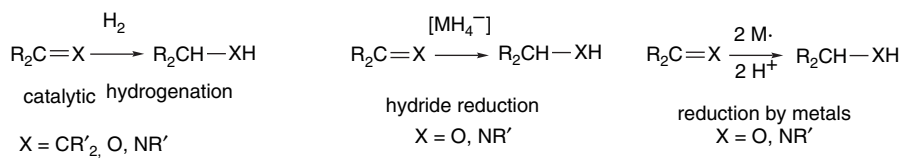
5

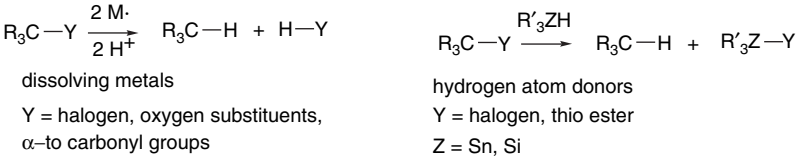
Reduction of Carbon-Carbon Multiple Bonds, Carbonyl Groups, and Other Functional Groups

Introduction

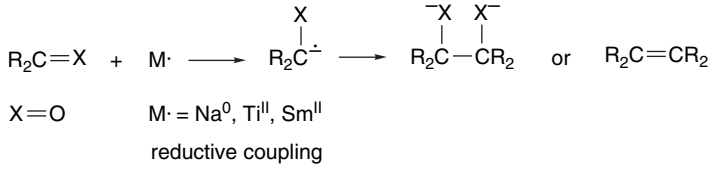
The subject of this chapter is reduction reactions that are especially important in synthesis. Reduction can be accomplished by several broad methods including addition of hydrogen and/or electrons to a molecule or by removal of oxygen or other electronegative substituents. The most widely used reducing agents from a synthetic point of view are molecular hydrogen and hydride derivatives of boron and aluminum, and these reactions are discussed in Sections 5.1 through 5.3. A smaller group of reactions transfers hydride from silicon or carbon, and these are the topic of Section 5.4. Certain reductions involving a free radical mechanism use silanes or stannanes as hydrogen atom donors, and these reactions are considered in Section 5.5. Other important procedures use metals such as lithium, sodium, or zinc as electron donors. Reduction by metals can be applied to carbonyl compounds and aromatic rings and can also remove certain functional groups.

Addition of Hydrogen

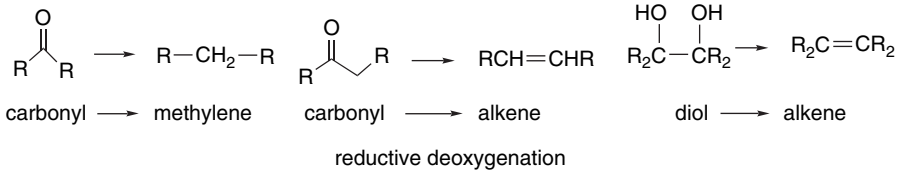




There are also procedures that form carbon-carbon bonds. Most of these reactions begin with an electron transfer that generates a radical intermediate, which then undergoes a coupling or addition reaction. These reactions are discussed in Section 5.6.

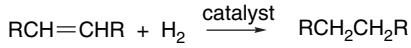


Reductive removal of oxygen from functional groups such as ketones and aldehydes, alcohols, α-oxy ketones, and diols are also important in synthesis. These reactions, which provide important methods for interconversion of functional groups, are considered in Section 5.7



5.1. Addition of Hydrogen at Carbon-Carbon Multiple Bonds

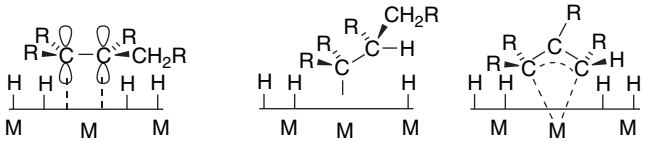
The most widely used method for adding the elements of hydrogen to carbon-carbon double bonds is catalytic hydrogenation. Except for very sterically hindered alkenes, this reaction usually proceeds rapidly and cleanly. The most common catalysts are various forms of transition metals, particularly platinum, palladium, rhodium, ruthenium, and nickel. Both the metals as finely dispersed solids or adsorbed on inert supports such as carbon or alumina (*heterogeneous catalysts*) and certain soluble complexes of these metals (*homogeneous catalysts*) exhibit catalytic activity. Depending upon conditions and catalyst, other functional groups are also subject to reduction under these conditions.



5.1.1. Hydrogenation Using Heterogeneous Catalysts

The mechanistic description of catalytic hydrogenation of alkene is somewhat imprecise, partly because the reactive sites on the metal surface are not as well

described as small-molecule reagents in solution. As understanding of the chemistry of soluble hydrogenation catalysts developed, it became possible to extrapolate the mechanistic concepts to heterogeneous catalysts. It is known that hydrogen is adsorbed onto the metal surface, forming metal hydrogen bonds similar to those in transition metal hydrides. Alkenes are also adsorbed on the catalyst surface and at least three types of intermediates have been implicated in hydrogenation. The initially formed intermediate is pictured as attached at both carbon atoms of the double bond by π-type bonding, as shown in **A**. The bonding involves an interaction between the alkene π and π* orbitals with corresponding acceptor and donor orbitals of the metal. A hydride can be added to the adsorbed group, leading to **B**, which involves a σ-type carbon-metal bond. This species can react with another hydrogen to give the alkane, which is desorbed from the surface. A third intermediate species, shown as **C**, accounts for double-bond isomerization and the exchange of hydrogen that sometimes accompanies hydrogenation. This intermediate is equivalent to an allyl group bound to the metal surface by π bonds. It can be formed from absorbed alkene by abstraction of an allylic hydrogen atom by the metal. The reactions of transition metals with organic compounds are discussed in Chapter 8. There are well-characterized examples of structures corresponding to each of the intermediates **A**, **B**, and **C** that are involved in hydrogenation. However, one issue that is left unresolved by this mechanism is whether there is cooperation between adjacent metal atoms, or if the reactions occur at a single metal center, which is usually the case with soluble catalysts.



A π-complex **B** σ-bond **C** π-allyl complex

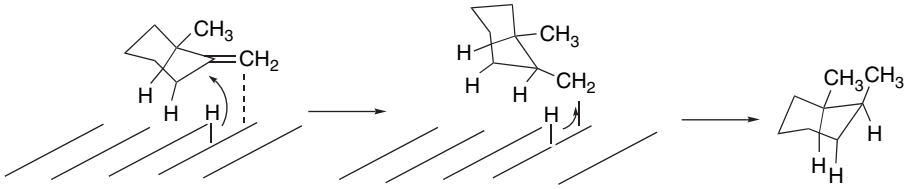
Catalytic hydrogenations are usually very clean reactions with little by-product formation, unless reduction of other groups is competitive, but careful study reveals that sometimes double-bond migration takes place in competition with reduction. For example, hydrogenation of 1-pentene over Raney nickel is accompanied by some isomerization to both *E*- and *Z*-2-pentene.[1] The isomerized products are converted to pentane, but at a slower rate than 1-pentene. Exchange of hydrogen atoms between the reactant and adsorbed hydrogen can be detected by isotopic exchange. Allylic positions undergo such exchange particularly rapidly.[2] Both the isomerization and allylic hydrogen exchange can be explained by the intervention of the π-allyl intermediate **C** in the general mechanism for hydrogenation. If hydrogen is added at the alternative end of the allyl system, an isomeric alkene is formed. Hydrogen exchange occurs if a hydrogen from the metal surface, rather than the original hydrogen, is transferred prior to desorption.

In most cases, both hydrogen atoms are added to the same face of the double bond (*syn* addition). If hydrogenation occurs by addition of hydrogen in two steps, as

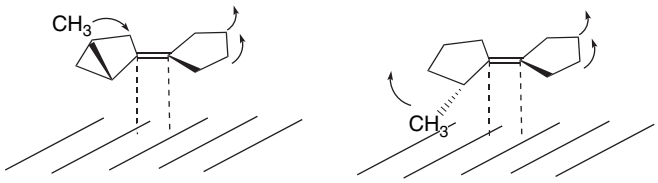
[1] H. C. Brown and C. A. Brown, *J. Am. Chem. Soc.*, **85**, 1005 (1963).
[2] G. V. Smith and J. R. Swoap, *J. Org. Chem.*, **31**, 3904 (1966).

implied by the above mechanism, the intermediate must remain bonded to the metal surface in such a way that the stereochemical relationship is maintained. Adsorption to the catalyst surface normally involves the less sterically congested side of the double bond, and as a result hydrogen is added from the less hindered face of the double bond. There are many hydrogenations in which hydrogen addition is not entirely *syn*, and independent corroboration of the stereochemistry is normally necessary.

Scheme 5.1 illustrates some hydrogenations in which the *syn* addition from the less hindered side is observed. Some exceptions are also included. Entry 1 shows the hydrogenation of an exocyclic methylene group. This reaction was studied at various H_2 pressures and over both Pt and Pd catalysts. 4-Methyl- and 4-*t*-butylmethylene cyclohexane also give mainly the *cis* product.[3] These results are consistent with a favored (2.3:1) equatorial delivery of hydrogen.



The Entry 2 reactant, 1,2-dimethylcyclohexene, was also studied by several groups and a 2:1–4:1 preference for *syn* addition was noted, depending on the catalyst and conditions. In the reference cited, the catalyst was prepared by reduction of a Pt salt with $NaBH_4$. A higher ratio of the *cis* product was noted at 0° C (5.2:1) than at 25° C (2.5:1). In Entry 3, the 2,6-dimethycyclohexene gives mainly *cis* product with a Pt catalyst but *trans* product dominates with a Pd catalyst. These three cases indicate that stereoselectivity for unhindered alkenes is modest and dependent on reaction conditions. Entries 4 and 5 involve more rigid and sterically demanding alkenes. In both cases, *syn* addition of hydrogen occurs from the less hindered face of the molecule. Entries 6 to 8 are cases in which hydrogen is added from the more-substituted face of the double bond. The compound in Entry 6 gives mainly *trans* product at high H_2 pressure, where the effects of alkene isomerization are minimized. This result indicates that the primary adsorption must be from the methyl-substituted face of the molecule. This may result from structural changes that occur on bonding to the catalyst surface. In the *cis* approach, the methyl substituent moves away from the cyclopentane ring as rehybridization of the double bond occurs. In the *trans* approach, the methyl group must move closer to the adjacent cyclopentane ring.

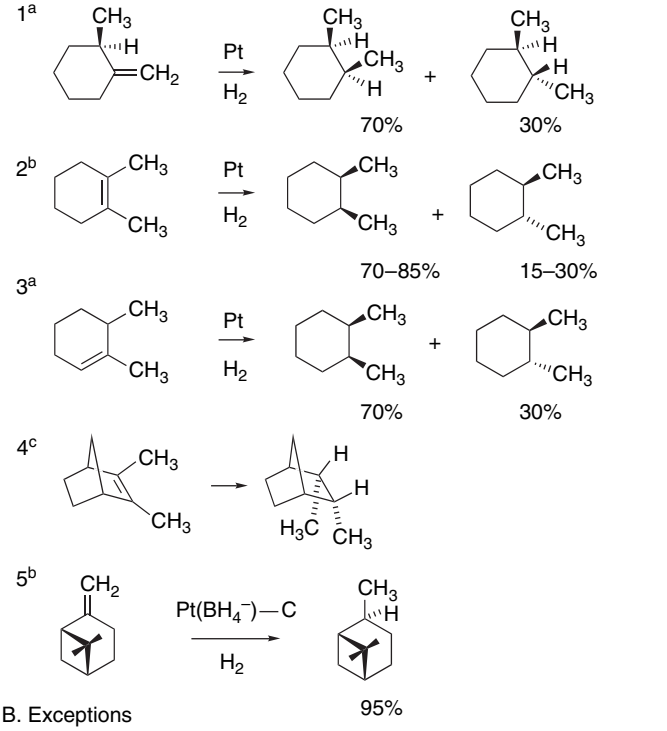


The preference for addition from the more hindered of the substituents in Entries 7 and 8 can be attributed to functional group interactions with the catalyst. Polar

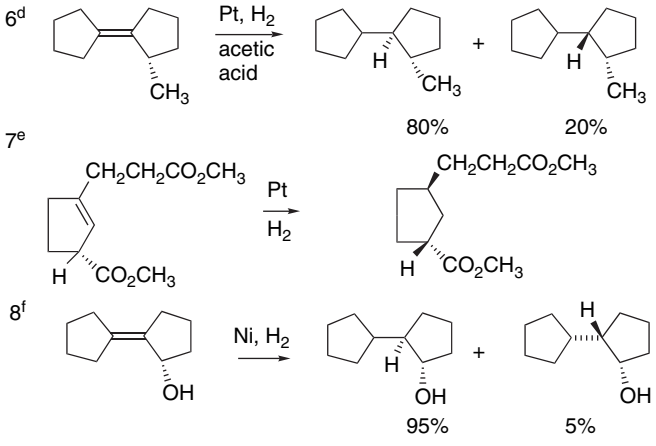
[3] J.-F. Sauvage, R. H. Baker, and A. S. Hussey, *J. Am. Chem. Soc.*, **82**, 6090 (1960).

Scheme 5.1. Stereochemistry of Hydrogenation of Some Alkenes

A. Examples of preferential *syn* addition from less hindered side



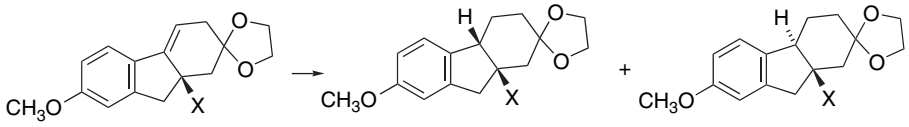
B. Exceptions



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. S. Siegel and J. R. Cozort, *J. Org. Chem.*, **40**, 3594 (1975).
e. J. P. Ferris and N. C. Miller, *J. Am. Chem. Soc.*, **88**, 3522 (1966).
f. S. Mitsui, Y. Senda, and H. Saito, *Bull. Chem. Soc. Jpn.*, **39**, 694 (1966).

groups sometimes favor *cis* addition of hydrogen, relative to the substituent. This is a very common observation for hydroxy groups, but less so for esters (*vide infra*).

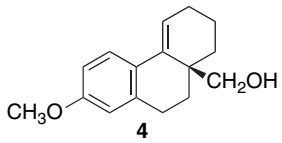
The facial stereoselectivity of hydrogenation is affected by the presence of polar functional groups that can govern the mode of adsorption to the catalyst surface. For instance, there are many of examples of hydrogen being introduced from the face of the molecule occupied by the hydroxy group, which indicates that the hydroxy group interacts with the catalyst surface. This behavior can be illustrated with the alcohol **1a** and the ester **1b**.[4] Although the overall shapes of the two molecules are similar, the alcohol gives mainly the product with a *cis* ring juncture (**2a**), whereas the ester gives a product with *trans* stereochemistry (**3b**). The stereoselectivity of hydroxy-directed hydrogenation is a function of solvent and catalyst. The *cis*-directing effect is strongest in nonpolar solvents such as hexane. This is illustrated by the results from compound **4**. In ethanol, the competing interaction of the solvent molecules evidently swamps out the effect of the hydroxymethyl group.



1a X = CH_2OH
1b X = CO_2CH_3

2a 94%
2b 15%

3a 6%
3b 85%



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Solvent	% *cis*	% *trans*
Hexane	61	39
DME	20	80
EtOH	6	94

Thompson and co-workers have explored the range of substituents that can exert directive effects using polycyclic systems. For ring system **1**, hydroxymethyl and formyl showed strong directive effects; cyano, oximino, and carboxylate were moderate; and carboxy, ester, amide, and acetyl groups were not directive (see Table 5.1).[4,5] As with **4**, the directive effects were shown to be solvent dependent. Strong donor solvents, such as ethanol and DMF, minimized the substituent-directing effect. Similar studies were carried out with ring system **5**.[6] The results are given in Table 5.1. It would be expected that the overall shape of the reactant molecule would influence the effectiveness of the directive effect. The trends in ring systems **1** and **5** are similar, although ring system **5** appears to be somewhat less susceptible to directive effects. These hydrogenations were carried out in hydroxylic solvents and it would be expected that the directive effects would be enhanced in less polar solvents.

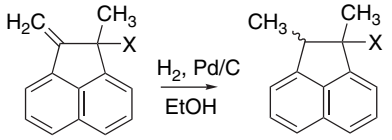
4. (a) H. W. Thompson, *J. Org. Chem.*, **36**, 2577 (1971); (b) H. W. Thompson, E. McPherson, and B. L. Lences, *J. Org. Chem.*, **41**, 2903 (1976).
5. H. W. Thompson and R. E. Naipawer, *J. Am. Chem. Soc.*, **95**, 6379 (1973).
6. H. W. Thompson and S. Y. Rashid, *J. Org. Chem.*, **67**, 2813 (2002).

Table 5.1. Substituent Directive Effects for Ring Systems 1 and 5

Substituent X	Ring system **1**[a]		Ring system **5**[b]	
	% cis (Directive)	*% trans* (Nondirective)	*% cis* (Directive)	*% trans* (Nondirective)
CH_2NH_2			87	13
$CH_2N(CH_3)_2$			62	38
CH_2OH	95	5	48	52
CH=O	93	7	42	58
CN	75	25	20	80
CH=NOH	65	35	45	55
CH_2OCH_3			44	56
$CH_2NHCOCH_3$			33	67
CO_2Na (or K)	55	45	30	70
CO_2H	18	82	17	83
CO_2CH_3	15	85	16	84
$CONH_2$	10	90	33	67
$COCH_3$	14	86	22	78

a. In methoxyethanol.
b. In ethanol.

The general ordering of aminomethyl > hydroxymethyl > CH=O > ester suggests that Lewis basicity is the dominant factor in the directive effect. Problem 5.2 involves considering the ordering of the various acyl substituents in more detail.



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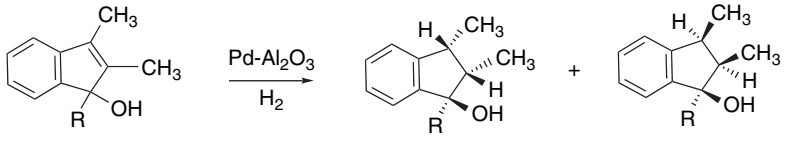
Substituted indenes provide other examples of substituent directive effects. Over Pd-alumina, the indenols **6a**-**c** show both *cis* stereoselectivity and a *syn* directive effect. The directive effect is reinforced by steric effects as the alkyl group becomes larger.[7]

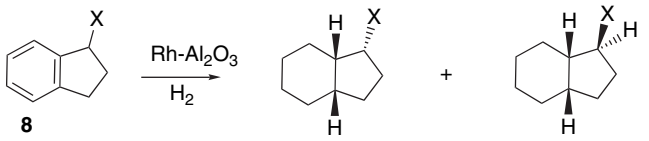


6 *trans,trans-**7*** *cis,cis-**7***

R		
CH_3	88	12
C_2H_5	97	3
$(CH_3)_2CH$	100	0

Several indanes (**8**) were reduced to hexahydroindanes over Rh-Al_2O_3. The stereochemistry of the ring junction is established at the stage of the reduction of the tetrasubstituted double bonds. Only the amino group shows a strong directive effect.[8]

7. K. Borszeky, T. Mallat, and A. Baiker, *J. Catalysis*, **188**, 413 (1999).
8. V. S. Ranade, G. Consiglio, and R. Prins, *J. Org. Chem.*, **65**, 1132 (2000); V. S. Ranade, G. Consiglio, and R. Prins, *J. Org. Chem.*, **64**, 8862 (1999).

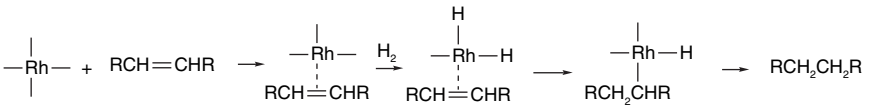


8

X	*cis,cis-***9**	*cis,trans-***9**
OH	67	33
CH_2OH	52	48
NH_2	1.5	98.5
CH_3	64	36
OCH_3	88	12
CO_2CH_3	85	15
$CONH_2$	81	19

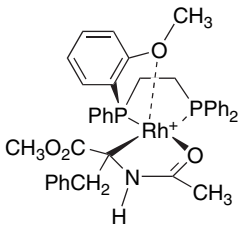
5.1.2. Hydrogenation Using Homogeneous Catalysts

In addition to solid transition metals, numerous soluble transition metal complexes are active hydrogenation catalysts.[9] One of the first to be used was *tris*-(triphenylphosphine)rhodium chloride, known as *Wilkinson's catalyst*.[10] Hydrogenation by homogeneous catalysts is believed to take place by initial formation of a π complex. The addition of hydrogen to the metal occurs by *oxidative addition* and increases the formal oxidation state of the metal by two. This is followed by transfer of hydrogen from rhodium to carbon to form an alkylrhodium intermediate. The final step is a second migration of hydrogen to carbon, leading to elimination of the saturated product (reductive elimination) and regeneration of active catalyst.

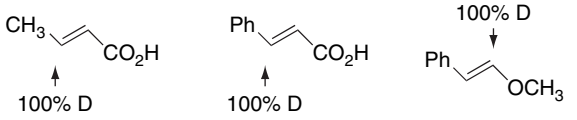


In some cases an alternative sequence involving addition of hydrogen at rhodium prior to complexation of the alkene may operate.[11] The phosphine ligands serve both to provide a stable soluble complex and to adjust the reactivity at the metal center. The σ-bonded intermediates have been observed for Wilkinson's catalyst[12] and for several other related catalysts.[13] For example, a partially hydrogenated structure has been isolated from methyl α-acetamidocinnamate.[14]

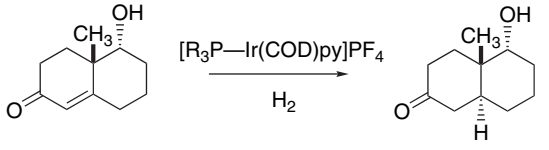
9. A. J. Birch and D. H. Williamson, *Org. React.*, **24**, 1 (1976); B. R. Jones, *Homogeneous Hydrogenation*, Wiley, New York, 1973.
10. J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).
11. I. D. Gridnev and T. Imamoto, *Acc. Chem. Res.*, **37**, 633 (2004).
12. D. Evans, J . A. Osborn and G. Wilkinson, *J. Chem. Soc. A*, 3133 (1968); V. S. Petrosyan, A. B. Permin, V. I. Bogdaskina, and D. P. Krutko, *J. Orgmet. Chem.*, **292**, 303 (1985).
13. H. Heinrich, R. Giernoth, J. Bargon, and J. M. Brown, *Chem. Commun.*, 1296 (2001); I. D. Gridnev, N. Higashi and T. Imamoto, *Organometallics*, **20**, 4542, (2001).
14. J. A. Ramsden, T. D. Claridge and J. M. Brown, *J. Chem. Soc., Chem. Commun.*, 2469 (1995).



The regioselectivity of the hydride addition step has been probed by searching for deuterium exchange into isomerized alkenes that have undergone *partial* reduction.[15] The results suggest that Rh is electrophilic in the addition step and that the hydride transfer is nucleophilic.



The stereochemistry of reduction by homogeneous catalysts is often controlled by functional groups in the reactant. Delivery of hydrogen occurs *cis* to a polar functional group. This behavior has been found to be particularly characteristic of an iridium-based catalyst that contains cyclooctadiene, pyridine, and tricyclohexylphosphine as ligands, known as the *Crabtree catalyst*.[16] Homogeneous iridium catalysts have been found to be influenced not only by hydroxy groups, but also by amide, ester, and ether substituents.[17]



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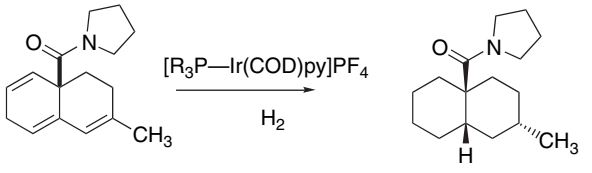
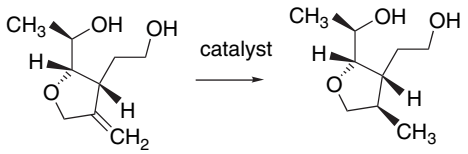


Ref. 19

15. J. Yu and J. B. Spencer, *J. Am. Chem. Soc.*, **119**, 5257 (1997); J. Yu and J. B. Spencer, *Tetrahedron*, **54**, 15821 (1998).
16. R. Crabtree, *Acc. Chem. Res.*, **12**, 331 (1979).
17. R. H. Crabtree and M. W. Davis, *J. Org. Chem.*, **51**, 2655 (1986); P. J. McCloskey and A. G. Schultz, *J. Org. Chem.*, **53**, 1380 (1988).
18. G. Stork and D. E. Kahne, *J. Am. Chem. Soc.*, **105**, 1072 (1983).
19. A. G. Schultz and P. J. McCloskey, *J. Org. Chem.*, **50**, 5905 (1985).

The Crabtree catalyst also exhibited superior stereoselectivity in comparison with other catalysts in reduction of an exocyclic methylene group.[20]



$[Ir(cod)(pyr)PR_3]\ PF_6$	> 99:1
$Rh(nbd)(dppb)\ BF_4$	90:10
$Rh(Ph_3P)_3Cl$	6:94
Pd/C	5:95

Presumably, the stereoselectivity in these cases is the result of coordination of iridium by the functional group. The crucial property required for a catalyst to be stereodirective is that it be able to coordinate with both the directive group and the double bond and still accommodate the metal hydride bonds necessary for hydrogenation. In the iridium catalyst illustrated above, the cyclooctadiene ligand (COD) in the catalysts is released by hydrogenation, permitting coordination of the reactant and reaction with hydrogen.

Scheme 5.2 gives some examples of hydrogenations carried out with homogeneous catalysts. Entry 1 is an addition of deuterium that demonstrates net *syn* addition with the Wilkinson catalyst. The reaction in Entry 2 proceeds with high stereoselectivity and is directed by steric approach control, rather than a substituent-directing effect. One potential advantage of homogeneous catalysts is the ability to achieve a high degree of selectivity among different functional groups. Entries 3 and 4 are examples that show selective reduction of the unconjugated double bond. Similarly in Entry 5, reduction of the double bond occurs without reduction of the nitro group, which is usually rapidly reduced by heterogeneous hydrogenation. Entries 6 and 7 are cases of substituent-directed hydrogenation using the iridium (Crabtree) catalyst. The catalyst used in Entry 8 is related to the Wilkinson catalyst, but on hydrogenation of norbornadiene (NBD) has two open coordination positions. This catalyst exhibits a strong hydroxy-directing effect. The Crabtree catalyst gave excellent results in the hydrogenation of 3-methylpentadeca-4-enone to *R*-muscone. (Entry 9) A number of heterogeneous catalysts led to 5–15% racemization (by allylic exchange).

5.1.3. Enantioselective Hydrogenation

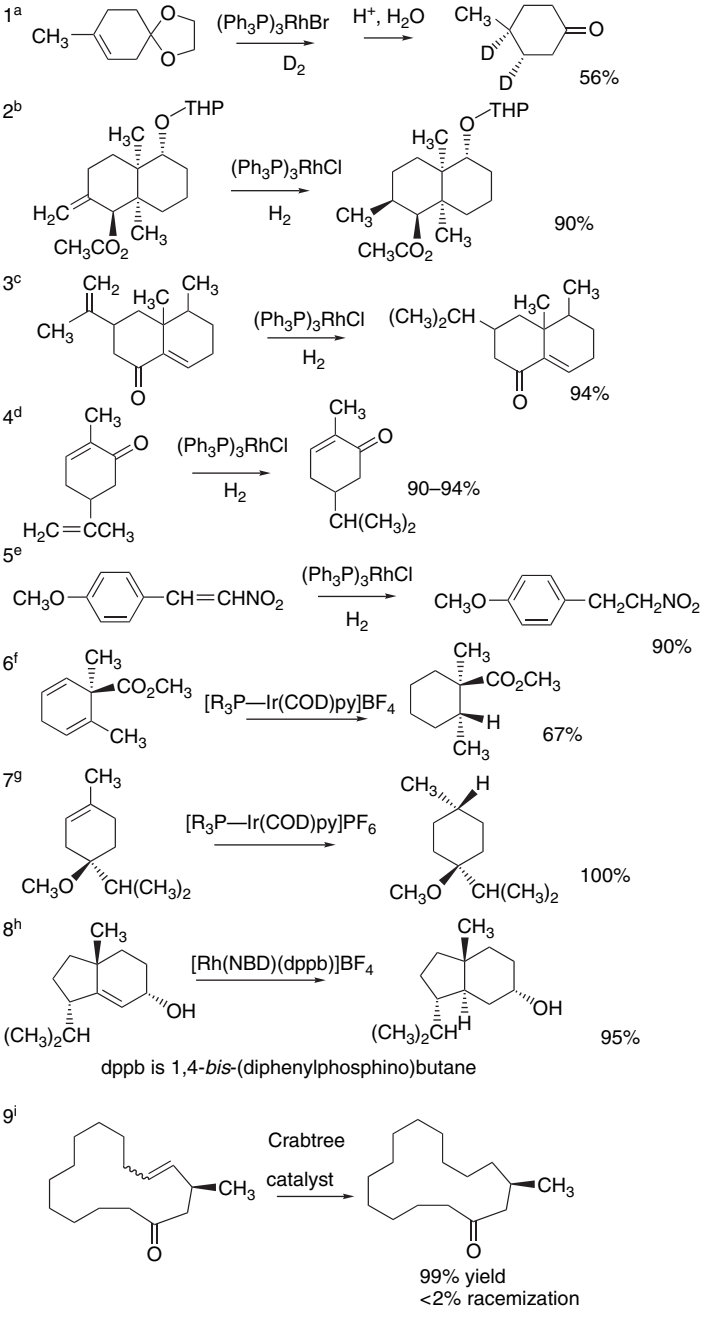
The fundamental concepts of enantioselective hydrogenation were introduced in Section 2.5.1 of Part A, and examples of reactions of acrylic acids and the important case of α-acetamido acrylate esters were discussed. The chirality of enantioselective hydrogenation catalysts is usually derived from phosphine ligands. A number of chiral phosphines have been explored in the development of enantioselective hydrogenation catalysts,[21] and it has been found that some of the most successful catalysts are derived from chiral 1, 1′-binaphthyldiphosphines, such as BINAP.[22]

[20] J. M. Bueno, J. M. Coteron, J. L. Chiara, A. Fernandez-Mayoralas, J. M. Fiandor, and N. Valle, *Tetrahedron Lett.*, **41**, 4379 (2000).

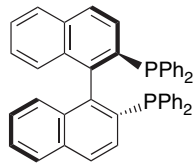
[21] B. Bosnich and M. D. Fryzuk, *Top. Stereochem.*, **12**, 119 (1981); W. S. Knowles, W. S. Chrisopfel, K. E. Koenig, and C. F. Hobbs, *Adv. Chem. Ser.*, **196**, 325 (1982); W. S. Knowles, *Acc. Chem. Res.*, **16**, 106 (1983).

[22] R. Noyori and H. Takaya, *Acc. Chem. Res.*, **23**, 345 (1990).

Scheme 5.2. Homogeneous Catalytic Hydrogenation

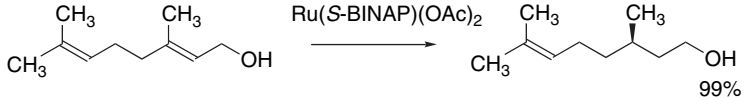


a. W. C. Agosta and W. L. Shreiber, *J. Am. Chem. Soc.*, **93**, 3947 (1971).
b. E. Piers, W. de Waal, and R. W. Britton, *J. Am. Chem. Soc.*, **93**, 5113 (1971).
c. M. Brown and L. W. Piszkiewicz, *J. Org. Chem.*, **32**, 2013 (1967).
d. R. E. Ireland and P. Bey, *Org. Synth*, **53**, 63 (1973).
e. R. E. Harmon, J. L. Parsons, D. W. Cooke, S. K. Gupta, and J. Schoolenberg, *J. Org. Chem.*, **34**, 3684 (1969).
f. A. G. Schultz and P. J. McCloskey, *J. Org. Chem.*, **50**, 5905 (1985).
g. R. H. Crabtree and M. W. Davies, *J. Org. Chem.*, **51**, 2655 (1986).
h. D. A. Evans and M. M. Morrissey, *J. Am. Chem. Soc.*, **106**, 3866 (1984).
i. C. Fehr, J. Galindo, I. Farris, and A. Cuenca, *Helv. Chim. Acta*, **87**, 1737 (2004).



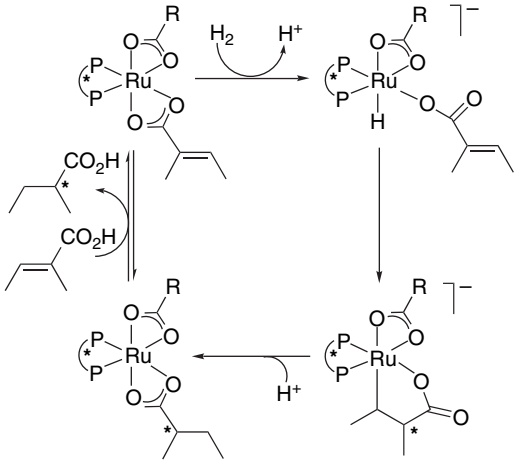
BINAP

Ruthenium complexes containing this ligand are able to reduce a variety of double bonds with e.e. above 95%. In order to achieve high enantioselectivity, the reactant must show a strong preference for a specific orientation when complexed with the catalyst. This ordinarily requires the presence of a functional group that can coordinate with the metal. The ruthenium-BINAP catalyst has been used successfully with unsaturated amides,[23] allylic and homoallylic alcohols,[24] and unsaturated carboxylic acids.[25]



99% e.e. Ref. 12

The mechanism of such reactions using unsaturated carboxylic acids and $Ru(BINAP)(O_2CCH_3)_2$ is consistent with the idea that coordination of the carboxy group establishes the geometry at the metal ion.[26] The configuration of the new stereocenter is then established by the hydride transfer. In this particular mechanism, the second hydrogen is introduced by protonolysis, but in other cases a second hydride transfer step occurs.



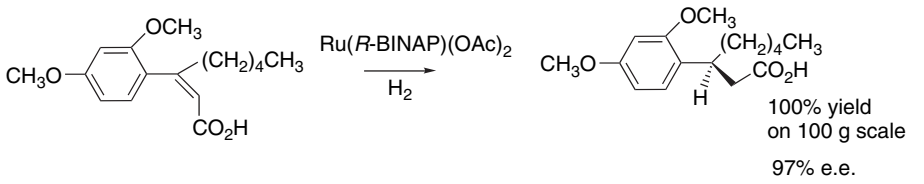
[23] R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta, and H. Takaya, *J. Am. Chem. Soc.*, **108**, 7117 (1986).

[24] H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara, and R. Noyori, *J. Am. Chem. Soc.*, **109**, 1596 (1987).

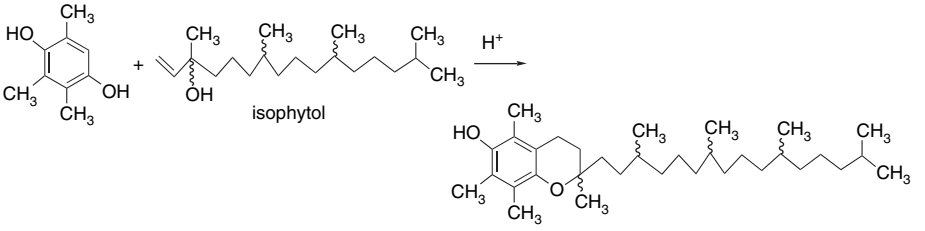
[25] T. Ohta, H. Takaya, M. Kitamura, K. Nagai, and R. Noyori, *J. Org. Chem.*, **52**, 3174 (1987).

[26] M. T. Ashby and J. T. Halpern, *J. Am. Chem. Soc.*, **113**, 589 (1991).

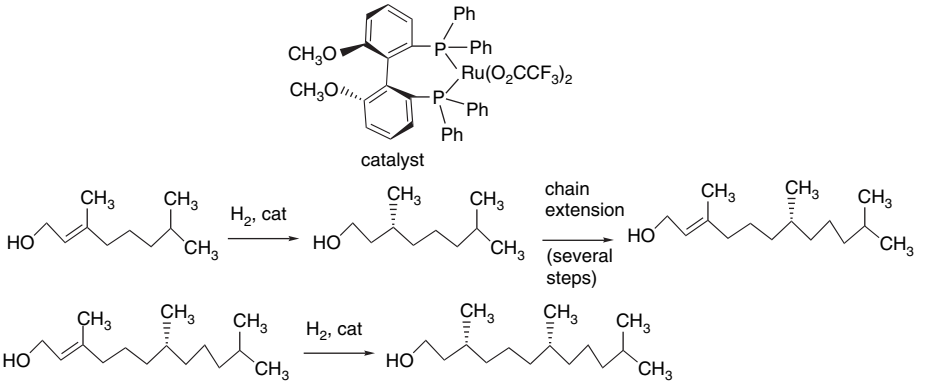
This reaction has been used in the large-scale preparation of an intermediate in the synthesis of a cholesterol acyl-transferase inhibitor.[27]



An enantioselective hydrogenation of this type is also of interest in the production of α-tocopherol (vitamin E). Totally synthetic α-tocopherol can be made in racemic form from 2,3,5-trimethylhydroquinone and racemic isophytol. The product made in this way is a mixture of all eight possible stereoisomers.

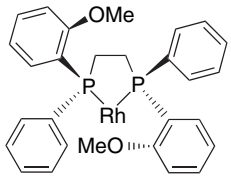


Tocopherol can be produced as the pure $2R, 4'R, 8'R$ stereoisomer from natural vegetable oils. This is the most biologically active of the stereoisomers. The correct side-chain stereochemistry can be obtained using a process that involves two successive enantioselective hydrogenations.[28] The optimum catalyst contains a 6, 6′-dimethoxybiphenyl phosphine ligand. This reaction has not yet been applied to the enantioselective synthesis of α-tocopherol because the cyclization step with the phenol is not enantiospecific.

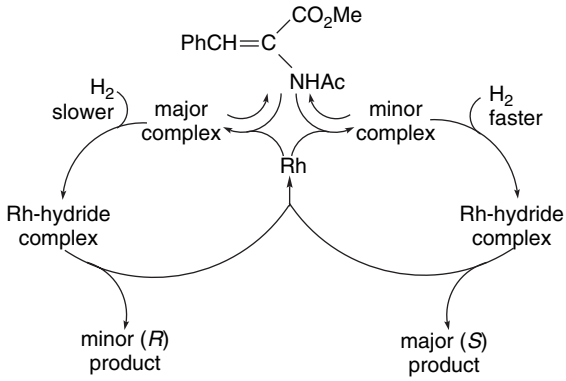


27. M. Murakami, K. Kobayashi, and K. Hirai, *Chem. Pharm. Bull.*, **48**, 1567 (2000).
28. T. Netscher, M. Scalione, and R. Schmid, in *Asymmetric Catalysis on an Industrial Scale: Challenges, Approaches and Solutions*, H. U. Blaser and E. Schmidt, eds., Wiley-VCH, Weinhem, 2004, pp. 71–89.

An especially important case is the enantioselective hydrogenation of α-amidoacrylic acids, which leads to α-aminoacids.[29] A particularly detailed study has been carried out on the mechanism of reduction of methyl *Z*-α-acetamidocinnamate by a rhodium catalyst with a chiral diphosphine ligand DIPAMP.[30] It has been concluded that the reactant can bind reversibly to the catalyst to give either of two complexes. Addition of hydrogen at rhodium then leads to a reactive rhodium hydride and eventually to product. Interestingly, the addition of hydrogen occurs most rapidly in the minor isomeric complex, and the enantioselectivity is due to this kinetic preference.



DIPAMP



A thorough computational study of this process has been carried out using B3LYP/ONIOM calculations.[31] The rate-determining step is found to be the formation of the rhodium hydride intermediate. The barrier for this step is smaller for the minor complex than for the major one. Additional details on this study can be found at:

Visual models and additional information on Asymmetric Hydrogenation can be found in the Digital Resource available at: Springer.com/carey-sundberg.

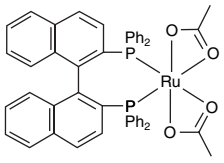
[29] J. Halpern, in *Asymmetric Synthesis*, Vol. 5, J. D. Morrison, ed., Academic Press, Orlando, FL, 1985; A. Pfaltz and J. M. Brown, in *Stereoselective Synthesis*, G. Helmchen, R. W. Hoffmann, J. Mulzer, and E. Schauman, eds., Thieme, New York, 1996, Part D, Sect. 2.5.1.2; U. Nagel and J. Albrecht, *Catalysis Lett.*, **5**, 3 (1998).

[30] C. R. Landis and J. Halpern, *J. Am. Chem. Soc.*, **109**, 1746 (1987).

[31] S. Feldgus and C. R. Landis, *J. Am. Chem. Soc.*, **122**, 12714 (2000).

Another mechanistic study, carried out using *S*-BINAP-ruthenium(II) diacetate catalyst, concluded that the mechanism shown in Figure 5.1 was operating.[32] The rate-determining step is the hydrogenolysis of intermediate **13**, which has an E_a of about 19 kcal/mol. This step also determines the enantioselectivity and proceeds with retention of configuration. The prior steps are reversible and the relative stability of $\mathbf{13}_R > \mathbf{13}_S$ determines the preference for the *S*-enantiomer. The energy relationships are summarized in Figure 5.2. The major difference between the major and minor pathways is in the precursors $\mathbf{12}_{re}$ (favored) and $\mathbf{12}_{si}$ (disfavored). There is a greater steric repulsion between the carboxylate substituent and the BINAP ligand in $\mathbf{12}_{si}$ than in $\mathbf{12}_{re}$ (Figure 5.3.).

A related study with a similar ruthenium catalyst led to the structural and NMR characterization of an intermediate that has the crucial Ru−C bond in place and also shares other features with the BINAP-ruthenium diacetate mechanism.[33] This mechanism, as summarized in Figure 5.4, shows the formation of a metal hydride prior to the complexation of the reactant. In contrast to the mechanism for acrylic acids shown on p. 378, the creation of the new stereocenter occurs at the stage of the addition of the second hydrogen.



(s)–BINAP–Ru(II)

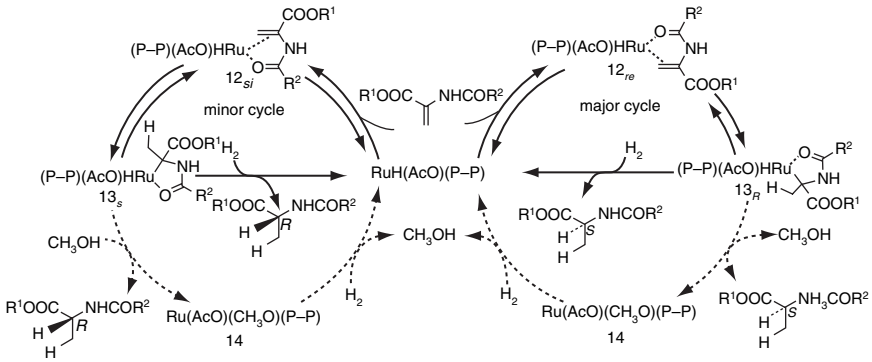


Fig. 5.1. Mechanism of ruthenium catalyzed enantioselective hydrogenation of α-acetamidoacrylate esters. Reproduced from *J. Am. Chem. Soc.*, **124**, 6649 (2002), by permission of the American Chemical Society.

32. M. Kitamura, M. Tsukamoto, Y. Bessho, M. Yoshimura, U. Kobs, M. Widhalm, and R. Noyori, *J. Am. Chem. Soc.*, **124**, 6649 (2002).
33. J. A. Wiles and S. H. Bergens, *Organometallics*, **17**, 2228 (1998); J. A. Wiles and S. H. Bergens, *Organometallics*, **18**, 3709 (1999).

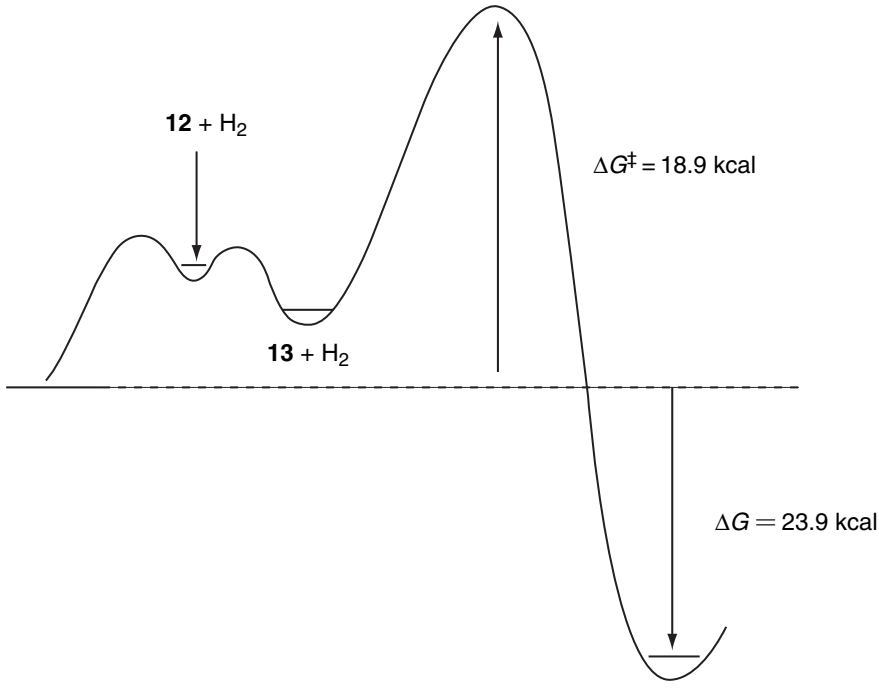


Fig. 5.2. Summary energy diagram for enantioselective ruthenium-catalyzed hydrogenation of α-acetamidoacrylate esters. Reproduced from *J. Am. Chem. Soc.*, **124**, 6649 (2002), by permission of the American Chemical Society.

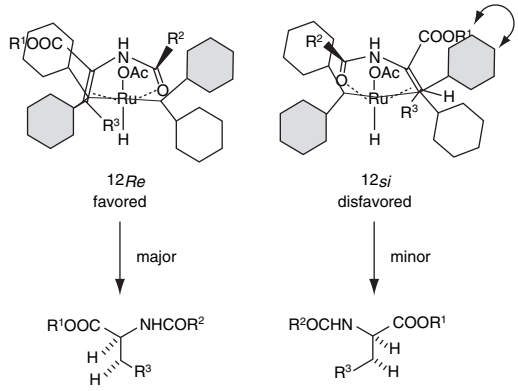


Fig. 5.3. (a) View of (*S*)-BINAP-ruthenium complex showing the chiral environment. (b) Relationship of reactant to chiral environment showing preferred orientation. The binaphthyl rings are omitted for clarity. Adapted from *J. Am. Chem. Soc.*, **124**, 6649 (2002), by permission of the American Chemical Society.

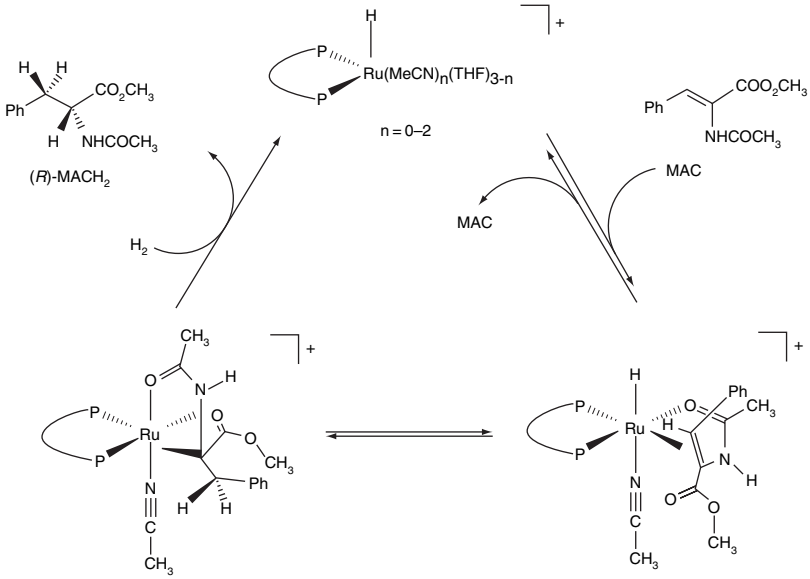
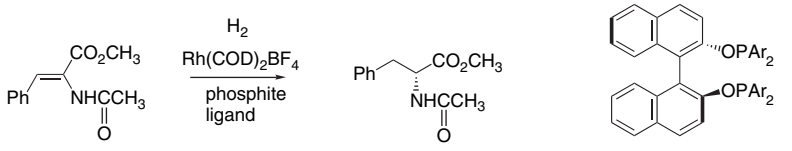


Fig. 5.4. Schematic mechanism for enantioselective hydrogenation of methyl acetamidocinnamate (MAC) over a cationic ruthenium catalyst. Reproduced from *Organometallics*, **18**, 3709 (1999), by permission of the American Chemical Society.

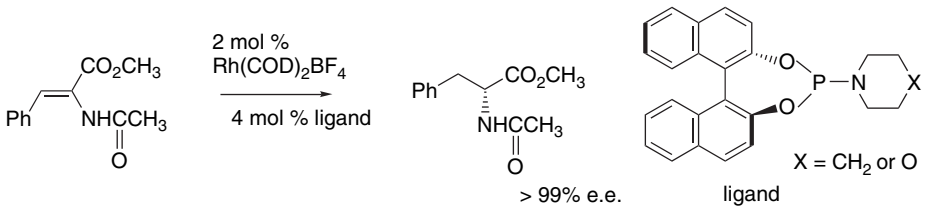
Catalyst reactivity and enantioselectivity can be affected by substituents on ligands. In the Rh-catalyzed hydrogenation of methyl *Z*-α-acetamidocinnamate, for example, BINOL phosphites with ERGs give much higher enantioselectivity than those with EWGs. The ligand substituents modify the electron density at the metal center and change the energy balance between the competing pathways. This example demonstrates the potential for fine-tuning of the catalysts by changes that are relatively remote from the catalytic site.[34]



Ar substituent	% e.e.
3,5-di-CF_3	31
4-CF_3	49
4-CH_3	93
3,5-di-CH_3	94
4-CH_3O	99

Many other catalysts and ligands have been examined for the enantioselective reduction of α-acetamidoacrylates and related substrates. Phosphoramidites derived from BINOL and the cyclic amines piperidine and morpholine give excellent results.[35]

34. I. Gergely, C. Hegedus, A. Szollosy, A. Monsees, T. Riermeier, and J. Bakos, *Tetrahedron Lett.*, **44**, 9025 (2003).
35. H. Bernsmann, M. van der Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. De Vries, and B. L. Feringa, *J. Org. Chem.*, **70**, 943 (2005).

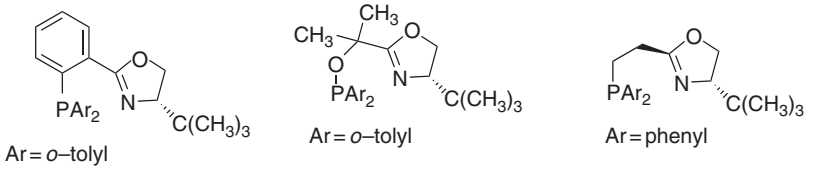


These ligands also give excellent results with dimethyl itaconate and α-arylenamides.

Scheme 5.3 shows the enantioselectivity of some hydrogenations of unsaturated acids and amides. Entries 1 to 5 are examples of hydrogenations of α-acetamidoacrylate and α-acetamidocinnamate esters. The catalyst in Entries 1 and 2 uses chiraphos as the chiral phosphine ligand and norbornadiene as the removable ligand. The catalyst in Entry 3 uses DIPAMP as the chiral ligand. BINAP is the ligand in Entry 4. The ligand in Entry 5, known as EtDuPHOS, gave highly selective reduction of the α,β-double bond in the conjugated system. Entries 6 and 7 show reduction of acrylate esters having other types of substituents that give good results with the DIPAMP catalyst. Entries 8 to 10 show examples of several alkylidene succinate half-esters.

There can be significant differences in the detailed structure and mechanism of these catalysts. For example, the geometry of the phosphine ligands may affect the reactivity at the metal ion, but the basic elements of the mechanism of enantioselection are similar. The phosphine ligands establish a chiral environment and provide an appropriate balance of reactivity and stability for the metal center. The reactants bind to the metal through the double bond and at least one other functional group, and mutual interaction with the chiral environment is the basis for enantioselectivity. The new stereocenters are established under the influence of the chiral environment.

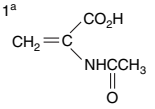
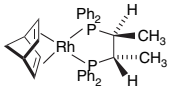
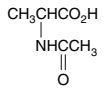
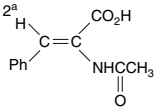
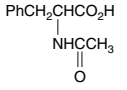
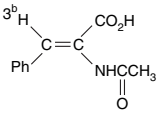
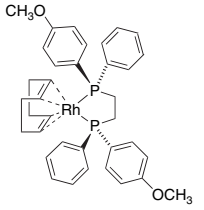
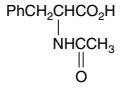
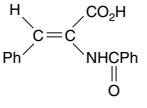
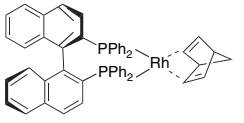
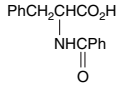
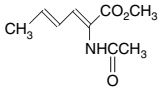
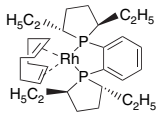
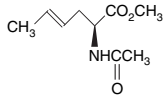
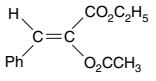
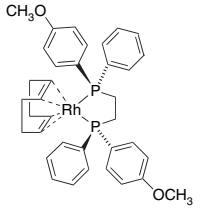
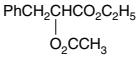
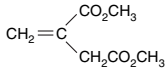
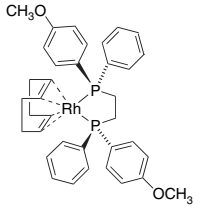
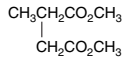
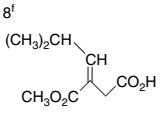
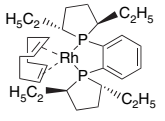
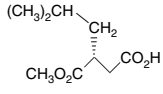
The enantioselective hydrogenation of unfunctionalized alkenes presents special challenges. Functionalized reactants such as acrylate esters can coordinate with the metal in the catalyst and this point of contact can serve to favor a specific orientation and promote enantioselectivity. Unfunctionalized alkenes do not have such coordination sites and enantioselectivity is based on steric factors. A number of iridium-based catalysts have been developed. One successful type of catalyst incorporates phosphine or phosphite groups and a chiral oxazoline ring as donors.[36] The catalysts also incorporate cyclooctadiene as a removable ligand. These catalysts are extremely sensitive to even weakly coordinating anions and the preferred anion for alkene hydrogenation is *tetrakis*-[(3,5-trifluoromethyl)phenyl]borate. Most of the examples to date have been with aryl-substituted double bonds.



A[37] **B**[38] **C**[39]

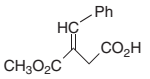
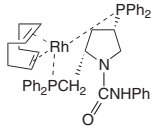
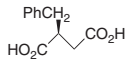
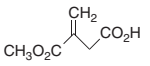
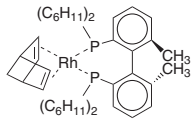
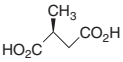
[36] G. Helmchen and A. Pfaltz, *Acc. Chem. Res.*, **33**, 336 (2000).
[37] F. Menges, M. Neuburger, and A. Pfaltz, *Org. Lett.*, **4**, 4713 (2002).
[38] S. P. Smidt, F. Menges, and A. Pfaltz, *Org. Lett.*, **6**, 2023 (2004).
[39] D. R. Hou, J. Reibenspies, T. J. Colacot, and K. Burgess, *Chem. Eur. J.*, **7**, 5391 (2001).

Scheme 5.3. Enantioselectivity for Catalytic Hydrogenation of Substituted Acrylic Acids

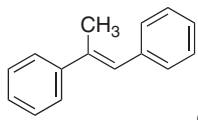
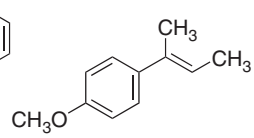
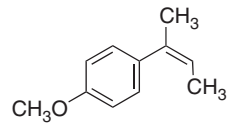
Reactant	Catalyst	Product	Configuration	% e.e.
1[a] 			*R*	90
2[a] 	Same as above		*S*	95
3[b] 			*R*	94
4[c] 			*S*	100
5[d] 			*R*	99.2
6[b] 			*S*	90
7[e] 			*R*	88
8[f] 			*R*	99

(*Continued*)

Scheme 5.3. (*Continued*)

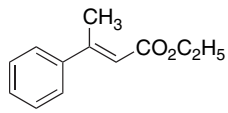
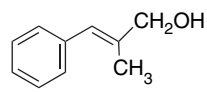
Reactant	Catalyst	Product	Configuration	% e.e.
9[g] 			*S*	>95
10[h] 			*S*	96

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. A. Miyashita, H. Takaya, T. Souchi, and R. Noyori, *Tetrahedron*, **40**, 1245 (1984).
d. M. J. Burk, J. G. Allen, and W. F. Kiesman, *J. Am. Chem. Soc.*, **120**, 657 (1998).
e. W. C. Christopfel and B. D. Vineyard, *J. Am. Chem. Soc.*, **101**, 4406 (1979).
f. M. J. Burk, F. Bienewald, M. Harris, and A. Zanotti-Gerosa, *Angew. Chem. Int. Ed. Engl.* **37**, 1931 (1998).
g. H. Jendralla, *Tetrahedron Lett.*, **32**, 3671 (1991).
h. T. Chiba, A. Miyashita, H. Nohira, and H. Takaya, *Tetrahedron Lett.*, **32**, 4745 (1991).

Catalyst	Percent e.e.		
A	98	81	63
B	98	91	66
C	89	86	75

These catalysts also provide excellent results with acrylate esters and allylic alcohols.

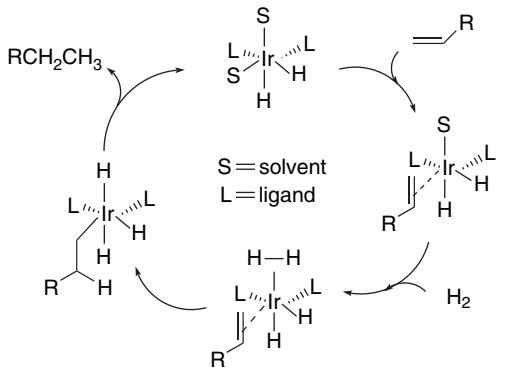



Catalyst	Percent e.e.	
A	84	96
B	94	97

These catalysts are activated by hydrogenation of the cyclooctadiene ligand, which releases cyclooctane and opens two coordination sites at iridium. The mechanism has been probed by computational studies.[40] It is suggested that the catalytic cycle involves

[40] P. Brandt, C. Hedberg, and P. G. Andersson, *Chem. Eur. J.*, **9**, 339 (2003).

the addition of two hydrogens to the alkene-catalyst complex, followed by formation of an alkyliridium intermediate and reductive elimination.



The enantioselectivity is thought to result from both steric blocking by the *t*-butyl substituent on the oxazoline ring and an attractive van der Waals interaction of an aryl ring and the oxazoline ring, as shown in Figure 5.5.

5.1.4. Partial Reduction of Alkynes

Partial reduction of alkynes to *Z*-alkenes is an important synthetic application of selective hydrogenation catalysts. The transformation can be carried out under heterogeneous or homogeneous conditions. Among heterogeneous catalysts, the one that

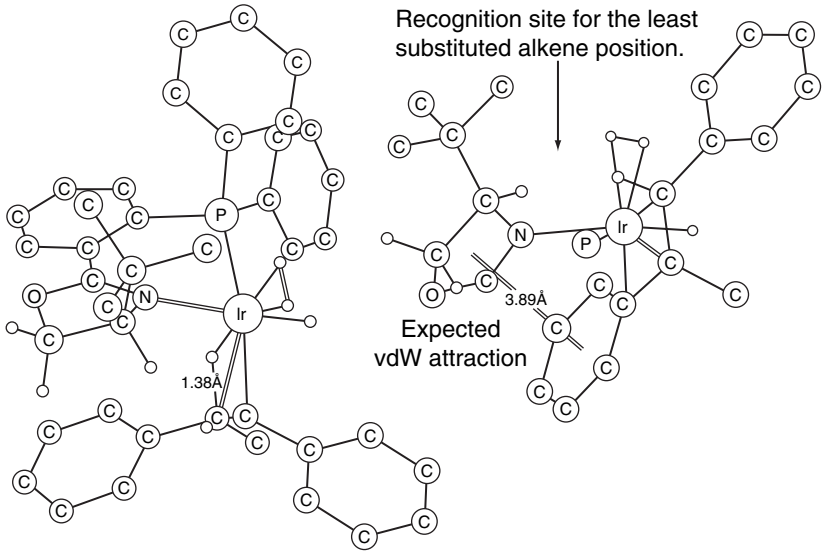
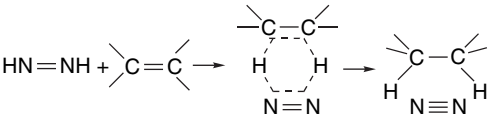


Fig. 5.5. Suggested basis of enantioselectivity in hydrogenation of α-methylstilbene by a phosphinoaryl oxazoline–iridium catalyst. Reproduced from *Chem. Eur. J.*, **9**, 339 (2003), by permission of Wiley-VCH.

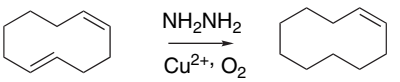
is most successful is *Lindlar's catalyst*, a lead-modified palladium-$CaCO_3$ catalyst.[41] A nickel-boride catalyst prepared by reduction of nickel salts with sodium hydride is also useful.[42] Rhodium catalysts have also been reported to show good selectivity.[43]

5.1.5. Hydrogen Transfer from Diimide

Catalytic hydrogenation transfers the elements of molecular hydrogen through a series of complexes and intermediates. Diimide, HN=NH, an unstable hydrogen donor that can be generated in situ, finds specialized application in the reduction of carbon-carbon double bonds. Simple alkenes are reduced efficiently by diimide, but other easily reduced functional groups, such as nitro and cyano are unaffected. The mechanism of the reaction is pictured as a concerted transfer of hydrogen via a nonpolar cyclic TS.



In agreement with this mechanism is the fact that the stereochemistry of addition is *syn*.[44] The rate of reaction with diimide is influenced by torsional and angle strain in the alkene. More strained double bonds react at accelerated rates.[45] For example, the more strained *trans* double bond is selectively reduced in *Z*,*E*-1,5-cyclodecadiene.



Ref. 46

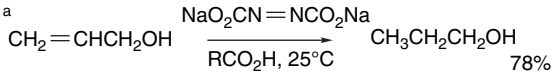
Diimide selectively reduces terminal over internal double bonds in polyunsaturated systems.[47]

Reduction by diimide can be advantageous when compounds contain functional groups that would be reduced by other methods or when they are unstable to hydrogenation catalysts. There are several methods for generation of diimide and they are illustrated in Scheme 5.4. The method in Entry 1 is probably the one used most frequently in synthetic work and involves the generation and spontaneous decarboxylation of azodicarboxylic acid. Entry 2, which illustrates another convenient method, thermal decomposition of *p*-toluenesulfonylhydrazide, is interesting in that it

41. H. Lindlar and R. Dubuis, *Org. Synth.*, **V**, 880 (1973).
42. 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).
43. R. R. Schrock and J. A. Osborn, *J. Am. Chem. Soc.*, **98**, 2143 (1976); J. M. Tour, S. L. Pendalwar, C. M. Kafka, and J. P. Cooper, *J. Org. Chem.*, **57**, 4786 (1992).
44. E. J. Corey, D. J. Pasto, and W. L. Mock, *J. Am. Chem. Soc.*, **83**, 2957 (1961).
45. E. W. Garbisch, Jr., S. M. Schildcrout, D. B. Patterson, and C. M. Sprecher, *J. Am. Chem. Soc.*, **87**, 2932 (1965).
46. J. G. Traynham, G. R. Franzen, G. A. Kresel, and D. J. Northington, Jr., *J. Org. Chem.*, **32**, 3285 (1967).
47. 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 5.4. Reductions with Diimide

1[a]



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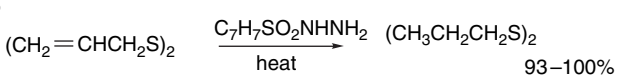

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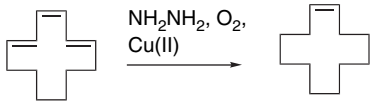

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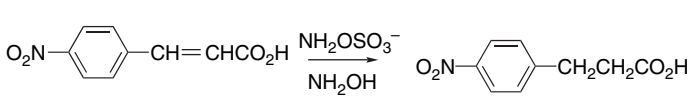
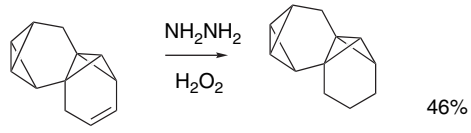


5[e]



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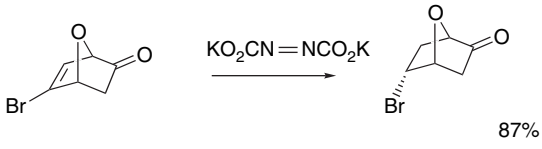

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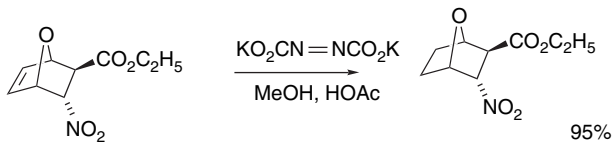
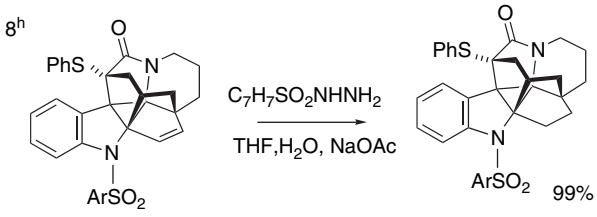
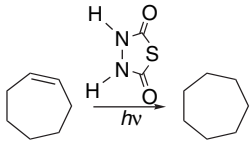


8[h]

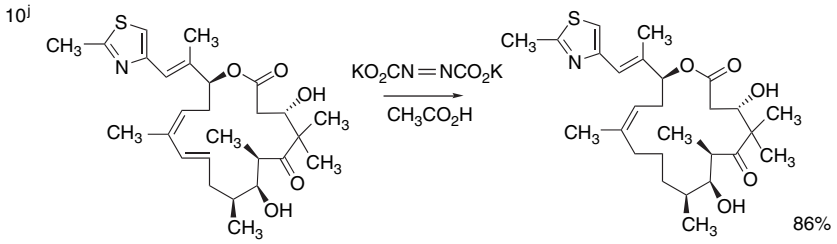


9[i]



(*Continued*)

Scheme 5.4. (*Continued*)



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, *Liebigs Ann. Chem.*, **712**, 240 (1969).
e. L. A. Paquette, A. R. Browne, E. Chamot, and J. F. Blount, *J. Am. Chem. Soc.*, **102**, 643 (1980).
f. J.-M. Durgnat and P. Vogel, *Helv. Chim. Acta*, **76**, 222 (1993).
g. P. A. Grieco, R. Lis, R. E. Zelle, and J. Finn, *J. Am. Chem. Soc.*, **108**, 5908 (1986).
h. P. Magnus, T. Gallagher, P. Brown, and J. C. Huffman, *J. Am. Chem. Soc.*, **106**, 2105 (1984).
i. M. Squillacote, J. DeFelippis, and Y. L. Lai, *Tetrahedron Lett.*, **34**, 4137 (1993).
j. K. Biswas, H. Lin, J. T. Njgardson, M. D. Chappell, T.-C. Chou, Y. Guan, W. P. Tong, L. He, S. B. Horwitz, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **124**, 9825 (2002).

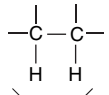
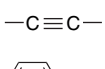
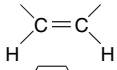
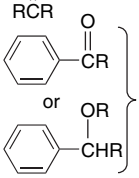
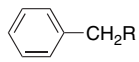
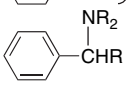
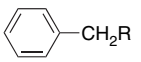
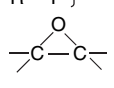
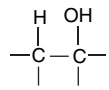
demonstrates that the very easily reduced disulfide bond is unaffected by diimide. Entry 3 involves generation of diimide by oxidation of hydrazine and also illustrates the selective reduction of *trans* double bonds in a medium-sized ring. Entry 4 shows that nitro groups are unaffected by diimide. Entries 5 to 7 involve sensitive molecules in which double bonds are reduced successfully. Entry 8, part of a synthesis of the kopsane group of alkaloids, successfully retains a sulfur substituent. Entry 9 illustrates a more recently developed diimide source, photolysis of 1,3,4-thiadiazolin-2,5-dione. Entry 10 is a selective reduction of a *trans* double bond in a macrocyclic lactone and was used in the synthesis of epothilone analogs.[48]

5.2. Catalytic Hydrogenation of Carbonyl and Other Functional Groups

Many other functional groups are also reactive under conditions of catalytic hydrogenation. Ketones, aldehydes, and esters can all be reduced to alcohols, but in most cases these reactions are slower than alkene reductions. For most synthetic applications, the hydride transfer reagents, discussed in Section 5.3, are used for reduction of carbonyl groups. The reduction of nitro compounds to amines, usually proceeds very rapidly. Amides, imines, and also nitriles can be reduced to amines. Hydrogenation of amides requires extreme conditions and is seldom used in synthesis, but reductions of imines and nitriles are quite useful. Table 5.2 gives a summary of the approximate conditions for catalytic hydrogenation of some common functional groups.

[48] For another example, see J. D. White, R. G. Carter, and K. F. Sundermann, *J. Org. Chem.*, **64**, 684 (1999).

Table 5.2. Conditions for Catalytic Reduction of Various Functional Groups[a]

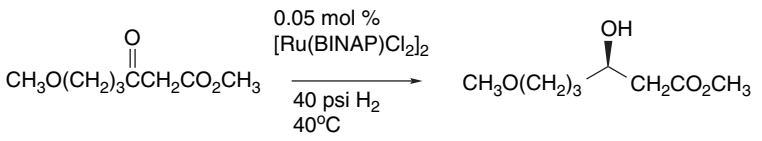
Reactant	Product	Catalyst	Conditions
		Pd, Pt, Ni, Ru, Rh	Rapid at room temperature (R.T.) and 1 atm except for highly substituted or hindered cases
		Lindlar	R. T. and low pressure, quinoline or lead added to deactivate catalyst
		Rh, Pt	Moderate pressure (5–10 atm), 50–100°C
		Ni, Pd	High pressure (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
		Pd	R. T., 1 atm. quinoline or other catalyst moderator used
	RCH_2OH	Pd, Ni, Ru	Very strenuous conditions required
	RCH_2OH	Cu–Cr, Ni	200°C, high pressure
	RCH_2NH_2	Ni, Rh	50–100°C, usually high pressure, NH_3 added to increase yield of primary amine
	RCH_2NH_2	Cu–Cr	Very strenuous conditions required
	RNH_2	Pd, Ni, Pt	R. T., 1–4 atm
	R_2CHNHR	Pd, Pt	R. T., 4–100 atm
		Pd	Order of reactivity: I > Br > Cl > F, bases promote reactions 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*, John Wiley & Sons, New York, 1978; P. N. Rylander, *Hydrogenation Methods*, Academic Press, Orlando FL, 1985.

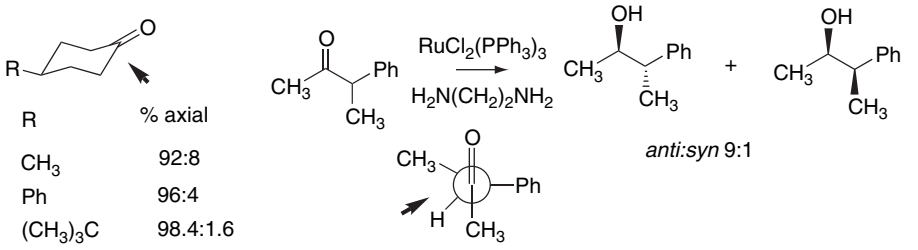
Many enantioselective catalysts have been developed for reduction of functional groups, particularly ketones. BINAP complexes of $Ru(II)Cl_2$ or $Ru(II)Br_2$ give good enantioselectivity in reduction of β-ketoesters.[49] This catalyst system has been shown to be subject to acid catalysis.[50] Thus in the presence of 0.1 mol % HCl, reduction proceeds smoothly at 40 psi of H_2 at 40° C.

[49] R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, and S. Akutagawa, *J. Am. Chem. Soc.*, **109**, 5856 (1987).

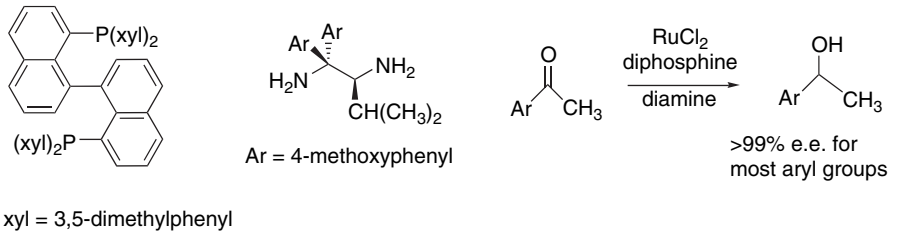
[50] S. A. King, A. S. Thompson, A. O. King, and T. R. Verhoeven, *J. Org. Chem.*, **57**, 6689 (1992).



For reduction of monofunctional ketones, the most effective catalysts include diamine ligands. The diamine catalysts exhibit strong selectivity for carbonyl groups over carbon-carbon double and triple bonds. These catalysts have a preference for equatorial approach in the reduction of cyclohexanones and for steric approach control in the reduction of acyclic ketones.[51]



Related catalysts include both a chiral BINAP-type phosphine and a chiral diamine ligand. A wide range of aryl ketones gave more than 95% enantioselectivity when substituted-1,1′-binaphthyl and ethylene diamines were used.[52]

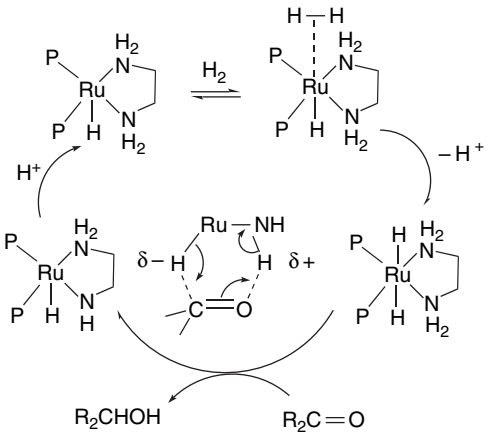


xyl = 3,5-dimethylphenyl

Cyclic and α,β-unsaturated ketones also gave high e.e. but straight-chain alkyl ketones did not.

The suggested catalytic cycle for the diamine catalysts indicates that the NH group of the diamine plays a direct role in the hydride transfer through a six-membered TS.[53] A feature of this mechanism is the absence of direct contact between the ketone and the metal. Rather, the reaction is pictured as a nucleophilic delivery of hydride from ruthenium, concerted with a proton transfer from nitrogen.

51. T. Ohkuma, H. Ooka, M. Yamakawa, T. Ikariya, and R. Noyori, *J. Org. Chem.*, **61**, 4872 (1996).
52. T. Ohkuma, M. Koizuma, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, and R. Noyori, *J. Am. Chem. Soc.*, **120**, 13529 (1998).
53. C. A. Sandoval, T. Ohkuma, Z. Muniz, and R. Noyori, *J. Am. Chem. Soc.*, **125**, 13490 (2003).



The catalyst used for these mechanistic studies has been characterized by X-ray crystallography, as shown in Figure 5.6. It is obtained as a hydrido ruthenium(II) species that is also coordinated by a $[BH_4]^-$ anion. The catalyst is prepared by exposing the DINAP-diamine $RuCl_2$ complex to excess $NaBH_4$.[54]

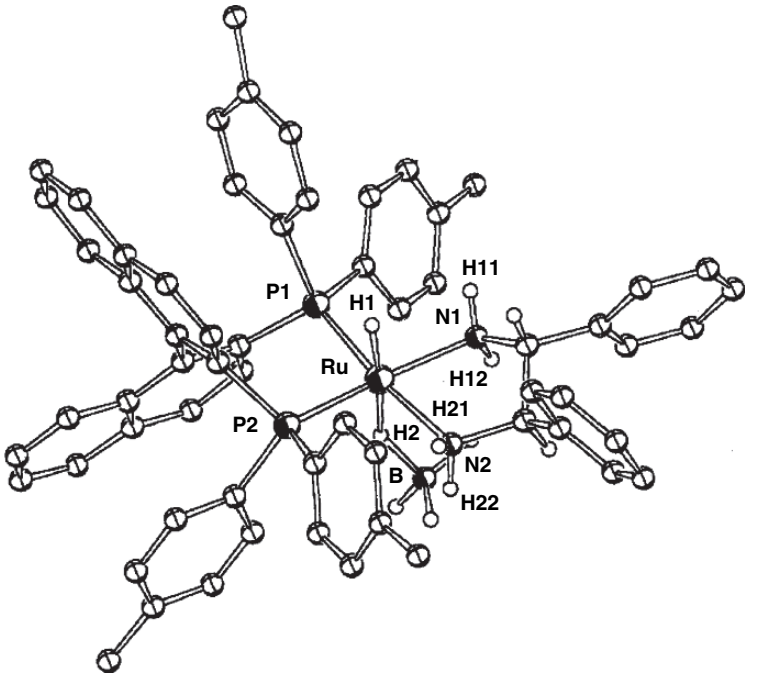
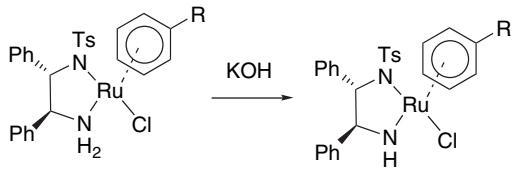


Fig. 5.6. Crystal structure of *tetrakis-P,P,P′P′*-(4-methylphenyl)-1,1′-binaphthyldiphosphine-1,2-diphenyl-1,2-ethanediamine ruthenium borohydride catalyst. Reproduced from *J. Am. Chem. Soc.*, **124**, 6508 (2002), by permission of the American Chemical Society.

54. T. Ohkuma, M. Koizumi, K. Muniz, G. Hilt, C. Kabuto, and R. Noyori, *J. Am. Chem. Soc.*, **124**, 6508 (2002).

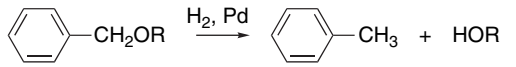
Several other versions of these catalysts have been developed. Arene complexes of monotosyl-1,2-diphenylethylenediamine ruthenium chloride give good results with α,β-ynones.[55] The active catalysts are generated by KOH. These catalysts also function by hydrogen transfer, with isopropanol serving as the hydrogen source. Entries 6 to 8 in Scheme 5.3 are examples.



Catalyst **D**: Arene = mesitylene
Catalyst **E**: Arene = *p*-cymene

Scheme 5.5 gives some examples of the application of these Ru(II)-diphosphine and diamine catalysts. Entries 1 and 2 are examples of the hydrogenation of β-dicarbonyl compounds with $Ru(BINAP)Cl_2$. Excellent enantioselectivity is observed, although elevated hydrogen pressure is required. Entry 3 proceeds in fair yield and enantioselectivity, and without reduction of the conjugated carbon-carbon double bond. Entry 4 uses the cymene complex catalyst **E** under hydrogen transfer conditions. Entry 5 involves tandem 1,4- and 1,2-reduction and was done under hydrogen transfer conditions, using formic acid as the hydride donor. Entries 6 to 8 show good yields and enantioselectivity for several alkynyl ketones of increasing structural complexity. In the latter two cases, only a single stereoisomer was observed.

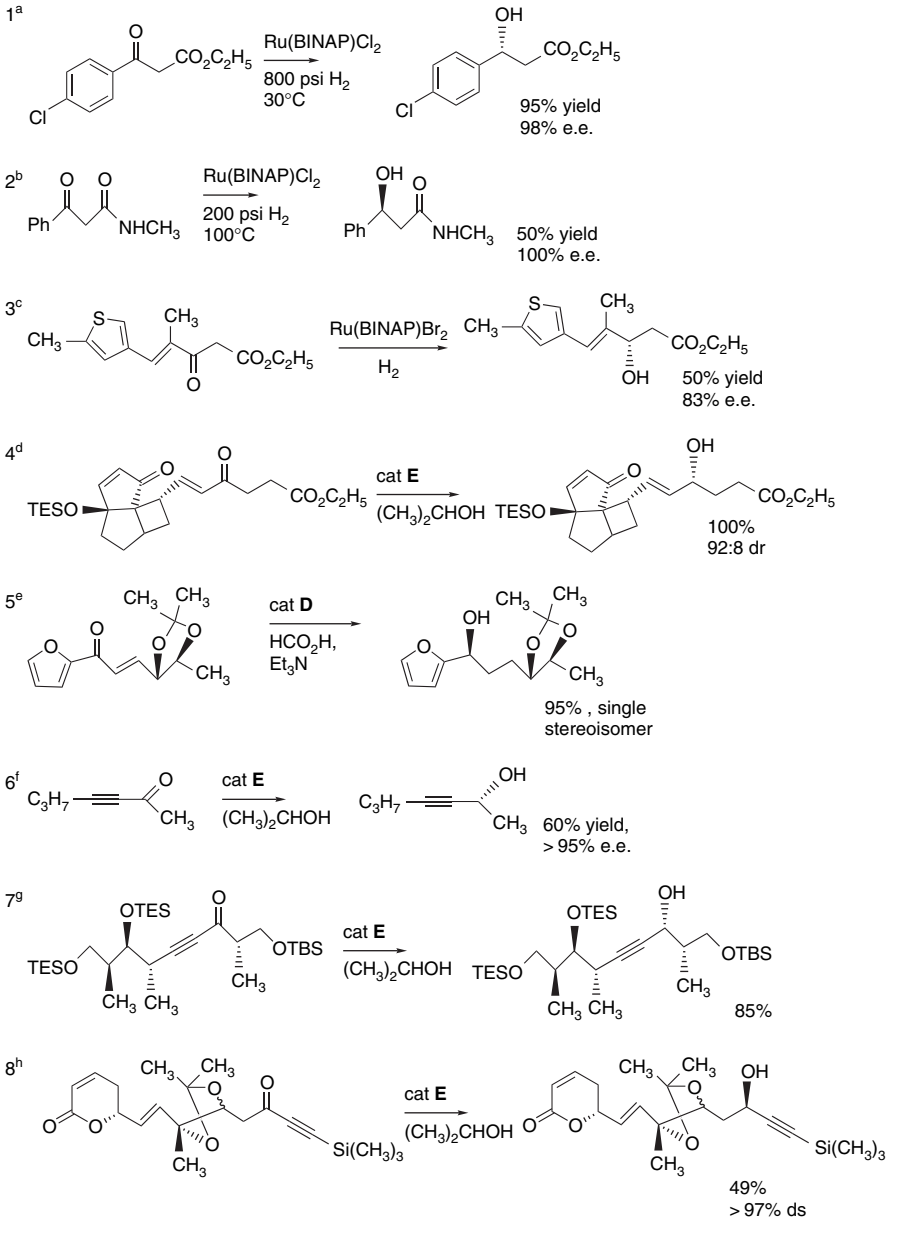
Certain functional groups can be entirely removed and replaced by hydrogen, a reaction known as *hydrogenolysis*. For example, aromatic halogen substituents are frequently removed by hydrogenation over transition metal catalysts. Aliphatic halogens are somewhat less reactive but hydrogenolysis is promoted by base.[56] The most useful type of hydrogenolysis reaction involves removal of oxygen functional groups at benzylic and allylic positions.[57]



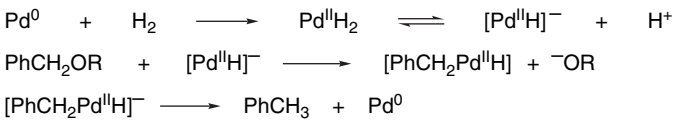
Hydrogenolysis of halides and benzylic groups presumably involves intermediates formed by *oxidative addition* to the active metal catalyst to generate intermediates similar to those involved in hydrogenation. The hydrogenolysis is completed by reductive elimination.[58] Many other examples of this pattern of reactivity are discussed in Chapter 8.

55. K. Matsumura, S. Hashiguchi, T. Ikariya, and R. Noyori, *J. Am. Chem. Soc.*, **119**, 8738 (1997).
56. A. R. Pinder, *Synthesis*, 425 (1980).
57. W. H. Hartung and R. Simonoff, *Org. React.*, **7**, 263 (1953); P. N. Rylander, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, New York, 1967, Chap. 25; P. N. Rylander, *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, New York, 1979, Chap. 15; P. N. Rylander, *Hydrogenation Methods*, Academic Press, Orlando, FL, 1985, Chap. 13.
58. The mechanism of benzylic hydrogenolysis has not been definitively established. For other possibilities, see R. B. Grossman, *The Art of Writing Reasonable Organic Mechanisms*, 2nd Edition, Springer, New York, 2003, pp. 309–310.

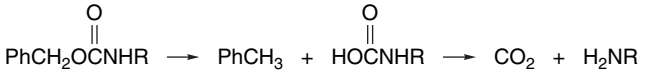
Scheme 5.5. Enantioselective Hydrogenation with Ruthenium Complex Catalysts



a. V. V. Thakur, M. D. Nikalje, and A. Sudalai, *Tetrahedron: Asymmetry*, **14**, 581 (2003).
b. H.-L. Huang, L. T. Liu, S.-F. Chen, and H. Ku, *Tetrahedron:Asymmetry*, **9**, 1637 (1998).
c. E. A. Reiff, S. K. Nair, B. S. N. Reddy, J. Inagaki, J. T. Henri, J. F. Greiner, and G. I. Georg, *Tetrahedron Lett.*, **45**, 5845 (2004).
d. H. Ito, M. Hasegawa, Y. Takenaka, T. Kobayashi, and K. Iguchi, *J. Am. Chem. Soc.*, **126**, 4520 (2004).
e. M. Li and G. O'Doherty, *Tetrahedron Lett.*, **45**, 6407 (2004).
f. N. Petry, A. Parenty, and J.-M. Campagne, *Tetrahedron: Asymmetry*, **15**, 1199 (2004).
g. J. A. Marshall and M. P. Bourbeau, *Org. Lett.*, **5**, 3197 (2003).
h. K. Fujii, K. Maki, M. Kanai, and M. Shibasaki, *Org. Lett.*, **5**, 733 (2003).



The facile cleavage of the benzyl-oxygen bond has made the benzyl group a useful protecting group in multistep syntheses. A particularly important example is the use of the carbobenzyloxy group in peptide synthesis. The protecting group is removed by hydrogenolysis. The substituted carbamic acid generated by the hydrogenolysis decarboxylates spontaneously to provide the amine (see Section 3.5.2).

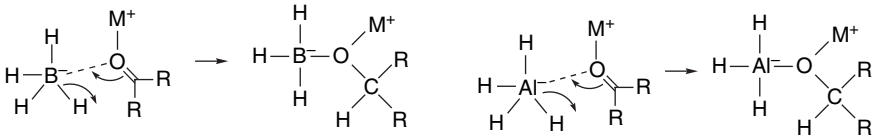


5.3. Group III Hydride-Donor Reagents

5.3.1. Comparative Reactivity of Common Hydride Donor Reagents

Most reductions of carbonyl compounds are done with reagents that transfer a hydride from boron or aluminum. The various reagents of this type that are available provide a considerable degree of chemo- and stereoselectivity. Sodium borohydride and lithium aluminum hydride are the most widely used of these reagents. Sodium borohydride is a mild reducing agent that reacts rapidly with aldehydes and ketones but only slowly with esters. It is moderately stable in hydroxylic solvents and can be used in water or alcoholic solutions. Lithium aluminum hydride is a much more powerful hydride donor, and it rapidly reduces esters, acids, nitriles, and amides, as well as aldehydes and ketones. Lithium aluminum hydride is strongly basic and reacts very rapidly (*violently*) with water or alcohols to release hydrogen. It must be used in anhydrous solvents, usually ether or tetrahydrofuran. The difference in the reactivity of these two compounds is due to properties of both the cations and the anions. Lithium is a stronger Lewis acid than sodium and AlH_4^- is a more reactive hydride donor than BH_4^-. Neither sodium borohydride nor lithium aluminum hydride reacts with isolated carbon-carbon double bonds. The reactivity of these reagents and some related reducing reagents is summarized in Table 5.3.

The mechanism by which the Group III hydrides effect reduction involves activation of the carbonyl group by coordination with a metal cation and nucleophilic transfer of hydride to the carbonyl group. Hydroxylic solvents also participate in the reaction,[59] and as reduction proceeds and hydride is transferred, the Lewis acid character of boron and aluminum becomes a factor.



[59] D. C. Wigfield and R. W. Gowland, *J. Org. Chem.*, **42**, 1108 (1977).

Table 5.3. Reactivity of Hydride-Donor Reducing Agents

	Reactant					
	Iminium ion	Acyl chloride	Aldehyde or ketone	Ester	Amide	Carboxylate salt
	Most reactive →					Least reactive
Hydride donor			Product[a]			
$LiAlH_4$[b]	Amine	Alcohol	Alcohol	Alcohol	Amine	Alcohol
Red-Al[c]		Alcohol	Alcohol	Alcohol	Amine	Alcohol
$LiAlH(OtBu)_3$[d]		Aldehyde[e]	Alcohol	Alcohol	Aldehyde[f]	
$NaBH_4$[b]	Amine		Alcohol	Alcohol[f]		
$NaBH_3CN$[g]	Amine					
B_2H_6[h]			Alcohol		Amine	Alcohol[i]
AlH_3[j]		Alcohol	Alcohol	Alcohol	Amine	Alcohol
Disiamylborane[k]			Alcohol		Aldehyde[e]	
DIBAlH			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. J. Seyden-Penne, *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, VCH Publishers, New York, 1991.
c. J. Malek, *Org. React.*, **34**, 1 (1985); **36**, 249 (1989).
d. H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **78**, 752 (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 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. Park, 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 through an acyloxyborane.
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. Res.*, **4**, 47 (1969); N. M. Yoon and Y. S. Gyoung, *J. Org. Chem.*, **50**, 2443 (1985).

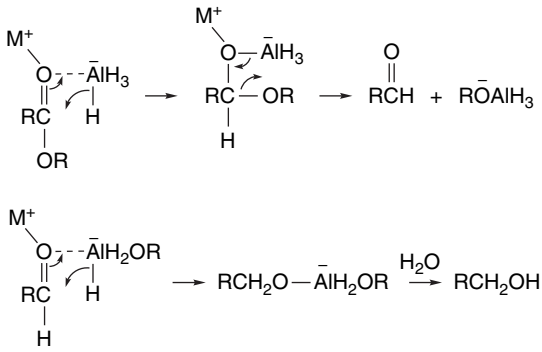
As all four of the hydrides can eventually be transferred, there are actually several distinct reducing agents functioning during the course of the reaction.[60] Although this somewhat complicates interpretation of rates and stereoselectivity, it does not detract from the synthetic utility of these reagents. Reduction with $NaBH_4$ is usually done in aqueous or alcoholic solution and the alkoxyboranes formed as intermediates are rapidly solvolyzed.

$$BH_4^- + R_2CO \longrightarrow R_2CHO\bar{B}H_3$$
$$R_2CHO\bar{B}H_3 + R_2CO \longrightarrow [R_2CHO]_2\bar{B}H_2$$
$$[R_2CHO]_2\bar{B}H_2 + R_2CO \longrightarrow [R_2CHO]_3\bar{B}H$$
$$[R_2CHO]_3\bar{B}H + R_2CO \longrightarrow [R_2CHO]_4\bar{B}$$
$$[R_2CHO]_4\bar{B} + 4\ SOH \longrightarrow 4\ R_2CHOH + \bar{B}(OS)_4$$

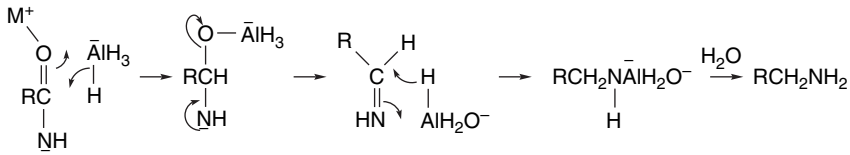
The mechanism for reduction by $LiAlH_4$ is very similar. However, since $LiAlH_4$ reacts very rapidly with protic solvents to form molecular hydrogen, reductions with this reagent must be carried out in aprotic solvents, usually ether or tetrahydrofuran.

60. B. Rickborn and M. T. Wuesthoff, *J. Am. Chem. Soc.*, **92**, 6894 (1970).

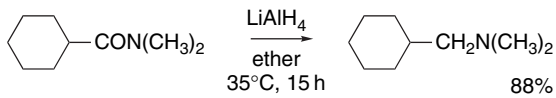
The products are liberated by hydrolysis of the aluminum alkoxide at the end of the reaction. Lithium aluminum hydride reduction of esters to alcohols involves an elimination step in addition to hydride transfers.



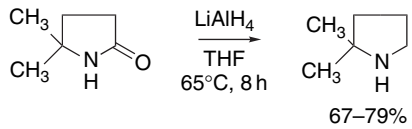
Amides are reduced to amines because the nitrogen is a poorer leaving group than oxygen at the intermediate stage of the reduction. Primary and secondary amides are rapidly deprotonated by the strongly basic $LiAlH_4$, so the addition step involves the conjugate base.



Reduction of amides by $LiAlH_4$ is an important method for the synthesis of amines.



Ref. 61

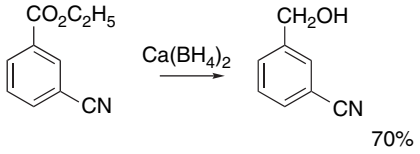


Ref. 62

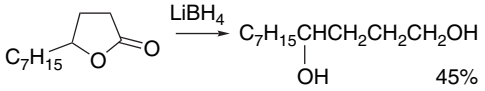
Several factors affect the reactivity of the boron and aluminum hydrides, including the metal cation present and the ligands, in addition to hydride, in the complex hydride. Some of these effects can be illustrated by considering the reactivity of ketones and aldehydes toward various hydride transfer reagents. Comparison of $LiAlH_4$ and $NaAlH_4$ has shown the former to be more reactive,[63] which is attributed to the greater

61. A. C. Cope and E. Ciganek, *Org. Synth.*, **IV**, 339 (1963).
62. R. B. Moffett, *Org. Synth.*, **IV**, 354 (1963).
63. E. C. Ashby and J. R. Boone, *J. Am. Chem. Soc.*, **98**, 5524 (1976); J. S. Cha and H. C. Brown, *J. Org. Chem.*, **58**, 4727 (1993).

Lewis acid strength and hardness of the lithium cation. Both $LiBH_4$ and $Ca(BH_4)_2$ are more reactive than sodium borohydride. This enhanced reactivity is due to the greater Lewis acid strength of Li^+ and Ca^{2+}, compared with Na^+. Both of these reagents can reduce esters and lactones efficiently.

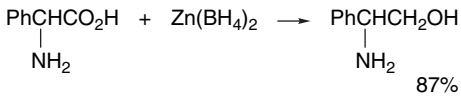


Ref. 64



Ref. 65

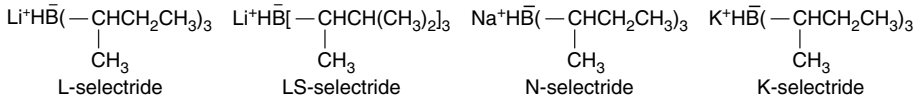
Zinc borohydride, which is also a useful reagent,[66] is prepared by reaction of $ZnCl_2$ with $NaBH_4$ in THF. Owing to the stronger Lewis acid character of Zn^{2+}, $Zn(BH_4)_2$ is more reactive than $NaBH_4$ toward esters and amides and reduces them to alcohols and amines, respectively.[67] $Zn(BH_4)_2$ reduces carboxylic acids to primary alcohols.[68] The reagent also smoothly reduces α-aminoacids to β-aminoalcohols.[69]



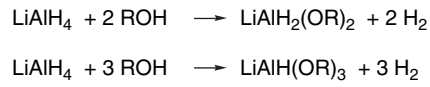
Sodium borohydride is sometimes used in conjunction with $CeCl_3$ (*Luche's reagent*).[70] The active reductants under these conditions are thought to be alkoxyborohydrides. Sodium cyanoborohydride is a useful derivative of sodium borohydride.[71] The electron-attracting cyano substituent reduces reactivity and only iminium groups are rapidly reduced by this reagent.

Alkylborohydrides are also used as reducing agents. These compounds have greater steric demands than the borohydride ion and therefore are more stereoselective in situations in which steric factors come into play.[72] These compounds are prepared by reaction of trialkylboranes with lithium, sodium, or potassium hydride.[73] Several of the compounds are available commercially under the trade name Selectrides®.[74]

64. H. C. Brown, S. Narasimhan, and Y. M. Choi, *J. Org. Chem.*
65. K. Soai and S. Ookawa, *J. Org. Chem.*, **51**, 4000 (1986).
66. S. Narasimhan and R. Balakumar, *Aldrichimica Acta*, **31**, 19 (1998).
67. S. Narasimhan, S. Madhavan, R. Balakumar, and S. Swamalakshmi, *Synth. Commun.*, **27**, 391 (1997).
68. S. Narasimhan, S. Madhavan, and K. G. Prasad, *J. Org. Chem.*, **60**, 5314 (1995); B. C. Ranue and A. R. Das, *J. Chem. Soc., Perkin Trans. 1*, 1561 (1992).
69. S. Narasimhan, S. Madhavan, and K. G. Prasad, *Synth. Commun.*, **26**, 703 (1996).
70. A. C. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, **103**, 5454 (1981).
71. C. F. Lane, *Synthesis*, 135 (1975).
72. H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972); S. Krishnamurthy and H. C. Brown, *J. Am. Chem. Soc.*, **98**, 3383 (1976).
73. H. C. Brown, S. Krishnamurthy, and J. L. Hubbard, *J. Am. Chem. Soc.*, **100**, 3343 (1978).
74. Selectride is a trade name of the Aldrich Chemical Company.

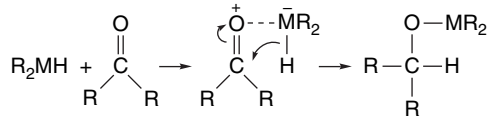


Derivatives of aluminum hydrides in which one or more of the hydrides is replaced by an alkoxide ion can be prepared by addition of the calculated amount of the appropriate alcohol.



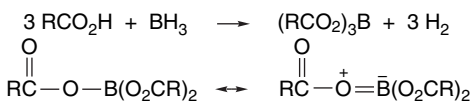
These reagents generally show increased solubility in organic solvents, particularly at low temperatures, and are useful in certain selective reductions.[75] Lithium tri-*t*-butoxyaluminum hydride and sodium *bis*-(2-methoxyethoxy)aluminum hydride (Red-Al)[76] are examples of these types of reagents that have synthetic use. Their reactivity toward carbonyl groups is summarized in Table 5.3.

Closely related to, but distinct from, the anionic boron and aluminum hydrides are the neutral boron (borane, BH_3) and aluminum (alane, AlH_3) hydrides. These molecules also contain hydrogen that can be transferred as hydride. Borane and alane differ from the anionic hydrides in being electrophilic species by virtue of the vacant *p* orbital and are Lewis acids. Reduction by these molecules occurs by an intramolecular hydride transfer in a Lewis acid-base complex of the reactant and reductant.



Alkyl derivatives of boron and alane can function as reducing reagents in a similar fashion. Two reagents of this type, disiamylborane and diisobutylaluminum hydride (DiBAlH) are included in Table 5.3. The latter is an especially useful reagent.

Diborane also has a useful pattern of selectivity. It reduces carboxylic acids to primary alcohols under mild conditions that leave esters unchanged.[77] Nitro and cyano groups are relatively unreactive toward diborane. The rapid reaction between carboxylic acids and diborane is the result of formation of a triacyloxyborane intermediate by protonolysis of the B—H bonds. The resulting compound is essentially a mixed anhydride of the carboxylic acid and boric acid in which the carbonyl groups have enhanced reactivity toward borane or acetoxyborane.



Diborane also reduces amides to amines (see Section 5.3.1.2).

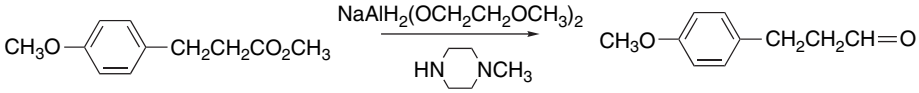
[75] J. Malek and M. Cerny, *Synthesis*, 217 (1972); J. Malek, *Org. React.*, **34**, 1 (1985).

[76] Red-Al is a trademark of the Aldrich Chemical Company.

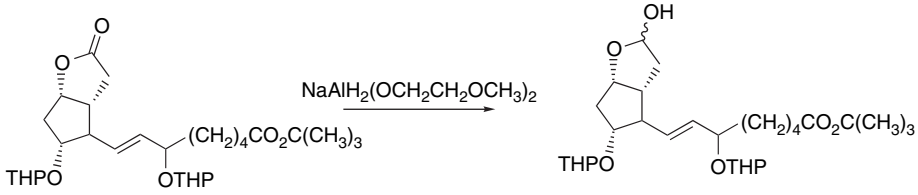
[77] N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).

In synthesis, the principal factors that affect the choice of a reducing agent are selectivity among functional groups (chemoselectivity) and stereoselectivity. Chemoselectivity can involve two issues. One may wish to effect a *partial reduction* of a particular functional group or it may be necessary to *reduce one group in preference to another*.[78] In the sections that follow, we consider some synthetically useful partial and selective reductions.

5.3.1.1. Partial Reduction of Carboxylic Acid Derivatives. One of the more difficult partial reductions is the conversion of a carboxylic acid derivative to an aldehyde without overreduction to the alcohol. Aldehydes are inherently more reactive than acids or esters, so the challenge is to stop the reduction at the aldehyde stage. Several approaches have been used to achieve this objective. One is to replace some of the hydrogens in the hydride with more bulky groups, thus modifying reactivity by steric factors. Lithium tri-*t*-butoxyaluminum hydride is an example of this approach.[79] Sodium tri-*t*-butoxyaluminum hydride can be used to reduce acid chlorides to aldehydes without overreduction to the alcohol.[80] The excellent solubility of sodium *bis*-(2-methoxyethoxy)aluminum hydride (Red-Al) makes it a useful reagent for selective reductions. The reagent is soluble in toluene even at $-70°$ C, and selectivity is enhanced by the low temperature. It is possible to reduce esters to aldehydes and lactones to lactols with this reagent.



Ref. 81

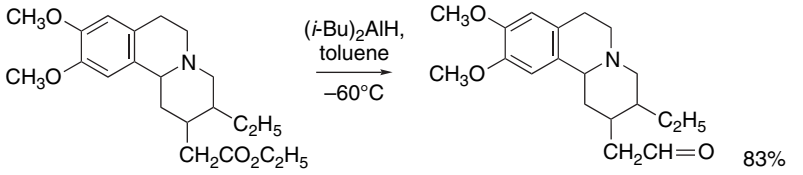


Ref. 82

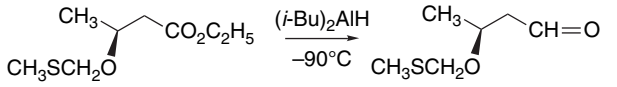
The most widely used reagent for partial reduction of esters and lactones at the present time is diisobutylaluminum hydride (DiBAlH).[83] By use of a controlled amount of the reagent at low temperature, partial reduction can be reliably achieved. The selectivity results from the relative stability of the hemiacetal intermediate that is formed. The aldehyde is not liberated until the hydrolytic workup and is therefore not

78. For more complete discussion of functional group selectivity of hydride reducing agents, see E. R. H. Walter, *Chem. Soc. Rev.*, **5**, 23 (1976).
79. H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **80**, 5377 (1958).
80. J. S. Cha and H. C. Brown, *J. Org. Chem.*, **58**, 4732 (1993).
81. R. Kanazawa and T. Tokoroyama, *Synthesis*, 526 (1976).
82. H. Disselnkoetter, F. Lieb, H. Oediger, and D. Wendisch, *Liebigs Ann. Chem.*, 150 (1982).
83. F. Winterfeldt, *Synthesis*, 617 (1975); N. M. Yoon and Y. G. Gyoung, *J. Org. Chem.*, **50**, 2443 (1985).

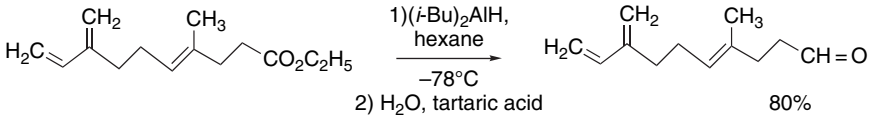
subject to overreduction. At higher temperatures, where the intermediate undergoes elimination, diisobutylaluminum hydride reduces esters to primary alcohols.



Ref. 84

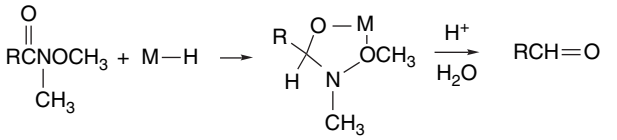


Ref. 85

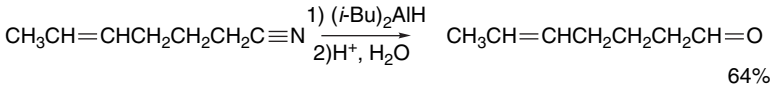


Ref. 86

Selective reduction to aldehydes can also be achieved using *N*-methoxy-*N*-methylamides.[87] $LiAlH_4$ and DiBAlH have both been used as the hydride donor. The partial reduction is again the result of the stability of the initial reduction product. The *N*-methoxy substituent leads to a chelated structure that is stable until acid hydrolysis occurs during workup.

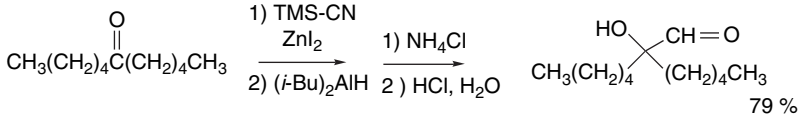


Another useful approach to aldehydes is by partial reduction of nitriles to imines. The reduction stops at the imine stage because of the low electrophilicity of the deprotonated imine intermediate. The imines are then hydrolyzed to the aldehyde. Diisobutylaluminum hydride seems to be the best reagent for this purpose.[88,89]

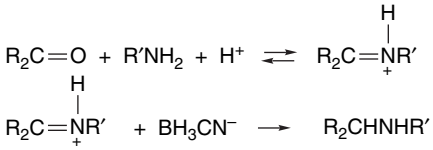


84. C. Szantay, L. Toke, and P. Kolonits, *J. Org. Chem.*, **31**, 1447 (1966).
85. G. E. Keck, E. P. Boden, and M. R. Wiley, *J. Org. Chem.*, **54**, 896 (1989).
86. P. Baeckstrom, L. Li, M. Wickramaratne, and T. Norin, *Synth. Commun.*, **20**, 423 (1990).
87. S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, **22**, 3815 (1981).
88. N. A. LeBel, M. E. Post, and J. J. Wang, *J. Am. Chem. Soc.*, **86**, 3759 (1964).
89. R. V. Stevens and J. T. Lai, *J. Org. Chem.*, **37**, 2138 (1972); S. Trofimenko, *J. Org. Chem.*, **29**, 3046 (1964).

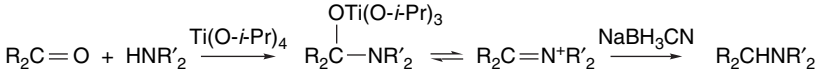
This method can be used in conjunction with addition of cyanide to prepare α-hydroxy aldehydes from ketones.[90]



5.3.1.2. Reduction of Imines and Amides to Amines. A second type of chemoselectivity arises in the context of the need to reduce one functional 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 choosing a reducing reagent with the appropriate level of reactivity. Sodium borohydride, for example, is very useful in this respect since it reduces ketones and aldehydes much more rapidly than esters. Sodium cyanoborohydride is used to reduce imines to amines, but this reagent is only reactive toward iminium ions. At pH 6–7, $NaBH_3CN$ is essentially unreactive toward carbonyl groups. When an amine and ketone are mixed together, equilibrium is established with the imine. At mildly acidic pH only the protonated imine is reactive toward $NaBH_3CN$.[91] This process is called *reductive amination*.

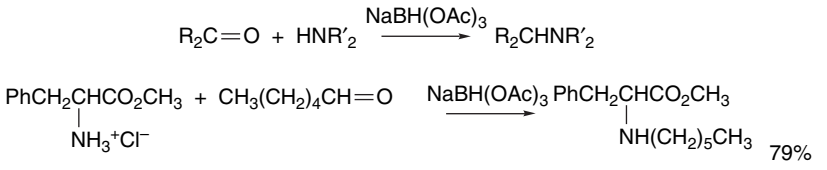


Reductive amination by $NaBH_3CN$ can also be carried out in the presence of $Ti(O\text{-}i\text{-}Pr)_4$. These conditions are especially useful for situations in which it is not practical to use the amine in excess (as is typically done under the acid-catalyzed conditions) or for acid-sensitive compounds. The $Ti(O\text{-}i\text{-}Pr)_4$ may act as a Lewis acid in generation of a tetrahedral adduct, which then may be reduced directly or via a transient iminium intermediate.[92]

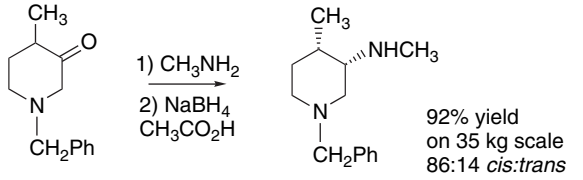


Sodium triacetoxyborohydride is an alternative to $NaBH_3CN$ for reductive amination. This reagent can be used with a wide variety of aldehydes or ketones with primary and secondary amines, including aniline derivatives.[93] This reagent has been used successfully to alkylate amino acid esters.[94]

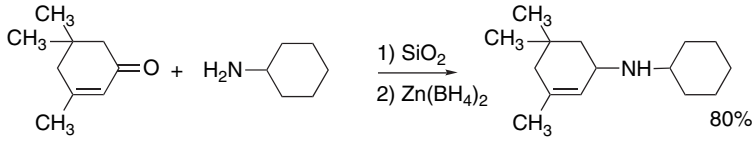
90. M. Hayashi, T. Yoshiga, and N. Oguni, *Synlett*, 479 (1991).
91. R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).
92. R. J. Mattson, K. M. Pham, D. J. Leuck, and K. A. Cowen, *J. Org. Chem.*, **55**, 2552 (1990).
93. A. F. Abdel-Magid, K. G. Carson, B. H. Harris, C. A. Maryanoff, and R. D. Shah, *J. Org. Chem.*, **61**, 3849 (1996).
94. J. M. Ramanjulu and M. M. Joullie, *Synth. Commun.*, **26**, 1379 (1996).



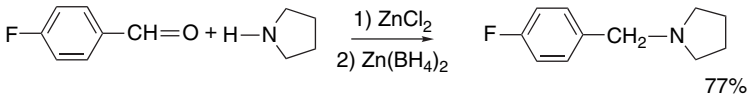
This method was used in a large-scale synthesis of 1-benzyl-3-methylamino-4-methylpiperidine.[95]



Zinc borohydride has been found to effect very efficient reductive amination in the presence of silica. The amine and carbonyl compound are mixed with silica and the powder is then treated with a solution of $Zn(BH_4)_2$. Excellent yields are also obtained for unsaturated aldehydes and ketones.[96]

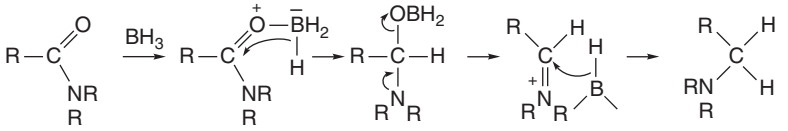


Aromatic aldehydes can be reductively aminated with the combination $Zn(BH_4)_2$-$ZnCl_2$,[97] and the $ZnCl_2$ assists in imine formation.



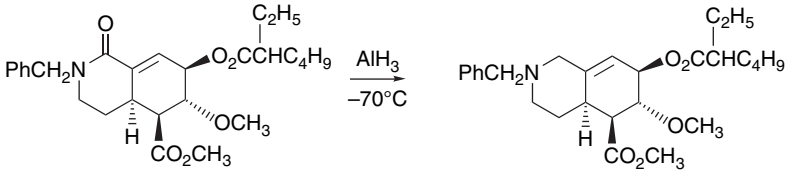
Amides are usually reduced to amines using $LiAlH_4$. Amides require vigorous reaction conditions for reduction by $LiAlH_4$, so that little selectivity can be achieved with this reagent. Diborane is also a useful reagent for reducing amides. Tertiary and secondary amides are easily reduced, but primary amides react only slowly.[98] The electrophilicity of borane is involved in the reduction of amides. The boron complexes at the carbonyl oxygen, enhancing the reactivity of the carbonyl center.

95. D. H. B. Ripin, S. Abele, W. Cai, T. Blumenkopf, J. M. Casavant, J. L. Doty, M. Flanagan, C. Koecher, K. W. Laue, K. McCarthy, C. Meltz, M. Munchoff, K. Pouwer, B. Shah, J. Sun, J. Teixera, T. Vries, D. A. Whipple, and G. Wilcox, *Org. Proc. Res. Dev.*, **7**, 115 (2003).
96. B. C. Ranu, A. Majee, and A. Sarkar, *J. Org. Chem.*, **63**, 370 (1998).
97. S. Bhattacharyya, A. Chatterjee, and J. S. Williamson, *Synth. Commun.*, **27**, 4265 (1997).
98. H. C. Brown and P. Heim, *J. Org. Chem.*, **38**, 912 (1973).



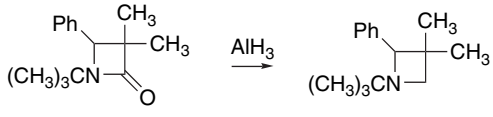
Diborane permits the selective reduction of amides in the presence of ester and nitro groups.

Alane is also a useful group for reducing amides and it, too, can be used to reduce amides to amines in the presence of ester groups.



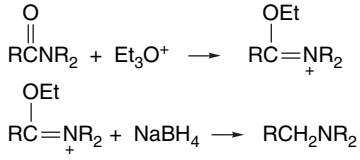
Ref. 99

The electrophilicity of alane is the basis for its selective reaction with the amide group. Alane is also useful for reducing azetidinones to azetidines. Most nucleophilic hydride reducing agents lead to ring-opened products. DiBAlH, AlH_2Cl, and $AlHCl_2$ can also reduce azetinones to azetidines.[100]



Ref. 101

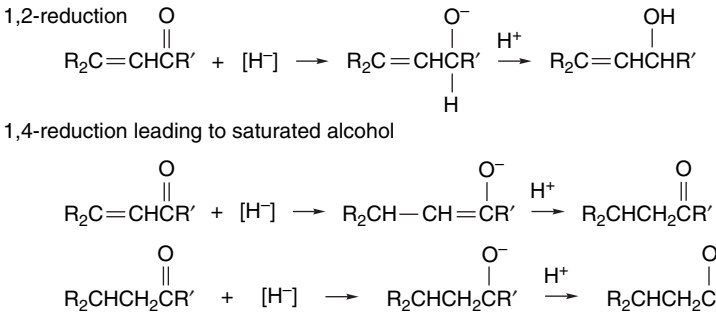
Another approach to reduction of an amide group in the presence of other groups that are more easily reduced is to convert the amide to a more reactive species. One such method is conversion of the amide to an O-alkyl derivative with a positive charge on nitrogen.[102] This method has proven successful for tertiary and secondary, but not primary, amides.



Other compounds that can be readily derived from amides that are more reactive toward hydride reducing agents are α-alkylthioimmonium ions[103] and α-chloroimmonium ions.[104]

99. S. F. Martin, H. Rueger, S. A. Williamson, and S. Grzejszczak, *J. Am. Chem. Soc.*, **109**, 6124 (1987).
100. I. Ojima, M. Zhao, T. Yamamoto, K. Nakanishi, M. Yamashita, and R. Abe, *J. Org. Chem.*, **56**, 5263 (1991).
101. M. B. Jackson, L. N. Mander, and T. M. Spotswood, *Aust. J. Chem.*, **36**, 779 (1983).
102. R. F. Borch, *Tetrahedron Lett.*, 61 (1968).
103. 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).
104. M. E. Kuehne and P. J. Shannon, *J. Org. Chem.*, **42**, 2082 (1972).

5.3.1.3. Reduction of α,β-*Unsaturated Carbonyl Compounds.* An important case of chemoselectivity arises in the reduction of α,β-unsaturated carbonyl compounds. Reaction can occur at the carbonyl group, giving an allylic alcohol or at the double bond giving a saturated ketone. These alternative reaction modes are called 1,2- and 1,4-reduction, respectively. If hydride is added at the carbonyl group, the allylic alcohol is usually not susceptible to further reduction. If a hydride is added at the β-position, the initial product is an enolate. In protic solvents this leads to the ketone, which can be reduced to the saturated alcohol. Both $NaBH_4$ and $LiAlH_4$ have been observed to give both types of product, although the extent of reduction to saturated alcohol is usually greater with $NaBH_4$.[105]



Several reagents have been developed that lead to exclusive 1,2- or 1,4-reduction. Use of $NaBH_4$ in combination with cerium chloride (*Luche reagent*) results in clean 1,2-reduction.[106] DiBAlH[107] and the dialkylborane 9-BBN[108] also give exclusive carbonyl reduction. In each case the reactivity of the carbonyl group is enhanced by a Lewis acid complexation at oxygen.

Selective reduction of the carbon-carbon double bond can usually be achieved by catalytic hydrogenation. A series of reagents prepared from a hydride reducing agent and copper salts also gives primarily the saturated ketone.[109] Similar reagents have been shown to reduce α,β-unsaturated esters[110] and nitriles[111] to the corresponding saturated compounds. The mechanistic details are not known with certainty, but it is likely that "copper hydrides" are the active reducing agents and that they form an organocopper intermediate by conjugate addition.

105. M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970); W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965).

106. J.-L. Luche, *J. Am. Chem. Soc.*, **100**, 2226 (1978); J.-L. Luche, L. Rodriguez-Hahn, and P. Crabbe, *J. Chem. Soc., Chem. Commun.*, 601 (1978).

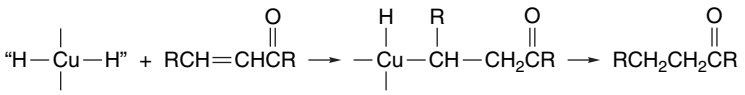
107. K. E. Wilson, R. T. Seidner, and S. Masamune, *J. Chem. Soc., Chem. Commun.*, 213 (1970).

108. K. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **42**, 1197 (1977).

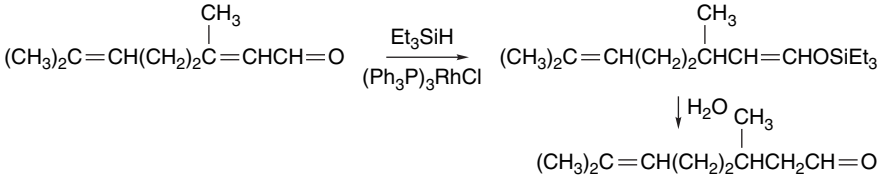
109. S. Masamune, G. S. Bates, and P. E. Georghiou, *J. Am. Chem. Soc.*, **96**, 3686 (1974); E. C. Ashby, J.-J. Lin, and R. Kovar, *J. Org. Chem.*, **41**, 1939 (1976); E. C. Ashby, J.-J. Lin, and A. B. Goel, *J. Org. Chem.*, **43**, 183 (1978); W. S. Mahoney, D. M. Brestensky, and J. M. Stryker, *J. Am. Chem. Soc.*, **110**, 291 (1988); D. M. Brestensky, D. E. Huseland, C. McGettigan, and J. M. Stryker, *Tetrahedron Lett.*, **29**, 3749 (1988); T. M. Koenig, J. F. Daeuble, D. M. Brestensky, and J. M. Stryker, *Tetrahedron Lett.*, **31**, 3237 (1990).

110. M. F. Semmelhack, R. D. Stauffer, and A. Yamashita, *J. Org. Chem.*, **42**, 3180 (1977).

111. M. E. Osborn, J. F. Pegues, and L. A. Paquette, *J. Org. Chem.*, **45**, 167 (1980).

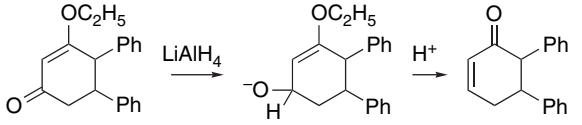


Combined use of $Co(acac)_2$ and DiBAlH also gives selective reduction for α,β-unsaturated ketones, esters, and amides.[112] Another reagent combination that selectively reduces the carbon-carbon double bond is Wilkinson's catalyst and triethylsilane. The initial product is the enol silyl ether.[113]



Unconjugated double bonds are unaffected by this reducing system.[114]

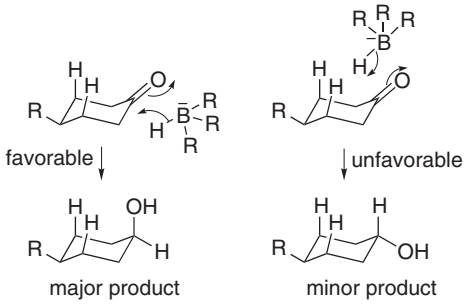
The enol ethers of β-dicarbonyl compounds are reduced to α,β-unsaturated ketones by $LiAlH_4$, followed by hydrolysis.[115] Reduction stops at the allylic alcohol, but subsequent acid hydrolysis of the enol ether and dehydration leads to the isolated product. This reaction is a useful method for synthesis of substituted cyclohexenones.



5.3.2. Stereoselectivity of Hydride Reduction

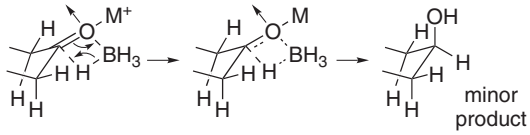
5.3.2.1. Cyclic Ketones. Stereoselectivity is a very important aspect of reductions by hydride transfer reagents. The stereoselectivity of the reduction of carbonyl groups is affected by the same combination of steric and stereoelectronic factors that control the addition of other nucleophiles, such as enolates and organometallic reagents to carbonyl groups. A general discussion of these factors is given in Section 2.4.1 of Part A. The stereochemistry of hydride reduction has been thoroughly studied with conformationally biased cyclohexanones. Some reagents give predominantly axial cyclohexanols, whereas others give the equatorial isomer. Axial alcohols are most likely to be formed when the reducing agent is a sterically hindered hydride donor because the equatorial direction of approach is more open and is preferred by bulky reagents. This is called *steric approach control*.[116]

112. T. Ikeno, T. Kimura, Y. Ohtsuka, and T. Yamada, *Synlett*, 96 (1999).
113. I. Ojima, T. Kogure, and Y. Nagai, *Tetrahedron Lett.*, 5035 (1972); I. Ojima, M. Nihonyanagi, T. Kogure, M. Kumagai, S. Horiuchi, K. Nakatsugawa, and Y. Nogai, *J. Organomet. Chem.*, **94**, 449 (1973).
114. H.-J. Liu and E. N. C. Browne, *Can. J. Chem.*, **59**, 601 (1981); T. Rosen and C. H. Heathcock, *J. Am. Chem. Soc.*, **107**, 3731 (1985).
115. 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).
116. W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

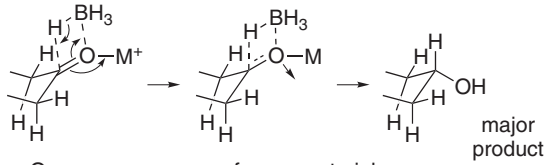


Steric Approach Control

With less hindered hydride donors, particularly $NaBH_4$ and $LiAlH_4$, conformationally biased cyclohexanones give predominantly the equatorial alcohol, which is normally the more stable of the two isomers. However, hydride reductions are exothermic reactions with low activation energies. The TS should resemble starting ketone, so product stability should not control the stereoselectivity. A major factor in the preference for the equatorial isomer is the torsional strain that develops in the formation of the axial alcohol.[117]



Torsional strain increases as oxygen passes through an eclipsed conformation



Oxygen moves away from equatorial hydrogens; no torsional strain

An alternative interpretation is that the carbonyl group π-antibonding orbital, which acts as the LUMO in the reaction, has a greater density on the axial face.[118] At the present time the importance of such orbital effects is not entirely clear. Most of the stereoselectivities that have been reported can be reconciled with torsional and steric effects being dominant.[119]

A large amount of data has been accumulated on the stereoselectivity of reduction of cyclic ketones.[120] Table 5.4 compares the stereoselectivity of reduction of several ketones by hydride donors of increasing steric bulk. The trends in the table illustrate

117. M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2205 (1968); M. Cherest and H. Felkin, *Tetrahedron Lett.*, 383 (1971).

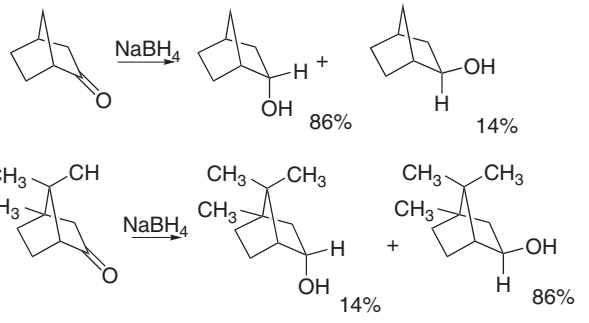
118. J. Klein, *Tetrahedron Lett.*, 4307 (1973); N. T. Ahn, O. Eisenstein, J.-M. Lefour, and M. E. Tran Huu Dau, *J. Am. Chem. Soc.*, **95**, 6146 (1973).

119. W. T. Wipke and P. Gund, *J. Am. Chem. Soc.*, **98**, 8107 (1976); J.-C. Perlburger and P. Mueller, *J. Am. Chem. Soc.*, **99**, 6316 (1977); D. Mukherjee, Y.-D. Wu, F. R. Fronczek, and K. N. Houk, *J. Am. Chem. Soc.*, **110**, 3328 (1988).

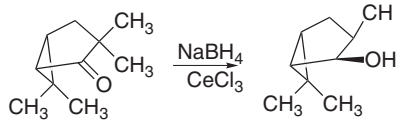
120. D. C. Wigfield, *Tetrahedron*, **35**, 449 (1979); D. C. Wigfield and D. J. Phelps, *J. Org. Chem.*, **41**, 2396 (1976).

the increasing importance of steric approach control as both the hydride reagent and the ketone become more highly substituted. The alkyl borohydrides have especially high selectivity for the least hindered direction of approach.

When a ketone is relatively hindered, as, for example, in the bicyclo[2.2.1]heptan-2-one system, steric approach control governs stereoselectivity even for small hydride donors.

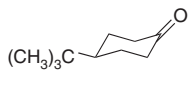
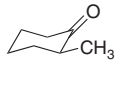
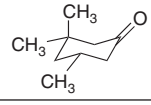
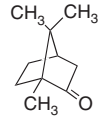


The $NaBH_4$-$CeCl_3$ reagent has been observed to give hydride delivery from the more hindered face of certain bicyclic ketones.[121]



91% 99:1 *exo*

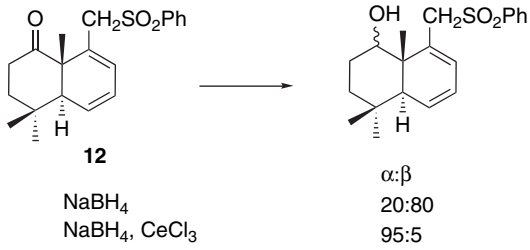
Table 5.4. Stereoselectivity of Hydride Reducing Agent

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	95	98	99
$LiAl(Ot\,Bu)_3H$	9	35[f]		94[f]	94[f]
L-Selectride	93[g]	98[g]	99.8[g]	99.6[g]	99.6[g]
LS-Selectride	>99[h]	>99[h]		>99[h]	NR[h]

a. Except where noted otherwise, data are from H. C. Brown and W. D. Dickason, *J. Am. Chem. Soc.*, **92**, 709 (1970). Data for many other cyclic ketones and other 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).

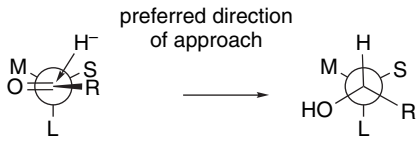
121. A. Krief and D. Surleraux, *Synlett*, 273 (1991).

Similarly, $NaBH_4$-$CeCl_3$ reverses the stereochemistry relative to $NaBH_4$ in the bicyclic ketone **12**.[122]



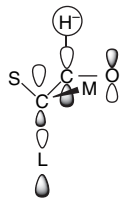
Thus, $NaBH_4$-$CeCl_3$ tends to give the *more stable* alcohol, but the origin of this stereoselectivity does not seem to have been established. It is thought that these reductions proceed through alkoxyborohydrides.[123] It is likely that equilibration occurs by reversible hydride transfer.

5.3.2.2. Acyclic Ketones. The stereochemistry of the 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 the Felkin conformational model of the TS,[63] which is based on a combination of steric and stereoelectronic effects.



S, M, L = relative size of substituents

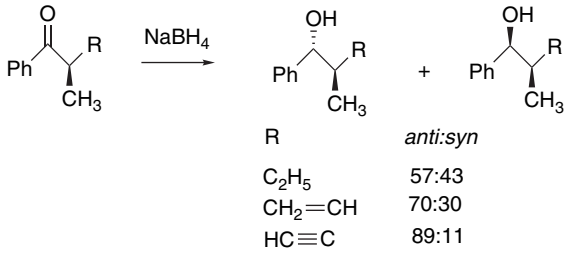
From a purely steric standpoint, minimal interaction with the groups L and M by approaching from the direction of the smallest substituent is favorable. The stereoelectronic effect involves the interaction between the approaching hydride ion and the LUMO of the carbonyl group. This orbital, which accepts the electrons of the incoming nucleophile, is stabilized when the group L is perpendicular to the plane of the carbonyl group.[124] This conformation permits a favorable interaction between the LUMO and the antibonding σ^* orbital associated with the C−L bond.



In the case of α-substituted phenyl ketones, the order of stereoselectivity is $C{\equiv}CH > CH{=}CH_2 > CH_2CH_3$.[125] These results indicate a stereoelectronic as well as a steric

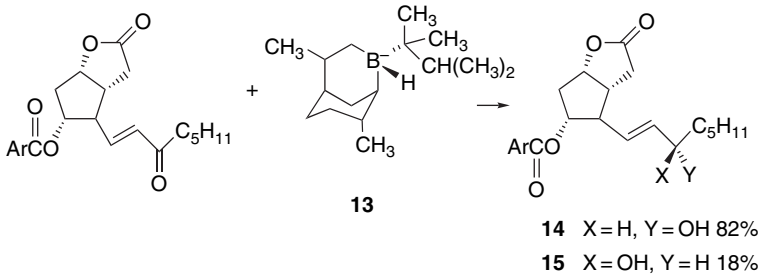
122. M. Leclaire and P. Jean, *Bull. Soc. Chim. Fr.*, **133**, 801 (1996).
123. A. C. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, **103**, 5454 (1981).
124. N. T. Ahn, *Top. Current Chem.*, **88**, 145 (1980).
125. M. Fujita, S. Akimoto, and K. Ogura, *Tetrahedron Lett.*, **34**, 5139 (1993).

component because the stereoselectivity corresponds to placing the unsaturated groups in the perpendicular position.



R	*anti:syn*
C_2H_5	57:43
$CH_2{=}CH$	70:30
$HC{\equiv}C$	89:11

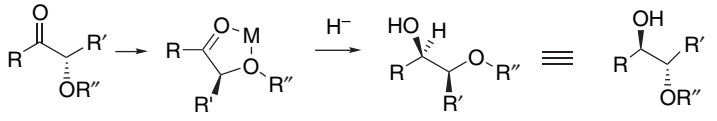
Steric factors arising from groups that are more remote from the center undergoing reduction can also influence the stereochemical course of reduction. Such steric factors are magnified by use of bulky reducing agents. For example, a 4.5:1 preference for stereoisomer **14** over **15** is achieved by using the trialkylborohydride **13** as the reducing agent in the reduction of a prostaglandin intermediate.[126]



13

14 X = H, Y = OH 82%
15 X = OH, Y = H 18%

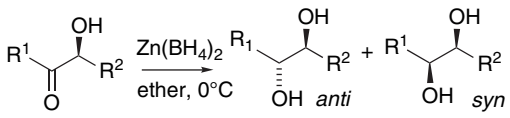
5.3.2.3. Chelation Control. The stereoselectivity of reduction of carbonyl groups can be controlled by chelation when there is a nearby donor substituent. In the presence of such a group, specific complexation among the substituent, the carbonyl oxygen, and the Lewis acid can establish a preferred conformation for the reactant. Usually hydride is then delivered from the less sterically hindered face of the chelate so the hydroxy group is *anti* to the chelating substituent.

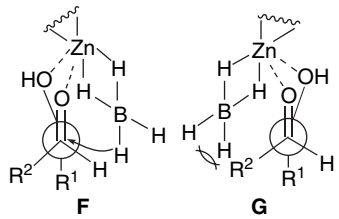


α-Hydroxy[127] and α-alkoxyketones[128] are reduced to *anti* 1,2-diols by $Zn(BH_4)_2$ through a chelated TS. This stereoselectivity is consistent with the preference for TS **F**

126. E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Am. Chem. Soc.*, **93**, 1491 (1971).
127. T. Nakata, T. Tanaka, and T. Oishi, *Tetrahedron Lett.*, **24**, 2653 (1983).
128. G. J. McGarvey and M. Kimura, *J. Org. Chem.*, **47**, 5420 (1982).

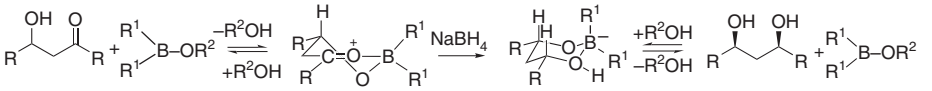
over **G**. The stereoselectivity increases with the bulk of substituent R^2. $LiAlH_4$ shows the same trend, but is not as stereoselective.



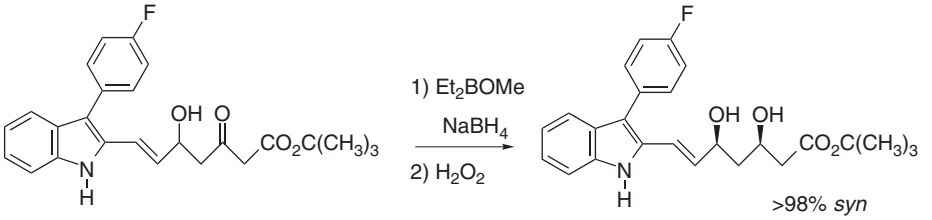


R^1	R^2	$Zn(BH_4)_2$ *anti:syn*	$LiAlH_4$ *anti:syn*
n-C_5H_{11}	CH_3	77:23	64:36
CH_3	*n*-C_5H_{11}	85:15	70:30
i-C_3H_7	CH_3	85:15	58:42
CH_3	*i*-C_3H_7	96:4	73:27
Ph	CH_3	98:2	87:13
CH_3	Ph	90:10	80:20

Reduction of β-hydroxy ketones through chelated TSs favors *syn*-1,3-diols. Boron chelates have been exploited to achieve this stereoselectivity.[129] One procedure involves in situ generation of diethylmethoxyboron, which then forms a chelate with the β-hydroxyketone. Reduction with $NaBH_4$ leads to the *syn*-diol.[130]



This procedure was used in the synthesis of the cholesterol-reducing drug lescol.[131] The diethylmethoxyboron can be prepared in situ from triethylboron and one equivalent of methanol.



Syn-1,3-diols can be obtained from β-hydroxyketones using LiI-$LiAlH_4$ at low temperatures.[132] β-Hydroxyketones also give primarily *syn*-1,3-diols when

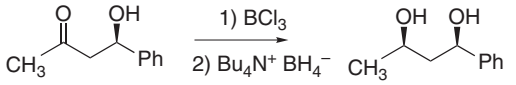
[129] K. Narasaka and F.-C. Pai, *Tetrahedron*, **40**, 2233 (1984); K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repic, and M. J. Shapiro, *Tetrahedron Lett.*, **28**, 155 (1987).

[130] K.-M. Chen, K. G. Gunderson, G. E. Hardtmann, K.Prasad, O. Repic, and M. J. Shapiro, *Chem. Lett.*, 1923 (1987).

[131] O. Repic, K. Prasad, and G. T. Lee, *Org. Proc. Res. Dev.*, **5**, 519 (2001).

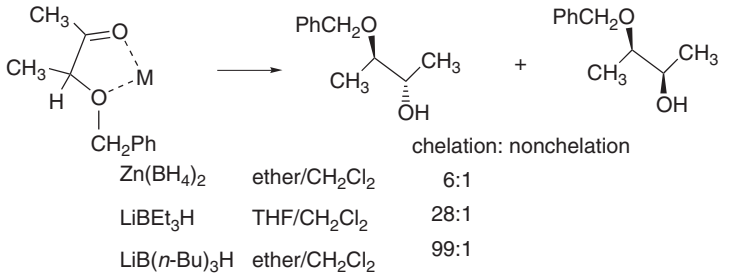
[132] Y. Mori, A. Takeuchi, H. Kageyama, and M. Suzuki, *Tetrahedron Lett.*, **29**, 5423 (1988).

chelates prepared with BCl_3 are reduced with quaternary ammonium salts of BH_4^- or BH_3CN^-.[133]

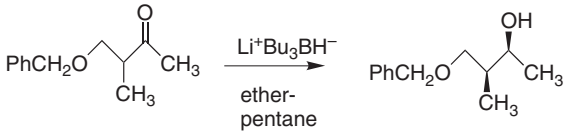


Similar results are obtained with β-methoxyketones using $TiCl_4$ as the chelating reagent.[134]

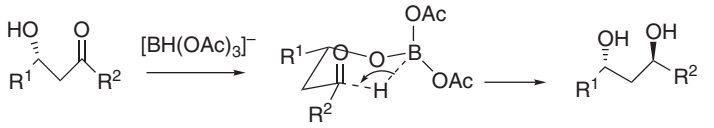
The effect of the steric bulk of the hydride reducing agent has been examined in the case of 3-benzyloxy-2-butanone.[135] The ratio of chelation-controlled product increased with the steric bulk of the reductant. This is presumably due to amplification of the steric effect of the methyl group in the chelated TS as the reductant becomes more sterically demanding. In these reactions, the degree of chelation control was also enhanced by use of CH_2Cl_2 as a cosolvent.



A survey of several of alkylborohydrides found that $LiBu_3BH$ in ether-pentane gave the best ratio of chelation-controlled reduction products from α- and β-alkoxy ketones.[134] In this case, the Li^+ cation acts as the Lewis acid. The alkylborohydrides provide an added increment of steric discrimination.

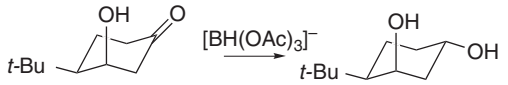


Tetramethylammonium triacetoxyborohydride gives *anti*-1,3-diols from β-hydroxy ketones.[136] These reactions are thought to occur by a rapid exchange that introduces the hydroxy group as a boron ligand.

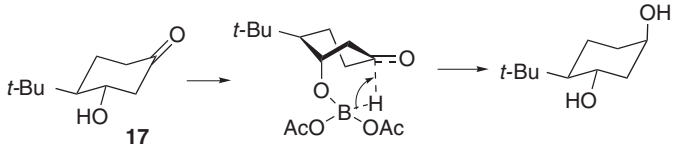


133. C. R. Sarko, S. E. Collibee, A. L. Knorr, and M. DiMare, *J. Org. Chem.*, **61**, 868 (1996).
134. C. R. Sarko, I. C. Guch, and M. DiMare, *J. Org. Chem.*, **59**, 705 (1994); G. Bartoli, M. C. Bellucci, M. Bosco, R. Dalpozzo, E. Marcantoni, and L. Sambri, *Tetrahedron Lett.*, **40**, 2845 (1999).
135. A.-M. Faucher, C. Brochu, S. R. Landry, I. Duchesne, S. Hantos, A. Roy, A. Myles, and C. Legualt, *Tetrahedron Lett.*, **39**, 8425 (1998).
136. D. A. Evans, K. T. Chapman, and E. M. Carreira, *J. Am. Chem. Soc.*, **110**, 3560 (1988).

Similarly, cyclic ketones **16** and **17** both give the *trans*-diol, as anticipated for intramolecular delivery of hydride. In the case of the equatorial alcohol, the reaction must occur through a nonchair conformer.

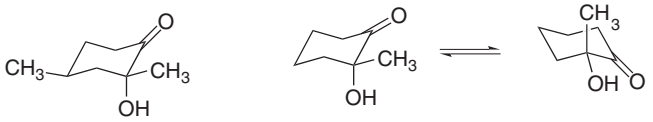


16



17

In 2-hydroxy-2,4-dimethylcyclohexanone there is a strong preference for equatorial attack by $LiAlH_4$, $NaBH_4$, and $Zn(BH_4)_2$.[137] In the case of the less conformationally biased 2-hydroxy-2-methylcyclohexanone, stereoselectivity is much weaker for these reductants, but is high for $NaB(OAc)_3H$. These results are attributed to prior complexation of the hydride at the hydroxy group with intramolecular delivery of hydride, leading to *anti*-diol. A 3-hydroxy substituent had a much weaker effect, except with $NaB(OAc)_3H$. This reagent presumably reacts more rapidly with hydroxy groups because of the greater lability of the acetoxy substituents, and in this case the reagent becomes a better hydride donor by replacing acetoxy with an alkoxide.

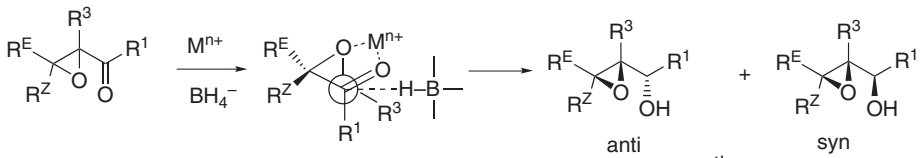


	% *anti*-diol		% *anti*-diol
$NaBH_4$	100	$NaBH_4$	57
$LiAlH_4$	100	$LiAlH_4$	74
$Zn(BH_4)_2$	100	$Zn(BH_4)_2$	75
$NaB(OAc)_3H$	100	$NaB(OAc)_3H$	97

Similar studies were carried out with methoxycyclohexanones.[138] 3-Methoxy groups showed no evidence of chelation effects with these reagents and the 2-methoxy group showed an effect only with $Zn(BH_4)_2$. This supports the suggestion that the effect of the hydroxy groups operates through deprotonated alkoxide complexes.

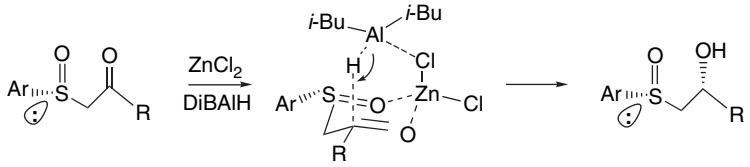
Chelation effects also come into play in the reduction of α,β-epoxyketones. Both $CaCl_2$ and $LaCl_3$ lead to enhanced *anti* stereoselectivity.[139] The same stereoselectivity is observed with $CeCl_3$ and with $Zn(BH_4)_2$.[140]

137. Y. Senda, N. Kikuchi, A. Inui, and H. Itoh, *Bull. Chem. Soc. Jpn.*, **73**, 237 (2000).
138. Y. Senda, H. Sakurai, S. Nakano, and H. Itoh, *Bull. Chem. Soc. Jpn.*, **69**, 3297 (1996).
139. M. Taniguchi, H. Fujii, K. Oshima, and K. Utimoto, *Tetrahedron*, **51**, 679 (1995).
140. K. Li, L. G. Hamann, and M. Koreeda, *Tetrahedron Lett.*, **33**, 6569 (1992).



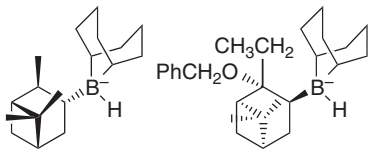
	anti:syn
$NaBH_4$	42:58
n-Bu_4NBH_4	48:52
$NaBH_4$–$CaCl_2$	92:8
$NaBH_4$–$LaCl_3$	92:8
$NaBH_4$–$CeCl_3$	>99:1
$Zn(BH_4)_2$	>99:1

β-Ketosulfoxides are subject to chelation control when reduced by DiBAlH in the presence of $ZnCl_2$.[141] This allows the use of chirality of the sulfoxide group to control the stereochemistry at the ketone carbonyl.



5.3.3. Enantioselective Reduction of Carbonyl Compounds

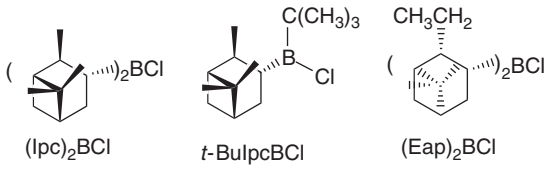
5.3.3.1. Reduction with Chiral Boranes. The reduction of an unsymmetrical ketone creates a new stereogenic center. Owing to the importance of hydroxy groups both in synthesis and in the properties of molecules, including biological activity, there has been a great deal of effort directed toward enantioselective reduction of ketones. One approach is to use chiral borohydride reagents.[142] Boranes derived from chiral alkenes can be converted to alkylborohydrides, and several such reagents are commercially available.[143]



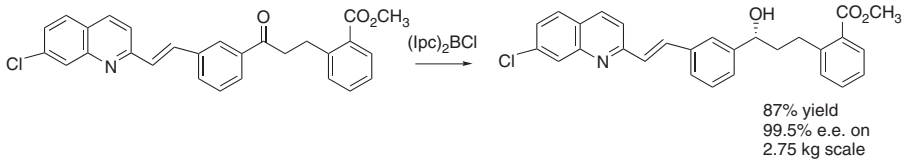
Chloroboranes have also been found useful for enantioselective reduction. Di-(isopinocampheyl)chloroborane,[144] $(Ipc)_2BCl$, and *t*-butyl(isopinocampheyl)

141. A. Solladie-Cavallo, J. Suffert, A. Adib, and G. Solladie, *Tetrahedron Lett.*, **31**, 6649 (1990).
142. M. M. Midland, *Chem. Rev.*, **89**, 1553 (1989).
143. Alpine-Hydride and NB-Enantride are trademarks of the Sigma-Aldrich Corporation.
144. H. C. Brown, J. Chandrasekharan, and P. V. Ramachandran, *J. Am. Chem. Soc.*, **110**, 1539 (1988); M. Zhao, A. O. King, R. D. Larsen, T. R. Verhoeven, and P. J. Reider, *Tetrahedron Lett.*, **38**, 2641 (1997); N. N. Joshi, C. Pyun, V. K. Mahindroo, B. Singaram, and H. C. Brown, *J. Org. Chem.*, **57**, 504 (1992).

chloroborane[145] achieve high enantioselectivity for aryl and branched dialkyl ketones. Di-(iso-2-ethylapopinocampheyl)chloroborane,[146] $(Eap)_2BCl$, shows good enantioselectivity for a wider range of alcohols.



For example, $(Ipc)_2BCl$ was found to be an advantageous in the enantioselective reduction in the large-scale preparation of L-699,392, a specific leukotriene antagonist of interest in the treatment of asthma.[147]



These reagents react through cyclic TSs and regenerate an alkene.

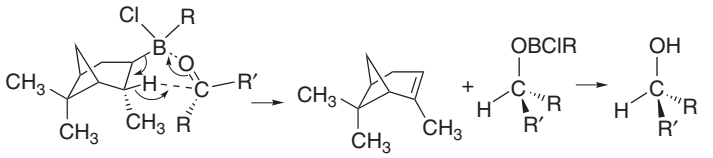
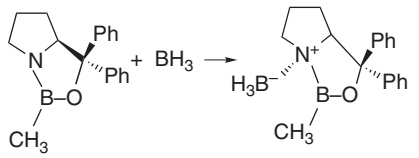


Table 5.5 gives some typical results for enantioselective reduction of ketones by alkylborohydrides and chloroboranes.

5.3.3.2. Catalytic Enantioselective Reduction of Ketones. An even more efficient approach to enantioselective reduction is to use a chiral catalyst. One of the most developed is the oxazaborolidine **18**, which is derived from the amino acid proline.[148] The enantiomer is also available. These catalysts are called the *CBS-oxazaborolidines*.



18

A catalytic amount (5–20 mol %) of the reagent, along with BH_3 as the reductant, can reduce ketones such as acetophenone and pinacolone in more than 95% e.e. An adduct of borane and **18** is the active reductant. This adduct can be prepared, stored,

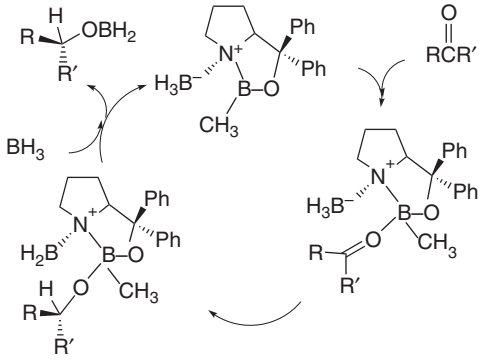
145. H. C. Brown, M. Srebnik, and P. V. Ramachandran, *J. Org. Chem.*, **54**, 1577 (1989).
146. H. C. Brown, P. V. Ramachandran, A. V. Teodorovic, and S. Swaminathan, *Tetrahedron Lett.*, **32**, 6691 (1991).
147. A. O. King, E. G. Corley, R. K. Anderson, R. D. Larsen, T. R. Verhoeven, P. J. Reider, Y. B. Xiang, M. Belley, Y. Leblanc, M. Labelle, P. Prasit, and R. J. Zamboni, *J. Org. Chem.*, **58**, 3731 (1993).
148. E. J. Corey, R. K. Bakhi, S. Shibata, C. P. Chen, and V. K. Singh, *J. Am. Chem. Soc.*, **109**, 7925 (1987); E. J. Corey and C. J. Helal, *Angew. Chem. Int. Ed. Engl.*, **37**, 1987 (1998); V. A. Glushkov and A. G. Tolstikov, *Russ. Chem. Rev.*, **73**, 581 (2004).

Table 5.5. Enantioselective Reduction of Ketones by Borohydrides and Chloroboranes

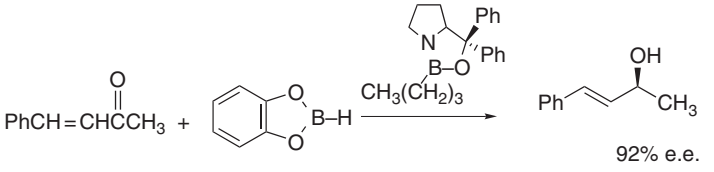
Reagent	Ketone	% e.e.	Configuration
Alpine-Hydride[a,b]	3-methyl-2-butanone	62	*S*
NB-Enantride[a,c]	2-octanone	79	*S*
$(Ipc)_2BCl$[d]	2-acetylnaphthalene	94	*S*
(*t*Bu)(Ipc)BCl[e]	acetophenone	96	*R*
$(Ipc)_2BCl$[f]	2,2-dimethylcyclohexanone	91	*S*
$(Eap)_2BCl$[g]	3-methyl-2-butanone	95	*R*

a. Trademark of Sigma-Aldrich Corporation.
b. H. C. Brown and G. G. Pai, *J. Org. Chem.*, **50**, 1384 (1985).
c. M. M. Midland and A. Kozubski, *J. Org. Chem.*, **47**, 2495 (1982).
d. M. Zhao, A. O. King, R. D. Larsen, T. R. Verhoeven, and A. J. Reider, *Tetrahedron Lett.*, **38**, 2641 (1997).
e. H. C. Brown, M. Srebnik, and P. V. Ramachandran, *J. Org. Chem.*, **54**, 1577 (1989).
f. H. C. Brown, J. Chandrasekharan, and P. V. Ramachandran, *J. Am. Chem. Soc.*, **110**, 1539 (1988).
g. H. C. Brown, P. V. Ramachandran, A. V. Teodorovic, and S. Swaminathan, *Tetrahedron Lett.*, **32**, 6691 (1991).

and used as a stoichiometric reagent if so desired.[149] The catalytic cycle depends on dissociation of the reduced product.



The corresponding *N*-butyloxazaborolidine is also frequently used as a catalyst. The enantioselectivity and reactivity of these catalysts can be modified by changes in substituent groups to optimize selectivity toward a particular ketone.[150] Catecholborane can also be used as the reductant.[151]



Both mechanistic and computational studies have been used to explore the catalytic process. A crystal structure of the catalysts is available (Figure 5.7).[152] The

149. D. J. Mahre, A. S. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley, and E. J. J. Grabowski, *J. Org. Chem.*, **58**, 2880 (1993).
150. A. W. Douglas, D. M. Tschaen, R. A. Reamer, and Y.-J. Shi, *Tetrahedron: Asymmetry*, **7**, 1303 (1996).
151. E. J. Corey and R. K. Bakshi, *Tetrahedron Lett.*, **31**, 611 (1990).
152. E. J. Corey, M. Azimiaora, and S. Sarshar, *Tetrahedron Lett.*, **33**, 3429 (1992).

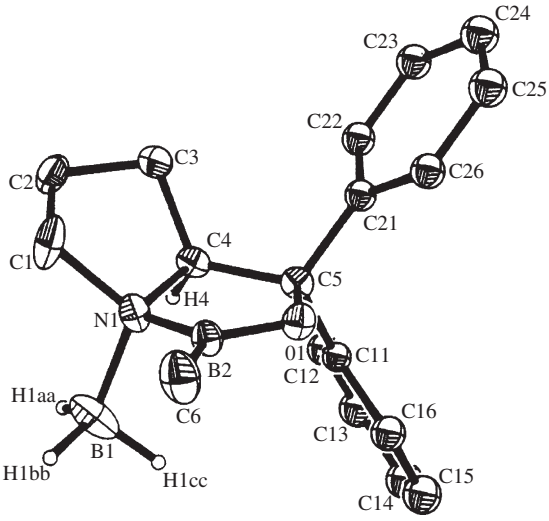
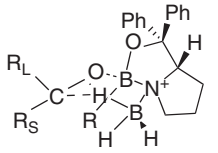


Fig. 5.7. Crystal structure of borane complex of α,α-diphenylprolinol oxazaborolidine catalysts. Reproduced from *Tetrahedron Lett.*, **33**, 3429 (1992), by permission of Elsevier.

orientation of the ketone is dictated by the phenyl groups and the relatively rigid geometry of the ring system. The enantioselectivity in these reductions is proposed to arise from a chairlike TS in which the governing steric interaction is with the alkyl substituent on boron.[153,154] There are experimental data indicating that the steric demand of the boron substituent influences enantioselectivity.[154]



There have been ab initio studies of the transition structure using several model catalysts and calculations at the HF/3-21G, HF/6-31G(*d*), and MP2/6-31G(*d*) levels.[155] The enantioselectivity is attributed to the preference for an *exo* rather than an *endo* approach of the ketone, as shown in Figure 5.8.

According to B3LYP/6-31G* computations of the intermediates and TSs, there are no large barriers to the reaction and it is strongly exothermic.[156] Measured E_a values are around 10 kcal/mol.[157] The complexation of borane to the catalyst shifts electron density from nitrogen to boron and enhances the nucleophilicity of the hydride. The

153. D. K. Jones, D. C. Liotta, I. Shikai, and D. J. Mathre, *J. Org. Chem.*, **58**, 799 (1993).
154. T. K. Jones, J. J. Mohan, L. C. Xavier, T. J. Blacklock, D. J. Mathre, P. Sohar, E. T. T. Jones, R. A. Beaner, F. E. Roberts, and E. J. J. Grabowski, *J. Org. Chem.*, **56**, 763 (1991).
155. G. J. Quallich, J. F. Blake, and T. M. Woodall, *J. Am. Chem. Soc.*, **116**, 8516 (1994).
156. G. Alagona, C. Ghio, M. Persico, and S. Tomas, *J. Am. Chem. Soc.*, **125**, 10027 (2003).
157. H. Jockel, R. Schmidt, H. Jope, and H. G. Schmalz, *J. Chem. Soc., Perkin Trans. 2*, 69 (2000).

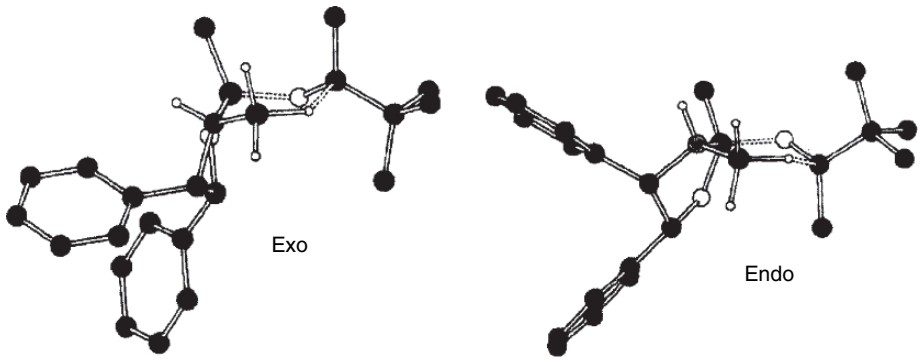
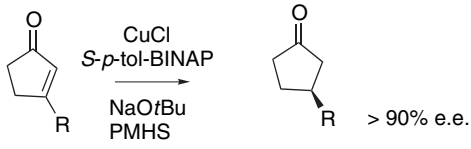


Fig. 5.8. Optimized (HF/3-21G) structures of the *exo* and *endo* transition states for reduction of *t*-butyl methyl ketone by model catalyst. The *exo* structure is favored by 2.1 kcal, in accord with an experimental e.e of 88%. Reproduced from *J. Am. Chem. Soc.*, **116**, 8516 (1994), by permission of the American Chemical Society.

complexation also diminishes the N–B delocalization present in the oxazaborolidine ring, with the bond length increasing from 1.410 to 1.498 Å, according to the computations. The computed structural parameters are close to those found by crystallography.

Scheme 5.6 shows some examples of enantioselective reduction of ketones using CBS-oxazaborolidine catalysts. The reaction in Entry 1 was carried out in the course of synthesis of a potential drug candidate. Entry 2 employs the catalyst to achieve stereoselective reduction at the C(15) center in a prostaglandin precursor. Entries 3 and 4 report high enantioselectivity in the reduction of cyclic ketones. Entries 5 and 6 are cases of acyclic ketones with adjacent functionality and are reduced with high enantioselectivity. Entries 7 and 8 are applications of the reaction to aromatic ketones done on a relatively large scale in the course of drug development. Entry 7 used an indane-derived aminoalcohol as the oxazaborolidine precursor, whereas the procedure in Entry 8 involves in situ generation of the CBS catalyst. Entries 9 to 14 show other examples of the reaction that were carried out in the course of multistage syntheses of complex molecules.

Enantioselective 1,4-reduction of enones can be done using a copper-BINAP catalyst in conjunction with silicon hydride donors.[158] Polymethylhydrosilane (PMHS) is one reductants that is used.

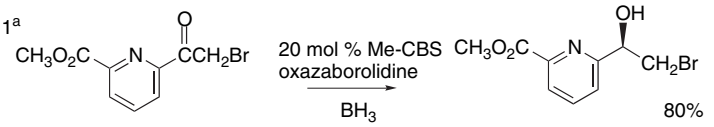


The reduction can also be effected with diphenylsilane and the intermediate silyl enol ethers can be alkylated in a tandem process.[159]

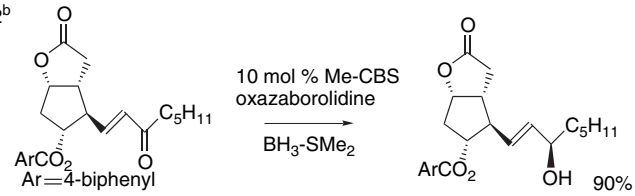
158. Y. Moritani, D. H. Appella, V. Jurkauskas, and S. L. Buchwald, *J. Am. Chem. Soc.*, **122**, 6797 (2000).
159. J. Yun and S. L. Buchwald, *Org. Lett.*, **3**, 1129 (2001).

Scheme 5.6. Enantioselective Reduction of Ketones Using CBS-Oxazaborolidine Catalysts

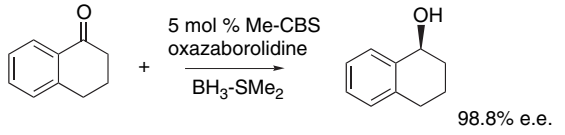
1[a]



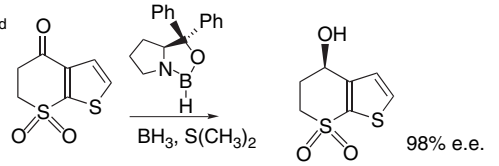
2[b]



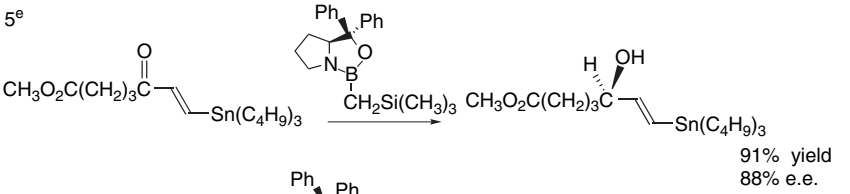
3[c]



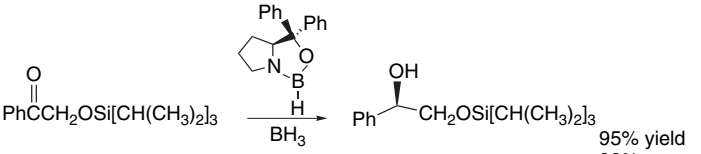
4[d]



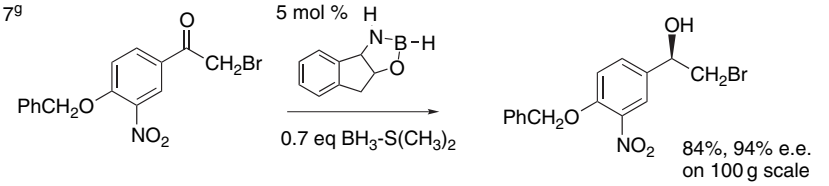
5[e]



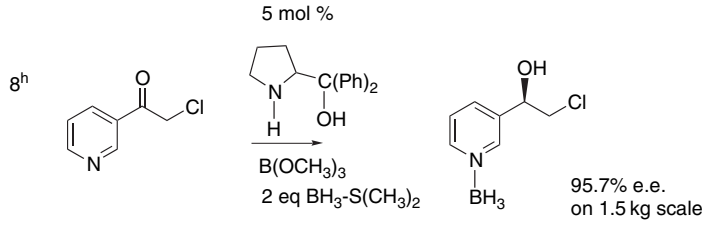
6[f]



7[g]



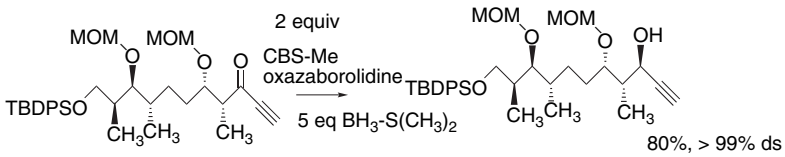
8[h]



(*Continued*)

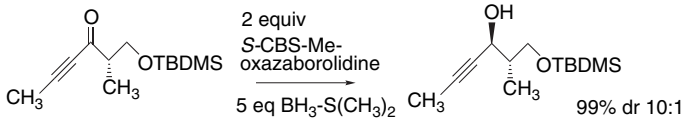
Scheme 5.6. (*Continued*)

9[i]



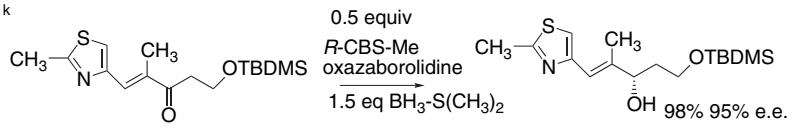
80%, > 99% ds

10[j]



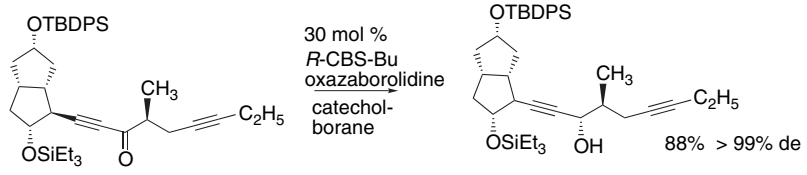
99% dr 10:1

11[k]



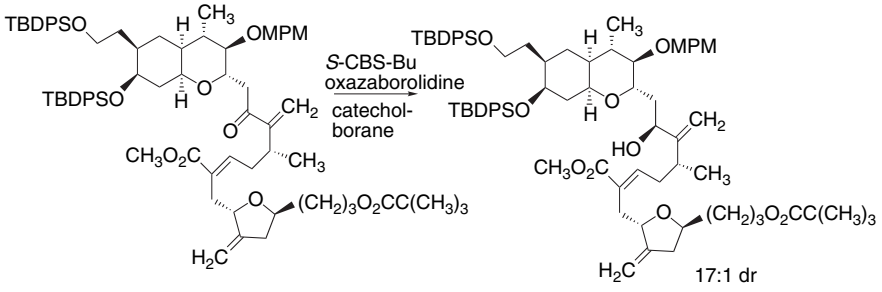
98% 95% e.e.

12[l]



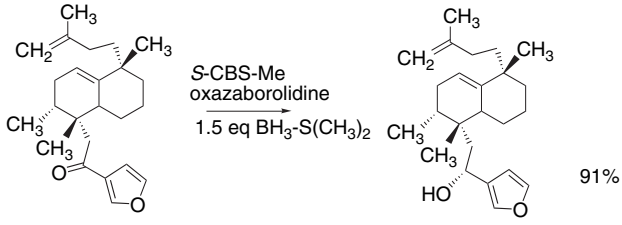
88% > 99% de

13[m]



17:1 dr

14[n]

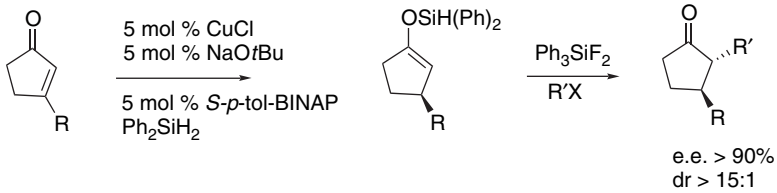


91%

(*Continued*)

Scheme 5.6. (*Continued*)

a. K. G. Hull, M. Visnick, W. Tautz, and A. Sheffron, *Tetrahedron*, **53**, 12405 (1997).
b. E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, and V. K. Singh, *J. Am. Chem. Soc.*, **109**, 7925 (1987).
c. D. J. Mathre, A. S. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley, and E. J. J. Grabowski, *J. Org. Chem.*, **58**, 2880 (1993).
d. T. K. Jones, J. J. Mohan, L. C. Xavier, T. J. Blacklock, D. J. Mathre, P. Sohar, E. T. T. Jones, R. A. Reamer, F. E. Roberts, and E. J. J. Grabowski, *J. Org. Chem.*, **56**, 763 (1991).
e. E. J. Corey, A. Guzman-Perez, and S. E. Lazerwith, *J. Am. Chem. Soc.*, **119**, 11769 (1997).
f. B. T. Cho and Y. S. Chun, *J. Org. Chem.*, **63**, 5280 (1998).
g. R. Hett, Q. K. Fang, Y. Gao, S. A. Wald, and C. H. Senanayake, *Org. Proc. Res. Dev.*, **2**, 96 (1998).
h. J. Duquette, M Zhang, L. Zhu, and R. S. Reeves, *Org. Proc. Res. Dev.*, **7**, 285 (2003).
i. L. Bialy and H. Waldmann, *Chem. Eur. J.*, **10**, 2759 (2004).
j. B. M. Trost, J. L. Guzner, O. Dirat, and Y. H. Rhee, *J. Am. Chem. Soc.*, **124**, 10396 (2002).
k. E. A. Reiff, S. K. Nair, B. S. N. Reddy, J. Inagaki, J. T. Henri, J. F. Greiner, and G. I. Georg, *Tetrahedron Lett.*, **45**, 5845 (2004).
l. M. Lerm, H.-J. Gais, K. Cheng, and C. Vermeeren, *J. Am. Chem. Soc.*, **125**, 9653 (2003).
m. D. P. Stamos, S. S. Chen, and Y. Kishi, *J. Org. Chem.*, **62**, 7552 (1997).
n. E. J. Corey and B. E. Roberts, *J. Am. Chem. Soc.*, **119**, 12425 (1997).



When necessary, the *trans*:*cis* ratio can be improved by base-catalyzed equilibration.

5.3.4. Reduction of Other Functional Groups by Hydride Donors

Although reductions of the common carbonyl and carboxylic acid derivatives are the most prevalent uses of hydride donors, these reagents can reduce a number of other groups in ways that are of synthetic utility. Halogen and sulfonate leaving groups can undergo replacement by hydride. Both aluminum and boron hydrides exhibit this reactivity, and lithium trialkylborohydrides are especially reactive.[160] The reduction is particularly rapid and efficient in polar aprotic solvents such as DMSO, DMF, and HMPA. Table 5.6 gives some indication of the reaction conditions. The normal factors in susceptibility to nucleophilic attack govern reactivity with I > Br > Cl being the order in terms of the leaving group and benzyl ~ allyl > primary > secondary > tertiary in terms of the substitution site.[161] For primary alkyl groups, it is likely that the reaction proceeds by an S_N2 mechanism. However, the range of halides that can be reduced includes aryl halides and bridgehead halides, which cannot react by the S_N2 mechanism.[162] The loss of stereochemical integrity in the reduction of vinyl halides suggests the involvement of radical intermediates.[163] Formation and subsequent

160. S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **45**, 849 (1980).
161. S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **47**, 276 (1982).
162. C. W. Jefford, D. Kirkpatrick, and F. Delay, *J. Am. Chem. Soc.*, **94**, 8905 (1972).
163. S. K. Chung, *J. Org. Chem.*, **45**, 3513 (1980).

Table 5.6. Reaction Conditions for Reductive Replacement of Halogen and Sulfonate Groups by Hydride Donors

	Approximate conditions for complete reduction	
Hydride donor	Halides	Sulfonates
$NaBH_3CN$[a]	$C_{12}H_{23}I$, HMPA, 25° C, 4 h	$C_{12}H_{23}O_3SC_7H_7$, HMPA, 70° C, 8 h
$NaBH_4$[b]	$C_{12}H_{23}Br$, DMSO, 85° C, 1.5 h	$C_{12}H_{23}O_3SC_7H_7$, DMSO, 85° C, 2 h
$LiAlH_4$[c,d]	$C_8H_{17}Br$, THF, 25° C, 1 h	$C_8H_{17}O_3SC_7H_7$, DME, 25° C, 6 h
$LiB(C_2H_5)_3H$[c]	$C_8H_{17}Br$, THF, 25° C, 3 h	

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).

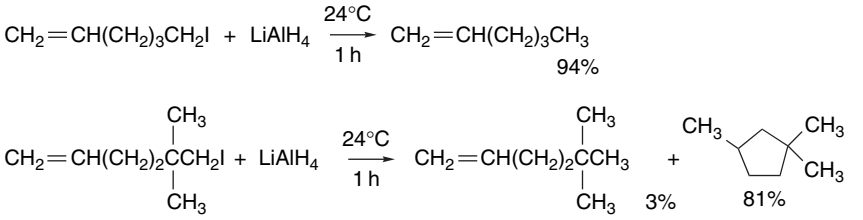
dissociation of a radical anion by one-electron transfer is a likely mechanism for reductive dehalogenation of compounds that cannot react by an S_N2 mechanism.

$$R{-}X + e^- \longrightarrow R{-}X^{\cdot-}$$

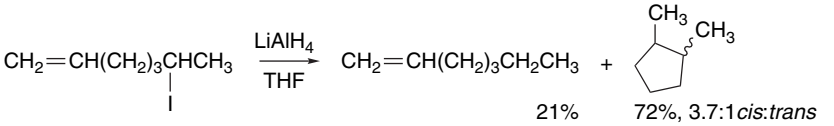
$$R{-}X^{\cdot-} \longrightarrow R\cdot + X^-$$

$$R\cdot + H^- \longrightarrow R{-}H + e^-$$

One experimental test for the involvement of radical intermediates is to study 5-hexenyl systems and look for the characteristic cyclization to cyclopentane derivatives (see Part A, Section 11.2.3). When 5-hexenyl bromide or iodide reacts with $LiAlH_4$, no cyclization products are observed. However, the more hindered 2,2-dimethyl-5-hexenyl iodide gives mainly cyclic product.[164]



Some cyclization also occurs with the bromide, but not with the chloride or the tosylate. The secondary iodide, 6-iodo-1-heptene, gives a mixture of cyclic and acyclic product in THF.[165]

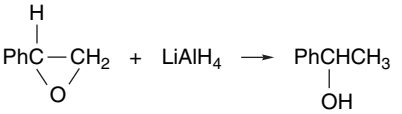


164. E. C. Ashby, R. N. DePriest, A. B. Goel, B. Wenderoth, and T. N. Pham, *J. Org. Chem.*, **49**, 3545 (1984).
165. E. C. Ashby, T. N. Pham, and A. Amrollah-Madjadabadi, *J. Org. Chem.*, **56**, 1596 (1991).

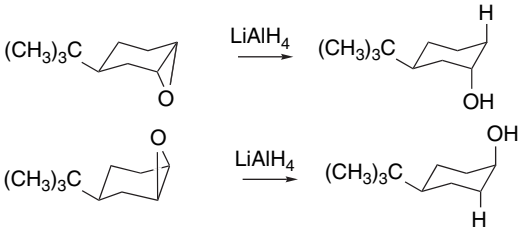
The occurrence of a radical intermediate is also indicated in the reduction of 2-octyl iodide by $LiAlD_4$ since, in contrast to the chloride or bromide, extensive racemization accompanies reduction.

The presence of transition metal ions has a catalytic effect on reduction of halides and tosylates by $LiAlH_4$.[166] Various "copper hydride" reducing agents are effective for removal of halide and tosylate groups.[167] The primary synthetic value of these reductions is for the removal of a hydroxy function after conversion to a halide or tosylate.

Epoxides are converted to alcohols by $LiAlH_4$ in a reaction that occurs by nucleophilic attack, and hydride addition at the less hindered carbon of the epoxide is usually observed.



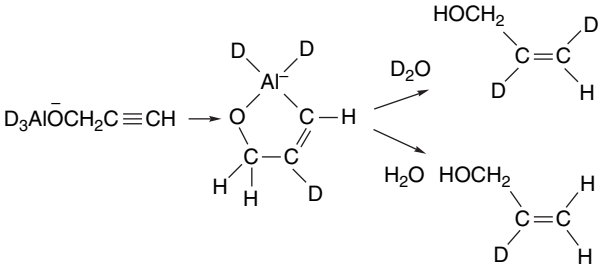
Cyclohexene epoxides are preferentially reduced by an axial approach by the nucleophile.[168]



Lithium triethylborohydride is a superior reagent for the reduction of epoxides that are relatively unreactive or prone to rearrangement.[169]

Alkynes are reduced to *E*-alkenes by $LiAlH_4$.[170] This stereochemistry is complementary to that of partial hydrogenation, which gives *Z*-isomers. Alkyne reduction by $LiAlH_4$ is greatly accelerated by a nearby hydroxy group. Typically, propargylic alcohols react in ether or tetrahydrofuran over a period of several hours,[171] whereas forcing conditions are required for isolated triple bonds.[172] This is presumably the result of coordination of the hydroxy group at aluminum and formation of a cyclic intermediate. The involvement of intramolecular Al–H addition has been demonstrated by use of $LiAlD_4$ as the reductant. When reduction by $LiAlD_4$ is followed by quenching with normal water, propargylic alcohol gives *Z*-3-^{2}H-prop-2-enol. Quenching with D_2O gives 2-^{2}H-3-^{2}H-prop-2-enol.[173]

166. E. C. Ashby and J. J. Lin, *J. Org. Chem.*, **43**, 1263 (1978).
167. 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).
168. 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).
169. H. C. Brown, S. C. Kim, and S. Krishnamurthy, *J. Org. Chem.*, **45**, 1 (1980); H. C. Brown, S. Narasimhan, and V. Somayaji, *J. Org. Chem.*, **48**, 3091 (1983).
170. E. F. Magoon and L. H. Slaugh, *Tetrahedron*, **23**, 4509 (1967).
171. N. A. Porter, C. B. Ziegler, Jr., F. F. Khouri, and D. H. Roberts, *J. Org. Chem.*, **50**, 2252 (1985).
172. H. C. Huang, J. K. Rehmann, and G. R. Gray, *J. Org. Chem.*, **47**, 4018 (1982).
173. J. E. Baldwin and K. A. Black, *J. Org. Chem.*, **48**, 2778 (1983).



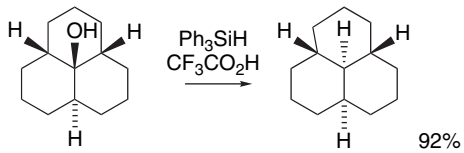
The efficiency and stereospecificity of reduction is improved by using a 1:2 mixture of $LiAlH_4$-$NaOCH_3$ as the reducing agent.[174] The mechanistic basis of this effect has not been explored in detail.

Scheme 5.7 illustrates these and other applications of the hydride donors. Entries 1 and 2 are examples of reduction of alkyl halides, whereas Entry 3 shows removal of an aromatic halogen. Entries 4 to 6 are sulfonate displacements, with the last example using a copper hydride reagent. Entry 7 is an epoxide ring opening. Entries 8 and 9 illustrate the difference in ease of reduction of alkynes with and without hydroxy participation.

5.4. Group IV Hydride Donors

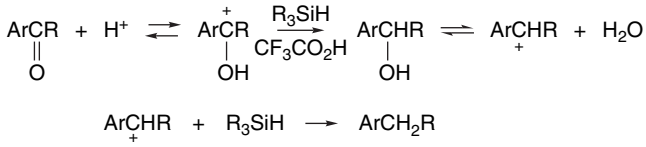
5.4.1. Reactions Involving Silicon Hydrides

Both Si−H and C−H compounds can function as hydride donors under certain circumstances. The silicon-hydrogen bond is capable of transferring a hydride to carbocations. Alcohols that can be ionized in trifluoroacetic acid are reduced to hydrocarbons in the presence of a silane.



Ref. 175

Aromatic aldehydes and ketones are reduced to alkylaromatics under similar conditions through reactions involving benzylic cations.[176]



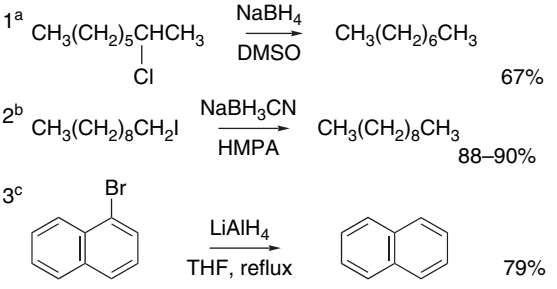
[174] E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 4245 (1967); B. B. Molloy and K. L. Hauser, *J. Chem. Soc., Chem. Commun.*, 1017 (1968).

[175] F. A. Carey and H. S. Tremper, *J. Org. Chem.*, **36**, 758 (1971).

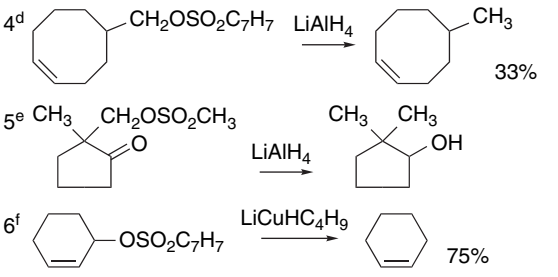
[176] C. T. West, S. J. Donnelly, D. A. Kooistra, and M. P. Doyle, *J. Org. Chem.*, **38**, 2675 (1973); M. P. Doyle, D. J. DeBruyn, and D. A. Kooistra, *J. Am. Chem. Soc.*, **94**, 3659 (1972); M. P. Doyle and C. T. West, *J. Org. Chem.*, **40**, 3821 (1975).

Scheme 5.7. Reduction of Other Functional Groups by Hydride Donors

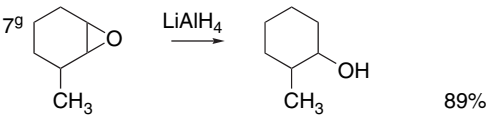
Halides



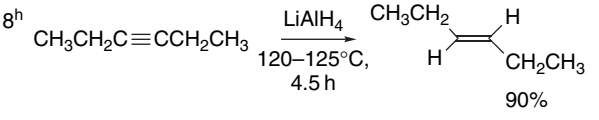
Sulfonates

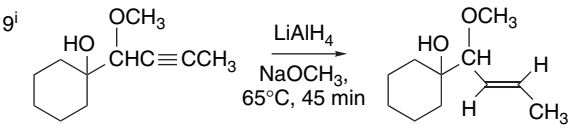


Epoxides



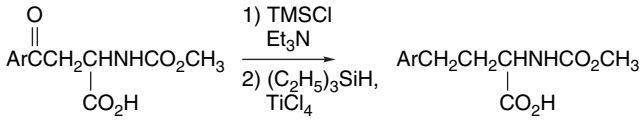
Acetylenes



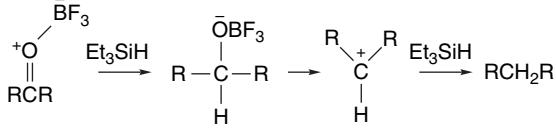


a. R. O. Hutchins, D. Hoke, J. Keogh, and D. Koharski, *Tetrahedron Lett.*, 3495 (1969); H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, **34**, 3923 (1969).
b. R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *Org. Synth.*, **53**, 107 (1973).
c. H. C. Brown and S. Krishnamurthy, *J. Org. Chem.*, **34**, 3918 (1969).
d. A. C. Cope and G. L. Woo, *J. Am. Chem. Soc.*, **85**, 3601 (1963).
e. A. Eshenmoser 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).
i. D. A. Evans and J. V. Nelson, *J. Am. Chem. Soc.*, **102**, 774 (1980).

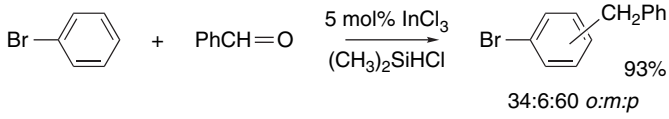
Aryl ketones are also reduced with triethylsilane and $TiCl_4$. This method can be used to prepare γ-arylaminoacids.[177]



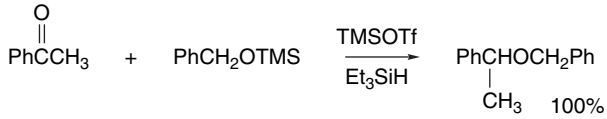
Aliphatic ketones can be reduced to hydrocarbons by triethylsilane and gaseous BF_3.[178] The BF_3 is a sufficiently strong Lewis acid to promote formation of a carbocation from the intermediate alcohol.



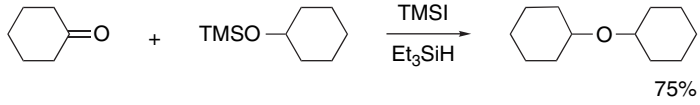
A combination of Friedel-Crafts alkylation and reduction can be achieved using $InCl_3$ and chlorodimethylsilane. The Lewis acid presumably promotes both the Friedel-Craft reaction and the subsequent reduction.[179]



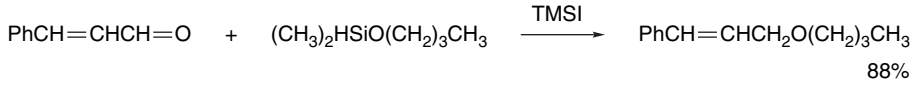
There are several procedures for reductive condensation of silyl ethers with carbonyl compounds to form ethers. One method uses TMSOTf as the catalyst.[180]



A number of related procedures have been developed. For example, TMSI can be used.[181]

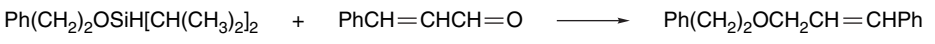


The trimethylsilyl group can be replaced by a dialkylsilyloxy group, in which case the silyl ether serves as the hydride donor.



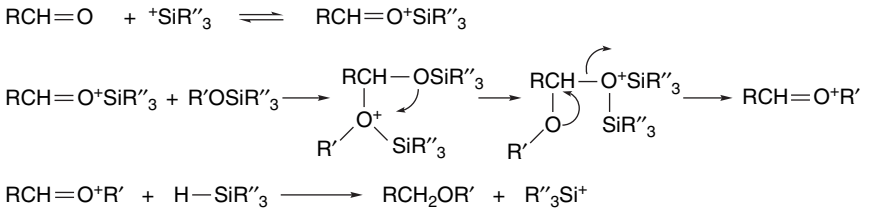
Ref. 182

177. M. Yato, K. Homma, and A. Ishida, *Heterocycles*, **49**, 233 (1998).
178. J. L. Frey, M. Orfanopoulos, M. G. Adlington, W. R. Dittman, Jr., and S. B. Silverman, *J. Org. Chem.*, **43**, 374 (1978).
179. T. Miyai, Y. Onishi, and A. Baba, *Tetrahedron Lett.*, **39**, 6291 (1998).
180. S. Hatakeyama, H. Mori, K. Kitano, H. Yamada, and M. Nishizawa, *Tetrahedron Lett.*, **35**, 4367 (1994).
181. M. B. Sassaman, K. D. Kotian, G. K. S. Prakash, and G. Olah, *J. Org. Chem.*, **52**, 4314 (1987).
182. K. Miura, K. Ootsuka, S. Suda, H. Nishikori, and A. Hosomi, *Synlett*, 313 (2002).

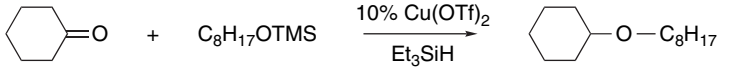


Ref. 183

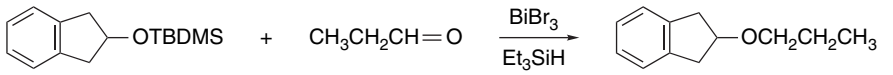
These reactions presumably proceed by catalytic cycles in which the carbonyl component is silylated. The silyl ether can then act as a nucleophile, and an oxonium ion is generated by elimination of a disilyl ether. The reduction of the oxonium ion regenerates the silyl cation, which can continue the catalytic cycle.



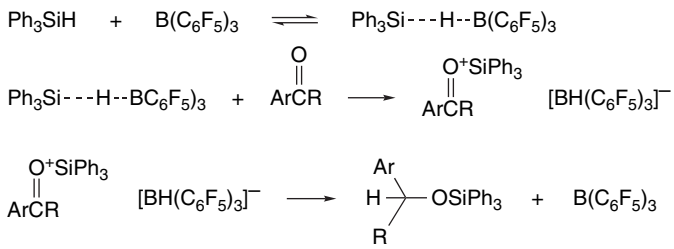
Various other kinds of Lewis acids can also promote the reaction. For example, $Cu(OTf)_2$ and Et_3SiH have been used to prepare a number of benzyl and alkyl ethers.[184]



The reductive condensation can also be carried out using $BiBr_3$ and Et_3SiH. The active catalyst under these conditions is Et_3SiBr, which is generated in situ.[185]

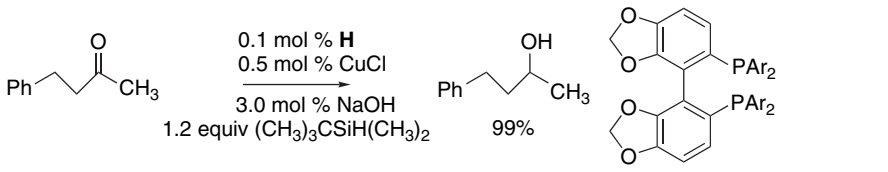


Reduction of ketones to triphenylsilyl ethers is effected by the unique Lewis acid perfluorotriphenylborane. Mechanistic and kinetic studies have provided considerable insight into the mechanism of this reaction.[186] The salient conclusion is that the hydride is delivered from a borohydride ion, not directly from the silane. Although the borane forms a Lewis acid-base complex with the ketone, its key function is in delivery of the hydride.



183. X. Jiang, J. S. Bajwa, J. Slade, K. Prasad, O. Repic, and T. J. Blacklock, *Tetrahedron Lett.*, **43**, 9225 (2002).
184. W.-C. Yang, X.-A. Lu, S. S. Kulkarni, and S.-C. Huang, *Tetrahedron Lett.*, **44**, 7837 (2003).
185. N. Komatsu, J. Ishida, and H. Suzuki, *Tetrahedron Lett.*, **38**, 7219 (1997).
186. D. J. Parks, J. M. Blackwell, and W. E. Piers, *J. Org. Chem.*, **65**, 3090 (2000).

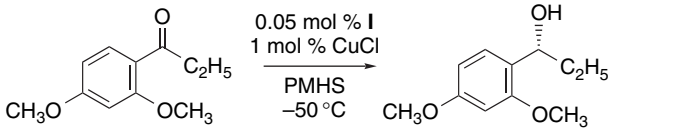
Copper-catalyzed systems have been developed that reduce ketones directly to silyl ethers. The reactions involve chiral biphenyl diphosphine type ligands and silane or siloxane hydride donors.[187]



H Ar = 3,5-dimethylphenyl

I Ar = 3,5-*bis*-(*t*-butyl)phenyl

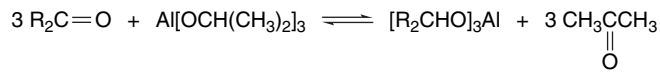
The reactions proceed with an e.e. of about 80% when the enantiopure ligand is used. Similar conditions using poly[oxy(methylsilylene)] (PMHS) as the hydride donor lead to reduction of aryl ketones with up to 98% e.e.[188]



98% yield
98% e.e.

5.4.2. Hydride Transfer from Carbon

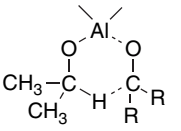
There are also reactions in which hydride is transferred from carbon. The carbon-hydrogen bond has little intrinsic tendency to act as a hydride donor, so especially favorable circumstances are required to promote this reactivity. Frequently these reactions proceed through a cyclic TS in which a new C−H bond is formed simultaneously with the C–H cleavage. Hydride transfer is facilitated by high electron density at the carbon atom. Aluminum alkoxides catalyze transfer of hydride from an alcohol to a ketone. This is generally an equilibrium process and the reaction can be driven to completion if the ketone is removed from the system, by, e.g., distillation, in a process known as the *Meerwein-Pondorff-Verley reduction*.[189] The reverse reaction in which the ketone is used in excess is called the *Oppenauer oxidation*.



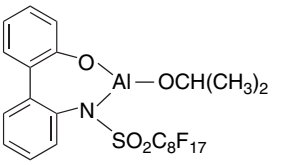
The reaction proceeds via a cyclic TS involving coordination of both the alcohol and ketone oxygens to the aluminum. Computational (DFT) and isotope effect studies are consistent with the cyclic mechanism.[190] Hydride donation usually takes place from

187. B. H. Lipshutz, C. C. Caires, P. Kuipers, and W. Chrisman, *Org. Lett.*, **5**, 3085 (2003).
188. B. H. Lipshutz, K. Noson, W. Chrisman, and A. Lower, *J. Am. Chem. Soc.*, **125**, 8779 (2003).
189. A. L. Wilds, *Org. React.*, **2**, 178 (1944); C. F. de Graauw, J. A. Peters, H. van Bekkum, and J. Huskens, *Synthesis*, 1007 (1994).
190. R. Cohen, C. R. Graves, S. T. Nguyen, J. M. L. Martin, and M. A. Ratner, *J. Am. Chem. Soc.*, **126**, 14796 (2004).

the less hindered face of the carbonyl group.[191] However, these conditions frequently promote equilibration of the alcohol stereoisomers.

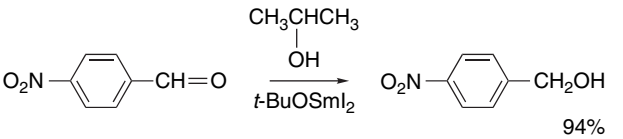


Recently, enantioselective procedures involving chiral catalysts have been developed. The combination of BINOL and $Al(CH_3)_3$ can achieve 80% e.e. in the reduction of acetophenone.[192] Compound **J** is also an effective catalyst.[193]



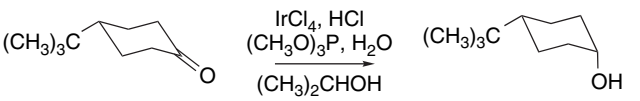
J

Certain lanthanide alkoxides, such as *t*-$BuOSmI_2$, have also been found to catalyze hydride exchange between alcohols and ketones.[194] Isopropanol can serve as the reducing agent for aldehydes and ketones that are thermodynamically better hydride acceptors than acetone.



Samarium metal in isopropanol also achieves reduction.[195] Like the Meerwein-Pondorff-Verley procedure, these conditions are believed to be under thermodynamic control and the more stable stereoisomer is the main product.[196]

Another reduction process, catalyzed by iridium chloride, is characterized by very high axial:equatorial product ratios for cyclohexanones and apparently involves hydride transfer from isopropanol.[197]



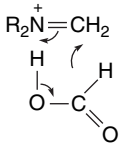
Formic acid can also act as a donor of hydrogen, and the driving force in this case is the formation of carbon dioxide. A useful application is the Clark-Eschweiler

191. F. Nerdel, D. Frank, and G. Barth, *Chem. Ber.*, **102**, 395 (1969).
192. E. J. Campbell, H. Zhou, and S. T. Nguyen, *Angew. Chem. Int. Ed. Engl.*, **41**, 1020 (2002).
193. T. Ooi, H. Ichikawa, and K. Maruoka, *Angew. Chem. Int. Ed. Engl.*, **40**, 3610 (2001).
194. J. L. Namy, J. Souppe, J. Collin, and H. B. Kagan, *J. Org. Chem.*, **49**, 2045 (1984).
195. S. Fukuzawa, N. Nakano, and T. Saitoh, *Eur. J. Org. Chem.*, 2863 (2004).
196. D.A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy, and T. J. Stout, *J. Am. Chem. Soc.*, **112**, 7001 (1990).
197. E. L. Eliel, T. W. Doyle, R. O. Hutchins, and E. C. Gilbert, *Org. Synth.*, **50**, 13 (1970).

reductive methylation of amines, in which heating a primary or secondary amine with formaldehyde and formic acid results in complete methylation to the tertiary amine.[198]

$$RNH_2 + CH_2{=}O + HCO_2H \longrightarrow RN(CH_3)_2 + CO_2$$

The hydride acceptor is the iminium ion that results from condensation of the amine with formaldehyde.



5.5. Reduction Reactions Involving Hydrogen Atom Donors

Reduction by hydrogen atom donors involves free radical intermediates and usually proceeds by chain mechanisms. Tri-*n*-butylstannane is the most prominent example of this type of reducing agent. Other synthetically useful hydrogen atom donors include hypophosphorous acid, dialkyl phosphites, and *tris*-(trimethylsilyl)silane. The processes that have found most synthetic application are reductive replacement of halogen and various types of thiono esters.

Tri-*n*-butylstannane is able to reductively replace halogen by hydrogen. Mechanistic studies indicate a free radical chain mechanism.[199] The order of reactivity for the halides is RI > RBr > RCl > RF, which reflects the relative ease of the halogen atom abstraction.[200]

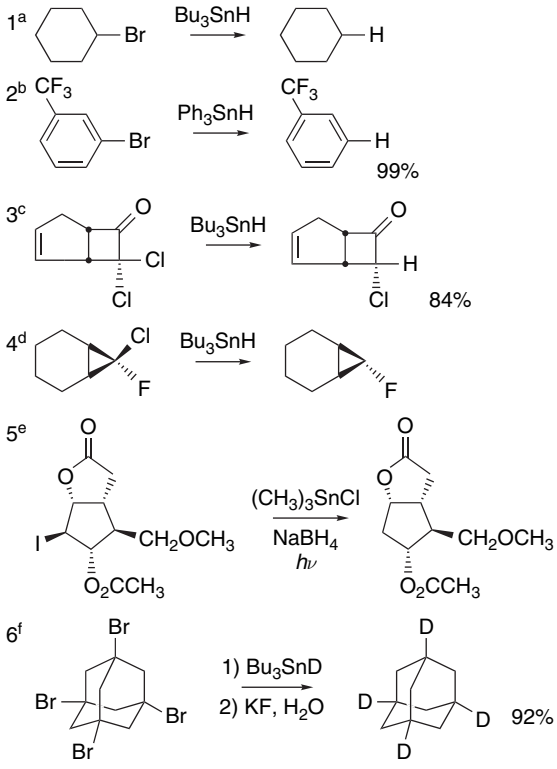
$$In\cdot + Bu_3SnH \longrightarrow In{-}H + Bu_3Sn\cdot \qquad (In\cdot = \text{initiator})$$
$$Bu_3Sn\cdot + R{-}X \longrightarrow R\cdot + Bu_3SnX$$
$$R\cdot + Bu_3SnH \longrightarrow RH + Bu_3Sn\cdot$$

Scheme 5.8 gives several examples of dehalogenation using tri-*n*-butylstannane. Entries 1 and 2 are examples from the early studies of this method. Entries 3 and 4 illustrate selective dehalogenation of polyhalogenated compounds. The stabilizing effect of the remaining halogen on the radical intermediate facilitates partial dehalogenation. These reactions also demonstrate stereoselectivity. In Entry 3, the stereochemical preference is for hydrogen abstraction from the more accessible face of the radical intermediate. Entry 4 shows retention of configuration at the fluorocyclopropyl carbon. (The stereoisomeric compound also reacts with retention of configuration.) This result indicates that hydrogen abstraction is faster than inversion for these cyclopropyl radicals (see Part A, Section 11.1.5).

A procedure that is catalytic in Bu_3SnH and uses $NaBH_4$ as the stoichiometric reagent has been developed.[201] This method has advantages in the isolation and purification of product. Entry 5 is an example of this procedure. The reaction was carried

198. M. L. Moore, *Org. React.*, **5**, 301 (1949); S. H. Pine and B. L. Sanchez, *J. Org. Chem.*, **36**, 829 (1971).
199. L. W. Menapace and H. G. Kuivila, *J. Am. Chem. Soc.*, **86**, 3047 (1964).
200. H. G. Kuivila and L. W. Menapace, *J. Org. Chem.*, **28**, 2165 (1963).
201. E. J. Corey and J. W. Suggs, *J. Org. Chem.*, **40**, 2554 (1975).

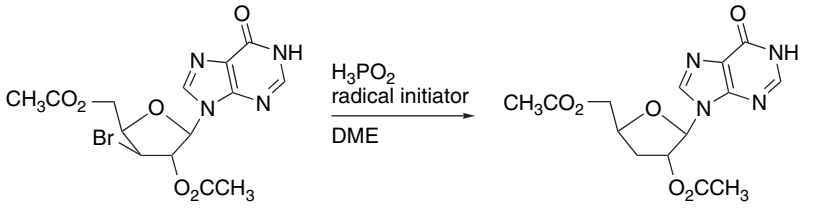
Scheme 5.8. Dehalogenation with Stannanes



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. J. 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. Jacobson, *J. Org. Chem.*, **44**, 449 (1979).

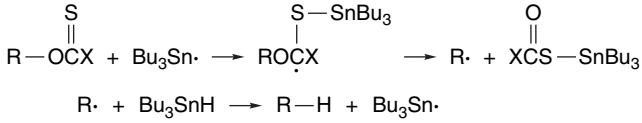
out under illumination to provide for chain initiation, and the reactant was prepared by an iodolactonization reaction. The sequence iodolactonization-dehalogenation is frequently used in the synthesis of five-membered lactones. Entry 6 illustrates the use of dehalogenation with deuterium incorporation. The addition of the fluoride salt facilitates workup by precipitation of tin by-products.

Hypophosphorous acid has been used as a hydrogen atom donor in the dehalogenation of nucleosides.[202]



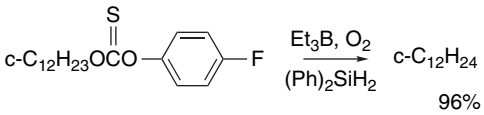
202. S. Takamatsu, S. Katayama, N. Hirose, M. Naito, and K. Izawa, *Tetrahedron Lett.*, **42**, 7605 (2001).

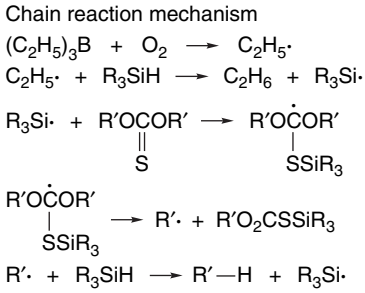
Tri-*n*-butyltin hydride also serves as a hydrogen atom donor in radical-mediated methods for reductive deoxygenation of alcohols via thiono esters.[203] The alcohol is converted to a thiocarbonyl derivative. These thiono esters undergo a radical reaction with tri-*n*-butyltin hydride. The resulting radicals fragment to give the alkyl radical, and the chain is propagated by hydrogen atom abstraction.



This procedure gives good yields from secondary alcohols and by appropriate adjustment of conditions can also be adapted to primary alcohols.[204]

Owing to the expense, toxicity, and purification problems associated with use of stoichiometric amounts of tin hydrides, there has been interest in finding other hydrogen atom donors.[205] The trialkylboron-oxygen system for radical generation (see Part A, Section 11.1.4) has been used with *tris*-(trimethylsilyl)silane or diphenylsilane as a hydrogen donor.[206]



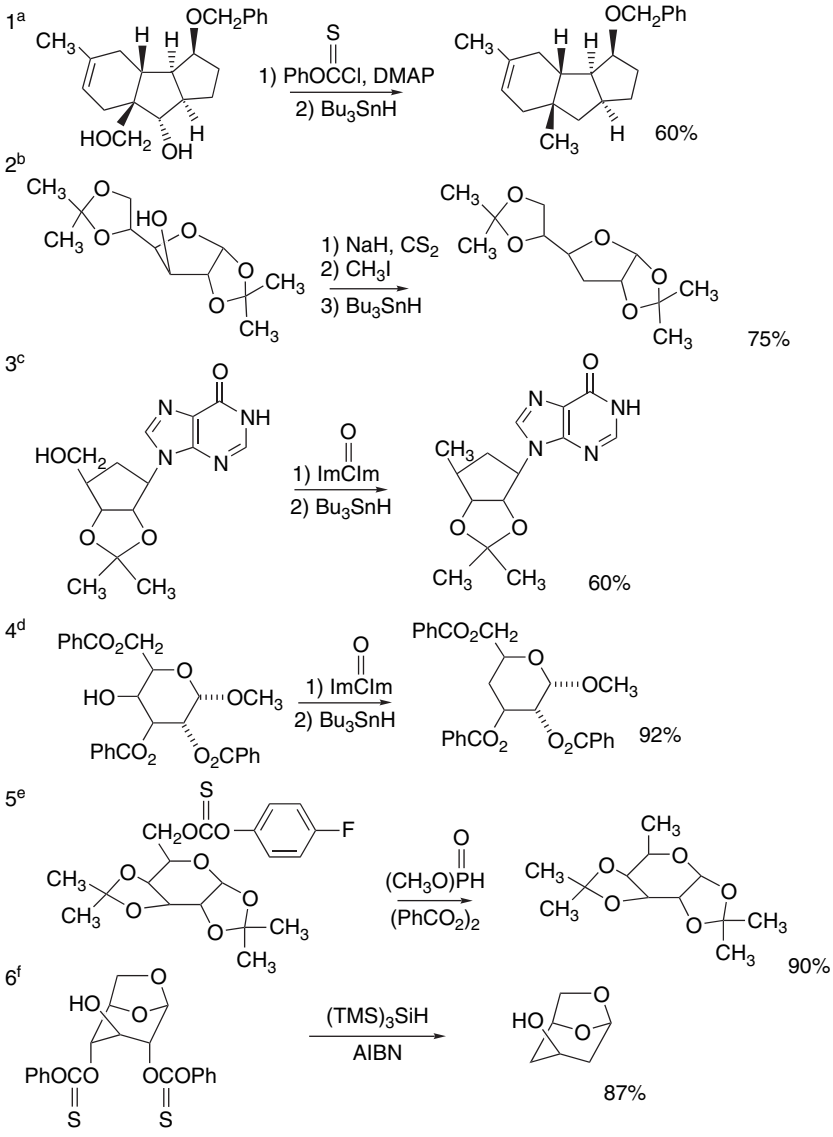


The alcohol derivatives that have been successfully deoxygenated include thionocarbonates and xanthates.[207] Peroxides can be used as initiators.[208]

Scheme 5.9 illustrates some of the conditions that have been developed for the reductive deoxygenation of alcohols. Entries 1 to 4 illustrate the most commonly used methods for generation of thiono esters and their reduction by tri-*n*-butylstannane. These include formation of thiono carbonates (Entry 1), xanthates (Entry 2), and thiono imidazolides (Entries 3 and 4). Entry 5 is an example of use of dimethyl phosphite as the hydrogen donor. Entry 6 uses *tris*-(trimethylsilyl)silane as the hydrogen atom donor.

[203] D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1574 (1975).For reviews of this method, see W. Hartwig, *Tetrahedron*, **39**, 2609 (1983); D. Crich and L. Quintero, *Chem. Rev.*, **89**, 1413 (1989).
[204] D. H. R. Barton, W. B. Motherwell, and A. Stange, *Synthesis*, 743 (1981).
[205] A. Studer and S. Amrein, *Synthesis*, 835 (2002).
[206] D. H. R. Barton, D. O. Jang, and J. C. Jaszberenyi, *Tetrahedron Lett.*, **31**, 4681 (1990).
[207] J. N. Kirwan, B. P. Roberts, and C. R. Willis, *Tetrahedron Lett.*, **31**, 5093 (1990).
[208] D. H. Barton, D. O. Jang, and J. C. Jaszberenyi, *Tetrahedron Lett.*, **33**, 7187 (1991).

Scheme 5.9. Deoxygenation of Alcohols via Thiono Esters and Related Derivatives



a. H. J. Liu and M. G. Kulkarni, *Tetrahedron Lett.*, **26**, 4847 (1985).
b. S. Iacono and J. R. Rasmussen, *Org. Synth.*, **64**, 57 (1985).
c. O. Miyashita, F. Kasahara, T. Kusaka, and R. Marumoto, *J. Antibiot.*, **38**, 98 (1985).
d. J. R. Rasmussen, C. J. Slinger, R. J. Kordish, and D. D. Newman-Evans, *J. Org. Chem.*, **46**, 4843 (1981).
e. D. H. R. Barton, D. O. Jang, and J. C. Jaszberenyi, *Tetrahedron Lett.*, **33**, 2311 (1992).
f. D. H. R. Barton, D. O. Jang, and J. C. Jaszberenyi, *Tetrahedron Lett.*, **33**, 6629 (1992).

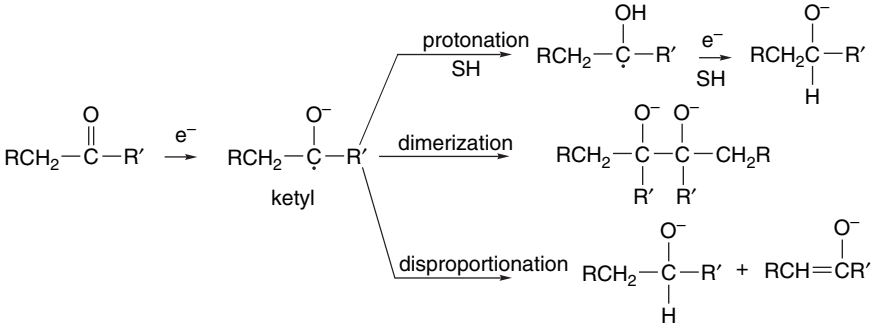
5.6. Dissolving-Metal Reductions

Another group of synthetically useful reductions employs a metal as the reducing agent. The organic reactant under these conditions accepts one or more electrons from the metal. The subsequent course of the reaction depends on the structure of the

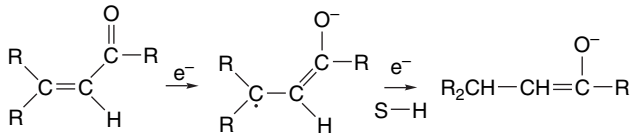
reactant and reaction conditions. Three broad types of reactions can be recognized and these are discussed separately. They include reactions in which the overall change involves: (a) net addition of hydrogen, (b) reductive removal of a functional group, and (c) formation of carbon-carbon bonds.

5.6.1. Addition of Hydrogen

5.6.1.1. Reduction of Ketones and Enones. Although the method has been supplanted for synthetic purposes by hydride donors, the reduction of ketones to alcohols in ammonia or alcohols provides mechanistic insight into dissolving-metal reductions. The outcome of the reaction of ketones with metal reductants is determined by the fate of the initial ketyl radical formed by a single-electron transfer. The radical intermediate, depending on its structure and the reaction medium, may be protonated, disproportionate, or dimerize.[209] In hydroxylic solvents such as liquid ammonia or in the presence of an alcohol, the protonation process dominates over dimerization. Net reduction can also occur by a disproportionation process. As is discussed in Section 5.6.3, dimerization can become the dominant process under conditions in which protonation does not occur rapidly.



α,β-Unsaturated carbonyl compounds are cleanly reduced to the enolate of the corresponding saturated ketone on reduction with lithium in ammonia.[210] Usually an alcohol is added to the reduction solution to serve as the proton source.

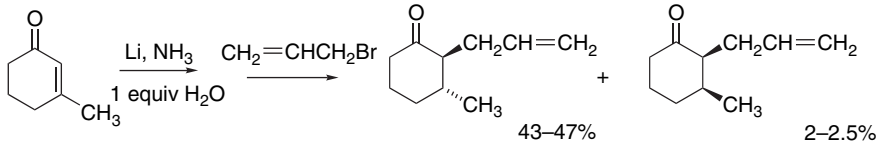


As noted in Chapter 1, this is one of the best methods for generating a specific enolate of a ketone. The enolate generated by conjugate reduction can undergo the characteristic alkylation and addition reactions that are discussed in Chapters 1 and 2. When this is the objective of the reduction, it is important to use only one equivalent of the proton donor. Ammonia, being a weaker acid than an aliphatic ketone, does

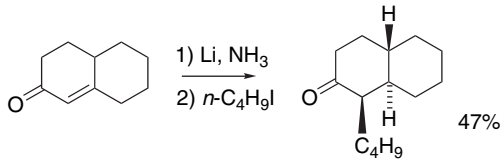
209. V. Rautenstrauch and M. Geoffroy, *J. Am. Chem. Soc.*, **99**, 6280 (1977); J. W. Huffman and W. W. McWhorter, *J. Org. Chem.*, **44**, 594 (1979); J. W. Huffman, P. C. Desai, and J. E. LaPrade, *J. Org. Chem.*, **48**, 1474 (1983).

210. D. Caine, *Org. React.*, **23**, 1 (1976).

not act as a proton donor toward an enolate, and the enolate remains available for subsequent reaction, as in the tandem alkylations shown below. 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.

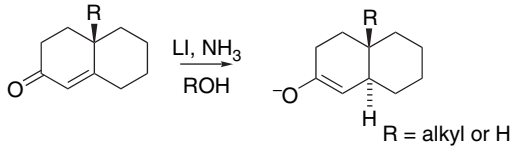


Ref. 211



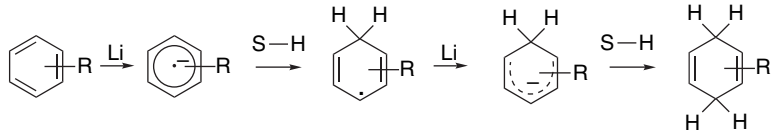
Ref. 212

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*.[213]



The stereochemistry is controlled by a stereoelectronic preference for protonation perpendicular to the enolate system and, given that this requirement is met, the stereochemistry normally corresponds to protonation of the most stable conformation of the dianion intermediate from its least hindered side.

5.6.1.2. Dissolving-Metal Reduction of Aromatic Compounds and Alkynes. Dissolving-metal systems constitute the most general method for partial reduction of aromatic rings. The reaction is called the *Birch reduction*,[214] and the usual reducing medium is lithium or sodium in liquid ammonia. An alcohol is usually added to serve as a proton source. The reaction occurs by two successive electron transfer/protonation steps.



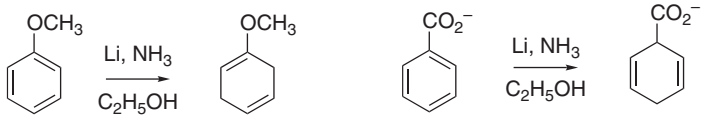
211. D. Caine, S. T. Chao, and H. A. Smith, *Org. Synth.*, **56**, 52 (1977).

212. G. Stork, P. Rosen, and N. L. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961).

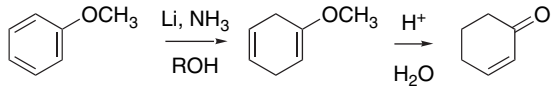
213. G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965); M. J. T. Robinson, *Tetrahedron*, **21**, 2475 (1965).

214. A. J. Birch and G. Subba Rao, *Adv. Org. Chem.*, **8**, 1 (1972); R. G. Harvey, *Synthesis*, 161 (1980); J. M. Hook and L. N. Mander, *Nat. Prod. Rep.*, **3**, 35 (1986); P. W. Rabideau, *Tetrahedron*, **45**, 1599 (1989); A. J. Birch, *Pure Appl. Chem.*, **68**, 553 (1996).

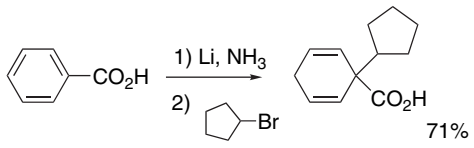
The isolated double bonds in the dihydro product are much less easily reduced than the conjugated ring, so the reduction stops at the dihydro stage. Alkyl and alkoxy aromatics, phenols, and benzoate anions are the most useful reactants for Birch reduction. In aromatic ketones and nitro compounds, the substituents are reduced in preference to the aromatic ring. Substituents also govern the position of protonation. Alkyl and alkoxy aromatics normally give the 2,5-dihydro derivative. Benzoate anions give 1,4-dihydro derivatives.



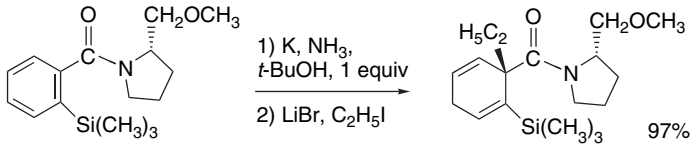
The structure of the products is determined by the site of protonation of the radical anion intermediate formed after the first electron transfer step. In general, ERG substituents favor protonation at the *ortho* position, whereas EWGs favor protonation at the *para* position.[215] Addition of a second electron gives a pentadienyl anion, which is protonated at the center carbon. As a result, 2,5-dihydro products are formed with alkyl or alkoxy substituents and 1,4-products are formed from EWG substituents. The preference for protonation of the central carbon of the pentadienyl anion is believed to be the result of the greater 1,2 and 4,5 bond order and a higher concentration of negative charge at C(3).[216] The reduction of methoxybenzenes is of importance in the synthesis of cyclohexenones via hydrolysis of the intermediate enol ethers.



The anionic intermediates formed in Birch reductions can be used in tandem alkylation reactions.



Ref. 217



Ref. 218

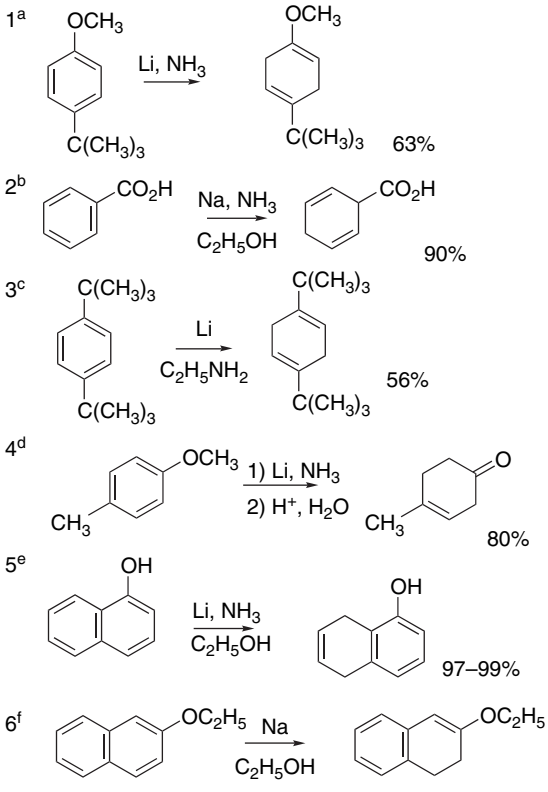
[215] A. J. Birch, A. L. Hinde, and L. Radom, *J. Am. Chem. Soc.*, **102**, 2370 (1980); H. E. Zimmerman and P. A. Wang, *J. Am. Chem. Soc.*, **112**, 1280 (1990).

[216] P. W. Rabideau and D. L. Huser, *J. Org. Chem.*, **48**, 4266 (1983); H. E. Zimmerman and P. A. Wang, *J. Am. Chem. Soc.*, **115**, 2205 (1993).

[217] P. A. Baguley and J. C. Walton, *J. Chem. Soc., Perkin Trans. 1*, 2073 (1998).

[218] A. G. Schultz and L. Pettus, *J. Org. Chem.*, **62**, 6855 (1997).

Scheme 5.10. Birch Reduction of Aromatic Rings

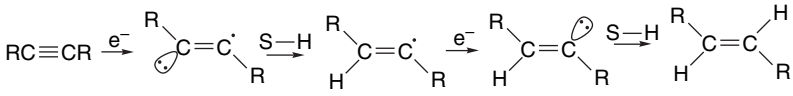


a. D. A. Bolon, *J. Org. Chem.* **35**, 715 (1970).
b. M. E. Kuehne and B. F. Lambert, *Org. Synth.*, **V**, 400 (1973).
c. H. Kwart and R. A. Conley, *J. Org. Chem.*, **38**, 2011 (1973).
d. E. A. Braude, A. A. Webb, and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3328 (1958); W. C. Agosta and W. L. Schreiber, *J. Am. Chem. Soc.*, **93**, 3947 (1971).
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 5.10 lists some examples of the use of the Birch reduction. Entries 1 and 2 illustrate the usual regioselectivity for alkoxy aromatics and for benzoic acid. Entry 3 uses an alkylamine as the solvent. In the case cited, the yield was much better than that obtained using ammonia. Entry 4 illustrates the preparation of a cyclohex-3-enone via the Birch reduction route. Entries 5 and 6 show an interesting contrast in the regioselectivity of naphthalene derivatives. The selective reduction of the unsubstituted ring may reflect the more difficult reduction of the ring having a deprotonated oxy substituent. On the other hand, empirical evidence indicates that ERG substituents in the 2-position direct reduction to the substituted ring.[219] The basis of this directive effect does not seem to have been developed in modern electronic terms.

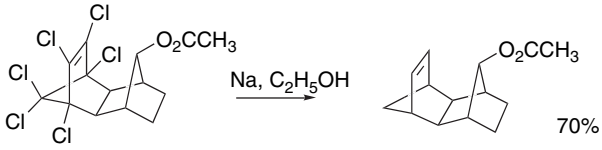
219. M. D. Soffer, R. A. Stewart, J. C. Cavagnol, H. E. Gellerson, and E. A. Bowler, *J. Am. Chem. Soc.*, **72**, 3704 (1950).

Reduction of acetylenes can be done with sodium in ammonia,[220] lithium in low molecular weight amines,[221] or sodium in HMPA containing *t*-butanol as a proton source,[222] all of which lead to the *E*-alkene. The reaction is assumed to involve successive electron transfer and protonation steps.



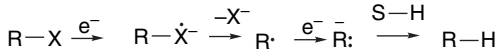
5.6.2. Reductive Removal of Functional Groups

The reductive removal of halogen can be accomplished with lithium or sodium. Tetrahydrofuran containing *t*-butanol is a useful reaction medium. Good results have also been achieved with polyhalogenated compounds by using sodium in ethanol.

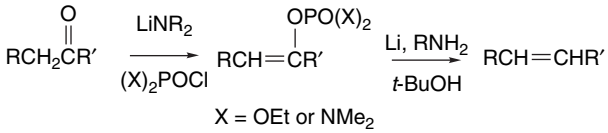


Ref. 223

An important synthetic application of this reaction is in dehalogenation of dichloro- and dibromocyclopropanes. The dihalocyclopropanes are accessible via carbene addition reactions (see Section 10.2.3). Reductive dehalogenation can also be used to introduce deuterium at a specific site. The mechanism of the reaction involves electron transfer to form a radical anion, which then fragments with loss of a halide ion. The resulting radical is reduced to a carbanion by a second electron transfer and subsequently protonated.

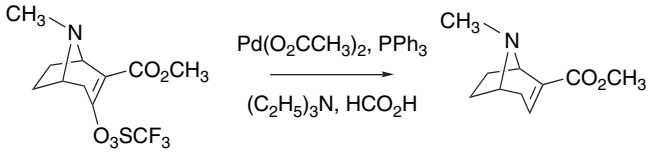


Phosphate groups can also be removed by dissolving-metal reduction. Reductive removal of vinyl phosphate groups is one method for conversion of a carbonyl compound to an alkene.[224] (See Section 5.7.2 for other methods.) The required vinyl phosphate esters are obtained by phosphorylation of the enolate with diethyl phosphorochloridate or *N*,*N*,*N*′,*N*′-tetramethyldiamidophosphorochloridate.[225]



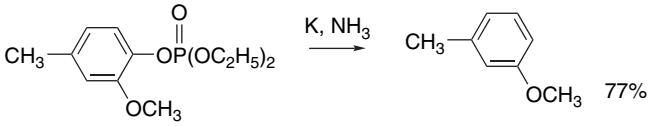
[220.] K. N. Campbell and T. L. Eby, *J. Am. Chem. Soc.*, **63**, 216, 2683 (1941); A. L. Henne and K. W. Greenlee, *J. Am. Chem. Soc.*, **65**, 2020 (1943).
[221.] R. A. Benkeser, G. Schroll, and D. M. Sauve, *J. Am. Chem. Soc.*, **77**, 3378 (1955).
[222.] H. O. House and E. F. Kinloch, *J. Org. Chem.*, **39**, 747 (1974).
[223.] B. V. Lap and M. N. Paddon-Row, *J. Org. Chem.*, **44**, 4979 (1979).
[224.] R. E. Ireland and G. Pfister, *Tetrahedron Lett.*, 2145 (1969).
[225.] R. E. Ireland, D. C. Muchmore, and U. Hengartner, *J. Am. Chem. Soc.*, **94**, 5098 (1972).

Ketones can also be reduced to alkenes via enol triflates. The use of $Pd(OAc)_2$ and triphenylphosphine as the catalyst and tertiary amines as the hydrogen donors is effective.[226]



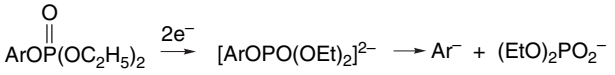
Ref. 227

Reductive removal of oxygen from aromatic rings can also be achieved by reductive cleavage of aryl diethyl phosphate esters.



Ref. 228

There are also examples in which phosphate esters of saturated alcohols are reductively deoxygenated.[229] Mechanistic studies of the cleavage of aryl dialkyl phosphates have indicated that the crucial C−O bond cleavage occurs after transfer of two electrons.[230]



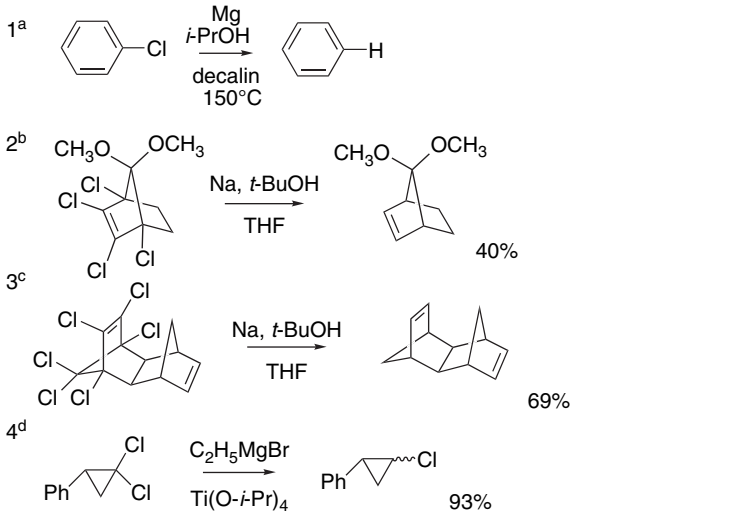
For preparative purposes, titanium metal can be used in place of sodium or lithium in liquid ammonia for both the vinyl phosphate[231] and aryl phosphate[232] cleavages. The titanium metal is generated in situ from $TiCl_3$ by reduction with potassium metal in tetrahydrofuran.

Scheme 5.11 shows some examples of these reductive reactions. Entry 1 is an example of conditions that have been applied to both alkyl and aryl halides. The reaction presumably proceeds through formation of a Grignard reagent, which then undergoes protonolysis. Entries 2 and 3 are cases of the dehalogenation of polyhalogenated compounds by sodium in *t*-butanol. Entry 4 illustrates conditions that were found useful for monodehalogenation of dibromo- and dichlorocyclopropanes. This method is not very stereoselective. In the example given, the ratio of *cis*:*trans* product was 1.2:1. Entries 5 to 7 are cases of dissolving-metal reduction of vinyl and aryl phosphates.

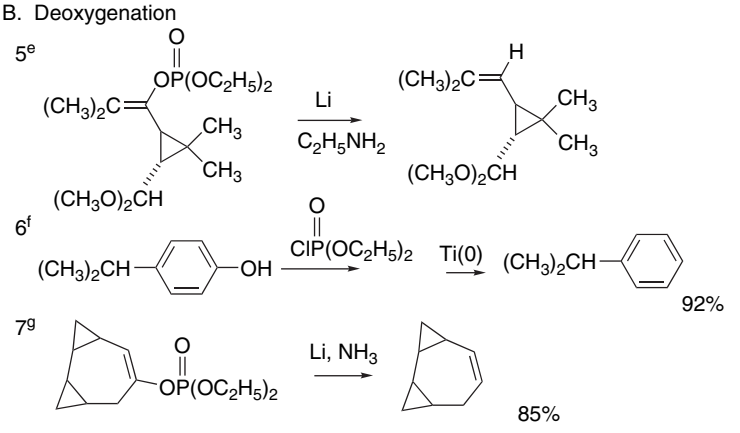
226. W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, **108**, 3033 (1986); L. A. Paquette, P. G. Meister, D. Friedrich, and D. R. Sauer, *J. Am. Chem. Soc.*, **115**, 49 (1993).
227. K. I. Keverline, P. Abraham, A. H. Lewin, and F. I. Carroll, *Tetrahedron Lett.* **36**, 3099 (1995).
228. R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 2314 (1973).
229. R. R. Muccino and C. Djerassi, *J. Am. Chem. Soc.*, **96**, 556 (1974).
230. S. J. Shafer, W. D. Closson, J. M. F. van Dijk, O. Piepers, and H. M. Buck, *J. Am. Chem. Soc.*, **99**, 5118 (1977).
231. S. C. Welch and M. E. Walters, *J. Org. Chem.*, **43**, 2715 (1978).
232. S. C. Welch and M. E. Walters, *J. Org. Chem.*, **43**, 4797 (1978).

Scheme 5.11. Reductive Dehalogenation and Deoxygenation by Dissolving Metals

A. Dehalogenation

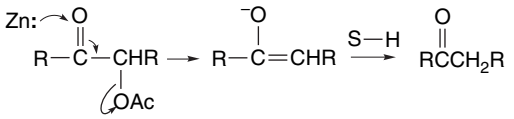


B. Deoxygenation

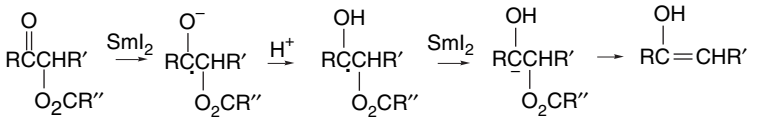


a. D. Bryce-Smith and B. J. Wakefield, *Org. Synth.*, **47**, 103 (1967).
b. P. G. Gassman and J. L. Marshall, *Org. Synth.*, **48**, 68 (1968).
c. B. V. Lap and M. N. Paddon-Row, *J. Org. Chem.*, **44**, 4979 (1979).
d. J. R. Al Duyayymi, M. S. Baird, I. G. Bolesov, V. Tversovsky, and M. Rubin, *Tetrahedron Lett.*, **37**, 8933 (1996).
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, **99**, 821 (1977).

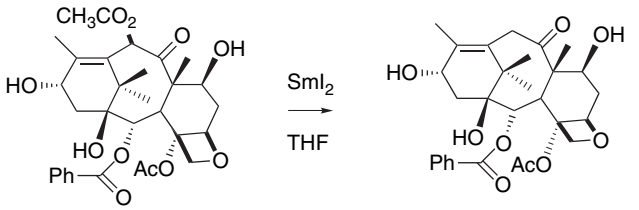
Both metallic zinc and aluminum amalgam are milder reducing agents than the alkali metals. These reductants selectively remove oxygen and sulfur functional groups α to carbonyl groups. The mechanistic picture that seems most generally applicable is a net two-electron reduction with expulsion of the oxygen or sulfur substituent as an anion. The reaction must be a concerted process, because the isolated functional groups are not reduced under these conditions.



Another useful reagent for reduction of α-acetoxyketones and similar compounds is samarium diiodide.[233] SmI_2 is a strong one-electron reducing agent, and it is believed that the reductive elimination occurs after a net two-electron reduction of the carbonyl group.



These conditions were used, for example, in the preparation of the anticancer compound 10-deacetoxytaxol.

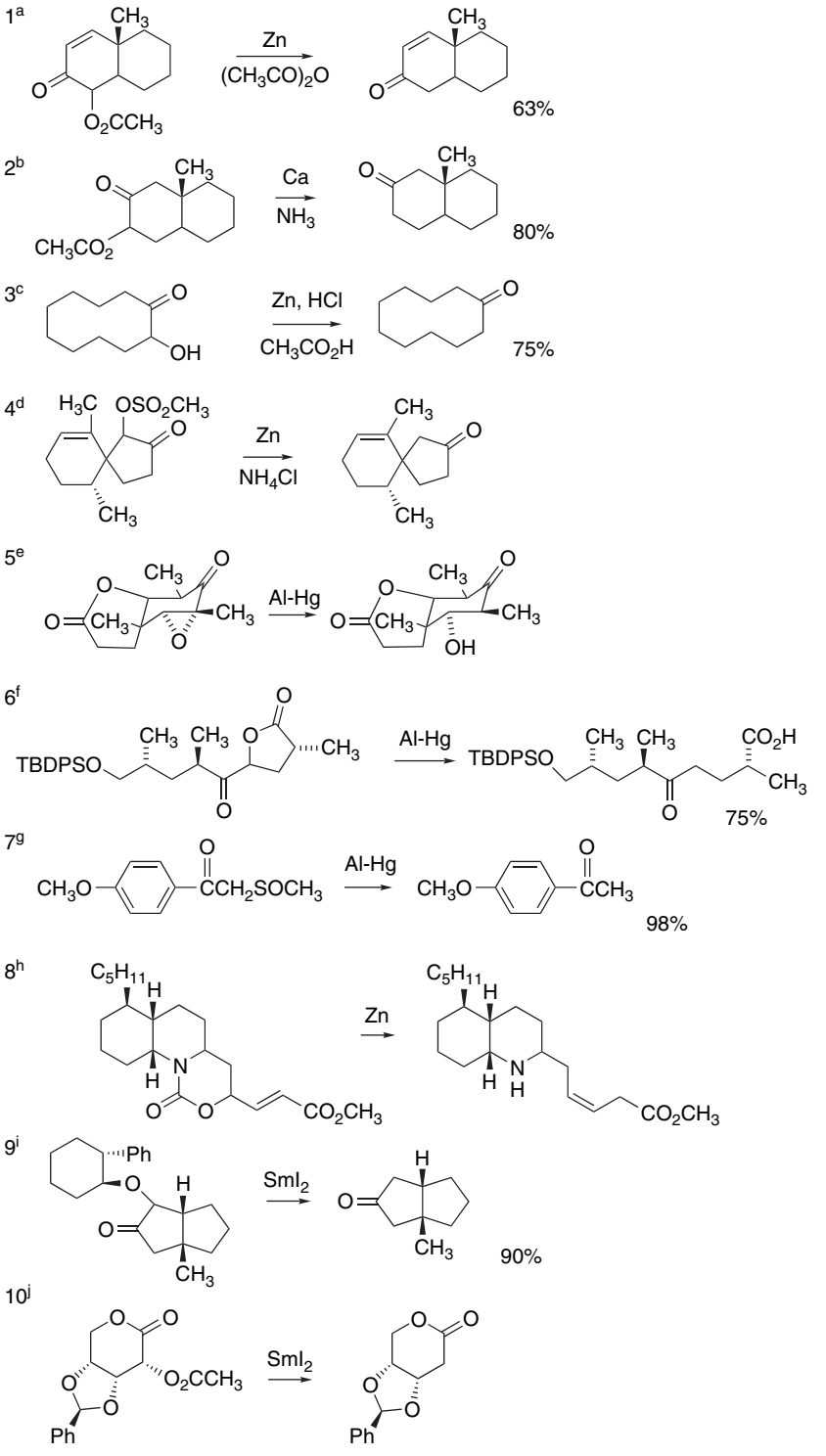


Ref. 234

Scheme 5.12 gives some examples of the reductive removal of functional groups adjacent to carbonyl groups. Entry 1 is an application of this reaction as it was used in an early steroid synthesis. The reaction in Entry 2 utilizes calcium in ammonia for the reduction. The reaction in Entry 3 converts the acyloin derived from dimethyl decanedicarboxylate into cyclodecanone. In the reaction in Entry 4, a sulfonate group is removed. In Entry 5 an epoxide is opened using aluminum amalgam, and in Entry 6 a lactone ring is opened. The latter reaction was part of a synthetic sequence in which the lactone intermediate was used to establish the stereochemistry of the acyclic product. The reaction in Entry 7 removes a sulfinyl group. Keto sulfoxides can be obtained by acylation of the anion of dimethylsulfoxide, so this reaction constitutes a general route to ketones (see Section 2.3.2). The reaction in Entry 8 is a *vinylogous* version of the reduction. The reductant in Entries 9 and 10 is SmI_2. In Entry 9, the 2-phenylcyclohexyloxy group that is removed was used earlier in the synthesis as a chiral auxiliary. Samarium diiodide is useful for deacetoxylation or dehydroxylation of α-oxygenated lactones derived from carbohydrates (Entry 10).[235] The reaction is also applicable to protected hydroxy groups, such as in acetonides. The reactions in Scheme 5.12 include quite a broad range of reductable groups, including some (e.g., ether) that are modest leaving groups.

233. G. A. Molander and G. Hahn, *J. Org. Chem.*, **51**, 1135 (1986).
234. R. A. Holton, C. Somoza, and K.-B. Chai, *Tetrahedron Lett.*, **35**, 1665 (1994).
235. S. Hanessian, C. Girard, and J. L. Chiara, *Tetrahedron Lett.*, **33**, 573 (1992).

Scheme 5.12. Reductive Removal of Functional Groups from α-Substituted Carbonyl Compounds



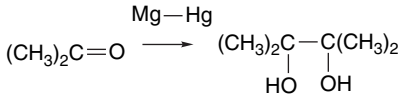
(*Continued*)

Scheme 5.12. (*Continued*)

a. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and M. W. 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.*, **1V**, 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).
i. J. Castro, H. Sorensen, A. Riera, C. Morin, A. Moyano, M. A. Pericas, and A. E. Greene, *J. Am. Chem. Soc.*, **112**, 9388 (1990).
j. S. Hanessian, C. Girard, and J. L. Chiara, *Tetrahedron Lett.*, **33**, 573 (1992).

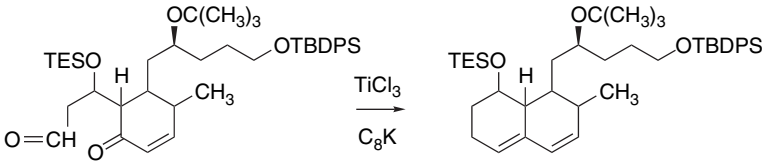
5.6.3. Reductive Coupling of Carbonyl Compounds

As reductions by metals often occur by one-electron transfers, radicals are involved as intermediates. When the reaction conditions are adjusted so that coupling competes favorably with other processes, the formation of a carbon-carbon bond can occur. The reductive coupling of acetone to 2,3-dimethylbutane-2,3-diol (pinacol) is an example of such a reaction.



Ref. 236

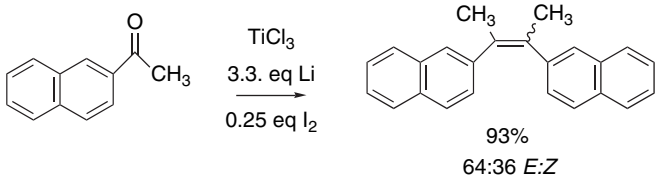
Reduced forms of titanium are currently the most versatile and dependable reagents for reductive coupling of carbonyl compounds. These reagents are collectively referred to as *low-valent titanium*. Either diols or alkenes can be formed, depending on the conditions.[237] Several different procedures have evolved for titanium-mediated coupling. One procedure involves prereduction of $TiCl_3$ with strong reducing agents such as $LiAlH_4$,[238] potassium on graphite (C_8K),[239] or Na-naphthalenide.[240b] The reductant prepared in this way is quite effective at coupling reactants with several oxygen substituents.



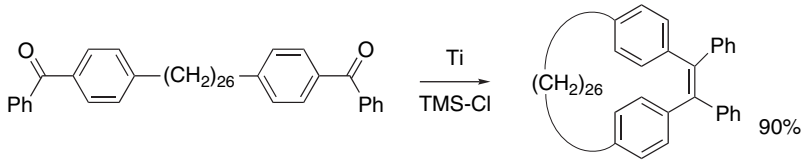
Ref. 240

236. R. Adams and E. W. Adams, *Org. Synth.*, **I**, 448 (1932).
237. J. E. McMurry, *Chem. Rev.*, **89**, 1513 (1989).
238. 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); J. E. McMurry, *Acc. Chem. Res.*, **16**, 405 (1983).
239. (a) A. Furstner and H. Weidmann, *Synthesis*, 1071 (1987); (b) D. L. J. Clive, C. Zhang, K. S. K. Murthy, W. D. Hayward, and S. Daigneault, *J. Org. Chem.*, **56**, 6447 (1991).
240. D. L. J. Clive, K. S. K. Murthy, A. G. H. Wee, J. S. Prasad, G. V. J. Da Silva, M. Majewski, P. C. Anderson, C. F. Evans, R. D. Haugen, L. D. Heerze, and J. R. Barrie, *J. Am. Chem. Soc.*, **112**, 3018 (1990).

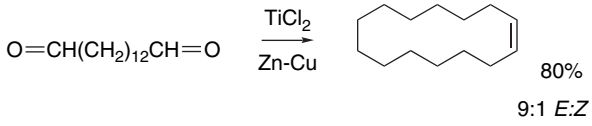
Another particularly reactive form of titanium is generated by including 0.25 equivalent of I_2. This reagent permits low-temperature reductive deoxygenation to alkenes.[241]



Titanium metal is also activated by TMS-Cl.[242] These conditions were used in a number of dimerizations and cyclizations, including the formation of a 36-membered ring.

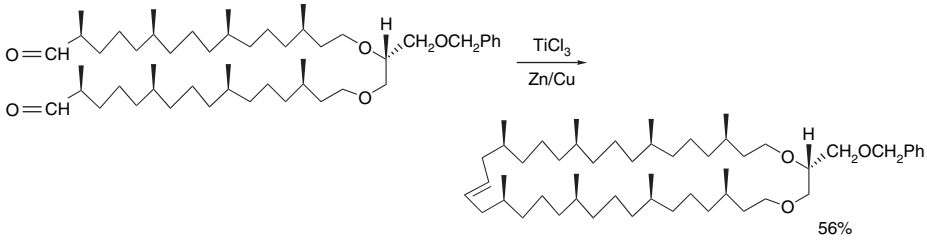


Another process that is widely used involves reduction by Zn-Cu couple. This reagent is especially reliable when prepared from $TiCl_3$ purified as a DME complex,[243] and is capable of forming normal, medium, and large rings with comparable efficiency.



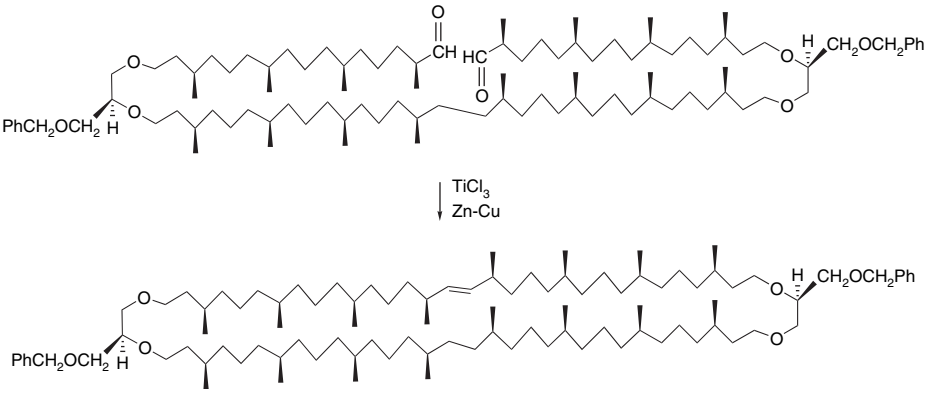
Ref. 244

The macrocyclization has proven useful in the formation of a number of natural products.[245] These conditions have been used to prepare 36- and 72-membered rings.



Ref. 246

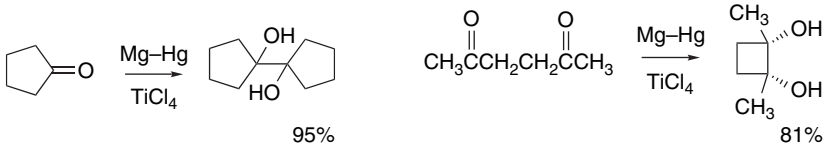
241. S. Talukadar, S. K. Nayak, and A. Banerji, *J. Org. Chem.*, **63**, 4925 (1998).
242. A. Furstner and A. Hupperts, *J. Am. Chem. Soc.*, **117**, 4468 (1995).
243. J. E. McMurry, T. Lectka, and J. G. Rico, *J. Org. Chem.*, **54**, 3748 (1989).
244. J. E. McMurry, J. R. Matz, K. L. Kees, and P. A. Bock, *Tetrahedron Lett.*, **23**, 1777 (1982).
245. J. E. McMurry, J. G. Rico, and Y. Shih, *Tetrahedron Lett.*, **30**, 1173 (1989); J. E. McMurry and R. G. Dushin, *J. Am. Chem. Soc.*, **112**, 6942 (1990).
246. T. Eguchi, K. Arakawa, T. Terachi, and K. Kakinuma, *J. Org. Chem.*, **62**, 1924 (1997).



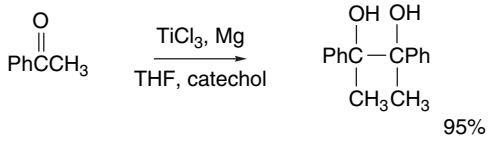
Ref. 247

The double bonds were reduced to the give the saturated compounds, so the double-bond configuration was not an immediate issue. It appears, however, that the *E*-double bonds are formed. The debenzylated derivatives of propan-1,2,3-triol occur as lipid components in various prokaryotes (archaebacteria) that grow under extreme thermal conditions.

Under other conditions, reduction leads to diols. Reductive coupling to diols can be done using magnesium amalgam[248] or zinc dust.[249]



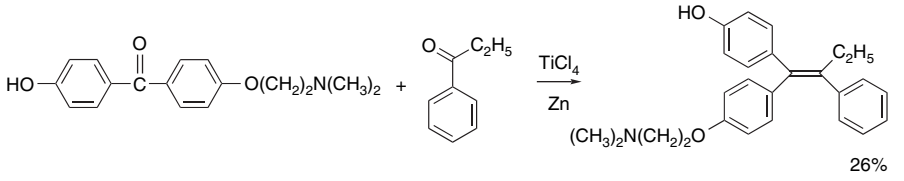
The most general procedures are based on low-valent titanium. Good yields of diols are obtained from aromatic aldehydes and ketones by adding catechol to the $TiCl_3$-Mg reagent prior to coupling.[250]



Both unsymmetrical alkenes and diols can be prepared by applying these methods to mixtures of two different carbonyl compounds. An excess of one component can be used to achieve a high conversion of the more valuable reactant. A mixed reductive

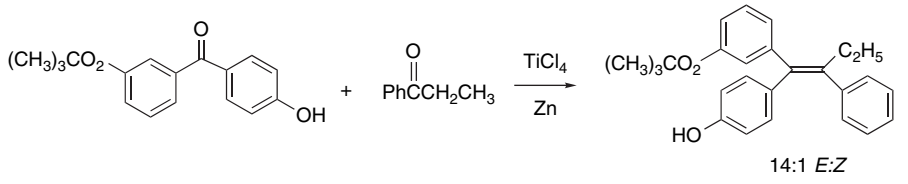
247. T. Eguchi, K. Ibaragi, and K. Kakinuma, *J. Org. Chem.*, **63**, 2689 (1998).
248. E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *J. Org. Chem.*, **41**, 260 (1976).
249. A. Furstner, A. Hupperts, A. Ptock, and E. Janssen, *J. Org. Chem.*, **59**, 5215 (1994).
250. N. Balu, S. K. Nayak, and A. Banerji, *J. Am. Chem. Soc.*, **118**, 5932 (1996).

deoxygenation with $TiCl_4$-Zn was used to prepare 4-hydroxytamoxifen, the active antiestrogenic metabolite of tamoxifen.



Ref. 251

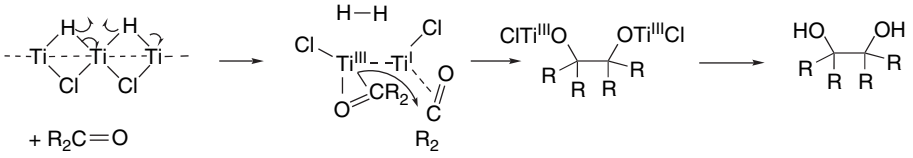
Stereoselectivity has been observed in some coupling reactions of this type. For example, coupling with 4-hydroxy-3′-pivaloyoxybenzophenone was stereoselective for the *E*-isomer.



Ref. 252

It is not clear at this time what factors determine stereoselectivity.

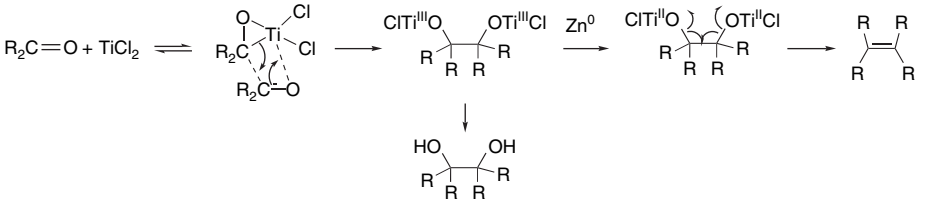
Titanium-mediated reductive couplings are normally heterogeneous, and it was originally thought that the reactions take place at the metal surface.[253] However, mechanistic study has suggested that Ti(II) may be the active species. Hydride reducing agents generate a solid having the composition $(HTi^{II}Cl)_n$ that effects reductive couplings. This species is believed to react with carbonyl compounds with elimination of hydrogen to generate a complexed form of the carbonyl compound. The ketone in this complex is considered to be analogous to a "ketone dianion"[254] and is strongly nucleophilic. This mechanism accounts for the characteristic "template effect" of the titanium reagents in promoting ring formation because it involves cooperating titanium ions.



It has been suggested that a similar mechanism operates under some conditions in which the reductant is generated in situ by a Zn-Cu couple.[255] The key intermediate in this mechanism is a complex of the carbonyl compound with $TiCl_2$. The formation

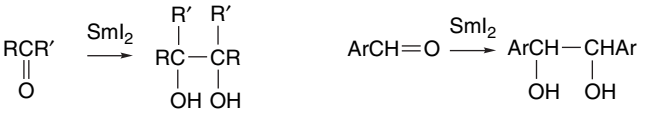
251. S. Gauthier, J. Mailhot, and F. Labrie, *J. Org. Chem.*, **61**, 3890 (1996).
252. S. Gauthier, J.-Y. Sanceau, J. Mailhot, B. Caron, and J. Cloutier, *Tetrahedron*, **56**, 703 (2000).
253. R. Dams, M. Malinowski, I. Westdrop, and H. Y. Geise, *J. Org. Chem.*, **47**, 248 (1982).
254. B. Bogdanovic, C. Kruger, and B. Wermeckes, *Angew. Chem. Int. Ed. Engl.*, **19**, 817 (1980).
255. A. Furstner and B. Bogdanovic, *Angew. Chem. Int. Ed. Engl.*, **35**, 2442 (1996).

of alkene involves a second reduction step, which can occur at elevated temperature in the presence of excess reactant.

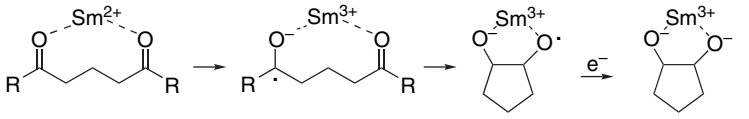


According to a DFT computational study, this mechanism is plausible.[256]

Samarium diiodide is another powerful one-electron reducing agent that can effect carbon-carbon bond formation under appropriate conditions.[257] Aromatic aldehydes and aliphatic aldehydes and ketones undergo pinacol-type coupling with SmI_2 or $SmBr_2$.

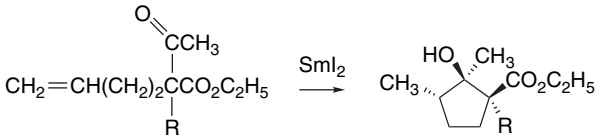


δ-Ketoaldehydes and 1,5-diketones are reduced to *cis*-cyclopentanediols.[258] 1,6-Diketo compounds can be cyclized to cyclohexanediols, again with a preference for *cis*-diols.[259] These reactions are believed to occur through successive one-electron transfer, radical cyclization, and a second electron transfer with Sm^{2+} serving as a tether and Lewis acid, as well as being the reductant.



Many of the compounds used have additional functional groups, including ester, amide, ether, and acetal. These groups may be involved in coordination to samarium and thereby influence the stereoselectivity of the reaction.

The ketyl intermediates in SmI_2 reductions can be trapped by carbon-carbon double bonds, leading, for example, to cyclization of δ,ε-enones to cyclopentanols.



Ref. 260

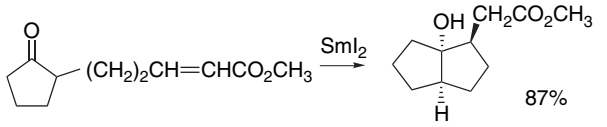
256. M. Stahl, U. Pidun, and G. Frenking, *Angew. Chem. Int. Ed. Engl.*, **36**, 2234 (1997).

257. G.A. Molander, *Org. React.*, **46**, 211 (1994); J. L. Namy, J. Souppe, and H. B. Kagan, *Tetrahedron Lett.*, **24**, 765 (1983); A. Lebrun, J.-L. Namy, and H. B. Kagan, *Tetrahedron Lett.*, **34**, 2311 (1993); H. Akane, T. Hatano, H. Kusui, Y. Nishiyama, and Y. Ishii, *J. Org. Chem.*, **59**, 7902 (1994).

258. G. A. Molander and C. Kemp, *J. Am. Chem. Soc.*, **111**, 8236 (1989); J. Uenishi, S. Masuda, and S. Wakabashi, *Tetrahedron Lett.*, **32**, 5097 (1991).

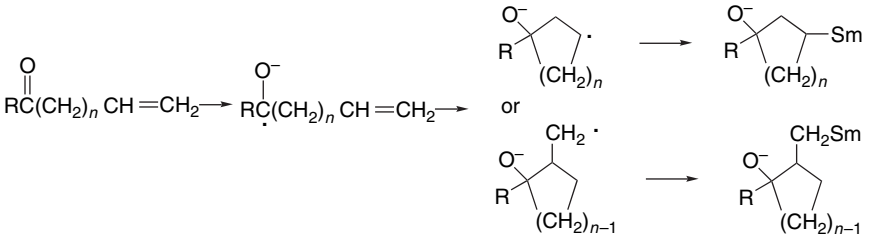
259. J. L. Chiara, W. Cabri, and S. Hanessian, *Tetrahedron Lett.*, **32**, 1125 (1991); J. P. Guidot, T. Le Gall, and C. Mioskowski, *Tetrahedron Lett.*, **35**, 6671 (1994).

260. G. Molander and C. Kenny, *J. Am. Chem. Soc.*, **111**, 8236 (1989).

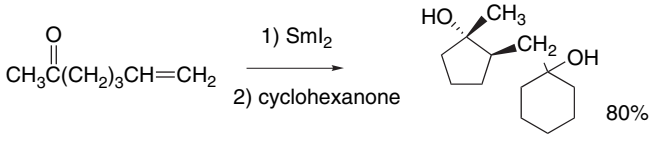


Ref. 261

SmI_2 has also been used to form cyclooctanols by cyclization of 7,8-enones.[262] These alkene addition reactions presumably proceed by addition of the ketyl radical to the double bond, followed by a second electron transfer.

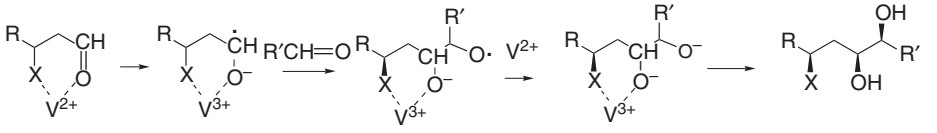


The initial products of such additions under aprotic conditions are organosamarium reagents and further (tandem) transformations are possible, including addition to ketones, anhydrides, or carbon dioxide.



Ref. 263

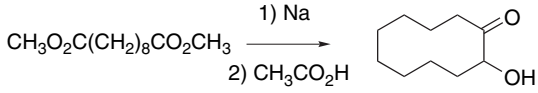
Another reagent that has found use in pinacolic coupling is prepared from VCl_3 and zinc dust.[264] This reagent is selective for aldehydes that can form chelated intermediates, such as β-formylamides, α-amidoaldehydes, α-phosphinoylaldehydes,[265] and δ-ketoaldehydes.[266] The vanadium reagent can be used for both homodimerization and heterodimerization. In the latter case, the reactive aldehyde is added to an excess of the second aldehyde. Under these conditions, the ketyl intermediate formed from the chelated aldehyde reacts with the second aldehyde.



The VCl_3-Zn reagent has also been used in cyclization reactions, as in Entries 4 and 5 in Scheme 5.13.

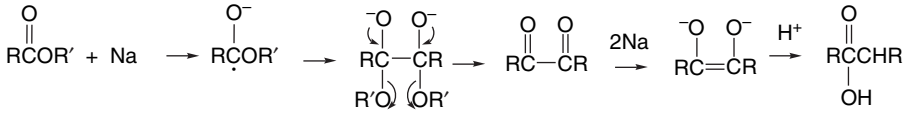
261. E. J. Enholm and A. Trivellas, *Tetrahedron Lett.*, **30**, 1063 (1989).
262. G. A. Molander and J. A. McKie, *J. Org. Chem.*, **59**, 3186 (1994).
263. G. A. Molander and J. A. McKie, *J. Org. Chem.*, **57**, 3132 (1992).
264. J. H. Freudenberg, A. W. Konradi, and S. F. Pedersen, *J. Am. Chem. Soc.*, **111**, 8014 (1989).
265. J. Park and S. F. Pedersen, *J. Org. Chem.*, **55**, 5924 (1990).
266. A. S. Raw and S. F. Pedersen, *J. Org. Chem.*, **56**, 830 (1991).

Another important reductive coupling is the conversion of esters to α-hydroxyketones (*acyloin condensation*).[267] This reaction is usually carried out with sodium metal in an inert solvent. Good results have also been obtained for sodium metal dispersed on solid supports.[268] Diesters undergo intramolecular reactions and this is also an important method for the preparation of medium and large carbocyclic rings.

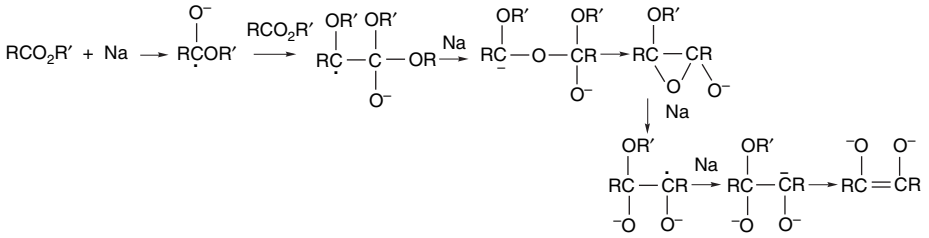


Ref. 269

There has been considerable discussion of the mechanism of the acyloin condensation. One formulation of the reaction envisages coupling of radicals generated by one-electron transfer.



An alternative mechanism bypasses the postulated α-diketone intermediate because its involvement is doubtful.[270]



Regardless of the details of the mechanism, the product prior to neutralization is the dianion of an α-hydroxy ketone, namely an enediolate. It has been found that the overall yields are greatly improved if trimethylsilyl chloride is present during the reduction to trap these dianions as trimethylsilyl ethers.[271] The silylated derivatives are much more stable to the reaction conditions than the enediolates. Hydrolysis during workup gives the acyloin product. This modified version of the reaction has been applied to cyclizations leading to small, medium, and large rings, as well as to intermolecular couplings.

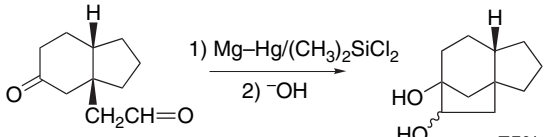
Scheme 5.13 provides several examples of reductive carbon-carbon bond formation, including formation of diols, alkenes, and acyloins. Entry 1 uses magnesium amalgam in the presence of dichlorodimethylsilane. The role of the silane may be to

267. J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. React.*, **23**, 259 (1976).
268. M. Makosza and K. Grela, *Synlett*, 267 (1997); M. Makosza, P. Nieczypor, and K. Grela, *Tetrahedron*, **54**, 10827 (1998).
269. N. Allinger, *Org. Synth.*, **IV**, 840 (1963).
270. J. J. Bloomfield, D. C. Owsley, C. Ainsworth, and R. E. Robertson, *J. Org. Chem.*, **40**, 393 (1975).
271. K. Ruhlmann, *Synthesis*, 236 (1971).

Scheme 5.13. Reductive Coupling of Carbonyl Compound

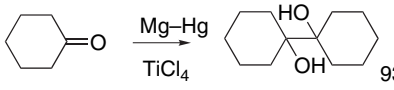
A. Diol formation

1[a]



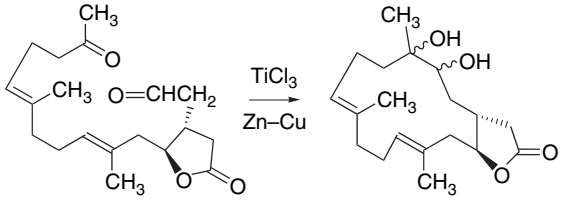
75%

2[b]



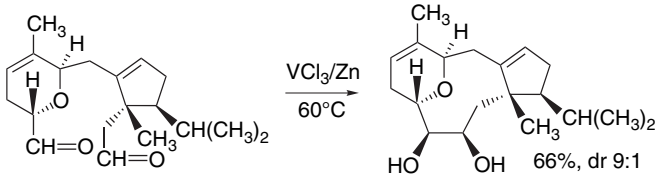
93%

3[c]



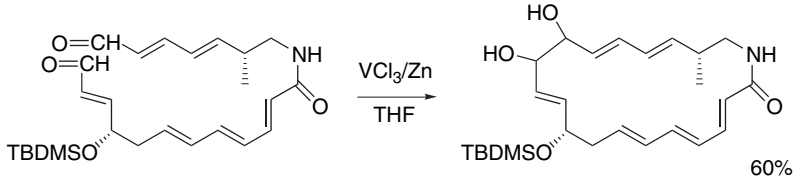
58%

4[d]



66%, dr 9:1

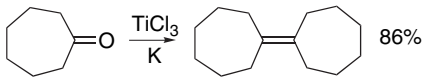
5[e]



60%

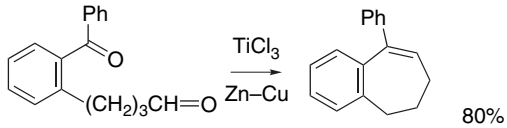
B. Alkene formation

6[f]



86%

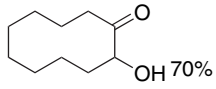
7[g]



80%

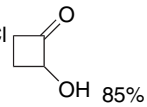
C. Acyloin formation

8[h] $CH_3O_2C(CH_2)_8CO_2CH_3$ — 1) Na, xylene; 2) CH_3CO_2H



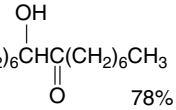
70%

9[i] $C_2H_5O_2CH_2CH_2CO_2C_2H_5$ — 1) Na, $(CH_3)_3SiCl$; 2) CH_3OH



85%

10[j] $CH_3(CH_2)_6CO_2C_2H_5$ — Na/NaCl, benzene → $CH_3(CH_2)_6CHC(CH_2)_6CH_3$



78%

(*Continued*)

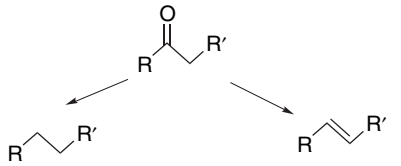
Scheme 5.13. (*Continued*)

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 and R. G. Dushin, *J. Am. Chem. Soc.*, **112**, 6942 (1990).
d. D. R. Williams and R. W. Heidebrecht, Jr., *J. Am. Chem. Soc.*, **125**, 1843 (2003).
e. M. Nazare and H. Waldmann, *Chem. Eur. J.*, **7**, 3363 (2001).
f. J. E. McMurry, M. P. Fleming, K. L. Kees, and L. R. Krepski, *J. Org. Chem.*, **43**, 3255 (1978).
g. C. B. Jackson and G. Pattenden, *Tetrahedron Lett.*, **26**, 3393 (1985).
h. N. L. Allinger, *Org. Synth.*, **IV**, 340 (1963).
i. J. J. Bloomfield and J. M. Nelke, *Org. Synth.*, **57**, 1 (1977).
j. M. Makosza and K. Grela, *Synlett*, 267 (1997).

trap the pinacol as a cyclic siloxane. The reaction in Entry 2 is thought to involve Ti(II) as the active reductant and to proceed by a mechanism of the type described on p. 447. These conditions were also successful for the reaction shown in Entry 1. Entry 3 involves formation of a 14-membered ring using a low-valent titanium reagent. The product is a mixture of all four possible diastereomeric diols in yields ranging from 7 to 21%. Entry 4 is an example of a pinacol reduction using a vanadium reagent prepared in situ from VCl_3 and Zn, which tends to give a high proportion of *cis*-diol as a result of chelation with vanadium. Entry 5 shows the synthesis of a sensitive polyunsaturated lactam. The *cis*-diol was formed in 60% yield. In this particular case, various low-valent titanium reagents were unsuccessful. Entries 6 and 7 describe conditions that lead to alkene formation. Entries 8 to 10 are acyloin condensations. The reaction in Entry 8 illustrates the classical conditions. Entry 9 is an example of the reaction conducted in the presence of TMS-Cl to trap the enediolate intermediate and make the reaction applicable to formation of a four-membered ring. The example in Entry 10 uses sodium in the form of a solid deposit on an inert material. This is an alternative to the procedures that require dispersion of molten sodium in the reaction vessel (Entries 8 and 9).

5.7. Reductive Deoxygenation of Carbonyl Groups

Several methods are available for reductive removal of carbonyl groups from organic compounds. Reduction to methylene groups or conversion to alkenes can be achieved.

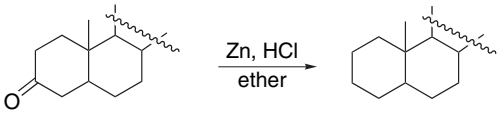


5.7.1. Reductive Deoxygenation of Carbonyl Groups to Methylene

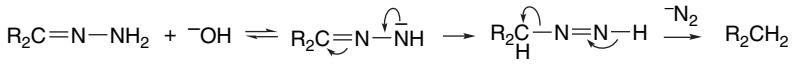
Zinc and hydrochloric acid form a classical reagent combination for conversion of carbonyl groups to methylene groups, a reaction known as the *Clemmensen reduction*.[272] The corresponding alcohols are not reduced under the conditions of the

[272.] E. Vedejs, *Org. React.*, **22**, 401 (1975).

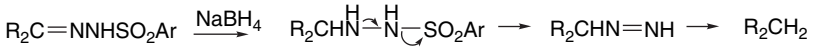
reaction, so they are evidently not intermediates. The Clemmensen reaction works best for aryl ketones and is less reliable with unconjugated ketones. The mechanism is not known in detail but may involve formation of carbon-zinc bonds at the metal surface.[273] The reaction is commonly carried out in hot concentrated hydrochloric acid with ethanol as a cosolvent. These conditions preclude the presence of acid-sensitive or hydrolyzable functional groups. A modification in which the reaction is run in ether saturated with dry hydrogen chloride gave good results in the reduction of steroidal ketones.[274]



The *Wolff-Kishner reaction*[275] is the reduction of carbonyl groups to methylene groups by base-catalyzed decomposition of the hydrazone of the carbonyl compound. It is thought that alkyldiimides are formed and then collapse with loss of nitrogen.[276]

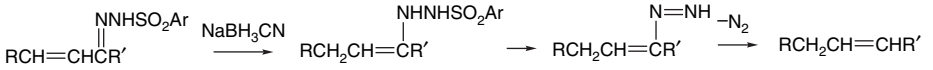


The reduction of tosylhydrazones by $LiAlH_4$ or $NaBH_4$ also converts carbonyl groups to methylene.[277] It is believed that a diimide is involved, as in the Wolff-Kishner reaction.



Excellent yields can also be obtained using $NaBH_3CN$ as the reducing agent.[278] The $NaBH_3CN$ can be added to a mixture of the carbonyl compound and *p*-toluenesulfonylhydrazide. Hydrazone formation is faster than reduction of the carbonyl group by $NaBH_3CN$ and the tosylhydrazone is reduced as it is formed. Another reagent that can reduce tosylhydrazones to give methylene groups is $CuBH_4(PPh_3)_2$.[279]

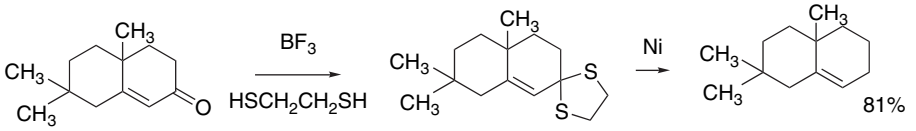
Reduction of tosylhydrazones of α,β-unsaturated ketones by $NaBH_3CN$ gives alkenes with the double bond located between the former carbonyl carbon and the α-carbon.[280] This reaction is believed to proceed by an initial conjugate reduction, followed by decomposition of the resulting vinylhydrazine to a vinyldiimide.



273. M. L. Di Vona and V. Rosnatti, *J. Org. Chem.*, **56**, 4269 (1991).
274. M. Toda, M. Hayashi, Y. Hirata, and S. Yamamura, *Bull. Chem. Soc. Jpn.*, **45**, 264 (1972).
275. D. Todd, *Org. React.*, **4**, 378 (1948); Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
276. T. Tsuji and E. M. Kosower, *J. Am. Chem. Soc.*, **93**, 1992 (1971). Alkyldiimides are also converted to hydrocarbons by a free radical mechanism; A. G. Myers, M. Movassaghi and B. Zheng, *Tetrahedron Lett.*, **38**, 6569 (1997).
277. L. Caglioti, *Tetrahedron*, **22**, 487 (1966).
278. R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).
279. B. Milenkov and M. Hesse, *Helv. Chim. Acta*, **69**, 1323 (1986).
280. R. O. Hutchins, M. Kacher, and L. Rua, *J. Org. Chem.*, **40**, 923 (1975).

Catecholborane or sodium borohydride in acetic acid can also be used as a reducing reagent in this reaction.[281]

Carbonyl groups can be converted to methylene groups by desulfurization of thioketals. The cyclic thioketal from ethanedithiol is commonly used. Reaction with excess Raney nickel causes hydrogenolysis of both C−S bonds.



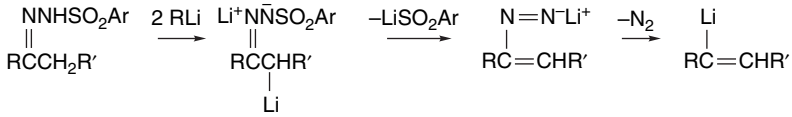
Ref. 282

Other reactive forms of nickel including nickel boride[283] and nickel alkoxide complexes[284] can also be used for desulfurization. Tri-*n*-butyltin hydride is an alternative reagent for desulfurization.[285]

Scheme 5.14 illustrates some representative carbonyl deoxygenations. Entries 1 and 2 are Clemmensen reductions of acyl phenols. Entry 3 is an example of the Wolff-Kishner reaction. Entry 4 describes modified conditions for the Wolff-Kishner reaction that take advantage of the strong basicity of the KO*t*Bu-DMSO combination. Entries 5 to 7 are examples of conversion of sulfonylhydrazones to methylene groups (Caglioti reaction). In addition to $LiAlH_4$, which was used in the original procedure, $NaBH_3CN$ (Entry 6) and catecholborane (Entry 7) can be used as reducing agents. Entries 8 and 9 are thioketal desulfurizations.

5.7.2. Reduction of Carbonyl Compounds to Alkenes

Ketone *p*-toluenesulfonylhydrazones are converted to alkenes on treatment with strong bases such as an alkyllithium or lithium dialkylamide.[286] Known as the *Shapiro reaction*,[287] this proceeds through the anion of a vinyldiimide, which decomposes to a vinyllithium reagent. Treatment of this intermediate with a proton source gives the alkene.



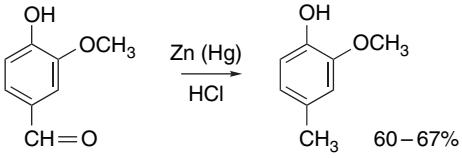
The Shapiro reaction has been particularly useful for cyclic ketones, but its scope includes acyclic systems as well. In the case of unsymmetrical acyclic ketones,

281. 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).
282. F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959).
283. W. E. Truce and F. M. Perry, *J. Org. Chem.*, **30**, 1316 (1965).
284. S. Becker, Y. Fort, and P. Caubere, *J. Org. Chem.*, **55**, 6194 (1990).
285. C. G. Gutierrez, R. A. Stringham, T. Nitasaka, and K. G. Glasscock, *J. Org. Chem.*, **45**, 3393 (1980).
286. R. H. Shapiro and M. J. Heath, *J. Am. Chem. Soc.*, **89**, 5734 (1967).
287. R. H. Shapiro, *Org. React.*, **23**, 405 (1976); R. M. Adington and A. G. M. Barrett, *Acc. Chem. Res.*, **16**, 53 (1983); A. R. Chamberlin and S. H. Bloom, *Org. React.*, **39**, 1 (1990).

Scheme 5.14. Carbonyl to Methylene Reductions

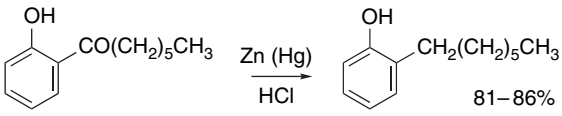
A. Clemmensen

1[a]



60–67%

2[b]



81–86%

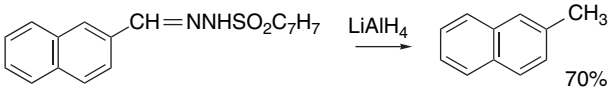
B. Wolff–Kishner

3[c] $HO_2C(CH_2)_4CO(CH_2)_4CO_2H \xrightarrow[KOH]{NH_2NH_2} HO_2C(CH_2)_9CO_2H$ 87–93%

4[d] $Ph-\underset{\underset{NNH_2}{\|}}{C}-Ph \xrightarrow[DMSO]{KOC(CH_3)_3} PhCH_2Ph$ 90%

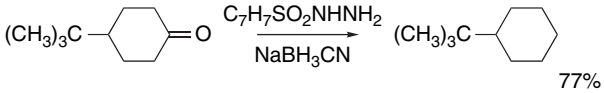
C. Tosylhydrazone reduction

5[e]



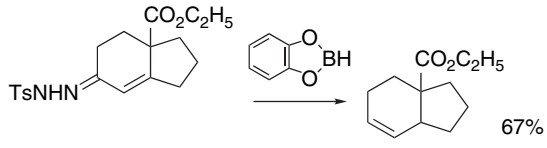
70%

6[f]



77%

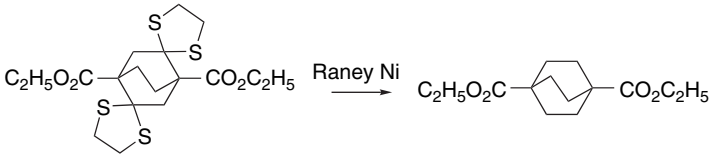
7[g]



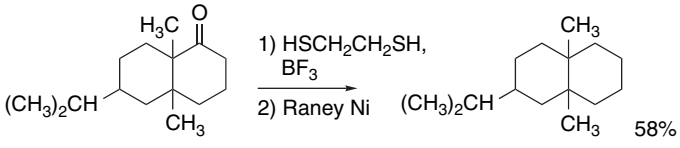
67%

D. Thioketal desulfurization

8[h]



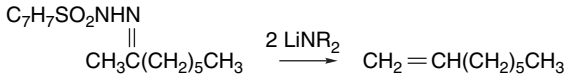
9[i]



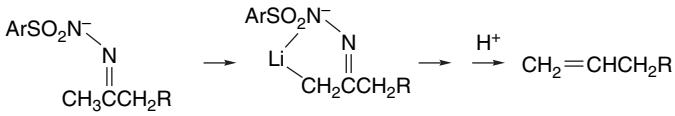
58%

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. M. N. Greco and B. E. Maryanoff, *Tetrahedron Lett.*, **33**, 5009 (1992).
h. J. D. Roberts and W. T. Moreland, Jr., *J. Am. Chem. Soc.*, **75**, 2167 (1953).
i. P. N. Rao, *J. Org. Chem.*, **36**, 2426 (1971).

questions of both regiochemistry and stereochemistry arise. 1-Octene is the exclusive product from 2-octanone.[288]

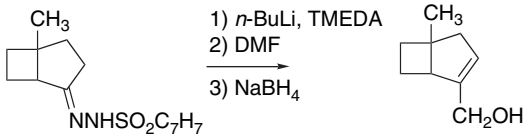


This regiospecificity has been shown to depend on the stereochemistry of the C=N bond in the starting hydrazone. There is evidently a strong preference for abstracting the proton *syn* to the arenesulfonyl group, probably because this permits chelation with the lithium ion.

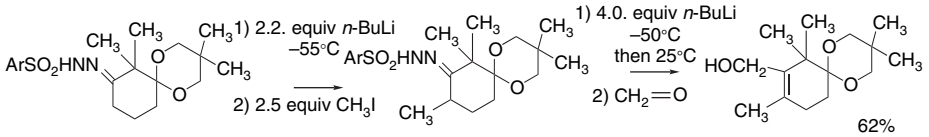


The Shapiro reaction converts the *p*-toluenesulfonylhydrazones of α, β-unsaturated ketones to dienes (see Entries 3 to 5 in Scheme 5.15).[289]

The vinyl lithium reagents generated in the Shapiro reaction can be used in tandem reactions. In the reaction shown below, a hydroxymethyl group was added by formylation followed by reduction.



In another example, a sequence of methylation-elimination-hydroxymethylation was used to install the functionality pattern found in the A-ring of taxol. The hydrazone dianion was generated and methylated at low temperature. The hydrazone was then deprotonated again using excess *n*-butyllithium and allowed to warm to room temperature, at which point formation of the vinyllithium occurred. Reaction with paraformaldehyde generated the desired product.[290]

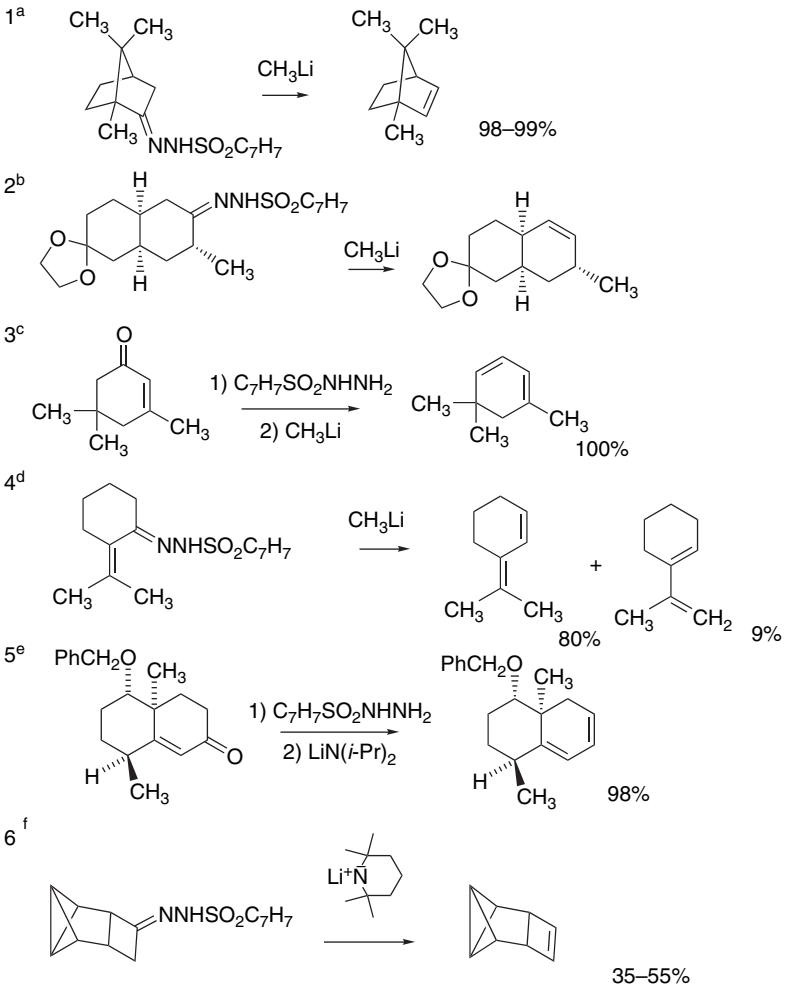


Ar = 2,4,6-trimethylphenyl

Scheme 5.15 shows some examples of the Shapiro reaction. Entry 1 is an example of the standard procedure, as documented in *Organic Syntheses*. Entry 2 illustrates the preference for the formation of the less-substituted double bond. Entries 3, 4, and 5 involve tosylhydrazone of α, β-unsaturated ketones. The reactions proceed by α′-deprotonation. Entry 6 illustrates the applicability of the reaction to a highly strained system.

288. K. J. Kolonko and R. H. Shapiro, *J. Org. Chem.*, **43**, 1404 (1978).
289. W. G. Dauben, G. T. Rivers, and W. T. Zimmerman, *J. Am. Chem. Soc.*, **99**, 3414 (1977).
290. O. P. Tormakangas, R. J. Toivola, E. K. Karvinen, and A. M. P. Koskinen, *Tetrahedron*, **58**, 2175 (2002).

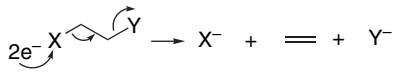
Scheme 5.15. Conversion of Ketones to Alkenes via Sulfonylhydrazones



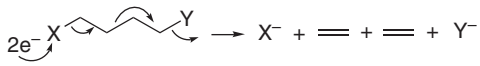
a. R. H. Shapiro and J. H. Duncan, *Org. Synth.*, **51**, 66 (1971).
b. W. L. Scott and D. A. Evans, *J. Am. Chem. Soc.*, **94**, 4779 (1972).
c. W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, and K. Tomer, *J. Am. Chem. Soc.*, **90**, 4762 (1968).
d. W. G. Dauben, G. T. Rivers, 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. R. Gream, and J. Meinwald, *J. Org. Chem.*, **42**, 927 (1977).

5.8. Reductive Elimination and Fragmentation

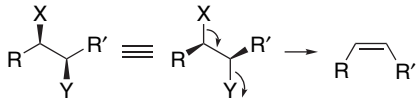
The presence of a potential leaving group β to the site of carbanionic character usually leads to β-elimination. In some useful synthetic procedures, the carbanionic character is generated by a reductive process.



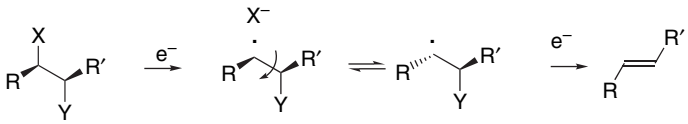
Similarly, carbanionic character δ to a leaving group can lead to β, γ-fragmentation.



A classical example of the β-elimination reaction is the reductive debromination of vicinal dibromides. Zinc metal is the traditional reducing agent.[291] A multitude of other reducing agents have been found to give this and similar reductive eliminations. Some examples are given in Table 5.7. Some of the reagents exhibit *anti* stereospecificity, whereas others do not. A stringent test for *anti* stereospecificity is the extent of *Z*-alkene formed from a *syn* precursor.



Anti stereospecificity is associated with a concerted reductive elimination, whereas single-electron transfer fragmentation leads to loss of stereospecificity and formation of the more stable *E*-stereoisomer.



As vicinal dibromides are usually made by bromination of alkenes, their utility for synthesis is limited, except for temporary masking of a double bond. Much more frequently it is desirable to convert a diol to an alkene, and several useful procedures have been developed. The reductive deoxygenation of diols via thiono carbonates was

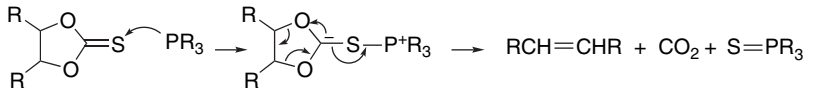
Table 5.7. Reagents for Reductive Dehalogenation

Reagent	*Anti* stereoselectivity
Zn, cat $TiCl_4$[a]	Yes
Zn, H_2NSNH_2[b]	?
$SnCl_2$, DiBAlH[c]	?
Sm, CH_3OH[d]	No
Fe, graphite[e]	Yes
C_2H_5MgBr, cat Ni(dppe)Cl_2[f]	No

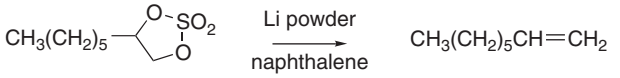
a. F. Sato, T. Akiyama, K. Ida, and M. Sato, *Synthesis*, 1025 (1982).
b. R. N. Majumdar and H. J. Harwood, *Synth. Commun.*, **11**, 901 (1981).
c. T. Oriyama and T. Mukaiyama, *Chem. Lett.*, 2069 (1984).
d. R. Yanada, N. Negoro, K. Yanada, and T. Fujita, *Tetrahedron Lett.*, **37**, 9313 (1996).
e. D. Savoia, E. Tagliavini, C. Trombini, and A. Umani-Ronchi, *J. Org. Chem.*, **47**, 876 (1982).
f. C. Malanga, L. A. Aronica, and L. Lardicci, *Tetrahedron Lett.*, **36**, 9189 (1995).

291. J. C. Sauer, *Org. Synth.*, **IV**, 268 (1965).

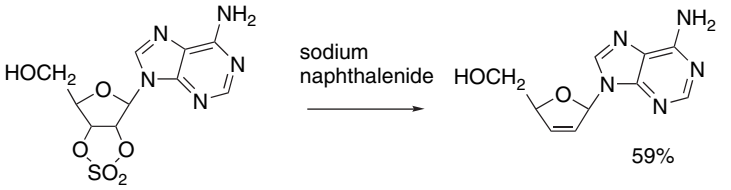
developed by Corey and co-workers.[292] Triethyl phosphite is useful for many cases, but the more reactive 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine can be used when milder conditions are required.[293] The reaction presumably occurs by initial P−S bonding followed by a concerted elimination of carbon dioxide and the thiophosphoryl compound.



Diols can also be deoxygenated via *bis*-sulfonate esters using sodium naphthalenide.[294] Cyclic sulfate esters are also cleanly reduced by lithium naphthalenide.[295]

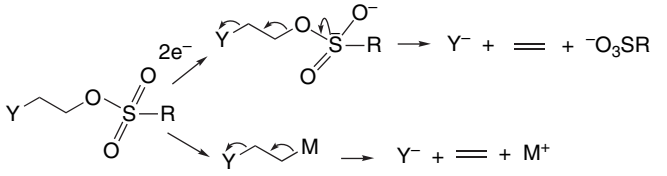


This reaction, using sodium naphthalenide, has been used to prepare unsaturated nucleosides.



Ref. 296

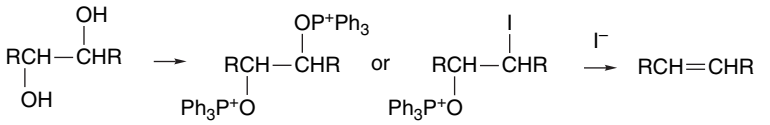
It is not entirely clear whether these reactions involve a redox reaction at sulfur or if they proceed by organometallic intermediates.



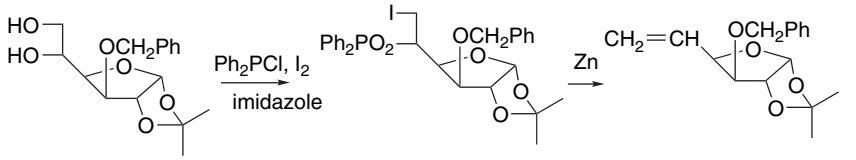
Iodination reagents combined with aryl phosphines and imidazole can also effect reductive conversion of diols to alkenes. One such combination is 2,4,5-triiodoimidazole, imidazole, and triphenylphosphine.[297] These reagent combinations

[292] E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, **85**, 2677 (1963); E. J. Corey, F. A. Carey, and R. A. E. Winter, *J. Am. Chem. Soc.*, **87**, 934 (1965).
[293] E. J. Corey and P. B. Hopkins, *Tetrahedron Lett.*, **23**, 1979 (1982).
[294] J. C. Carnahan, Jr., and W. D. Closson, *Tetrahedron Lett.*, 3447 (1972); R. J. Sundberg and R. J. Cherney, *J. Org. Chem.*, **55**, 6028 (1990).
[295] D. Guijarro, B. Mancheno, and M. Yus, *Tetrahedron Lett.*, **33**, 5597 (1992).
[296] M. J. Robins, E. Lewandowska, and S. F. Wnuk, *J. Org. Chem.*, **63**, 7375 (1998).
[297] P. J. Garegg and B. Samuelsson, *Synthesis*, 813 (1979); Y. Watanabe, M. Mitani, and S. Ozaki, *Chem. Lett.*, 123 (1987).

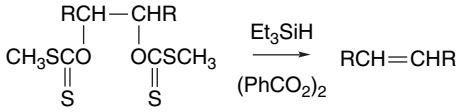
are believed to give oxyphosphonium intermediates, which then can serve as leaving groups, forming triphenylphosphine oxide as in the Mitsunobu reaction (see Section 3.2.3). The iodide serves as both a nucleophile and reductant.



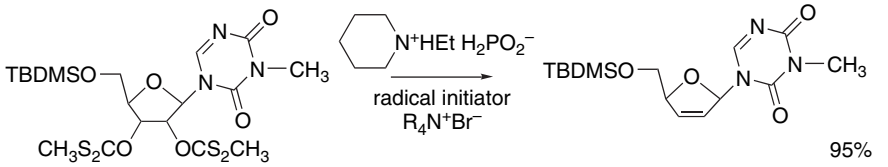
In a related procedure, chlorodiphenylphosphine, imidazole, iodine, and zinc cause reductive elimination of diols.[298] β-Iodophosphinate esters can be shown to be intermediates in some cases.



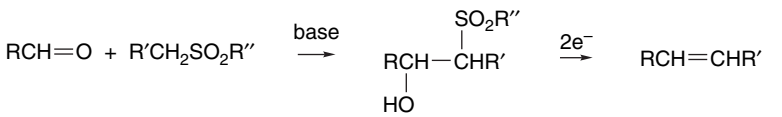
Another alternative for conversion of diols to alkenes is the use of the Barton radical fragmentation conditions (see Section 5.5) with a silane hydrogen atom donor.[299]



N-Ethylpiperidinium hypophosphite has been used as a reductant in deoxygenation of nucleoside diol xanthates in aqueous solution.[300]



The reductive elimination of β-hydroxysulfones is the final step in the *Julia-Lythgoe alkene synthesis* (see Section 2.4.3).[301] The β-hydroxysulfones are normally obtained by an aldol addition.



[298] Z. Liu, B. Classon, and B. Samuelsson, *J. Org. Chem.*, **55**, 4273 (1990).

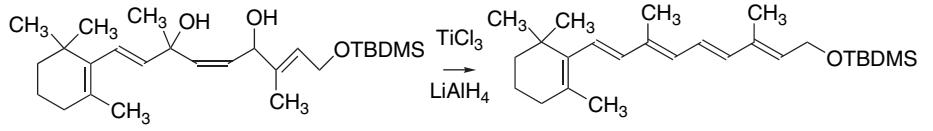
[299] D. H. R. Barton, D. O. Jang, and J. C. Jaszberenyi, *Tetrahedron Lett.*, **32**, 2569 (1991); D. H. R. Barton, D. O. Jang, and J. C. Jaszberenyi, *Tetrahedron Lett.*, **32**, 7187 (1991).

[300] D. O. Jang and D. H. Cho, *Tetrahedron Lett.*, **43**, 5921 (2002).

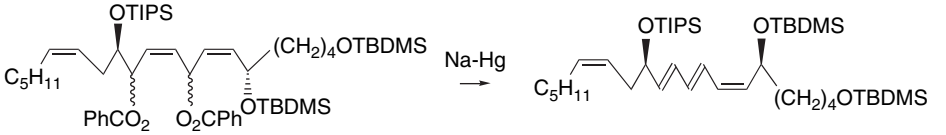
[301] P. Kocienski, *Phosphorus and Sulfur*, **24**, 97 (1985).

Several reducing agents have been used for the elimination, including sodium amalgam[302] and samarium diiodide.[303] The elimination can also be done by converting the hydroxy group to a xanthate or thiocarbonate and using radical fragmentation.[304]

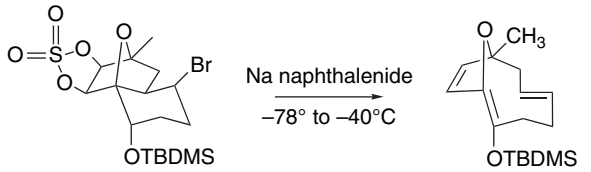
Reductive elimination from 2-en-1,4-diol derivatives has been used to generate 1,3-dienes. Low-valent titanium generated from $TiCl_3$-$LiAlH_4$ can be used directly with the diols. This reaction has been used successfully to create extended polyene conjugation.[305]



Benzoate esters of 2-en-1,4-diols undergo reductive elimination with sodium amalgam.[306]



The β,γ-fragmentation is known as Grob fragmentation. Its synthetic application is usually in the construction of medium-sized rings by fragmentation of fused-ring systems. The reaction below results in both a reductive fragmentation and deoxygenation via a cyclic sulfate.



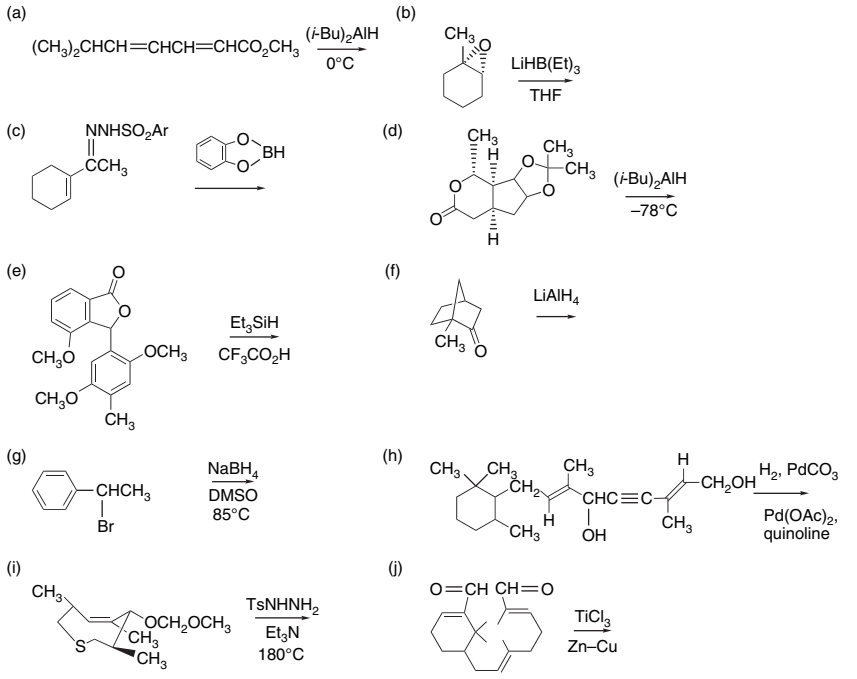
Ref. 307

302. P. J. Kocienski, B. Lythgoe, and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1045 (1980); A. Armstrong, S. V. Ley, A. Madin, and S. Mukherjee, *Synlett*, 328 (1990); M. Kagayama, T. Tamura, M. H. Nantz, J. C. Roberts, P. Somfai, D. C. Whritenour, and S. Masamune, *J. Am. Chem. Soc.*, **112**, 7407 (1990).
303. A. S. Kende and J. S. Mendoza, *Tetrahedron Lett.*, **31**, 7105 (1990); I. E. Marko, F. Murphy, and S. Dolan, *Tetrahedron Lett.*, **37**, 2089 (1996); G. E. Keck, K. A. Savin, and M. A. Weglarz, *J. Org. Chem.*, **60**, 3194 (1995).
304. D. H. R. Barton, J. C. Jaszberenyi, and C. Tachdjian, *Tetrahedron Lett.*, **32**, 2703 (1991).
305. G. Solladie, A. Givardin, and G. Lang, *J. Org. Chem.*, **54**, 2620 (1989); G. Solladie and V. Berl, *Tetrahedron Lett.*, **33**, 3477 (1992).
306. G. Solladie, A. Urbano, and G. B. Stone, *Tetrahedron Lett.*, **34**, 6489 (1993).
307. W. B. Wang and E. J. Roskamp, *Tetrahedron Lett.*, **33,** 7631 (1992).

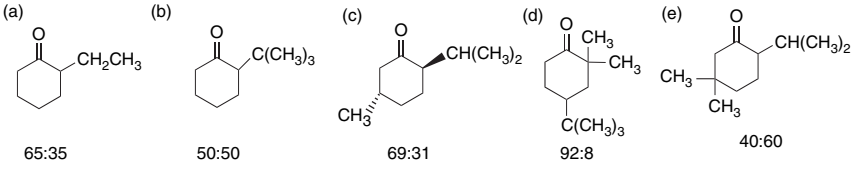
Problems

(*References for these problems will be found on page 1278.*)

5.1. Give the product(s) to be expected from the following reactions. Be sure to specify all facets of stereochemistry.

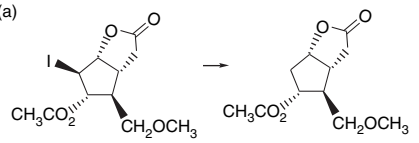


5.2. The data below give the ratio of equatorial:axial alcohol by $NaBH_4$ reduction of each cyclohexanone derivative under conditions in which 4-*t*-butylcyclohexanone gives an approximately 85:15 ratio. Analyze the effect of the substituents in each case.

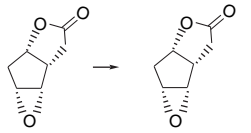


5.3. Indicate reaction conditions that would accomplish each of the following transformations in a single step:

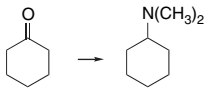
(a)



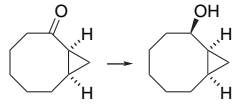
(b)



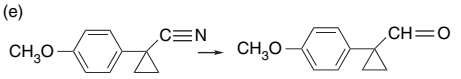
(c)



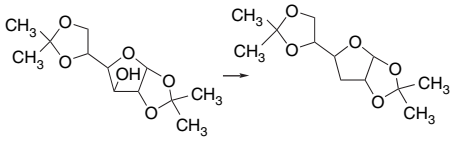
(d)



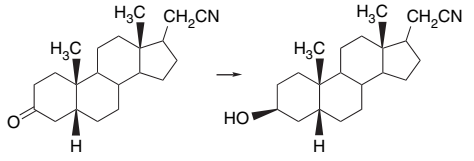
(e)



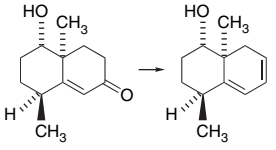
(f)



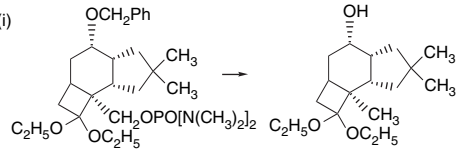
(g)



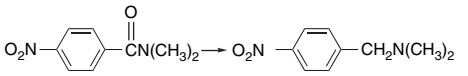
(h)



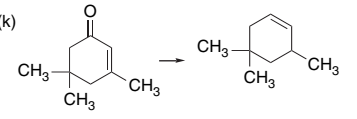
(i)



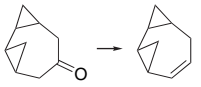
(j)



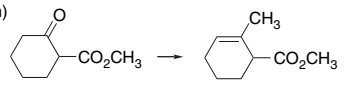
(k)



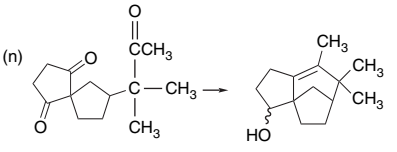
(l)



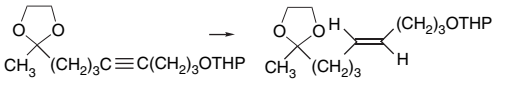
(m)



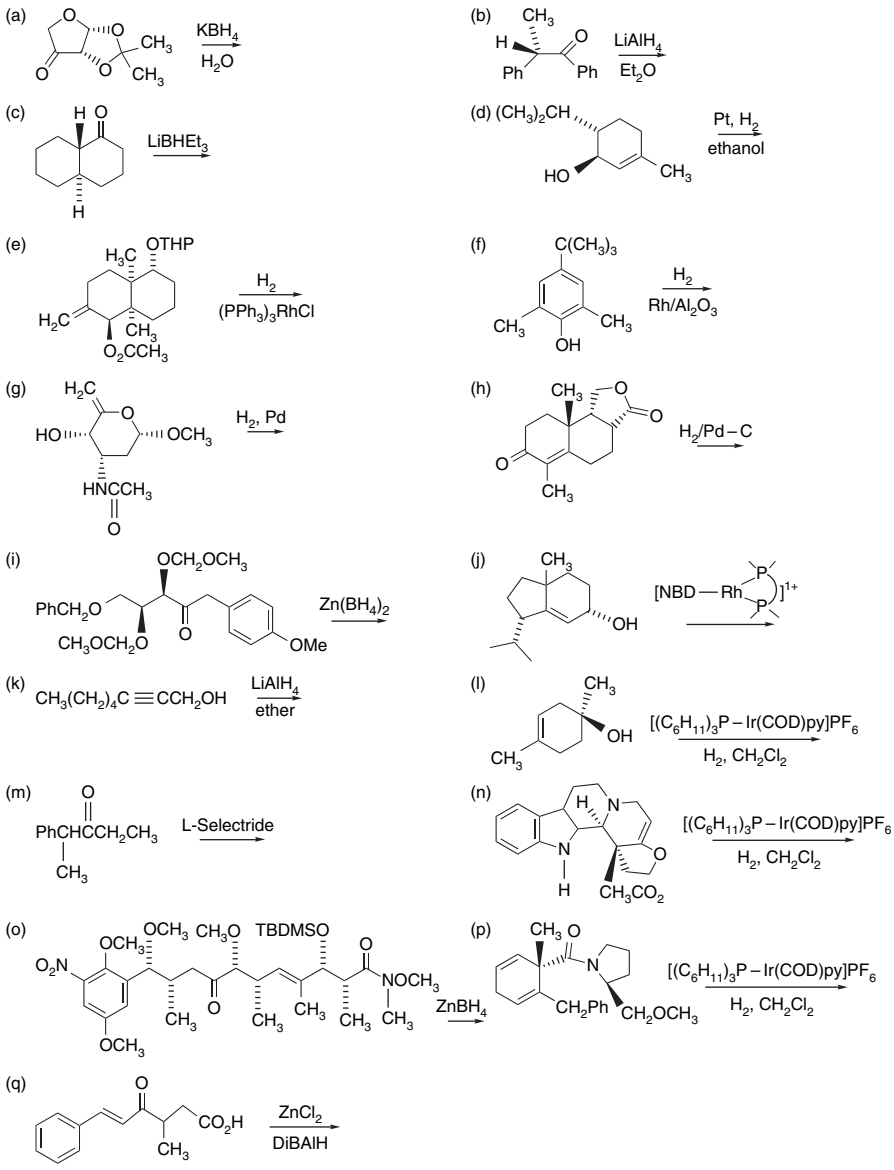
(n)



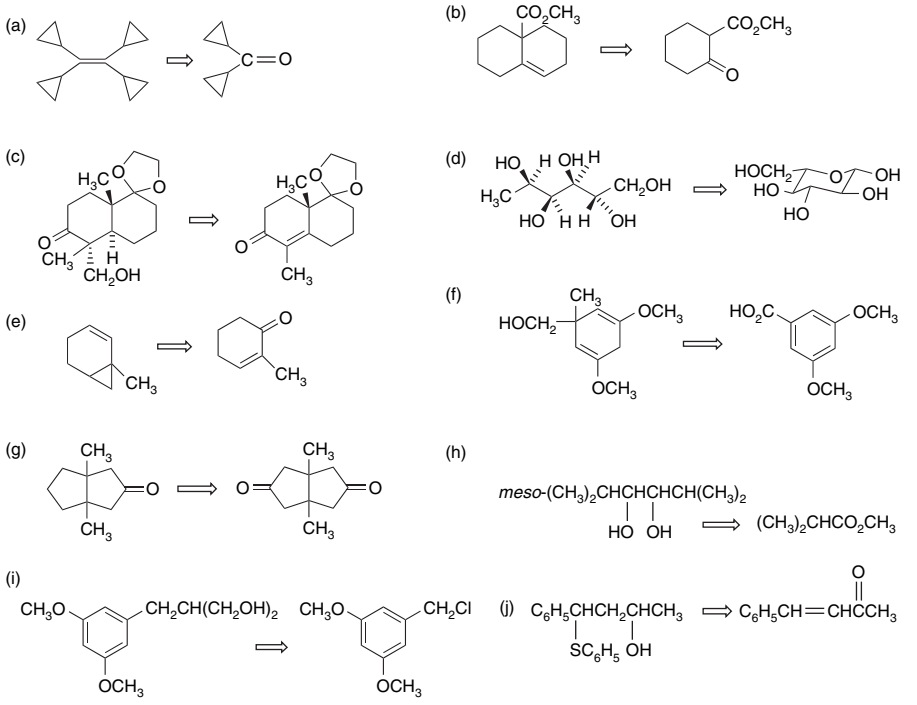
(o)



5.4. Predict the stereochemistry of the products from the following reactions and justify your prediction.



5.5. Suggest a convenient method for carrying out the following syntheses. The compound on the left is to be made from the one on the right (retrosynthetic notation). No more than three steps should be necessary.

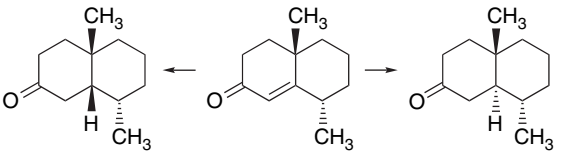


5.6. Offer an explanation to account for the observed differences in the rate of the following reactions:

a. $LiAlH_4$ reduces 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 $LiAlH(t\text{-}OBu)_3$, the addition of one methyl group at C(3) has little effect, but a second group on the same carbon has a large effect. The addition of a third methyl group at C(5) has no effect and the addition of a second methyl at C(5) has only a small effect.

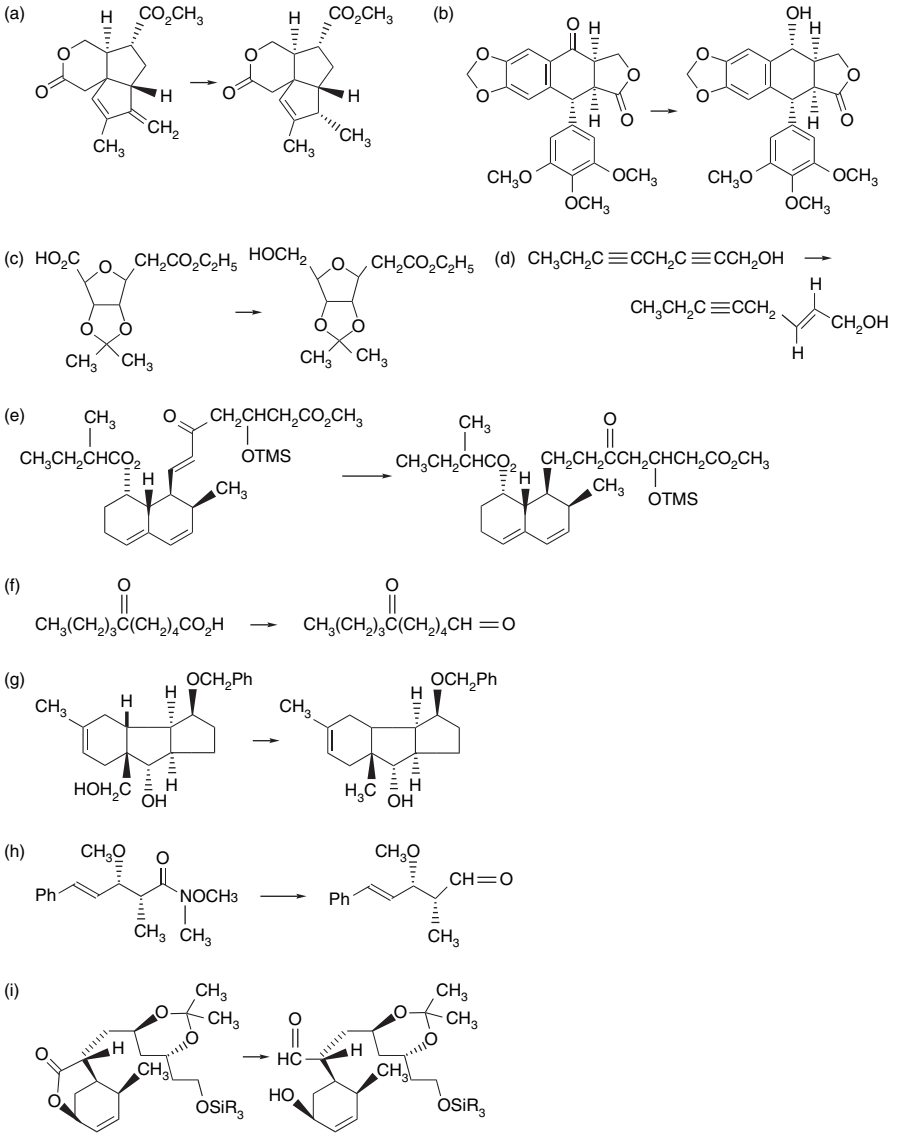
Ketone	Rel. rate
Cyclohexanone	439
3-Methylcyclohexanone	280
3,3-Dimethylcyclohexanone	17.5
3,3,5-Trimethylcyclohexanone	17.4
3,3,5,5-Tetramethylcyclohexanone	8.9

5.7. Suggest reaction conditions appropriate for stereoselective conversion of the octalone shown to each of the diastereomeric decalones.

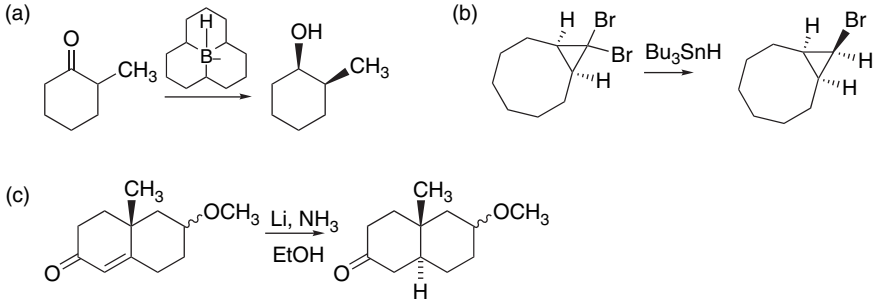


5.8. The fruit of a shrub that grows in Sierra Leone is very toxic and has been used as a rat poison. The toxic principal has been identified as *Z*-18-fluoro-9-octadecenoic acid. Suggest a synthesis from 8-fluorooctanol, 1-chloro-7-iodoheptane, acetylene, and any other necessary organic or inorganic reagents.

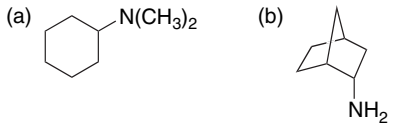
5.9. Each of the following compounds contains more than one potentially reducible group. Indicate a reducing agent that will be suitable for effecting the desired reduction. Explain the basis for the expected selectivity.



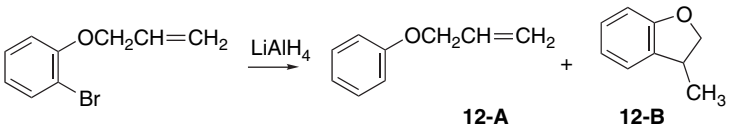
5.10. Explain the basis of the observed stereoselectivity for the following reactions:



5.11. A valuable application of sodium cyanoborohydride is in the synthesis of amines by reductive amination. What combination of carbonyl and amine components would give the following amines by this method?

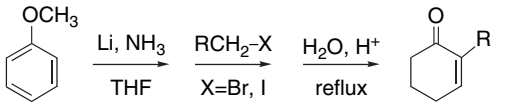


5.12. The reduction of allyl *o*-bromphenyl ether by $LiAlH_4$ has been studied in several solvents. In ether, two products **12-A** and **12-B** are formed. The ratio **12-A**:**12-B** increases with increasing $LiAlH_4$ concentration. When $LiAlD_4$ is used as the reductant, about half of product **12-B** is monodeuterated. Provide a mechanistic rationale for these results. What is the predicted location of the deuterium in the **12-B**? Why is the product not completely deuterated?



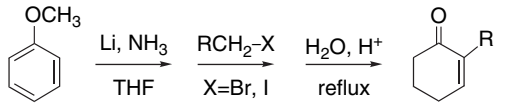
5.13. Each of the following parts describes a synthetic sequence in which Birch reduction is employed to convert aromatic rings to partially saturated products.

a. A simple synthesis of 2-substituted cyclohexenones from 2-methoxybenzoic acid has been developed. The reaction sequence entails Birch reduction, tandem alkylation, and acid hydrolysis. Although the yields are only 25–30%, it can be 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 sequence.

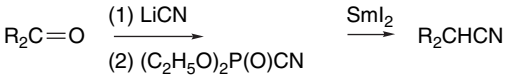


b. Birch reduction of 3,4,5-trimethoxybenzoic acid gives a dihydrobenzoic acid in 94% yield, but it has only *two* methoxy substituents. Suggest a plausible structure for this product based on the mechanism of the Birch reduction.

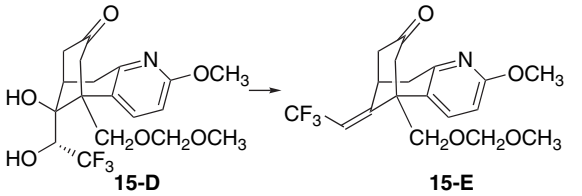
c. The cyclohexenone **13-C** has been prepared in a one-pot process starting with 4-methylpent-3-en-2-one. The reagents that are added in succession are 4-methoxyphenyllithium, Li, and NH_3, followed by acidic workup. Show the intermediates that are involved in the process.



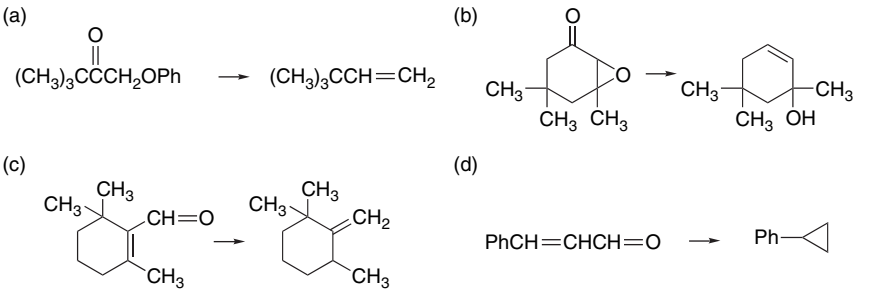
5.14. Ketones can be converted to nitriles by the following sequence of reagents. Indicate the intermediate stages of the reaction.



5.15. In the synthesis of fluorinated analogs of the acetylcholinesterase inhibitor, huperzine A, it was necessary to accomplish reductive elimination of the diol **15-D** to **15-E**. Of the methods for diol reduction, which seems most compatible with the other functional groups in this compound?



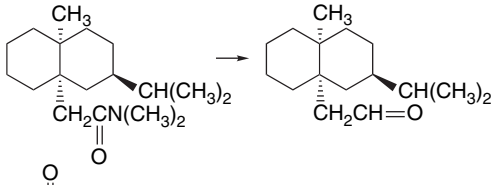
5.16. Wolff-Kishner reduction of ketones bearing other functional groups sometimes gives products other than the expected methylene reduction product. Several examples are given below. Indicate a mechanism for each reaction.



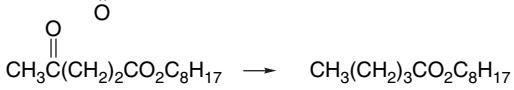
5.17. Suggest reagents and reaction conditions that would be suitable for each of the following selective or partial reductions:

(a)

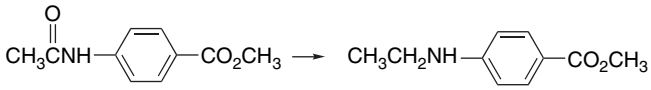
(b)



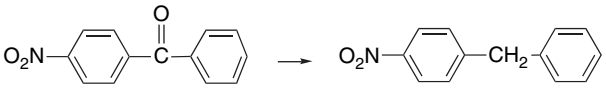
(c)



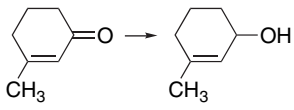
(d)



(e)

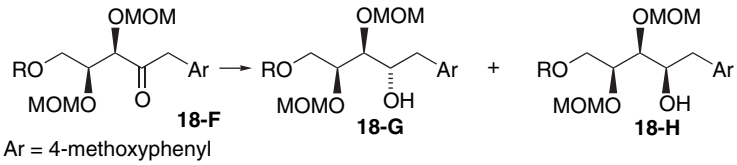


(f)



(g)

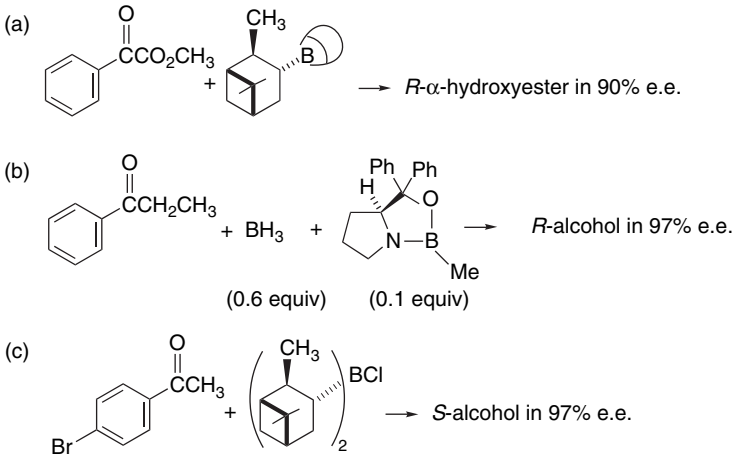
5.18. The reduction of the ketone **18-F** gives product **18-G** in preference to **18-H** with *increasing* stereoselectivity in the order $NaBH_4 < LiAlH_2(OCH_2CH_2OCH_3)_2 < Zn(BH_4)_2$. With L-Selectride, however, **18-H** is favored. Account for the dependence of the stereoselectivity on the various reducing agents.



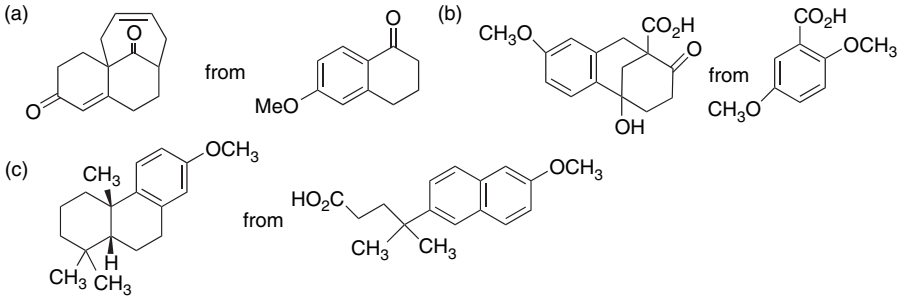
18-F **18-G** **18-H**

Ar = 4-methoxyphenyl
R = benzyl
MOM = methoxymethyl

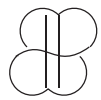
5.19. The following reducing agents effect enantioselective reduction of ketones. Propose a transition structure that is in accord with the observed enantioselectivity.



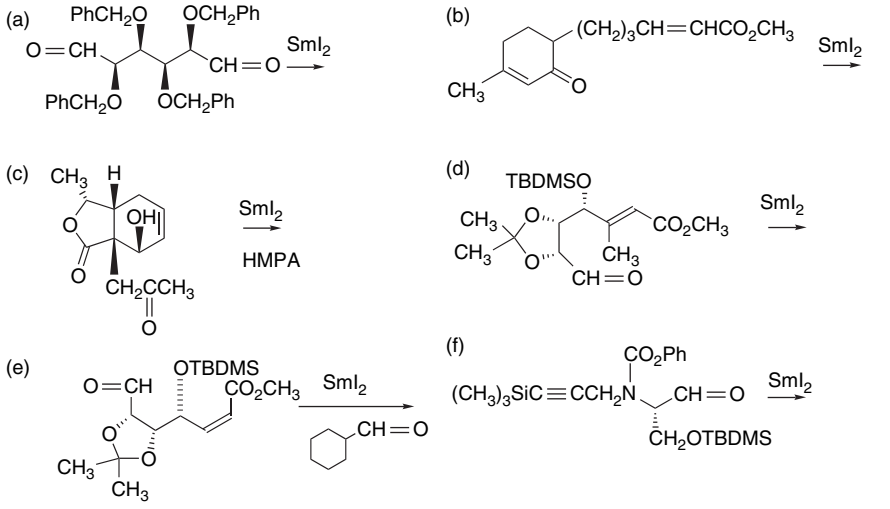
5.20. By retrosynthetic analysis, devise a sequence of reactions that would accomplish the following transformations:



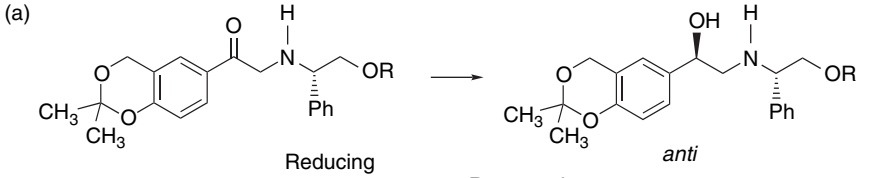
5.21. A group of topologically unique molecules called "betweenanenes" has been synthesized. Successful synthesis of such molecules depends on effective means of closing large rings. Suggest an overall strategy (details not required) to synthesize such molecules. Suggest types of reactions that might be considered for formation of the large rings.



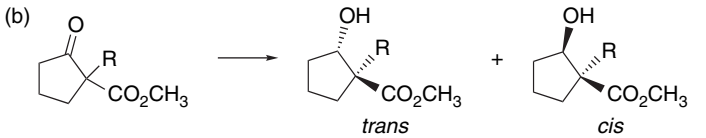
5.22. Give the products expected from the following reactions with Sm(II) reagents.



5.23. Provide an explanation based on a transition structure for the trends in stereoselectivity revealed by the following data.



Reducing agent	R	*anti:syn*
$NaBH_4$	H	2:1
$NaBH_4/CaCl_2$	H	10:1
$NaBH_4/CaCl_2$	CH_3	4.5:1



R	$NaBH_4$	$NaBH_4/CaCl_2$
	trans:cis	*trans:cis*
$CH_3CH_2CH_2$	1:1.9	1:99
$PhCH_2$	1:2.0	1:12
$CH_3CH_2CH{=}CH$	1:2.3	1:7