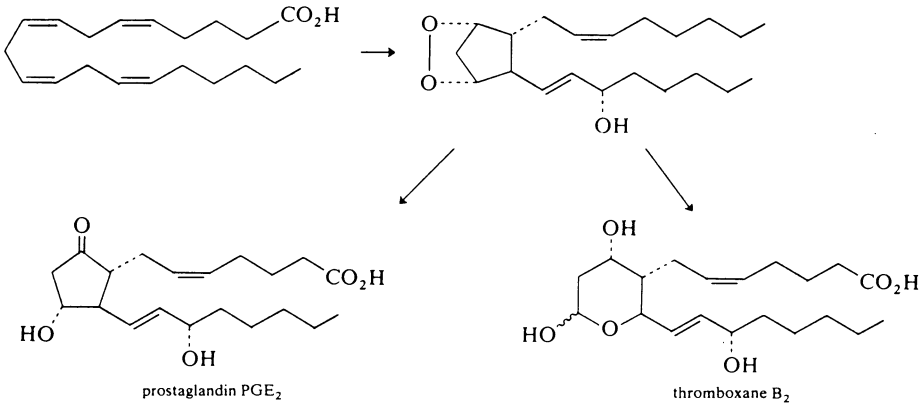




a. R. E. Ireland, J. D. Godfrey, and S. Thaisrivongs, *J. Am. Chem. Soc.* **103**, 2446 (1981).

11.8. Thromboxane B_2

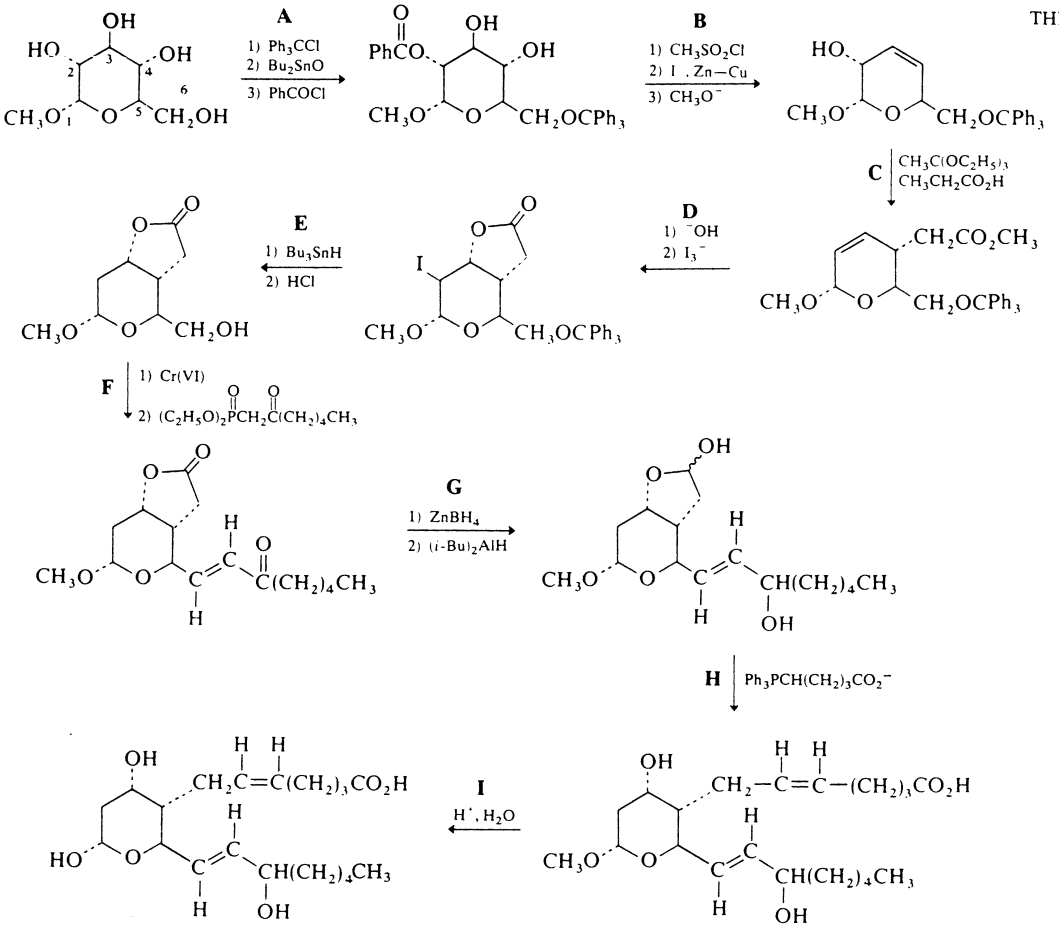
Thromboxane B_2 is an alternative reaction product of the chemical transformation of the endo peroxide intermediate which gives rise to prostaglandins. This

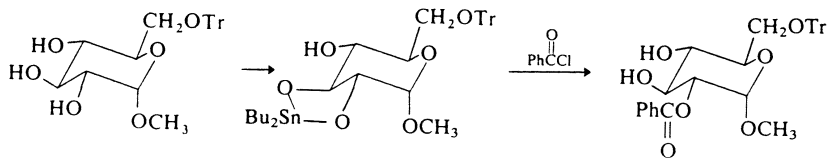


family of compounds has profound physiological activity and the minimal amounts which are available from natural sources have prompted considerable effort at synthesis. For study of biological activity, stereochemical purity and optical activity are absolutely essential since the presence of alternative stereoisomers can easily confuse the interpretation of the results. Scheme 11.25 illustrates the synthesis of thromboxane B_2 in optically pure form, using glucose as the starting material. Several groups of researchers have contributed to this synthesis[69–73] and there is an alternative route from glucose to thromboxane B_2.[74] The objective of the synthesis is the utilization of the absolute configuration of glucose to control the configuration of the subsequent transformation products. As the synthesis is developed it is possible to directly control the configuration of the three chiral centers in the pyran ring. The fourth chiral center, which is in the side chain, must be controlled by other means. In step **A** differential protection of the hydroxyl groups of glucose is achieved. The primary alcohol is selectively protected by the trityl group. This preference for reaction at the primary hydroxyl group is well known and is steric in origin. The selective benzoylation is a characteristic of the cyclic tin ester formed upon reaction with dibutyltin oxide.[75] The two free hydroxyl

69. N. L. Holdrer and B. Fraser-Reid, *Can. J. Chem.* **51**, 3357 (1973).
70. E. J. Corey, M. Shibasaki, and J. Knolle, *Tetrahedron Lett.*, 1625 (1977).
71. O. Hernandez, *Tetrahedron Lett.*, 219 (1978).
72. N. A. Nelson and R. W. Jackson, *Tetrahedron Lett.*, 3275 (1976).
73. R. C. Kelly, I. Schletter, and S. J. Stein, *Tetrahedron Lett.*, 3279 (1976).
74. S. Hanessian and P. Lavallee, *Can. J. Chem.* **55**, 562 (1977).
75. R. M. Munavu and H. H. Szmant, *J. Org. Chem.* **41**, 1832 (1976).

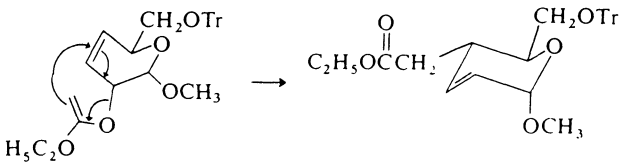
Scheme 11.25. Synthesis of Thromboxane B_2 from Methyl Glucoside





groups are then reductively removed, generating a double bond. This takes place by conversion to a diiodide, via the mesylate, followed by reduction with zinc. The

C-2 hydroxyl group is then freed from the benzoate ester by reaction with methoxide. This hydroxyl group then controls the configuration of the carbon–carbon bond established at C-4 by virtue of the concerted intramolecular Claisen rearrangement. This center, in turn, can control the C–O bond stereochemistry



established at C-3 by virtue of the high stereospecificity of the iodolactonization in step **D**. The configuration of C-5 remains unperturbed through these transformations. Steps **E** and **F** set the stage for introduction of the side chain by a method perfected in earlier research on the prostaglandins.[76] The reduction of the carbonyl group is not highly diastereoselective, but the isomers can be separated.

General References

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76. E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Am. Chem. Soc.* **92**, 397 (1970).

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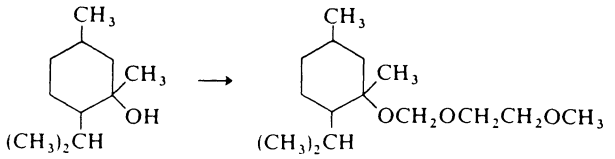
B. Fraser-Reid and R. C. Anderson, *Fortschritte Chem. Org. Naturstoffe* **39**, 1 (1980).

Problems

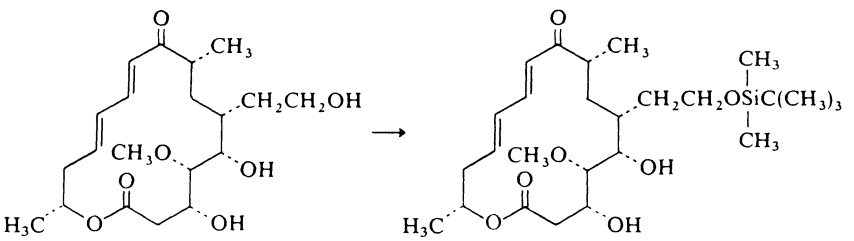
(*References for these problems will be found on page 630.*)

1. Indicate conditions which would be appropriate for the following transformations involving introduction or removal of protecting groups.

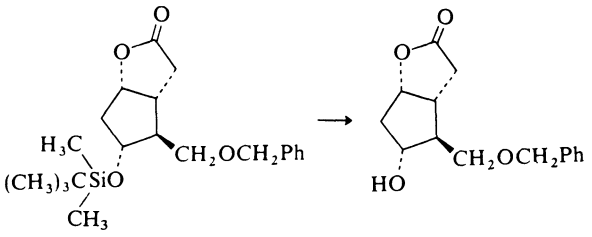
(a)



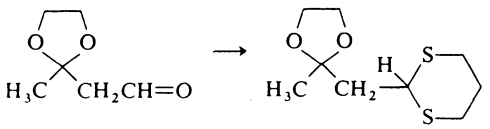
(b)



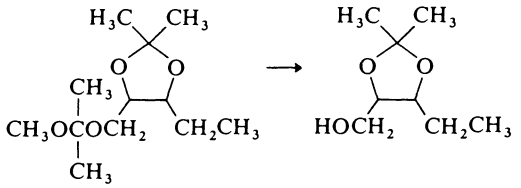
(c)



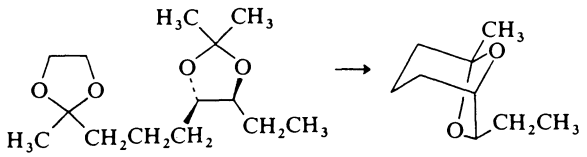
(d)



(e)

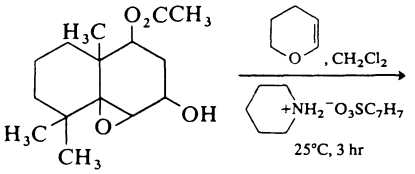


(f)

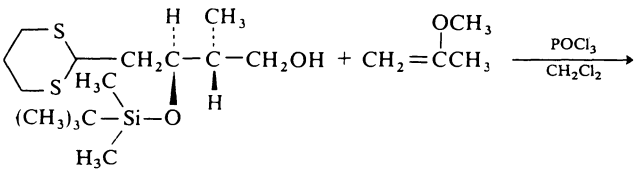


2. Indicate the product to be expected under the following reaction conditions.

(a)



(b)



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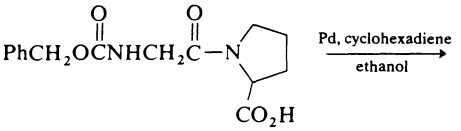

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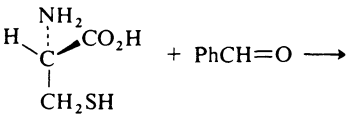
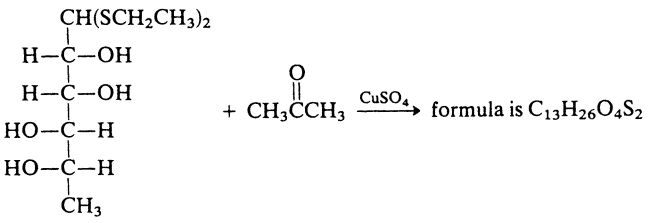
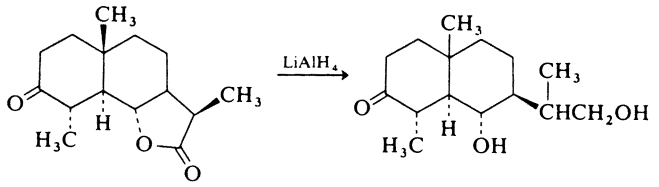
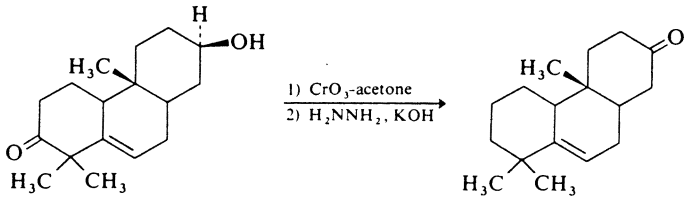
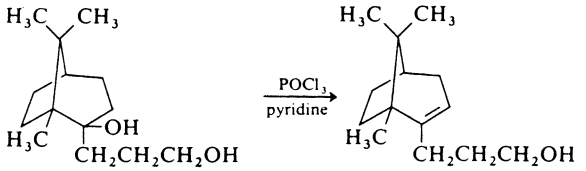


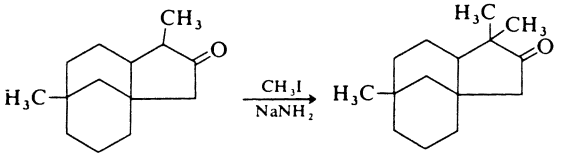
(e) 

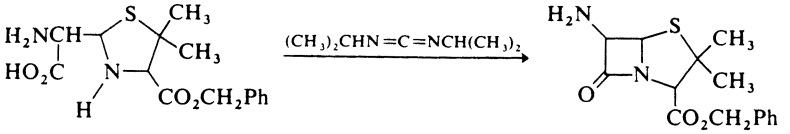
3. In each of the synthetic transformations shown, the reagents are appropriate, but the reactions will not be practical as they are written. What modification would be necessary to permit each transformation to be carried out to give the desired product?

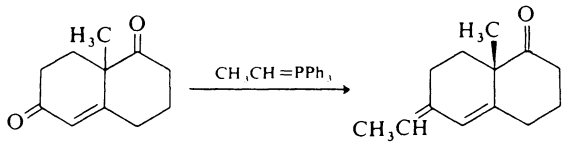
(a) 

(b) 

(c) 

(d) 

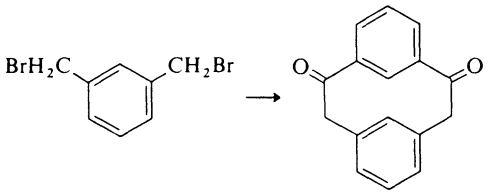
(e) 

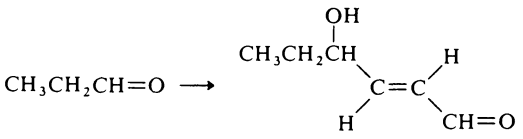
(f) 

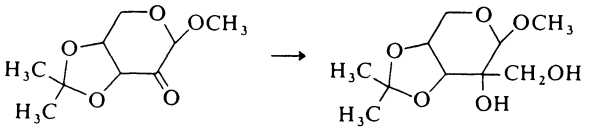
4. Under certain circumstances, each of the following groups can serve as a temporary protecting group for secondary amines by acting as a removable tertiary substituent. Suggest conditions which might be appropriate for subsequent removal of each group.

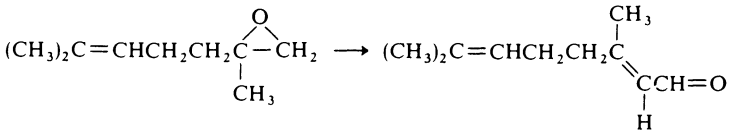
(a) $PhCH_2-$ (b) $CH_2{=}CHCH_2-$ (c) $CH_2{=}CH-$ (d) $PhCH_2OCH_2-$

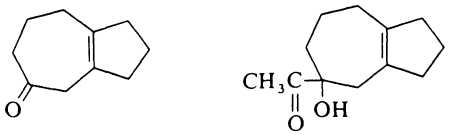
5. Show how synthetic equivalent groups might be used to efficiently carry out the following transformations.

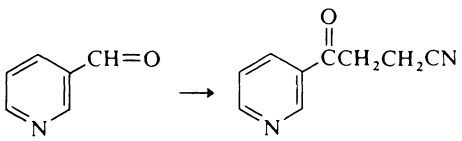
(a) 

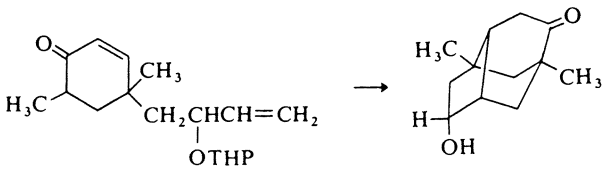
(b) 

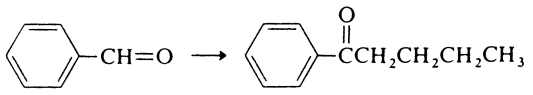
(c) 

(d) 

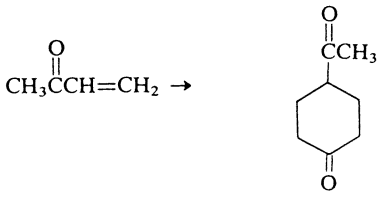
(e) 

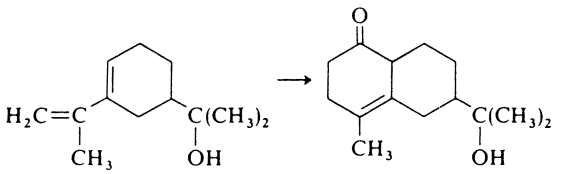
(f) 

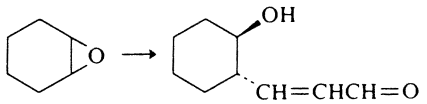
(g) 

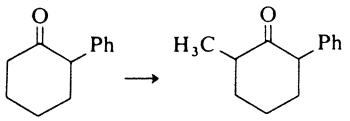
(h) 

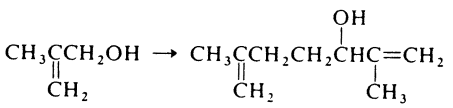
6. Indicate a reagent or short reaction sequence that would accomplish each of the following synthetic transformations:

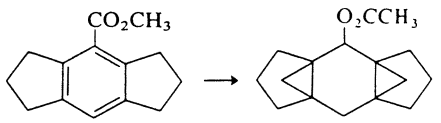
(a) 

(b) 

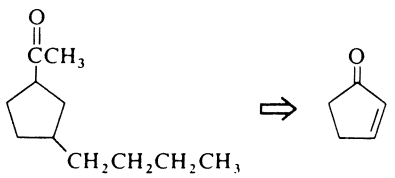
(c) 

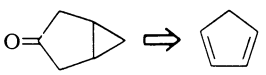
(d) 

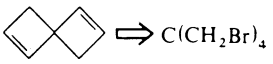
(e) 

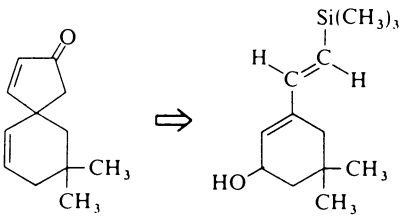
(f) 

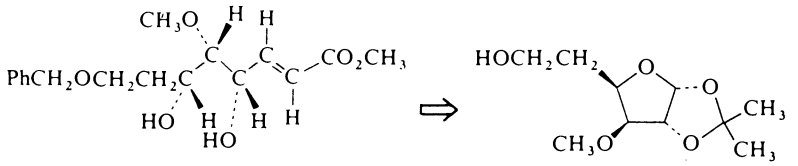
7. Indicate a reagent or short reaction sequence which could accomplish synthesis of the material shown on the left from the starting material on the right.

(a) 

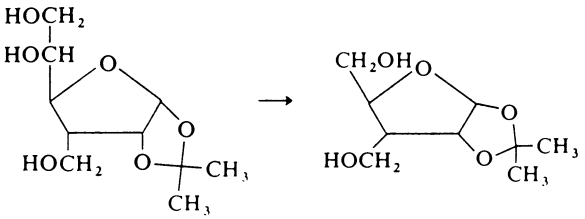
(b) 

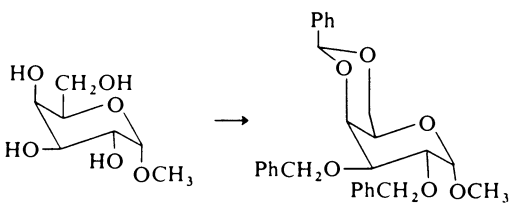
(c) 

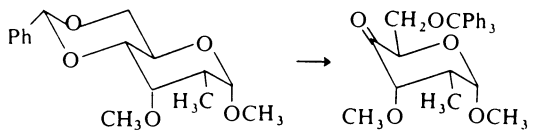
(d) 

(e) 

8. Because they are readily available from natural sources in optically pure form, carbohydrates are very useful starting materials for the synthesis of optically pure substances. However, the high number of similar functional groups present in carbohydrates requires versatile techniques for selective protection and selective reaction. Show how appropriate manipulation of protecting groups and/or selective reagents might be employed to effect the desired transformations.

(a) 

(b) 

(c) 

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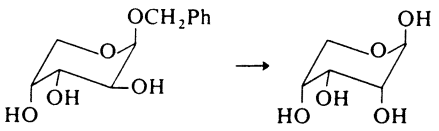
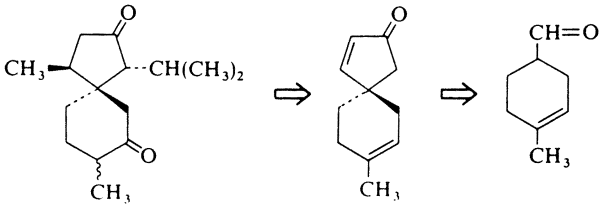


9. Synthetic transformations which are parts of total syntheses of natural products are outlined by a general retrosynthetic outline. For each retrosynthetic disconnection, suggest a reagent or short sequence of reactions which could accomplish the forward synthetic reaction. The proposed route should be diastereoselective but need not be enantioselective.

(a)



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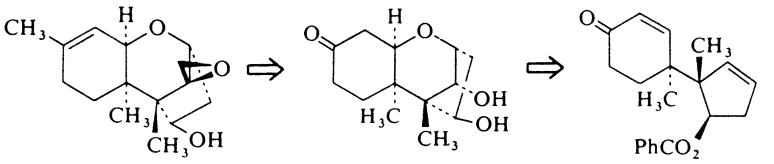

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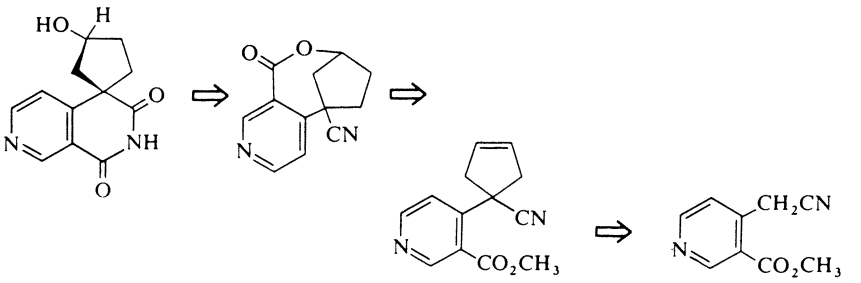

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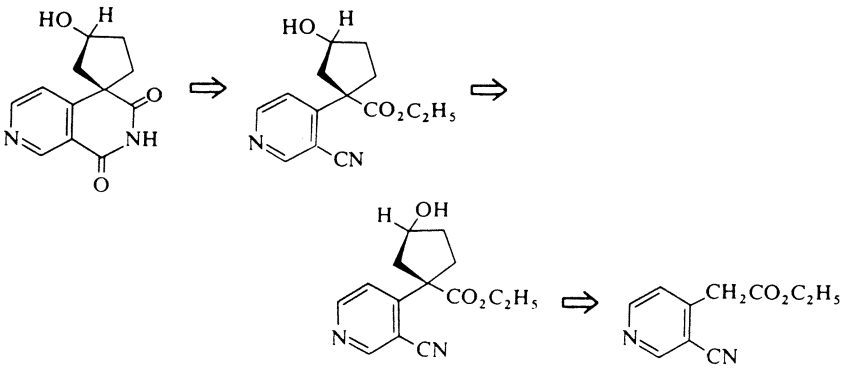


10. Diels–Alder reactions are attractive for many synthetic applications, particularly because of their predictable stereochemistry. There are, however, significant limitations on the type of compound which can serve as a dienophile or diene. As a result, the idea of synthetic equivalency has been exploited in this area. For each of the reactive dienophiles and dienes given below, suggest one or more transformations which might be carried out on a Diels–Alder adduct derived from it that would lead to a product not directly attainable by a Diels–Alder reaction. Give the structure of the diene or dienophile "synthetic equivalent" and indicate why the direct Diels–Alder reaction would not be possible.

Dienophiles

(a) $CH_2{=}CH\overset{+}{P}Ph_3$

(b) $CH_2{=}CH\overset{+}{S}Ph$ (O$^-$)

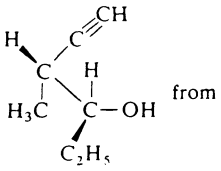
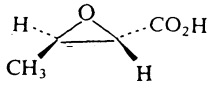
(c) $CH_2{=}C(CO_2C_2H_5)(O_2CCH_3)$

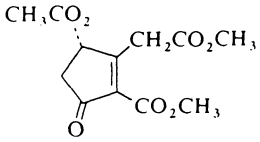
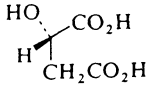
Dienes

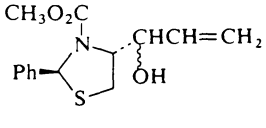
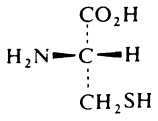
(d) $CH_2{=}C(OSi(CH_3)_3){-}CH{=}CHOCH_3$

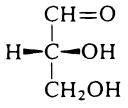
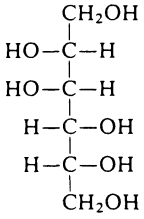
(e) $CH_2{=}C(SPh){-}C{=}CH_2$ (O_2CCH_3)

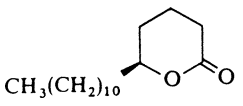
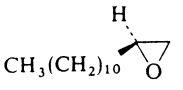
11. One approach to the synthesis of optically pure materials is to start with an available optically pure material and effect the synthesis by a series of stereospecific reactions. Devise a sequence of reactions which would be appropriate for the following syntheses based on optically pure starting materials.

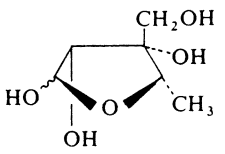
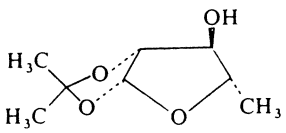
(a)  from 

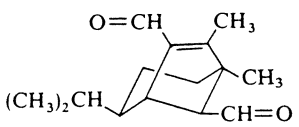
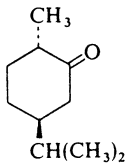
(b)  from 

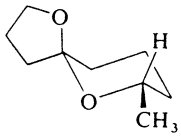
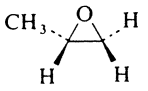
(c)  from 

(d)  from 

(e)  from 

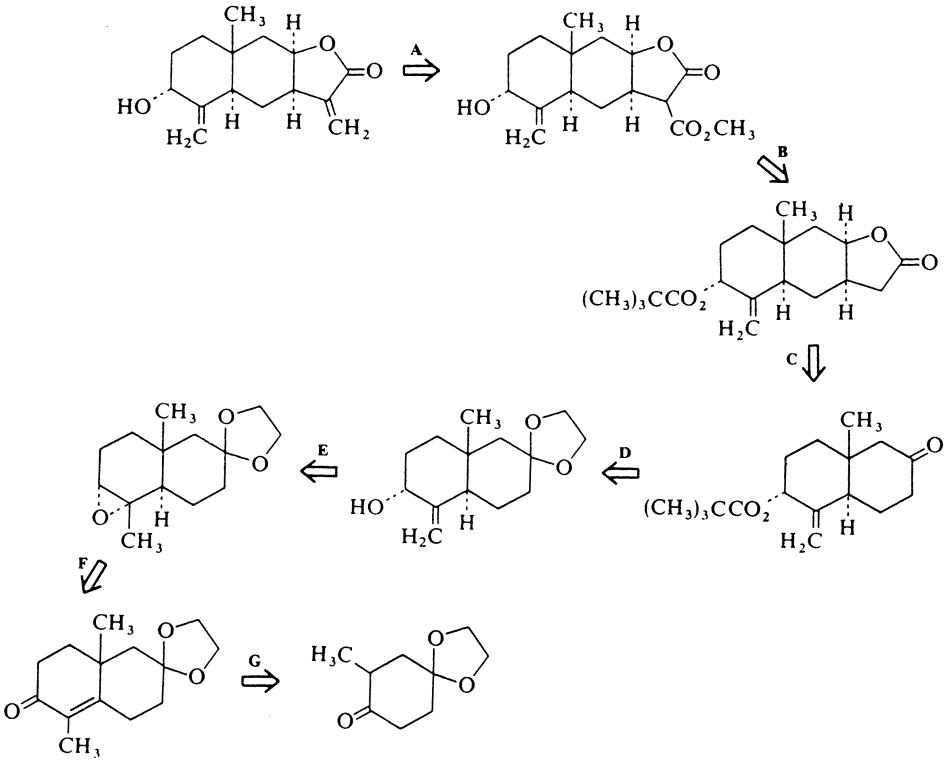
(f)  from 

(g)  from 

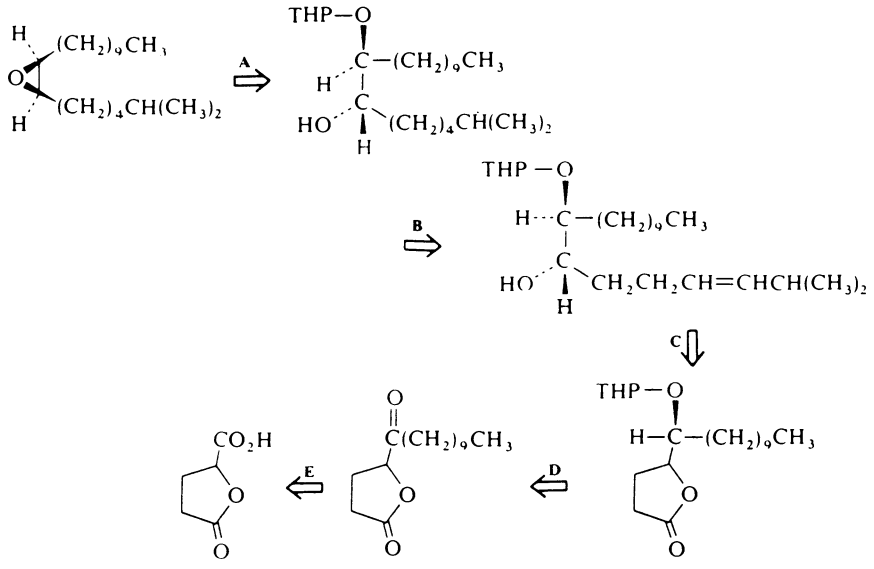
(h)  from 

12. Several natural product syntheses are outlined in retrosynthetic form. Suggest a reaction or short reaction series which could accomplish each lettered transformation in the forward synthetic direction. The structures shown refer to racemic materials.

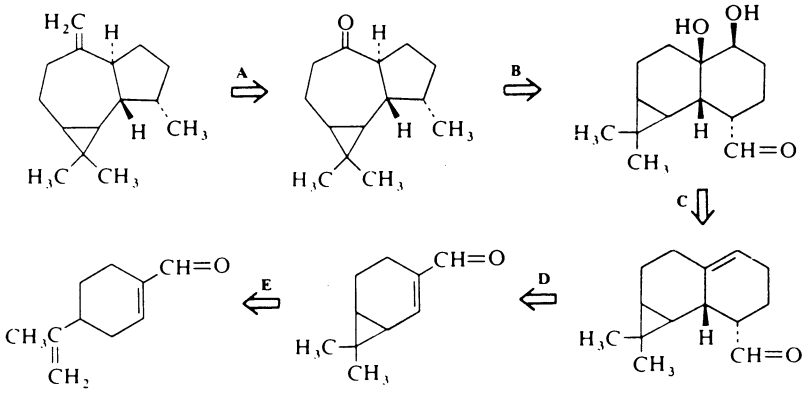
(a) Isotelekin



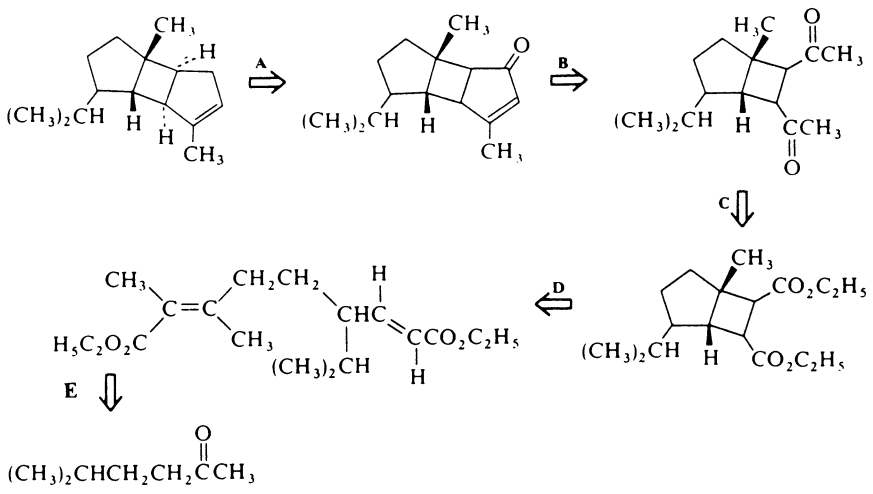
(b) Disparlure



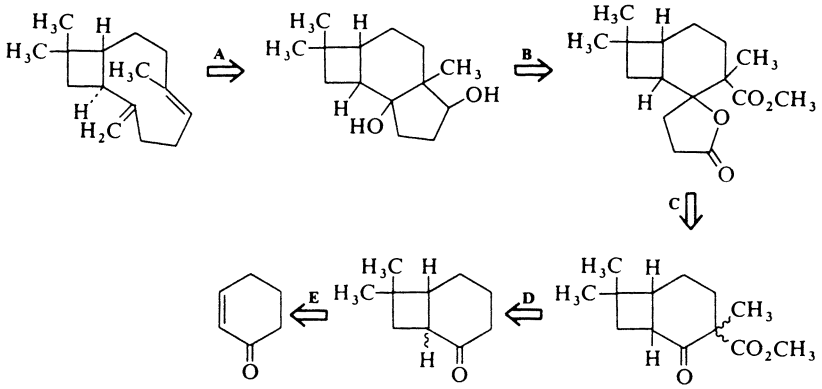
(c) Aromandrene



(d) α-Bourbonene

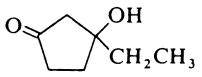


(e) Caryophyllene



13. Perform a retrosynthetic analysis for each of the following molecules. Develop at least three outline schemes. Discuss the relative merits of the three schemes and develop a fully elaborated synthetic plan for the one you consider to be most promising.

(a)



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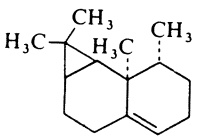

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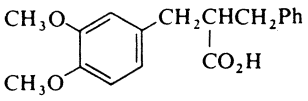

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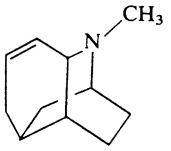

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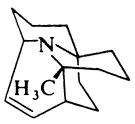

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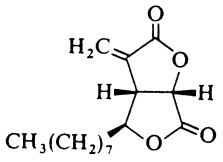

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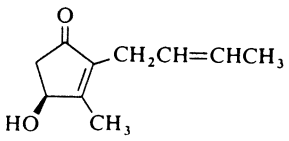

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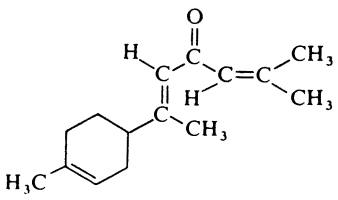

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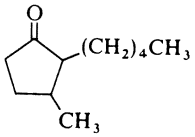

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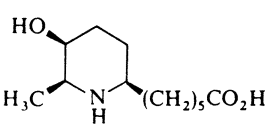
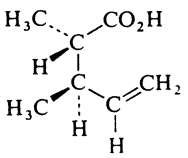
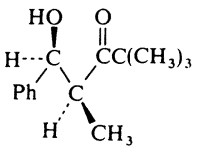
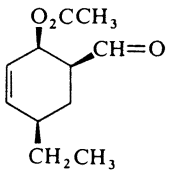
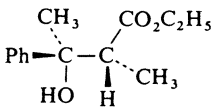


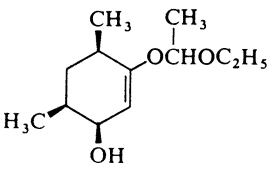
14. Suggest methods that would be expected to achieve a diastereoselective synthesis of the following compounds.

(a) 

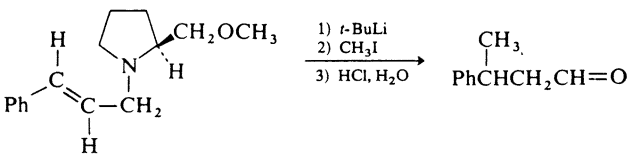
(b) 

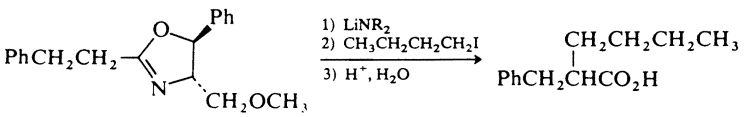
(c) 

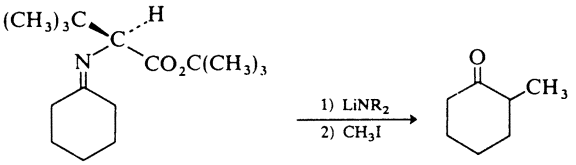
(d) 

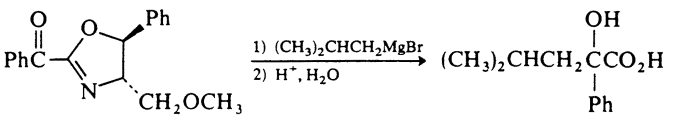
(e) 

15. By careful consideration of transition state geometry using models, predict the *absolute configuration* of the major product for each asymmetric synthesis. Explain the basis of your prediction.

(a) 

(b) 

(c) 

(d) 

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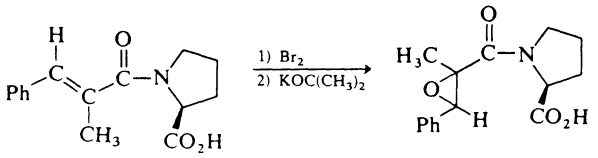

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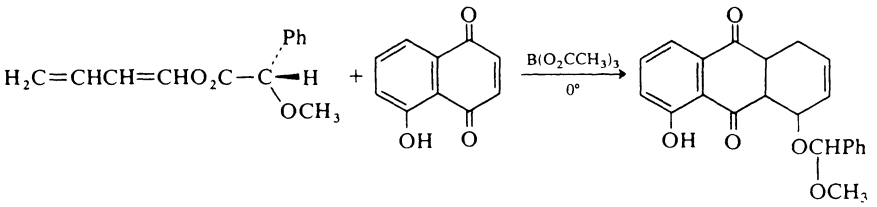

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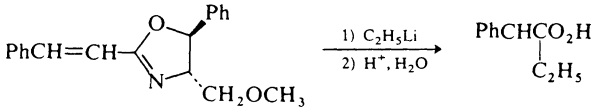

References for Problems

Chapter 1

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