J. Seyden-Penne

Reductions by the Alumino- and Borohydrides in Organic Synthesis

Foreword by H.C. Brown

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PREFACE

Alumino- and borohydrides and, on a lesser scale, the boranes, form a part of the chemist's classic arsenal of reducing agents employed in organic synthesis. A number of these compounds are commercially available, but the study of their properties and the introduction of improved reagents or new reaction conditions continue to be important areas of research. Modern organic synthesis itself has to be selective, above all when it deals with elaborate multifunctional molecules. The reagents chosen at each stage of the chemical transformation must not therefore affect other functional groups in the molecule, preferably without even temporary protection. Moreover, the functional groups can influence the reaction process by controlling, for instance, a particular regioselectivity or stereoselectivity. In this book, we compare the potential of the main commercial hydrides or hydrides resulting from simple modification of these materials. They are easy to use, so that the reader can select, given the synthetic goal, the right reagent for the desired reduction. The emphasis then lies in:

- compatibility between the reduction of the group in question and the other functional groups present in the molecule;
- the possibility of partial reduction;
- the regio- and stereoselectivity of reductions that are induced, in particular, by other neighboring groups.

This work has been developed from a preparatory Ph.D. course given at Orsay for many years. The framework of the course material, which has aroused the interest of researchers confronted with problems involving reduction, has been extended with recent references, but the bibliography is far from being exhaustive. We refer, therefore, to some specialist articles, to some reviews, and to publications that contain bibliographical collections.

Finally, only the most common functional groups are reviewed.

Especially good in describing some experimental protocols is a recent compendium on reductions in organic chemistry is the book by M. Hudlicky,

Reductions in Organic Chemistry (1984), to which we eventually make reference.

This book has three parts:

1. Enumeration of the most useful reagents, indicating their stability and solubility characteristics as well as their principal applications.
2. Presentation of the reactivity of the functional groups toward reducing reagents, with special reference to problems of stereochemistry and compatibility.
3. Synoptic tables permitting access by hydride reduction to the main functional groups of organic chemistry by the reagents discussed in the text.

This book would not have come to fruition had it not been for the competence and assistance of Henriette Mandville, to whom I especially offer my thanks.

FOREWORD

The publication in 1939 of my Ph.D. Thesis (1938) at the University of Chicago (1935), "Hydrides of Boron. XI. The Reaction of Diborane with Organic Compounds Containing a Carbonyl Group," (Herbert C. Brown, H. I. Schlesinger and Anton B. Burg, *J. Am. Chem. Soc.* **1939**, *61*, 673-680), opened the hydride era for the reduction of functional groups in organic chemistry. This was followed by the discovery of the alkali metal hydride route to diborane, the synthesis of lithium and sodium borohydride, and many applications of these reagents for the reduction of organic compounds.

Over the years, many additional hydride reagents have been developed. Many new applications have been discovered and published. It became evident that only specialists in the field could possess the information to select the most favorable reagent for a specific reduction. It also became evident that help was needed for the average synthetic chemist. A possible solution to this problem appeared to be the publication of a companion volume to my book, *Organic Synthesis via Boranes* (Wiley, 1975). I invited Professor Nung Min Yoon of the Department of Chemistry of Sogang University in Seoul, South Korea, to come to Purdue University for a year on his next sabbatical. He industriously assembled and organized all of the available reduction data, but my exceptionally busy post-Nobel schedule did not provide the time I had envisaged to work on the book.

Consequently, I was delighted to learn that a book filling this void had been published in France by J. Seyden-Penne, and that VCH Publishers was planning to publish a translation that would help the English-speaking chemist.

In the past, I was anguished to read that chemists I respect were using hydride reagents that were not the most favorable reagents for the chemical transformations desired. Fortunately, this volume, *Reductions by the Alumino- and Borohydrides in Organic Synthesis* by J. Seyden-Penne, concisely organizes the pertinent information on the numerous hydride reagents now available, as well as the data on their applications, such that the chemist should find it relatively easy to select the most favorable regent for the desired transformation. This book should be in the personal library of every chemist engaged in organic synthesis. I look forward to reading the literature with much less discomfort than in the past.

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BRIEF NOMENCLATURE

AcOEt	ethyl acetate
Ar	aryl
Bn	benzyl
BOC	benzyloxycarbonyl
Bz	benzoyl
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
Et_2O	diethyl ether
HMPT	hexamethylphosphorotriamide
i-Pr	isopropyl
Me	methyl
MeCN	acetonitrile
MEM	methoxymethyl
Ph	phenyl
sec-Bu	*sec*-butyl
t-Bu	*tert*-butyl
THF	tetrahydrofuran
Tol	*p*-methylphenyl

PART I

DESCRIPTION AND CHARACTERISTICS OF THE MAIN REAGENTS

DESCRIPTION AND CHARACTERISTICS OF THE MAIN REAGENTS

This chapter lists and describes the characteristics of the main reagents. Cross-references are made, to the corresponding sections (§) of Part II, for more complete details.

1. LITHIUM ALUMINOHYDRIDE: $LiAlH_4$ (LAH)

This reagent is soluble in ethers. In Et_2O, it forms tight ion pairs, as in dioxane, but in THF and in DME it forms loose ion pairs [AD1, WS1]. It is used either in solution, as a suspension, in a solid–liquid phase transfer medium (benzene, 15-crown-5) [GL4, DC1], or adsorbed on silica gel [KH2, KH3]: its reducing power is so diminished under the latter conditions that it can reduce ketoesters to hydroxyesters or amide esters into amide alcohols [KS5].

$LiAlH_4$ reacts violently with water and must be handled away from moisture. Decomposition of an excess of LAH can be carried out either by treatment with water-saturated Et_2O or by addition of AcOEt, which is reduced to EtOH before treatment with water. Crude reaction mixtures can be treated either in acid or basic media, by complexation with tartaric acid, or even by the addition of a stoichiometric quantity of water to form LiOH and $Al(OH)_3$, which precipitate and are coated by solid $MgSO_4$ and Na_2SO_4 through which they are filtered [HUD]. If the reaction leads to amino alcohols, which are good ligands for aluminum, it is sometimes difficult to recover the product of the reduction, but

treatment by $(HOCH_2CH_2)_3N$ before the addition of water allows isolation of the product in good yield [PJ1].

This reagent shows very high reducing power and does not appear consequently to be very selective, even when the conditions of medium and temperature are varied.

Alcohols and phenols react with LAH: in using known amounts of these reagents, one obtains alkoxyaluminum hydrides whose reducing power can be modulated (see below).

By reaction with amines and especially pyridine, one produces a special reagent, lithium tetrakis *N*-dihydropyridinoaluminohydride [LL1].

There is a review devoted to the rearrangement observed during reduction by LAH [C2].

2. LITHIUM ALKOXYALUMINOHYDRIDES

The reaction of stoichiometric quantities of alcohols with LAH, leads to the formation of alkoxyaluminohydrides. The problem most often encountered is the resulting disproportionation according to the following equilibria [HM3]:

$$LiAlH_4 + ROH \rightleftharpoons Li(RO)AlH_3 + H_2\uparrow$$

$$Li(RO)AlH_3 + ROH \rightleftharpoons Li(RO)_2AlH_2 + H_2\uparrow$$

$$Li(RO)_2AlH_2 + ROH \rightleftharpoons Li(RO)_3AlH + H_2\uparrow$$

$$Li(RO)_3AlH + ROH \rightleftharpoons ROLi + (RO)_3Al + H_2\uparrow$$

Because of this disproportionation, some solutions of alkoxyaluminohydrides contain essentially the alcoholates and LAH; thus they present the same characteristics as LAH itself. This is especially the case when R = Et or *i*-Pr [WS1].

The following reagents are nevertheless stable:

- $Li(MeO)_3AlH$, dimer in THF [M1, M3, BK5]: its interest resides in the 1–2 attack of α-enones (§2.2.8).
- $Li(t\text{-}BuO)_3AlH$ (LTBA), monomer in THF: its reductive properties have been well studied [M1, M3, BK5, W3]; its principal applications are the reduction of acid chlorides and imidazolides to aldehydes at low temperature. Because of its bulkiness, a high stereoselectivity during the reduction of carbonyl compounds makes the reaction often more interesting than with LAH. At low temperature, aldehydes can be reduced in the presence of ketones, even an only slightly hindered ketone in the presence of more hindered ones (§2.2.1). Likewise, LTBA attacks

saturated ketones more rapidly than α-enones (§2.2.8). LTBA leaves ethers, acetals, epoxides, chlorides and bromides, and nitro derivatives inert; aliphatic esters are reduced only slowly, in contrast, phenyl esters are converted into aldehydes (§2.2.4).

- Formed from a tertiary alcohol, the reagent $LiAlH(OCEt_3)_3$ has been suggested: it reduces aldehydes selectively in the presence of ketones [K4].
- $Li(EtO)_3AlH$ (LTEA) and $Li(EtO)_2AlH_2$ can be produced in situ and have some interesting properties, but because they rapidly undergo disproportionation, they must be used very soon after their formation against sufficiently reactive substrates: they reduce nitriles into imines, which can then be hydrolyzed to aldehydes (§3.3) or else tertiary amides into aldehydes (§2.2.7).
- Reducing agents having special properties, obtained by the reaction of alkoxyaluminohydrides with CuBr [SS1, CA1] reduce the double and triple bonds of α,β-unsaturated carbonyl compounds (§2.2.8, 3.2, 3.4) and allow one to obtain *N*-acyldihydro-1,4-pyridines (§2.3.3.3).

3. SODIUM BIS(METHOXYETHOXY)ALUMINOHYDRIDE: $Na(OCH_2CH_2OCH_3)_2AlH_2$ (Red-Al)†

An interesting feature of this reagent is its solubility in aromatic hydrocarbons. It is also soluble in ethers. Most frequently, one uses a benzene solution to which are added various solvents. The reaction of Red-Al in water is less violent than that of LAH, which facilitates work-up. Hydrolysis can be carried out in acidic or basic media or with a minimal amount of water, as for LAH: in the last case, the addition of a small amount of acid, to neutralize the NaOH that forms, is recommended.

The peculiarities of Red-Al are the following: it easily reduces halogenated derivatives even if acetylenic (§1.1); tertiary amides lead to aldehydes (§2.2.7); and propargylic alcohols and amines are reduced to corresponding allylic alcohols and amines (§3.1). Epoxides remain intact unless they carry an alcohol functional group at the α-position: the reduction is then regioselective (§1.3). Aromatic nitriles are reduced, but aliphatic nitriles are not affected (§3.3).

In the presence of CuBr, in THF, Red-Al gives rise to an interesting reagent [SS1] that is especially good for selective reduction of the carbon–carbon double and triple bonds of unsaturated ketones, esters, or nitriles (§ 2.2.8, 3.2, 3.4).

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†[M1, MC1, W3]

4. DIISOBUTYL ALUMINUM HYDRIDE: *i*-Bu_2AlH (DIBAH)[†]

This compound is both soluble and stable in toluene or hexane. It is also soluble in ethers (Et_2O, THF, DME, glymes), but it forms solutions that are stable only at low temperature. It is a particularly strong Lewis acid. At high temperature, it leads to the hydroalumination of the C—C double and triple bonds [HH1]. The usual treatment after reduction consists of addition of MeOH, then water, to the solution, followed by separation of the aluminum salts that have precipitated. Alternatively, a treatment with dilute aqueous HCl can be done followed by extraction.

This reagent presents the following characteristics: It allows carbon–halogen bonds to remain unperturbed (§1.1). It can cleave aromatic ethers (ArOMe) to give phenols (§1.4) and acetals to give ethers (§1.4). Nitriles are reduced to imines, from which one obtains aldehydes (§3.3, 3.4). Esters are generally reduced selectively to aldehydes at low temperatures; if they are α,β-unsaturated, however, one obtains allylic alcohols (§2.2.4, 2.2.8). Lactones are reduced to lactols (§2.2.4) and imides to α′-hydroxyamides (§2.2.7). DIBAH is the reagent of choice for selectively reducing the carbonyl of α,β-unsaturated aldehydes and ketones (§2.2.4, 3.2) in toluene at low temperature. By way of contrast, in the presence of HMPT with the possible addition of a catalytic quantity of MeCu, DIBAH reduces α,β-ethylenic ketones and esters to saturated ketones and esters (§2.2.8) and α,β-acetylenic ketones and esters to α,β-ethylenic derivatives (§3.2).

Because of the Lewis acid properties of DIBAH, the reduction of functionalized carbonyl compounds often shows an interesting stereoselectivity (§2.2.3).

5. ALUMINUM HYDRIDES AlH_3 :

ALUMINUM CHLOROHYDRIDES: AlH_2Cl, $AlHCl_2$[‡]

AlH_3, $AlHCl_2$, and AlH_2Cl are obtained by reaction of a limited quantity of $AlCl_3$ with a solution of LAH/Et_2O. These reagents are just as sensitive as LAH toward water and must be decomposed under the same conditions as LAH. The ready

[†][BK5, W1, W3, YG1]
[‡][W3, BYI, BK5, EB1, E2]

generation of a dimethylethylamine-AlH_3 or *N*-methylpyrrolidine-AlH_3 complex, which can be used in toluene-THF and whose reducing properties are similar to those of AlH_3/THF, has been described [MP2].

These reagents are strong Lewis acids that cleave THF and acetals (§1.4). Nevertheless, they leave bromo- and chloroderivatives intact (§1.1); the regioselectivity of the opening of epoxides is opposite to that which is observed for LAH/THF (§1.3). Diarylcarbinols can be reduced to hydrocarbons (§1.4), and α,β-unsaturated carbonyl compounds to allylic alcohols (§2.2.8); the reduction of amides to amines is easier than with LAH (§2.2.7), especially in the case of α,β-ethylenic amides or the β-lactams. These reagents do not reduce the NO_2 groups.

Aluminum bis(*N*-methylpiperazino)hydride, obtained by combining 2 equivalents of *N*-methylpiperazine and a solution of AlH_3 in THF, is especially recommended for the reduction of esters or acids to aldehydes (§2.2.4, 2.2.5) [MM3].

The structure of lithium dimethylaminohydridoaluminates in various solutions in Et_2O, THF, or DME has been studied [BN6].

6. SODIUM AND POTASSIUM BOROHYDRIDES: $NaBH_4$, KBH_4[†]

The sodium and potassium borohydrides are soluble in water, alcohols, glymes, and DMF; they are not very soluble in Et_2O; and slightly soluble in cold THF, but more soluble under heating. Basic aqueous solutions are relatively stable, but solutions in MeOH or EtOH are rapidly decomposed to borates: the latter then reduce only very reactive substrates. Solutions in *i*-PrOH or glymes are more stable and are often used. If the substrates or products of the reaction are fragile in an alkaline medium, the solutions can be buffered by $B(OH)_3$ [DS1]. They are useful in phase transfer systems (liquid/liquid or solid/liquid) [ML1] on solid supports in the presence of THF or Et_2O [BI1], on resins [NS1], or in microemulsions [JW1].

An increase in the degree of reducing power of $NaBH_4$ in hot THF by addition of MeOH after reflux has recently been suggested [SO1].

The most frequent treatment, after reduction, is the addition of an acid. During the formation of alkoxyboranes or aminoboranes, the decomposition of these intermediates may require heating in a strong acid medium or even treatment by H_2O_2 in an alkaline medium [PS1, HUD] — a problem that often arises with reducing reagents derived from boron.

Sodium and potassium borohydrides are above all used for reducing al-

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[†] [BK5, W3, W4, PS1]

dehydes and ketones (§2.2.1, 2.2.2); α,β-ethylenic ketones are converted to mixtures [W3]. In alcoholic media or THF, they leave epoxides, esters and lactones, acids, amides, and most nitro compounds unreacted, but they do reduce halides (§1.1), anhydrides (§2.2.5), pyridinium salts (§2.2.3), the double bonds conjugated to two electron-withdrawing groups (§2.2.8, 3.4), and C—Pd and C—Hg bonds (§4.3). However, in the presence of hot MeOH in THF, $NaBH_4$ reduces esters to alcohols [SO1].

Compounds able to undergo solvolysis to sufficiently stable cations are reduced by $NaBH_4$ in alcoholic media, via these carbocations possibly in the presence of acid: diarylketones (§2.2) or the di- or triarylcarbinols are reduced to hydrocarbons (§1.4), imines and the iminium salts are reduced to amines (§2.3.1, 2.3.2), and imides to α′-hydroxyamides (§2.2.7).

In the presence of organic acids, the sodium and potassium borohydrides form acyloxyborohydrides that show some remarkable characteristics [GN1]; their reactivity depends on the quantity of acid present, which leads to either monoacyloxy- ($NaRCOOBH_3$) or trisacyloxyborohydrides [$Na(RCOO)_3BH$]. The reduction can be performed in the presence of a cosolvent (dioxane, THF, EtOH) or in pure organic acid (AcOH, CF_3COOH most frequently). Acyloxyborohydrides are easily decomposed by water. Aldehydes and ketones react more slowly than with the borohydrides in alcoholic media [GN1]. Given an acidic medium, they reduce di- and triarylketones and alcohols to hydrocarbons (§1.4, 2.2.1), acetals to ethers (§1.4), and nitriles to amines (§3.3). Their most interesting application consists of the reduction of —C═N— double bonds to amines: imines, oximes, enamines, iminium salts, and numerous nitrogen heterocyclic compounds are hence reduced (§2.3.1–2.3.4). These are the conditions of choice for effecting reductive aminations (§2.3.1) or the reductions of tosylhydrazines to hydrocarbons (§2.3.4). Depending on the case, $NaBH_4$ may be used, but it is preferable to substitute $NaCNBH_3$ while operating under the same conditions [GN1].

Under the action of Lewis acids such as BF_3 and $AlCl_3$, the borohydrides are converted into boranes, which then become the reducing agent.

7. LITHIUM BOROHYDRIDE: $LiBH_4$[†]

$LiBH_4$ is soluble in alcohols and ethers. In an Et_2O or THF medium, the Li^+ cation is a stronger Lewis acid than Na^+, which gives this reagent an increased reducing power: epoxides, esters, and lactones may then be reduced (§1.3, 2.2.4);

[†][BK5, W3, PS1]

amides and nitriles remain intact unless one adds hot DME or MeOH. Under these conditions, tertiary amides give alcohols and nitriles give amines (§3.3).

$LiBH_4$ can also be activated by adding $(MeO)_3B$ or Et_3B in Et_2O: esters are more rapidly reduced, and tertiary amides and nitriles are affected; but the sulfones, sulfoxides, and the NO_2 groups remain intact [BN3, YP2].

8. TETRABUTYLAMMONIUM BOROHYDRIDES: n-$Bu_4N^+BH_4^-$ †

These reagents are soluble in alcohols, ethers, CH_2Cl_2, and toluene. In hot CH_2Cl_2, they decompose slowly to borane. They are usable on solid supports [BI1].

An n–$Bu_4N^+BH_4^-$ is a very mild reducing agent. The reactivity order in CH_2Cl_2 is as follows: RCOCl > RCHO > RCOR′ >> RCOOR′, esters being reduced only under reflux. Such reagents permit reduction of aldehydes selectively in the presence of ketones (§2.2.1). In organic acid media, they lead to tetrabutylammonium acyloxyborohydrides, which, under reflux in C_6H_6, reduce aldehydes selectively without affecting the ketones (§2.2.1) [GN1].

9. ZINC BOROHYDRIDE: $Zn(BH_4)_2$ ‡

Zinc borohydride [BK5, W3, ON1, KH1], which exists in the dimeric form, is obtained by adding $ZnCl_2/Et_2O$ to a solution of $LiBH_4/Et_2O$. This relatively strong Lewis acid reduces α,β-ethylenic ketones to allylic alcohols (§2.2.8). As good chelating agent, it can be used in some very stereoselective reductions of ketones having a heteroatom at the α- or β-position, especially α- and β-ketoesters, ketoamides, or even epoxyketones (§2.2.3). The ester, amide, and nitrile groups and the halogens are not affected; however, the reduction of tertiary halides can be carried out [KH1].

A complex $Zn(BH_4)_2$,•1.5 DMF has been described [HJ1]; it shows a greater selectivity than $Zn(BH_4)_2/Et_2O$ and does not react with the α-enones: in MeCN this complex allows the reduction of aldehydes in the presence of ketones, the reduction of some sterically unhindered ketones in the presence of other less accessible ketones, or even the reduction of aliphatic ketones in the presence of aromatic ones (§2.2.1).

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†[PS1, RG1]
‡[BK5, W3, ON1, KH1]

10. SODIUM AND TETRABUTYLAMMONIUM CYANOBOROHYDRIDES: $NaCNBH_3$, n-Bu_4NCNBH_3[†]

The Na and TBA cyanoborohydrides are soluble in water, alcohols, organic acids, THF, and polar aprotic solvents. They are insoluble in Et_2O and hydrocarbons and may be used under phase transfer conditions [HM1]. One feature of the cyanoborohydrides is their stability in acid media at about pH 3: it is thus necessary to treat the crude reaction mixture with a strong acid to decompose the intermediates formed.

These reagents are interesting because aldehydes and ketones are affected in acidic media only, which permits the reduction of carbon–halogen bonds (§1.1) without affecting carbonyl groups, esters, or nitriles.

In organic acid media, $NaCNBH_3$ is converted to acyloxycyanoborohydrides whose reactivity is comparable to that of $NaBH_4/CF_3COOH$, especially concerning the reduction of imines to amines, tosylhydrazones to saturated hydrocarbons, oximes to hydroxylamines, or reductive amination: depending on the case, $NaBH_4$ or $NaCNBH_3$ is recommended (§2.3.1–2.3.4) [GN1].

11. ZINC CYANOBOROHYDRIDE[‡]

Zinc cyanoborohydride is formed by reaction of $ZnCl_2/Et_2O$ in a solution of $NaCNBH_3/Et_2O$ [KO1] or even by the action of ZnI_2 on $NaCNBH_3/CH_2Cl_2$ [LD1].

In ether media (Et_2O or THF), the nature of the reagent is ill-defined, but it reduces aldehydes, ketones, and acid chlorides, but leaves esters, anhydrides, and amides unchanged. In MeOH, the reduction of enamines and imines to amines may be effected in the same way as the reduction of tosylhydrazones to hydrocarbons (§2.3.4).

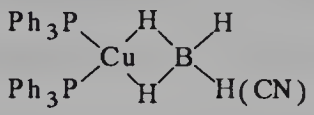
The reagent formed by reaction of ZnI_2 with $NaCNBH_3$ in CH_2Cl_2 allows the reduction of aromatic aldehydes and ketones, as well as benzylic, allylic, and tertiary alcohols to hydrocarbons, probably by a radical process [LD1] (§1.4). Some comparable reductions are carried out in ether media starting from tertiary, benzylic, or allylic halides (§1.1).

[†][BK5, W3, L1, HN1, PS1]

[‡][KO1, LD1]

12. CUPROUS BISDIPHENYL PHOSPHINEBOROHYDRIDE AND CYANOBOROHYDRIDE†

These cuprous borohydrides are isolated complexes of the structure



which transfer only a single hydride.

In neutral media, they leave the carbonyl derivatives intact but reduce tosylhydrazones to the corresponding hydrocarbons under reflux of $CHCl_3$ (§2.3.4). The reduction is compatible with α-enone, epoxide, or lactone groups present in the molecule [GL3]. In cold acetone, these reagents reduce acid chlorides to aldehydes [FH1] (§2.2.6). In the presence of Lewis acids or gaseous HCl in CH_2Cl_2, they reduce aldehydes and ketones; the selective reduction of aldehydes in the presence of ketones can also be realized (§2.2.1). These reagents also reduce aromatic azides to amines (§4.2).

13. LITHIUM TRIETHYLBOROHYDRIDE: $LiEt_3BH$‡

$LiEt_3BH$ is soluble in ethers (Et_2O, THF, glymes) and hydrocarbons. Rapidly decomposed by water or alcohols, it must be handled away from moisture. The work-up of the crude reaction mixture consists of hydrolysis, possibly in the presence of acid, followed by the action of alkaline H_2O_2 to oxidize Et_3B, which is a by-product of the reduction, to EtOH and boric acid soluble in water.

Besides being much more reactive than $LiBH_4$, the triethyl compound shows an analogous reactivity spectrum. It reacts particularly well with primary and secondary alkyl halides and tosylates, even when hindered, with an inversion of configuration (§1.1), and with epoxides at the least sterically hindered site (§1.3). It reduces ammonium salts to tertiary amines. The reduction of imines and ketones, cyclic or functionalized, by $LiEt_3BH$/THF, can be very stereoselective (§2.2.2, 2.3.1), but in general Li(*sec*-Bu)$_3$BH is preferable. Tertiary amides are reduced to aldehydes, then to alcohols (§2.2.7), and nitriles to imines,

†[FH1, FH2, DF1, HM2, SP1, W4]
‡[BK5, BK6, W3, BN4, KB3, KB5]

hydrolyzable to give aldehydes (§3.3). The use of KEt_3BH for chemoselective reduction of carboxylic acid esters has been suggested [YY1].

14. LITHIUM AND POTASSIUM TRI(*sec*-BUTYL)BOROHYDRIDES (L AND K SELECTRIDES): Li or K (*sec*-Bu)$_3$BH[†]

The L and K selectrides are soluble in ether media (Et_2O, THF, glymes). The treatment after reduction is identical to that employed for $LiEt_3BH$.

The principal interest of these reagents resides in their bulkiness, such that the reductions of slightly hindered cyclic ketones and imines occurs on the equatorial face (§2.2.2, 2.3.1) and aliphatic carbonyl compounds are reduced with a high stereoselectivity (§2.2.2). The L and K selectrides reduce selectively the C=C bond of α-enones and α,β-ethylenic esters unless the β-position is disubstituted (§ 2.2.8); in the latter case, the carbonyl of the α-enones is reduced.

15. POTASSIUM TRIISOPROPOXYBOROHYDRIDE: K(*i*-PrO)$_3$BH[‡]

This borohydride, obtained in THF by adding 3 moles of *i*-PrOH to a solution of KBH_4, essentially reduces aldehydes, ketones, and halogenated derivatives. Its principal interest is the reduction of the haloboranes RR'BCl or RR'BBr to boranes RR'BH. This process allows sequential hydroborations, first by a halogenoborane, which is reduced to a hydrogenoborane that can then undergo a new hydroboration, giving access to mixed trialkylboranes. This reagent also transfers KH toward similarly hindered trialkylboranes, thereby forming KR_3BH.

16. LITHIUM ALKYLBOROHYDRIDES

The properties of two types of reagents have been explored: Li(*n*-Bu)BH_3 [KM2]

[†][W3, BK5]
[‡][BC3]

and the borobicyclononane Li 9-BBN-H [BM1, KB1]. No peculiarity has been pointed out in relation to other reducing agents.

The treatment of the crude reaction mixture after reduction by Li 9-BBN-H requires the action of H_2O_2 in an alkaline medium to convert the borane formed to water-soluble or volatile compounds.

17. BORANE: BH_3 †

Rarely utilized in its gaseous dimeric form (B_2H_6), borane is generally employed as a solvate with THF or Me_2S. BH_3•THF is employed in ether media. BH_3•Me_2S is soluble in ethers, hydrocarbons, and CH_2Cl_2.

Borane reduces carboxylic acids in the cold without attacking esters, nitriles, and halogenated derivatives (§2.2.5). It easily reduces amides (§2.2.7).

An important limitation is hydroboration of carbon–carbon double and triple bonds [BK7, HH1, L2].

18. AMINE-BORANES: R_3N-BH_3 ‡

These complexes are more stable than the borane complexes with ether or Me_2S. They are soluble in water and alcohols and stable in the presence of acetic acid. Their decomposition requires the action of a strong acid and often even heating, or a decomplexation by an amino alcohol.

With respect to reactivity the amine-boranes lie somewhere between BH_3•THF and $NaBH_4$. They reduce aldehydes and ketones without affecting ester, ether, SPh, and NO_2 groups. The reduction of ketones can be expedited by the addition of Lewis acids or carried out in acetic acid [PS1]. On alumina or silica supports, amine-boranes can selectively reduce aldehydes without affecting keto groups [BS1]. Amino acids can be reduced to amino alcohols, without epimerization if they are chiral [PS1].

Ph_2NH•BH_3 is a recommended reagent because its stability and its reactivity are superior to those of amine-boranes formed from aliphatic amines [CU1].

Pyridine-borane reacts poorly with carbonyl compounds and has been suggested for carrying out reductive aminations (§2.3.1) [PR2].

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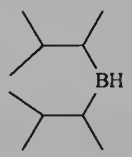
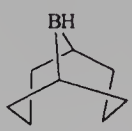
†[PS1, L2, BK5, HC1]
‡[A1, PS1]

19. SUBSTITUTED BORANES†

Substituted boranes are obtained by hydroboration of relatively hindered olefins such as the trimethylethylene, tetramethylethylene, and 1,5-cyclooctadiene, which, by action of BH_3, lead respectively to diisoamylborane, thexylborane, and 9-BBN:

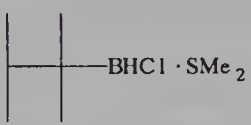
diisoamylborane: Sia_2BH = 

thexylborane: $ThexBH_2$ = 

9-BBN: 

which are used in THF.

Thexylchloroborane, obtained by reaction of $ClBH_2{\bullet}SMe_2$ with tetramethylethylene

$ThexBHCl{\bullet}SMe_2$ = 

in solution in CH_2Cl_2 or in THF, where it is less stable, is also recommended. The crude reaction mixture is hydrolyzed in a hot acid medium.

The reagents reflect their sterically hindered and Lewis acid character. This is why the reduction of relatively hindered acyclic ketones by Sia_2BH shows the opposite selectivity to that observed with the alumino- or borohydrides (§2.2.2) [HW1]; the reduction of hindered cyclanones by $ThexBHCl{\bullet}SMe_2$ leads to the least stable alcohol [BN5]. α,β-Ethylenic aldehydes and ketones are reduced by 9-BBN or $ThexBHCl{\bullet}SMe_2$ to allylic alcohol, the selectivity being better than that observed with $BH_3{\bullet}SMe_2$ or $ThexBH_2$ (§2.2.8). Acids are selectively reduced to aldehydes by $ThexBHCl{\bullet}SMe_2$ [BC5] (§2.2.5). Tertiary amides are reduced by 9-BBN to alcohols and by Sia_2BH and $ThexBH_2$ to aldehydes (§2.2.7), while BH_3 transforms these tertiary amides to amines and ThexBHCl reacts with them slowly.

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† [BK5, BN5]

20. ALUMINO- AND BOROHYDRIDES IN PRESENCE OF TRANSITION METAL SALTS†

Solutions or suspensions of LAH in Et_2O or THF in the presence of $FeCl_3$, $CoCl_2$, $TiCl_3$, or $NiCl_2$ [GO3, AL1] are used as reducing agents. Similarly, Li or $NaBH_4$ in MeOH or DMF may be used in the presence of salts of complexes containing nickel, cobalt, tin, palladium, or lanthanides [GO3, W4]: their structure is often not well known.

Each reagent shows some particular characteristics, but a certain number of results merit emphasis:

- the reduction of alkenes by LAH/$FeCl_2$, $CoCl_2$, $TiCl_3$ or $NiCl_2$, or $NaBH_4/CoCl_2$, all of which do not touch aromatic derivatives (§2.1);
- the reduction of the aromatic moieties by $NaBH_4/RhCl_3$ in EtOH;
- the reduction of aromatic nitrogen-containing heterocycles by $NaBH_4/NiCl_2$ in MeOH, which does not perturb aromatic carbon-containing rings (§2.3.3);
- the reduction of aromatic or alicyclic halogenated derivatives by $NaBH_4/NiCl_2$ in DMF either in the presence of Ph_3P or by LAH in the presence of various transition metal salts (§1.1);
- the reduction of nitriles and nitro derivatives to amines by $NaBH_4/CoCl_2$ in MeOH (§3.3, 4.1);
- the reduction of nitro derivatives and of oximes to amines by $NaBH_4/NiCl_2$ (§2.3.4, 4.1);
- the reduction of arylketones to hydrocarbons by $NaBH_4/PdCl_2$ in MeOH (§2.2.1);
- the reduction of allylic acetates to saturated hydrocarbons by $NaBH_4/NiCl_2$ (§1.2);
- the reduction of α-enones to allylic alcohols by $NaBH_4/CeCl_3$ in MeOH (§2.2.8).

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†[W4, GO3, AL1]

PART II

REDUCTION OF THE MAIN FUNCTIONAL GROUPS

CHAPTER 1

CLEAVAGE OF THE CARBON–HETEROATOM SIMPLE BOND

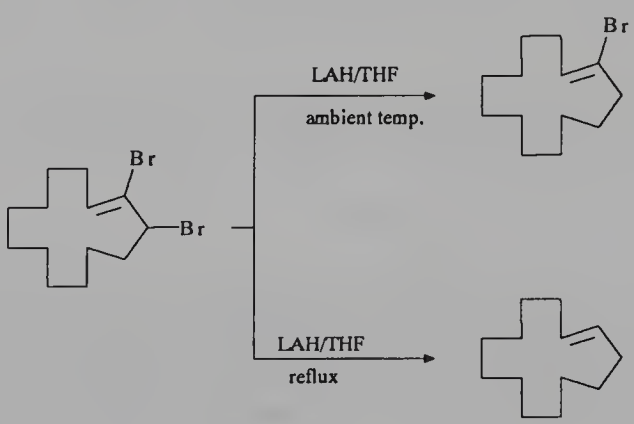
1.1. HALIDES $\rangle C-X$

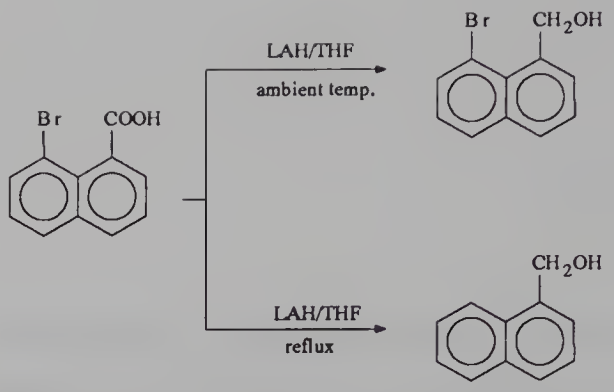
LAH/THF reduces to hydrocarbons chlorides, bromides, and iodides, whatever their degree of substitution may be (primary, secondary, tertiary, aromatic, vinyl, and cyclopropyl). The order of reactivity is iodide > bromide > chloride:

$$ArCH_2X \approx \text{allyl} > RCH_2X > R_2CHX > R_3CX$$

In fact, the aliphatic and alicyclic iodides and bromides are reduced at room temperature, while the aromatic, vinyl, and cyclopropyl bromides as well as the chlorides can be reduced only under reflux.

As an example, the following selective reductions can be performed [P1]:





In the presence of $CeCl_3$ in cold DME or under reflux in THF, LAH reduces all the halides [GO2].

The mechanism of this reduction is a bimolecular nucleophilic substitution for the reaction of LAH with most primary and secondary halides [BK5, PC1]. A single-electron transfer (SET) has been stressed in the reduction of primary iodides [AD3, AG1], although some doubts have been cast [PC1] on this mechanism in the case of bromocyclopropanes [HW2] and aromatic or vinyl halides [C1], especially in the presence of $CeCl_3$ [GO2]. In this case, some rearrangements may be observed.

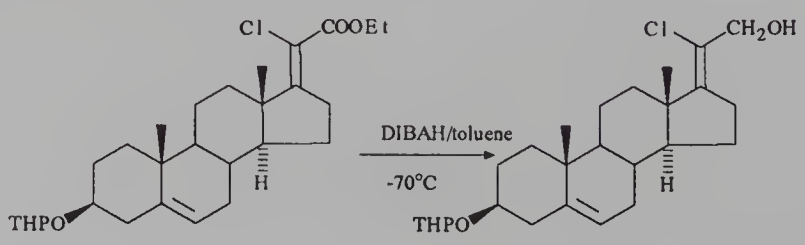
The alkoxyaluminohydrides reduce aliphatic and alicyclic iodides and bromides but not the corresponding chlorides, except for Red-Al in benzene, which reduces all halides, as well as the cyclopropyl and aromatic derivatives. The reduction of 1-bromoalkynes by the latter reagent does not give a mixture, unlike other aluminohydrides. Difluoroalkenes, meanwhile, are converted to the monofluoro derivatives [M1]:

$$RC{\equiv}C\text{–}Br \xrightarrow[Red\text{-}Al/C_6H_6]{} RC{\equiv}CH$$

$$PhCH{=}CF_2 \xrightarrow[Red\text{-}Al/C_6H_6,0°C]{} PhCH{=}CHF$$

$$PhCH{=}CF_2 \xrightarrow[Red\text{-}Al/C_6H_6,reflux]{} PhCH{=}CH_2$$

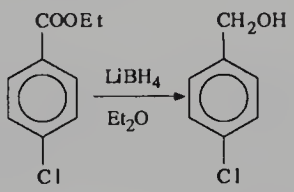
On the other hand, the selective reduction of an α,β-ethylenic-α-chloro ester [DW1] comes from the failure of DIBAH in cold toluene to react with halogenated derivatives [YG1].



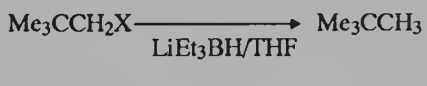
The reduction of the fluorides requires the electrophilic assistance of a Lewis acid in breaking the C—F bond: AlH_3/Et_2O and LAH/$CeCl_3$/DME are adequate reducing agents [P1, GO2]. AlH_3, however, leaves the aliphatic C—Br and C—Cl bonds intact [PC1].

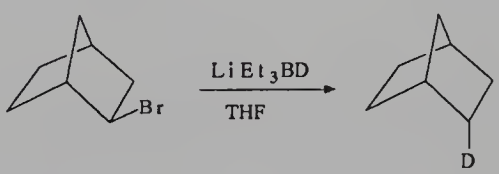
The alkaline borohydrides are less reactive toward halides. $NaBH_4$ in DME or DMSO or in the presence of polyethylene glycols [SF2] reduces only primary or secondary bromides upon heating; with chlorides the reaction is even slower [PS1]. The dibromocyclopropanes can be selectively reduced to monobromocyclopropanes by heating with $NaBH_4$/DMF [PS1]. The reduction of aromatic halides under these conditions requires UV irradiation: these reductions undoubtedly take place via a radical pathway. Reduction of primary, secondary, and aryl bromides and iodides by $NaBH_4$ in hot toluene in the presence of benzo-15-crown-5 and a polymer bound tin halide catalyst has been described [BW1]. Aryl bromides and iodides are also dehalogenated by $NaBH_4$-$CuCl_2$/MeOH [NH1], while chlorides and fluorides remain unaffected. Aryl bromides are inert in the presence of $NaBH_4/ZrCl_4$/THF [IS1].

$LiBH_4$ leaves the halogens inert in the following selective reduction [BK5]:

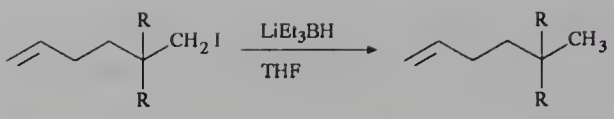


$LiEt_3BH$ in THF is the reagent of choice for the reduction of primary and secondary halides; the latter takes place by an S_N2 mechanism with configuration inversion, without rearrangement or cyclization as shown in the following examples [BK1]:



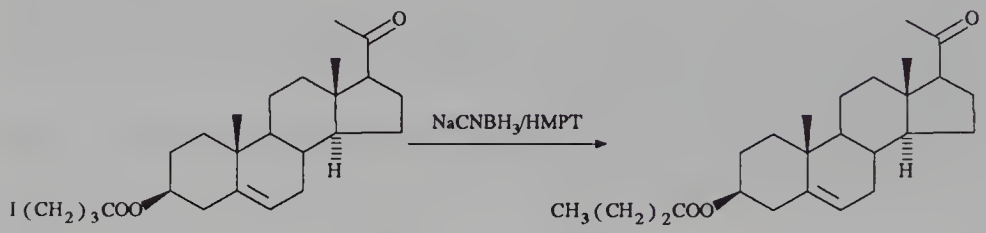


The neopentyl or norbornyl systems, which easily undergo rearrangement, thereby remain unchanged. Similarly, as shown in the following example [AG1], hexene-5-yl iodide, capable of cyclization via a radical pathway, is transformed into a linear olefin, without modification of the carbon skeleton.



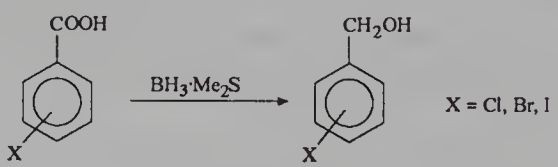
It is convenient to use 2 equivalents of $LiEt_3BH$ per molecule to reduce a halide molecule. In fact, the by-product of the reduction is BEt_3, which forms a complex $LiEt_3BH$ $[Et_3BH...BEt_3]^-Li^+$, which is much less reactive. The aromatic and tertiary halides remain intact under these conditions [BK1].

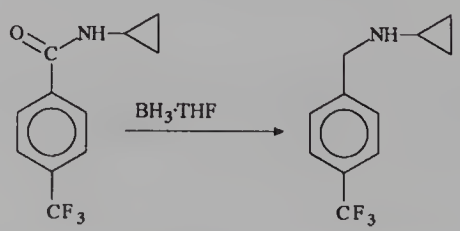
The selective reduction of the primary halides can also be accomplished with $NaCNBH_3$ in HMPT or DMSO or even by $NaBH_4$ in warm DMSO. Epoxides, nitriles, amides, ketones, and esters are not affected under these conditions [HK1, L1], as illustrated by the following:



n-$Bu_4N^+CNBH_3^-$ shows itself to be even more selective, since it reduces only the primary iodides and bromides, leaving the chlorides alone [P1].

Borane leaves the halides intact in an ether medium, wherein the following selective reduction takes place [P1]:



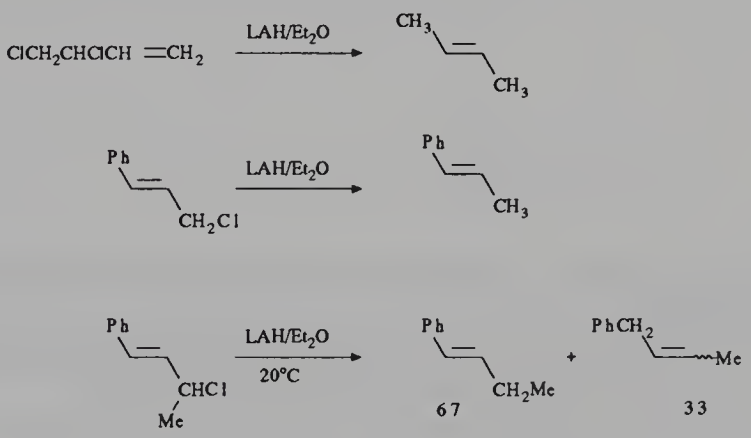


In the presence of transition metal complexes such as $(Ph_3P)_4Ni$, halogenated aromatic derivatives are reduced by $NaBH_4$/DMF [W4] or $PdCl_2/NaBH_4$/MeOH [GO2]. The DDT and 2,4D types of pesticides are also reduced by $Ni_2B/NaBH_4$ in alcohol [GO2].

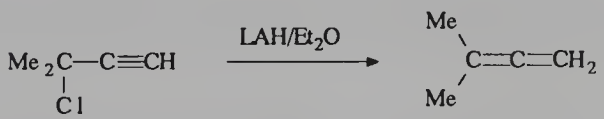
In a protic medium (alcohol or aqueous diglyme), tertiary halides undergo solvolysis and lead to the corresponding carbocations, reducible by $NaBH_4$. If the carbocations are able to undergo rearrangement much faster than reduction, a rearranged alkane product is obtained [BB1]. Borane in CF_3COOH shows a similar behavior [MM1].

$$R_3C{-}X \xrightarrow[MeOH]{} R_3C^+ \xrightarrow[NaBH_4]{} R_3C{-}H$$

When associated with a Lewis acid such as $Zn(BH_4)_2$, $NaCNBH_3/ZnI_2$ or $NaCNBH_3/SnCl_2$ can also induce, in ether, the cleavage of the C—X bond of the halides, which lead to sufficiently stable carbocations. An analogous mechanism can be proposed to understand the reaction of LAH with the secondary allylic chlorides in ether, a process that takes place with rearrangement [HN2], while primary derivatives are reduced without rearrangement [HN2].



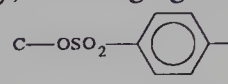
Similarly, propargylic chlorides are converted to allenes:

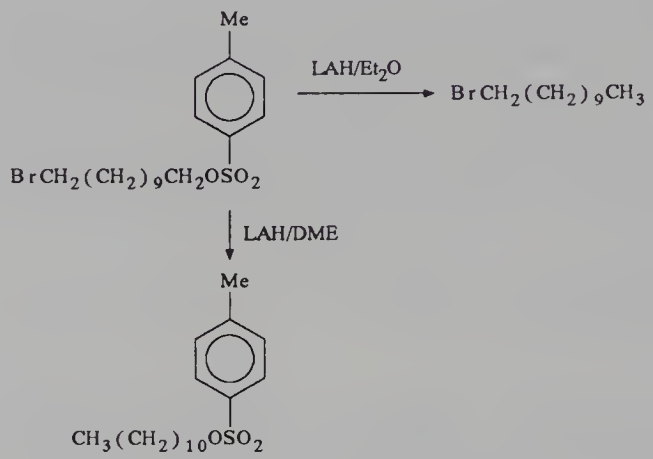


$Zn(BH_4)_2/Et_2O$ reduces the tertiary and benzylic halides at the corresponding carbon sites, but the allylic derivatives give polymers [KH1].

However, $NaCNBH_3/ZnI_2/Et_2O$ or $NaCNBH_3$ in the presence of $SnCl_2$ selectively reduces the tertiary, benzylic, and allylic halides without affecting the primary or secondary halides, esters, and amides [KK1, KK6]. The -ate complex formed by the reaction of *n*-BuLi with 9-BBN in hexane has an identical behavior: the tertiary, allylic, and benzylic halides are reduced; the primary and secondary halides remain intact [TY1].

1.2. SULFONATES AND ESTERS: $\geq C-OSO_2R$; $\geq C-OCOR$

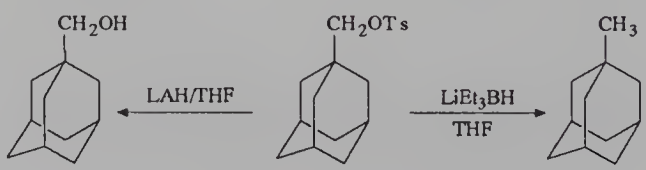
LAH/Et_2O reduces sulfonates, requiring the electrophilic assistance of the Li^+ cation in the cleavage of the C—O bond. This is why, on changing the solvent, it is possible to reduce at will the C—Br bond or  of the following bifunctional compound [K1]:



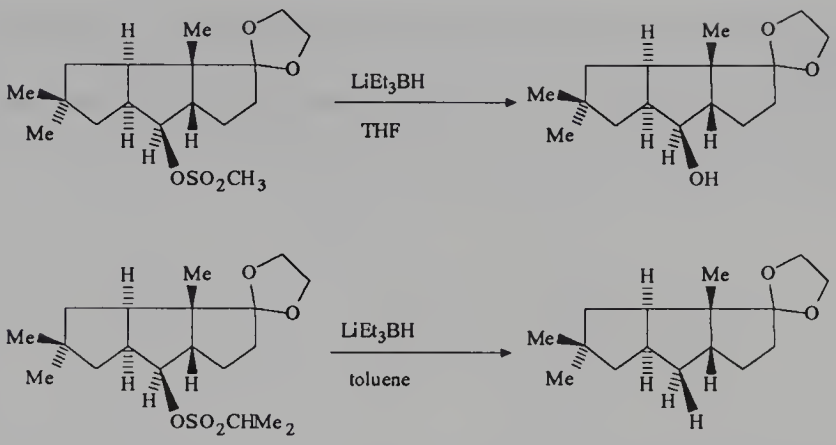
In DME, where the Li^+ cation is well solvated, electrophilic assistance does not manifest itself.

The use of $LiBH_4$, $LiEt_3BH$, or DIBAH in THF also reduces primary and secondary sulfonates to hydrocarbons [YG1, BN3, KB1, BK5].

However, if the substrate is too sterically hindered, the attack of the reducing reagent takes place on the sulfur and one obtains the corresponding alcohol [WS2, GL5, SH4]: this phenomenon is less sensitive than the result obtained when one uses $LiEt_3BH$, as shown in the following example [KB1]:

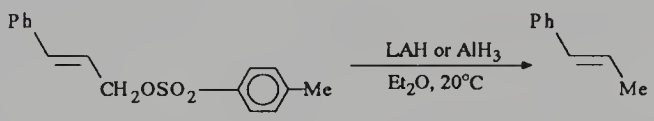


In one reported case [HS3], however, a hindered mesylate, when reacted with $LiEt_3BH$, did not produce the alkane but rather the corresponding alcohol. The authors thereby recommend the use of isopropanesulfonate Me_2CHSO_2OR which, when treated with $LiEt_3BH$, is not attacked at the sulfonate site.

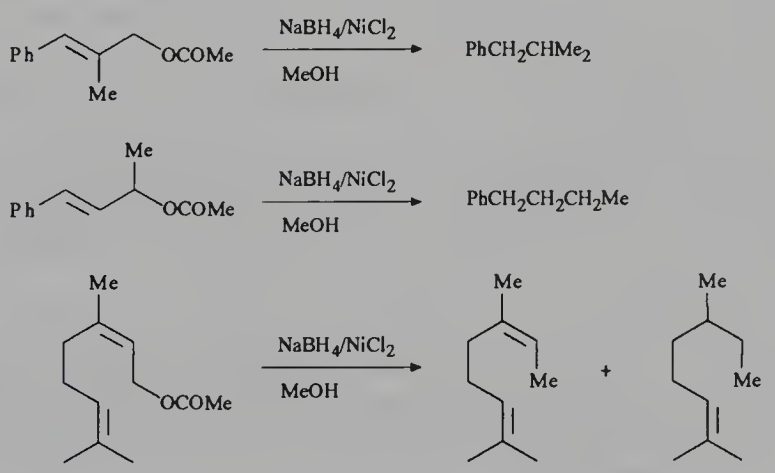


$NaBH_4$ in hot DMSO can also reduce the primary sulfonates [HH2, PS1]: this method has been applied to various sugar derivatives [WW1, KS2].

Primary allylic tosylates are reduced to the corresponding olefins by LAH or AlH_3 [HN2]; secondary tosylates do not react at all.



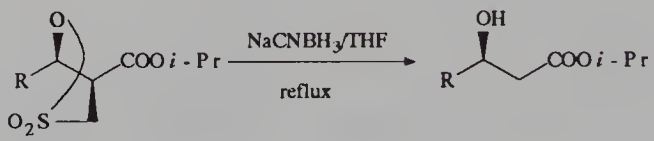
The acetates, whether primary or secondary, allylic, propargylic, or benzylic, are also reduced by $NaBH_4/NiCl_2$/MeOH to hydrocarbons [I2, HP2], but the double bond, in general, is not preserved.

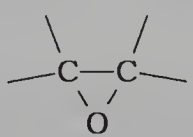


The problems of solvolysis and possible rearrangements are similar to those of halides.

For example [KN1], the reduction of a tricyclic tosylate, whose structure is such that its double bond can participate to the reaction, leads to the formation of a cyclopropane via an intermediate carbocation.

Cyclic sulfates of 1,2-diols are reduced to monoalcohols by $NaCNBH_3$ in refluxing THF at pH 4–5 if symmetrical (R = COO*i*-Pr), or regioselectively to a β-hydroxyester by $NaBH_4$/MeCONMe$_2$ when R = alkyl [GS3].



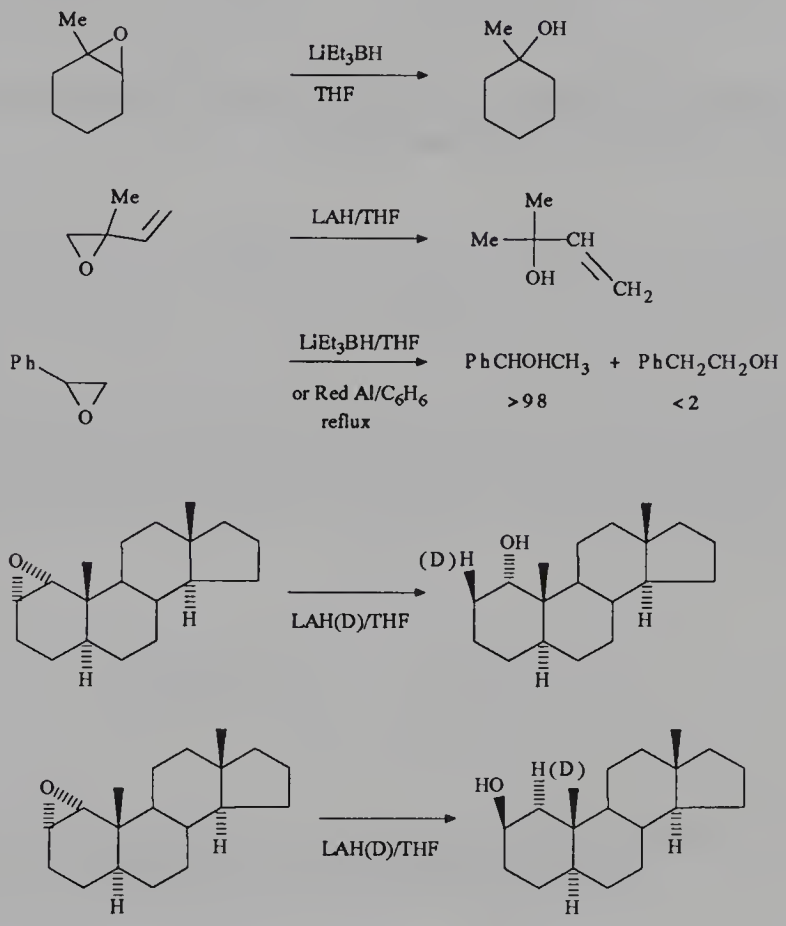
1.3. EPOXIDES: 

The cleavage of the C—O bond of epoxides requires the electrophilic assistance of a reagent, which can either be a Lewis acid (Li^+) or behave as such (AlH_3, DIBAH) unless it is too hindered. Thus, the reduction of epoxides by the borohydrides is very slow [BK5] unless one adds strong Lewis acid to them: $NaCNBH_3$ in the presence of BF_3-Et_2O [HT1], or $LiBH_4$ in the presence of BEt_3 [YO1] or 

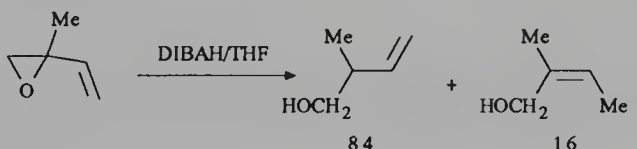
[BN3]. The reduction by BH_3 is also assisted by the presence of BF_3•Et_2O [PS1, L2], but it is more difficult when it is carried out with bulky substituted boranes (Sia_2BH, 9-BBN, or ThexBHCl) [BK5, BN5, G4]. Red-Al is not very efficient either, except when the epoxides carry an alcohol functional group at the α-position [FK1, M1].

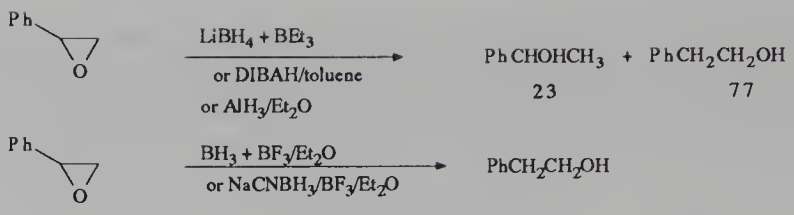
The regioselectivity of the opening of disymmetrical epoxides depends essentially on the strength of the Lewis acid–base interaction between the partners. If this interaction is rather weak, the reduction takes place at the least sterically hindered carbon site. Such is the case when one uses LAH or $LiEt_3BH$ in THF or Li 9-BBN-H [G4].

The mechanism of the reaction is S_N2 assisted by the Lewis acid; its stereoselectivity is thereby a *trans*-diaxial opening (Furst–Plattner rule) [G4], as shown in the following examples [RP1, BK5, BK6, W1, BN4, BM1].

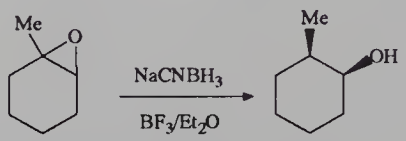


When one uses a stronger Lewis acid, the regioselectivity is reversed: the hydride attack takes place preferentially on the carbon that is better able to stabilize a carbocation: such is the case when one uses BH_3 or $NaCNH_3$ in the presence of BF_3, AlH_3/Et_2O or DIBAH in THF, toluene, or hexane, or else $LiBH_4/BEt_3$ [HT1, YO1, YG1, PS1, L2, W1, M1, G4, E2].

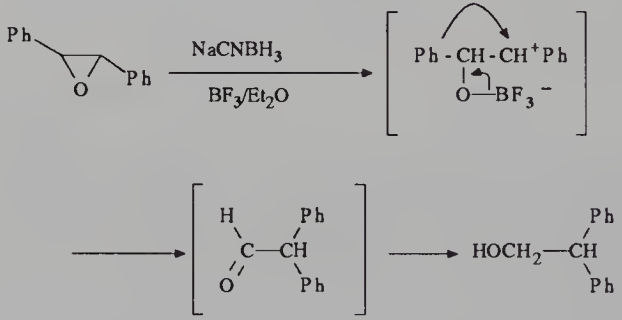




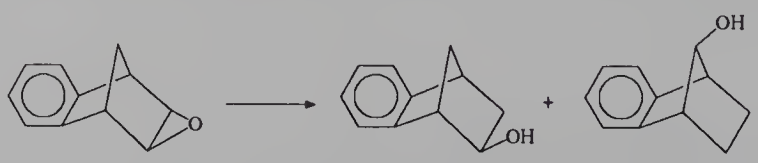
The reduction of the epoxide of 1-methyl cyclohexene under these conditions leads to *cis*-2-methyl cyclohexanol [HT1].



In certain cases, whenever the Lewis acidity of the reagent is high enough and whenever the structure of the molecule is favorable, the reaction involves the formation of a carbocation, which can undergo intramolecular migration, leading, for example, to an aldehyde that is later reduced, as shown in the example below [HT1].



The carbocation can rearrange in a different way when the alcohol obtained has a modified carbon skeleton. However, the use of LiEt3BH allows one to minimize these rearrangements, as the following example shows [G4].

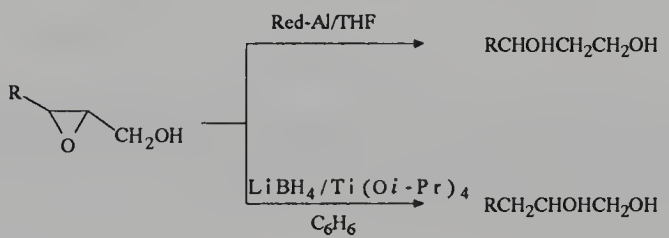


LAH	15	85
$LiEt_3BH$	93	<0.1

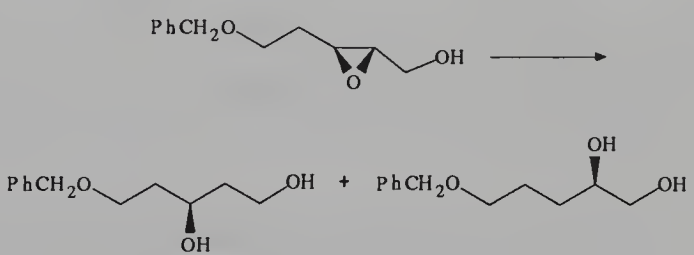
Epoxides undergo decomposition under the influence of the acyloxyboranes in organic acid [MM1]. Being bulky, LTBA/THF leaves the epoxide unattacked in the cold and leads to the selective reduction shown below [M1]: the primary alcohol that is formed undergoes lactonization, but the epoxide and the ester are not reduced.

The presence of a functional group in the vicinity of the epoxide can influence the regioselectivity of the reduction. Such is the case for the epoxy-2,3 alcohols, which are quite interesting because they can be obtained in an optically active form by asymmetric epoxidation of the corresponding allylic alcohols [KS3].

The action of LAH/THF or better yet of Red-Al in the same solvent [V1, MM2] or preferably in DME [GS4] selectively leads to the 1,3-diols, while DIBAH [FK1] or $LiBH_4/(i\text{-}PrO)_4Ti/C_6H_6$ [DL1] gives access to the 1,2-diols.

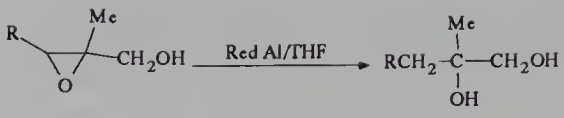


The hydride attack is stereospecific, and in the following chiral molecule, the reaction proceeds with configuration inversion [FK1].

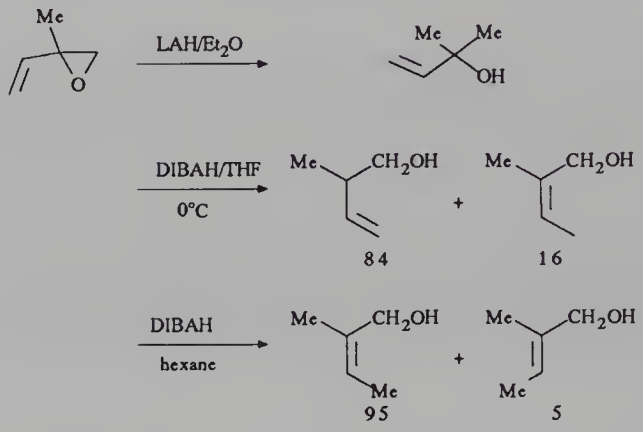


Red-Al/THF	98	2
DIBAH/hexane	7	93

The limitation of the method is steric hindrance: if the carbon atom bearing the primary alcohol is disubstituted, one obtains, with Red-Al, the other regioisomer [V1].

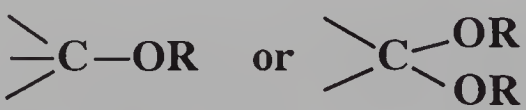


The vinylic epoxides can be reduced by attack on the epoxide carbon atoms according to the usual rules, or they can undergo conjugate reduction, as demonstrated in the following example [LK1].



LAH attacks the epoxide at the least substituted carbon, and DIBAH/THF mainly attacks the epoxide at the most substituted carbon, whereas DIBAH/hexane only gives the conjugate reduction.

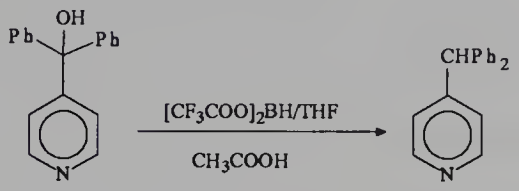
1.4. ALCOHOLS, ETHERS, AND ACETALS



1.4.1. Alcohols

Alcohols are generally converted to alcoholates by the alumino- and borohydrides. The cleavage of the C—O bond can take place with warming with Red-Al [M1], or it can occur under solvolytic conditions, in which starting with appropriate alcohols such as benzylic or allylic alcohols gives stable carbocations. The carbocations thus formed are then reduced to hydrocarbons. Therefore, the diaryl- and triarylcarbinols are reduced by $NaBH_4/CF_3COOH$ [GN1] or $(CF_3COO)_2BH/THF/CF_3COOH$ [MM1].

$$ArCHOHAr' \xrightarrow[NaBH_4/CF_3COOH]{} ArCH_2Ar'$$

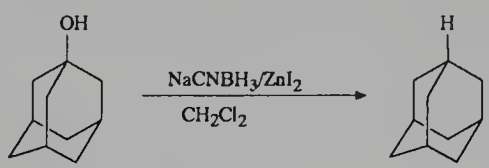


When using suitable experimental conditions, electron-donating substituted primary benzyl alcohols can also be reduced to substituted toluenes [NB2]. However, $NaBH_4/CF_3SO_3H/Et_2O$ is far superior to the $NaBH_4/CF_3COOH$ system in reducing 2-aryladamantanols to the corresponding hydrocarbons [OW1]. Adamantylmethanol, under the same conditions, leads to homoadamantane. Similarly, other carbocyclic substituted methanols give ring-expanded cycloalkanes [OW2].

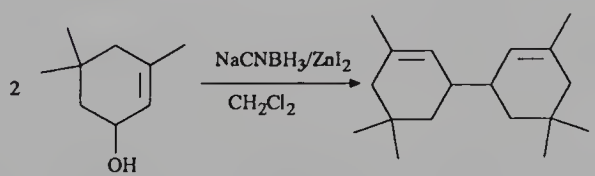
$NaBH_4/AlCl_3/THF$ or AlH_3/Et_2O also reduces the diarylcarbinols or the arylalkylcarbinols to hydrocarbons [OS2, M1, E2].

$$PhCHOHMe \xrightarrow[NaBH_4/AlCl_3/THF]{} PhCH_2Me$$

In the presence of $NaCNBH_3/ZnI_2$, the allylic, benzylic, and even tertiary alcohols are reduced to hydrocarbons via the corresponding carbocations [LD1].

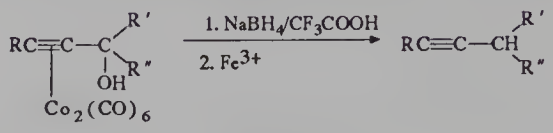


In some cases, the reaction results in dimerization, probably by a radical process.



The cobalt complexes derived from propargylic alcohols are reduced by $NaBH_4/CF_3COOH$ to hydrocarbons via the corresponding carbocations, which,

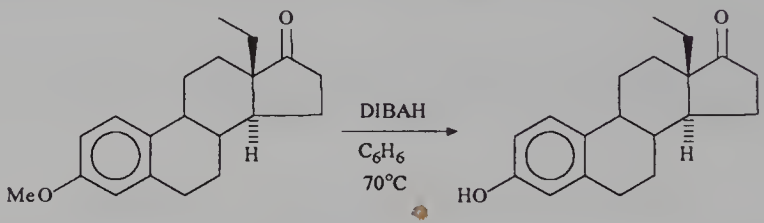
after decomplexation, allow substituted acetylenes, which are much less easily prepared otherwise, to be readily obtained [N3].



The reduction can also be carried out by $BH_3/Me_2S/CF_3COOH$ [PL1].

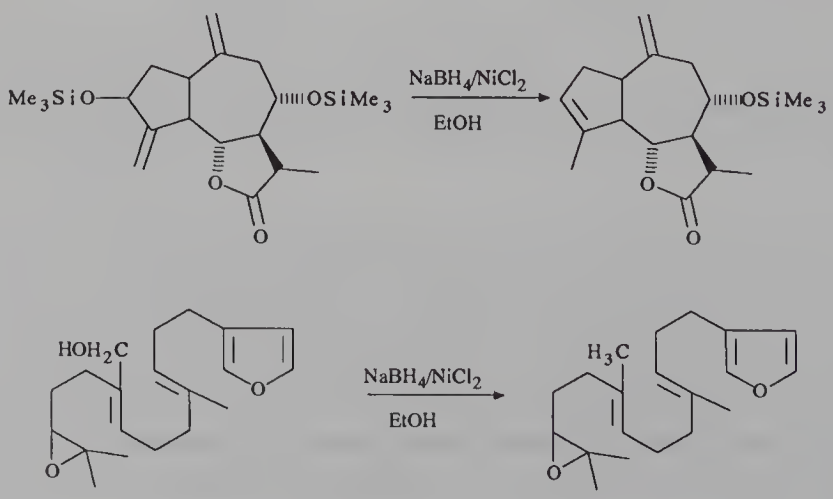
1.4.2. Ethers

Aliphatic ethers are generally inert in the presence of alumino- and borohydrides. Aromatic ethers can be cleaved to give phenols using DIBAH [W1, MH2], while benzylic ethers are cleaved by Red-Al/xylene under reflux [M1].



The hindered ketone is not reduced in the example above.

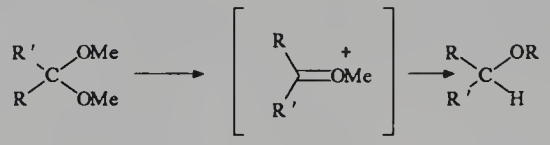
In the presence of $Pd(PPh_3)_4$, allylic ethers are reduced by LAH/THF (§ 4.3). The methylated or trimethylsilylated allylic ethers are reduced to the corresponding unsaturated hydrocarbons by $NaBH_4/NiCl_2/EtOH$ [GO_2]: lactones and epoxides remain intact under these conditions, just like the ethers of saturated alcohols.



Trimethylsilyl ethers ($ROSiMe_3$) are cleaved by aluminohydrides and borohydrides [G3]. Aluminohydrides and DIBAH also reduce some dissymmetrical methylated silyl ethers [F1, CG1, CG2]. However, more hindered silyl ethers such as $ROSiMe_2t$-Bu or $ROSiPh_2t$-Bu seem to resist these reducing reagents, particularly if the reactions are carried out at low temperature [G3].

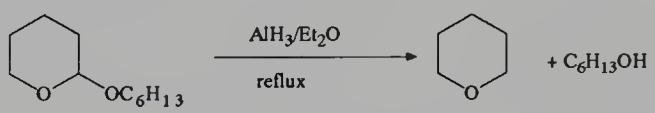
1.4.3. Acetals and Orthoesters

Acetals associate to DIBAH at low temperatures and are cleaved into ethers only at room temperature or under heating, depending on the case [W1, TA1]. Similarly, orthoesters are cleaved by DIBAH at 0°C [TN1]. The reducing agents AlH_3 [EB1, E2, MK3], BH_3•THF [L2, HUD, PS1], $AlBr_2H$, $AlCl_2H$ [MF1], and $ClBH_2$•Me_2S [BB3], have sufficient Lewis acid character to convert acetals to ethers. The mechanism of these reductions involves the formation of an oxonium ion, which is then reduced:

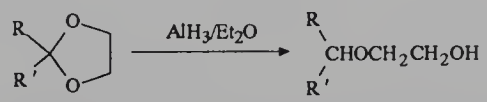


On the other hand, LAH and $LiEt_3BH$ leave acetals untouched, except in the presence of $TiCl_4$ [MA1, NG2] or other Lewis acids that induce the formation of tricoordinated aluminohydrides.

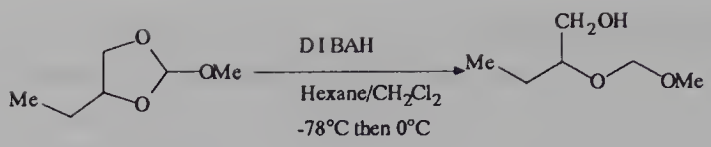
An application of these reactions is the regeneration of alcohols from the ethers of THF or tetrahydropyranyl (OTHP), used as protecting groups. By reaction with AlH_3, most frequently formed in situ starting from LAH in ether solution by adding some $AlCl_3$• or BF_3•Et_2O, one obtains the expected alcohols except if the latter are likely to form carbocations, which are in turn reduced (tertiary, benzylic, allylic alcohols).



Under the same conditions, dioxolanes lead to glycol monoethers.



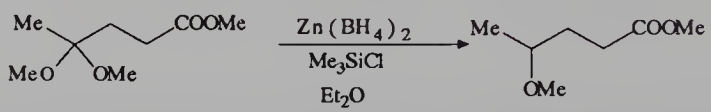
The cleavage of orthoesters is regioselective when they are dissymmetrical: primary alcohols are formed rather than secondary ones [TN1],



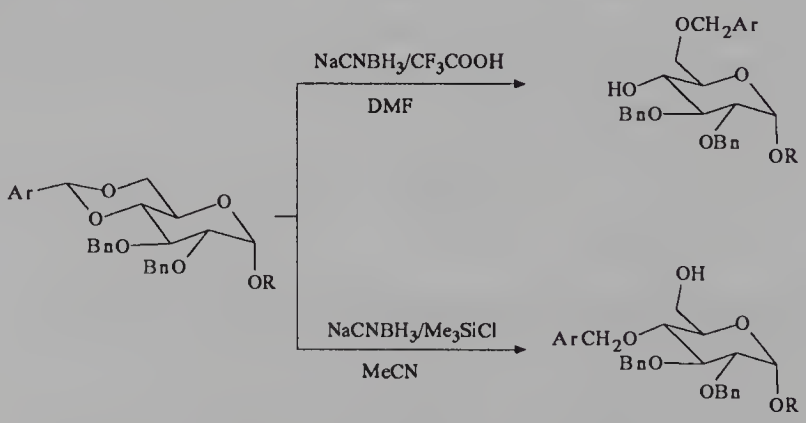
Other reducing reagents leave acetal intact [M1,BK5] except in acid media, where the oxonium ions are likely to be generated: $NaCNBH_3$/MeOH/HCl [NG2, HJ3], $NaBH_4/CF_3COOH$/THF, $NaCNBH_3/CF_3COOH$/DMF, or $NaCNBH_3/Me_3SiCl$/MeCN [JS1, GN1, MK3]. The last three reagents cleave only the dioxolane derivatives of aromatic ketones, whereas the first is more reactive and is more generally used.

$$CH_3(CH_2)_8CH(OMe)_2 \xrightarrow[NaCNBH_3/MeOH/HCl,\ 0°C]{} CH_3(CH_2)_8CH_2OMe$$

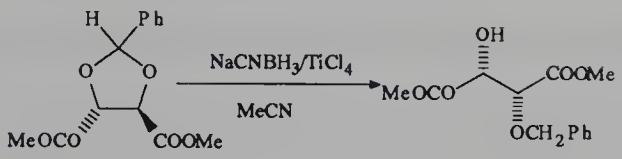
At ambient temperature, $Zn(BH_4)_2/Et_2O$ in the presence of trimethylsilyl chloride, transforms acetals and ketals into ethers. Under these conditions, esters remain intact, but the double bonds are reduced [KU1].



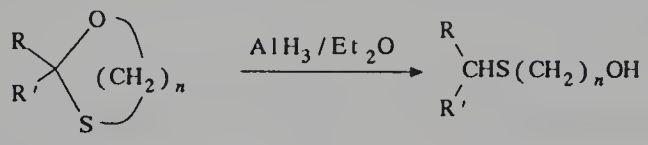
According to the experimental conditions, the regioselectivity of the cleavage can vary [JS1], as shown by the following example taken from sugar chemistry:



$NaCNBH_3/TiCl_4$ can also be used for such a purpose. Esters are left unchanged under these conditions; for instance, a benzylidene acetal formed from tartaric acid can be transformed into a chiral monoether [AS1].

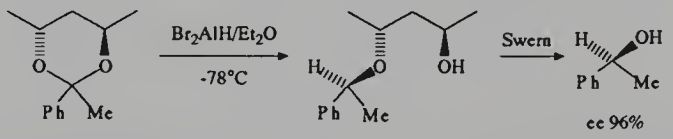


Other examples are described in the literature [MA1]. The carbon–oxygen bond of hemithioketals is hydrogenolyzed by AlH_3/Et_2O, while the C—S bond remains unchanged [E2].

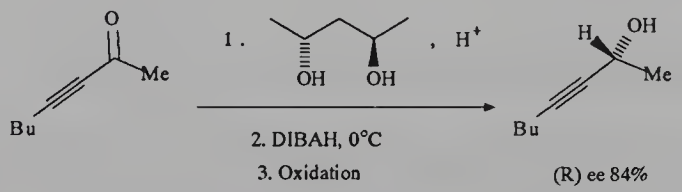


Dithianes, by way of contrast, are not affected by aluminohydrides, borohydrides, or boranes [NG2].

The treatment of the acetal derivatives of chiral diols by DIBAH or rather by $AlBr_2H$ or $AlCl_2H$, obtained by combining 3 equivalents of AlX_3 with LAH/Et_2O, leads to an enantioselective cleavage in ether/alcohol, which can then be oxidized to an optically active alcohol by Swern reagent [MF1, MI1]. The following example is illustrative.



The method is applicable to acetals of the α,β-acetylenic ketones [IM1]:

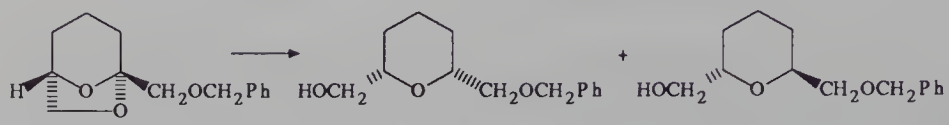


The other enantiomer can then be obtained by using $Et_3SiH/TiCl_4$ on the same acetal of a chiral diol [IM1, IM2, MI1].

This methodology constitutes, in fact, a reduction of ketones to chiral alcohols, which is complementary to the reduction effected by the chiral alumino- and borohydrides (§ 2.2.2).

The stereoselectivity of the reduction of bicyclic 1,3-dioxolanes has been studied [KU2, KU3]: DIBAH leads predominantly to trans-substituted isomers,

while $Et_3SiH/TiCl_4$ or $Zn(BH_4)_2/TiCl_4/CH_2Cl_2$ gives the reverse stereoselectivity.

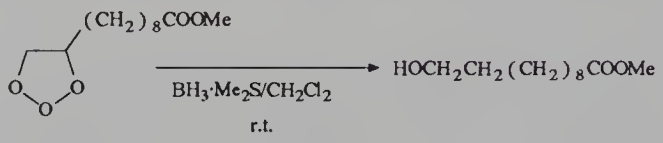


DIBAH	4	96
$Et_3Si/TiCl_4$	99	1
or $Zn(BH_4)_2/TiCl_4$		

Other reagents, such as $AlBr_2H$ or $AlCl_2H$, are less stereoselective [KU4].

1.4.4. Ozonides

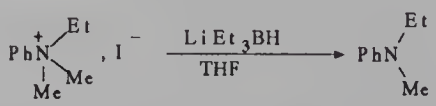
Ozonides are reduced to alcohols by $LiAlH_4$ [MS3] and $NaBH_4$ in alcohols [HUD, CH4]. However, it appears that the best reagent is $BH_3{\cdot}Me_2S/CH_2Cl_2$ at room temperature, a method that is compatible with carboxylic esters [FG1].



Ozonolysis of olefins, followed by reduction, can be performed sequentially in a one-flask operation.

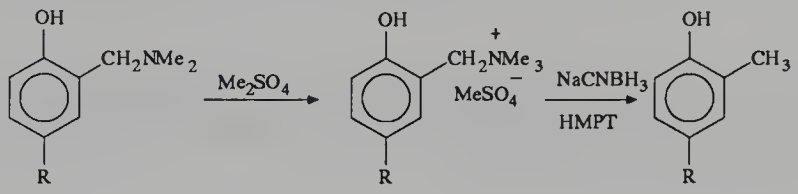
1.5. AMMONIUM SALTS: $—N^+R_3, X^-$

LAH/THF reduces ammonium salts to amines. However, the best reagent for this reaction is $LiEt_3BH$/THF at 25°C. The methylammonium salts are selectively demethylated [CP1, BK5, PS1, NM1].



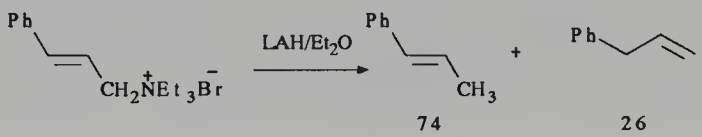
This method has found numerous applications in synthesizing natural products [NM1].

The reduction of ammonium salts, formed by reacting Me_2SO_4 with Mannich benzylic bases, by $NaCNBH_3$/HMPT at 70°C, leads to methylated aromatic derivatives [YI1].

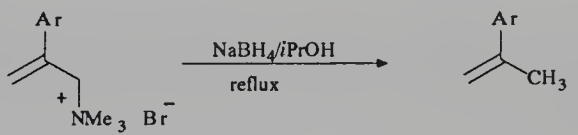


This method preserves the R group in the following cases: Cl, COOEt, CH_2CN, and NO_2.

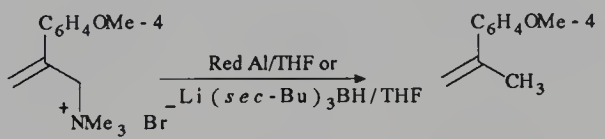
Starting with allylic derivatives, LAH in an ether medium can lead to mixtures of regioisomers [HN2].



If gentler reducing agents are used, however, the reaction can be regioselective [GL6]:



Ar = C_6H_5, 4-ClC_6H_4, 4-$MeOC_6H_4$, $\alpha C_{10}H_7$



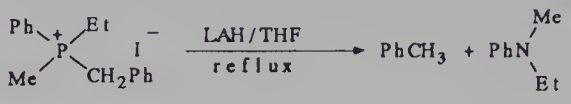
$NaCNBH_3$/*i*-PrOH under reflux does not react at all.

1.6. PHOSPHORUS DERIVATIVES: >C — P

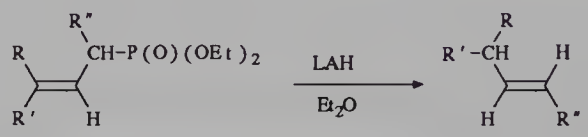
Examples of simple C—P bond cleavage that have been described include the following.

Phosphonium salts are reduced to phosphines by LAH/THF under reflux:

the broken bond corresponds in producing the most stable carbanion, as shown in the following example [H2]:

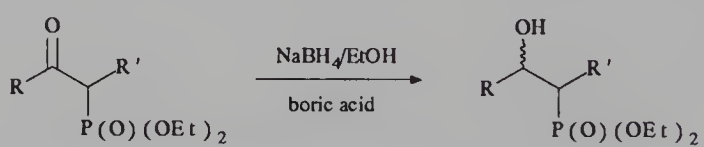


The P—C bonds of phosphonates or allylic phosphonium salts can also be cleaved by LAH/Et_2O: the reduction involves an allylic transposition and leads to a *trans*-olefin [HJ2, HN2, KN2]:



LBTA can also cleave selectively the P—C bond of acyl phosphonates, while preserving the other functional groups [DS1]:

Nevertheless, the reduction of similar compounds by $NaBH_4$/EtOH/boric acid does preserve the C—P bond and leads to diastereomeric α-phosphorylated alcohols [DS1, BS5]:



R' = COOEt or Ph

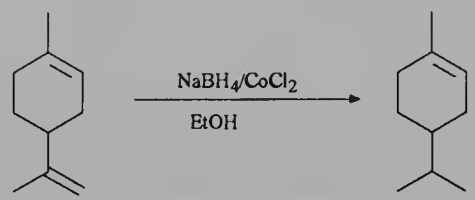
CHAPTER 2

REDUCTION OF DOUBLE BONDS

2.1. NONCONJUGATED CARBON–CARBON DOUBLE BONDS: $\rangle C=C\langle$

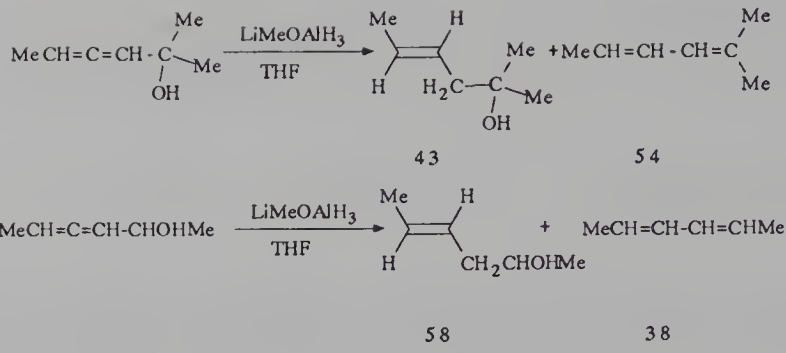
Boranes add to carbon–carbon double bonds even if they are not activated by an electron-withdrawing group. The hydroboration reactions lie outside our scope here, nevertheless, we should know that these reagents are the ones not to use when we want to preserve the C=C bonds in a molecule unless it is particularly hindered. However, $[CF_3COOH]_2BH{\bullet}THF$ leaves the double bonds of styrene and of 1-decene intact, as well as that of $Ph_2C{=}CH_2$ [MM1].

The other hydrides and borohydrides do not affect the isolated C=C bonds except in the presence of transition metals [W4, M1, GO2], as shown in the following example, where only the most hindered double bond is reduced:



The unsubstituted and substituted styrenes can still be reduced by hot $LiEt_3BH$ in THF, but the selectrides Li(*sec*-Bu)$_3$BH and K(*sec*-Bu)$_3$BH leave them intact.

The double bonds of certain allene alcohols can also be reduced, as shown in the following examples [M1].



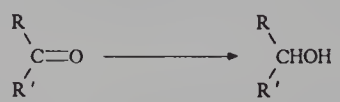
The reduction of the double bonds conjugate to electron-withdrawing groups is examined later (§2.2.8).

2.2. CARBON–OXYGEN DOUBLE BONDS: $>C{=}O$

2.2.1. Aldehydes and Ketones

Generally aldehydes and ketones are reduced to primary and secondary alcohols by all the reagents studied with the following exceptions:

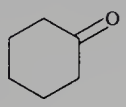
- by sodium and ammonium cyanoborohydrides in neutral or basic protic media [L1], allowing the reduction of halides while leaving the carbonyl fragments intact (§1.1);
- by $(Ph_3P)_2CuBH_4$ in neutral media, whereby the selective reduction of acid chlorides is possible [FH1] (§2.2.6). The reduction of aldehydes by this complex, however, takes place in an acid medium or in the presence of Lewis acids.



Although single-electron transfer is highlighted in the reduction of more or less hindered aromatic ketones by AlH_3, BH_3, or LAH-pyridine [AG2], the reductions of aldehydes and ketones by alumino- and borohydrides and boranes occur mostly as a nucleophilic attack of hydride on the carbonyl carbon. The study of this process has been the object of numerous theoretical [N2, HW1, ES1, W2] and mechanistic [CB1, W2, W4] studies.

In certain cases, the reduction can take place without acid catalysis (*n*-$Bu_4N^+BH_4^-$ or by phase transfer), but most frequently it requires the coordination of the carbonyl by a Lewis acid before nucleophilic attack. The latter may imply

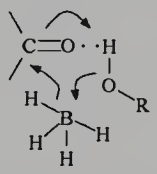
that the cation is associated with the reagent, an acid, or even the boron or aluminum atom of the tricoordinate reagent (AlH_3, DIBAH, boranes). The importance of this phenomenon has been shown by the introduction of coordinating macrocyclic molecules into solutions of LAH and $LiBH_4$, which considerably retards the reduction of carbonyl compounds in an ether medium [HP1, DC1]. This effect is more important when the lower unoccupied molecular orbital (LUMO) of the carbonyl compound lies higher in energy: electrophilic assistance by the Li^+ cation leads to a lowering of its energy. The observed sequence is the following [LS2]:



> *p*-ClC_6H_4CHO > C_6H_5CHO > *p*-$CH_3C_6H_4CHO$

In protic media, it is the solvent that plays the role of the acid catalyst in providing electrophilic assistance by hydrogen bonding [W2, ES1, PS1].

In alcoholic media, it has been shown that the transition state of the reduction by borohydrides implies an alcohol molecule that is converted to the corresponding borate.



In addition, reductions by LAH in ether solvents imply a transition state close to the reactants [N2, HW1], whereas for cases involving borohydrides, the transition state occurs later along the reaction coordinate [W2, ES1, YH1, CB1]: with reagents having tetracoordinated aluminum or boron species, the formation of the C—H bond is the rate-determining step. Chloral (Cl_3CCHO), whose lowest-lying vacant orbital is low in energy, is indeed reduced more rapidly than pivalaldehyde [$(CH_3)_3CCHO$], for which this orbital lies higher in energy [BK5].

A review of these mechanistic approaches has recently been published [W6].

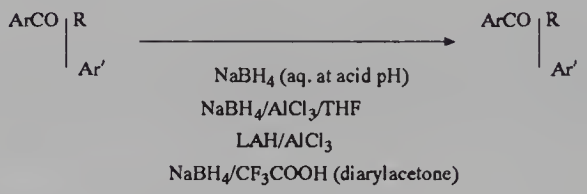
In contrast, when one uses reducing agents whose central atom is tricoordinated and thus has a strong Lewis acidity (boranes, AlH_3, DIBAH), the coordination of the reactants with the carbonyl oxygen is the dominant factor: pivalaldehyde, whose carbonyl oxygen is more basic, reacts more rapidly with BH_3•THF than does chloral [BK5]. This difference in behavior has some important implications with regard to the stereoselectivity of these reductions by these two types of reagent (§2.2.2).

Aldehydes and ketones may be reduced to alcohols by LAH in an ether medium at low temperature [BK5], by LAH on a solid support [KH2, W4], and by alkoxyaluminohydrides [M1], AlH_3/Et_2O, Red-Al/C_6H_6 [M1], borohydrides in the solid state [TK2], in alcoholic media or ethers or glymes [BK5], by boranes

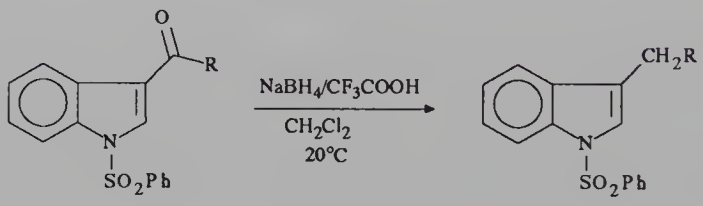
and acyl oxyboranes [BK5, PS1, MM1, GN1], and by trialkylborohydrides [BK5], and -ate complexes [BM1].

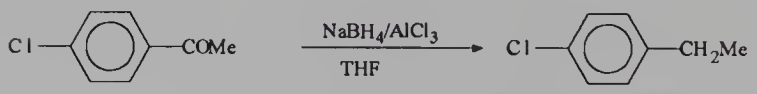
The reduction by alkaline cyanoborohydrides only takes place at pH values less than 4 [L1]. The reduction of ketones by $Zn(CNBH_3)_2$ is efficient only in Et_2O [KK5] and is relatively slow when $NaBH_4$ is used in organic acid media [GN1]. These reductions are in general so sensitive to steric hindrance around the carbonyl, that the severity of experimental conditions must be changed.

In acid media, or in the presence of Lewis acids, diaryl ketones or alkylaryl ketones are reduced by LAH or $NaBH_4$ to the corresponding hydrocarbons [GK1, GN1, OS2, E2]:



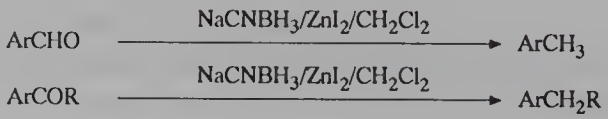
$LAH/AlCl_3$ gives poorer yields, as illustrated below [KG1, GN1, KL1]:





However, $NaBH_4/ZrCl_4/THF$ reduces PhCHO and $PhCOCH_3$ to the corresponding alcohols [IS1]. Flavanones are reduced by $NaCNBH_3/CF_3COOH$ either to flavanes or 1,3-diarylpropanes, depending on their substituents [LB1].

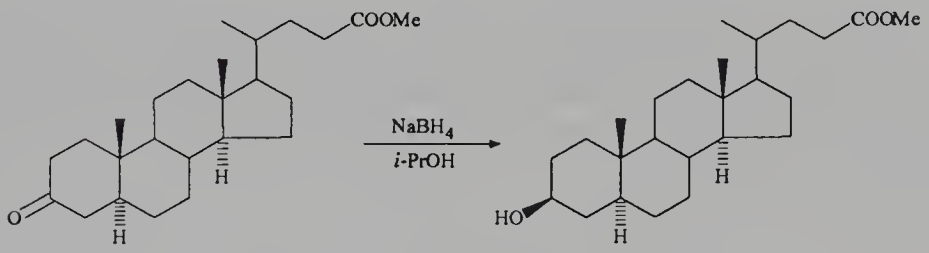
Aromatic aldehydes and ketones with electron-donating substituents are also reduced to hydrocarbons by BH_3•THF [L2] and $NaCNBH_3/ZnI_2/CH_2Cl_2$ [LD1].



$NaBH_4$/MeOH in the presence of $PdCl_2$ gives analogous results [GO2].

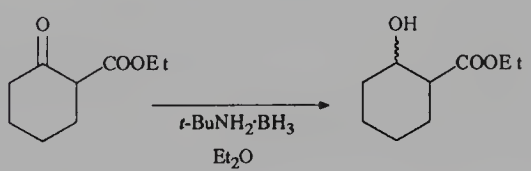
While arylalkyl ketones (ArCOR) do not react with $Me_3N{\bullet}BH_3$, they lead to benzyl bromides ($ArCHBrCH_3$) when the reaction is run in the presence of Br_2 [LG1]. Moreover, *t*-$BuNH_2{\bullet}BH_3/AlCl_3/CH_2Cl_2$ reduces arylalkyl ketones to the corresponding hydrocarbons ($ArCH_2R$). This transformation is compatible with having ester groups, as well as chloro, bromo, nitro, and phenyl thiosubstituents in the aryl ring; however, carboxylic acids are reduced to primary alcohols [LT1].

It is possible to reduce aldehydes and ketones selectively in the presence of isolated double bonds, halides, sulfonates, acetals, esters, amides, or nitriles, acids and NO_2-containing groups by using $NaBH_4$ or *n*-$Bu_4N^+BH_4^-$ in different media [PS1, WG2]. The following examples illustrate this compatibility:

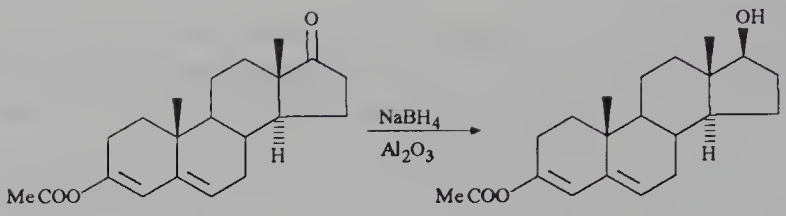


The in situ formation of the lactone results from the sole reduction of the ketone.

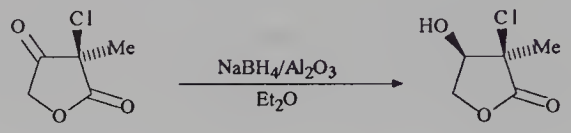
Likewise, the amine-boranes allow the reduction of ketones in the presence of esters [A1]:



$NaBH_4$ on alumina appears to be a very gentle reducing agent. Under these conditions the possible hydrolysis of esters, owing to the basicity of $NaBH_4$ aqueous–alcoholic solutions, can be avoided. This is particularly interesting for the case of enol acetates, which are fragile in protic media, as shown in the following example [W4]:

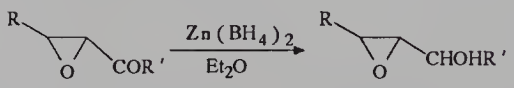


The selective reduction of the following chlorinated ketolactone is another illustration of this [WV1]:



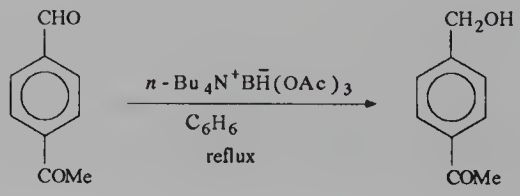
LAH on silica gel also reduces ketoesters to hydroxyesters in Et_2O [KH3].

The reduction of epoxy ketones to epoxy alcohols is easily accomplished by action of $Zn(BH_4)_2/Et_2O$ or $NaBH_4$/MeOH, sometimes in the presence of $CeCl_3$: the stereoselectivity of the reaction is usually high [NT1, BC2, CP3, BB6] (§2.2.3):



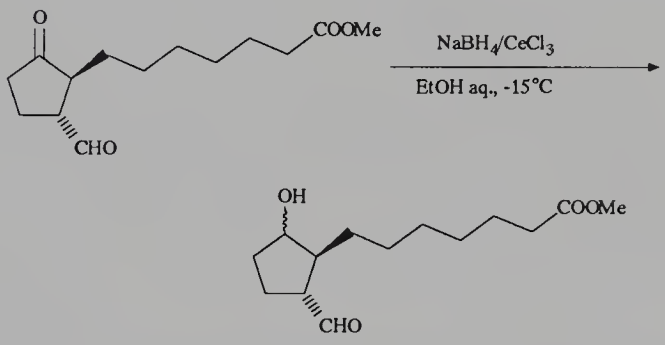
The selective reduction of aldehydes in the presence of ketones has been suggested using the following systems:

- $NaBH_4$/cold *i*-PrOH [BK5] or in EtOH/CH_2Cl_2 (3:7) at –78°C [WR2];
- *n*-$Bu_4N^+BH_4^-$/CH_2Cl_2 [SP1, RG1];
- *n*-$Bu_4N^+CNBH_3^-$ in an aqueous 0.1 *N* HCl solution [W3];
- $(Ph_3P)_2CuBH_4$ in acid medium [FH1];
- $NaBH(OCOCH_3)_3$ or better *n*-$Bu_4N^+B^-(OCOCH_3)_3/C_6H_6$ under reflux [GF1, GN1, NG1] as shown in the example below, unless the molecule bears an alcoholic functional group at the α- or β- position to the ketone, which is then also reduced [SM2];

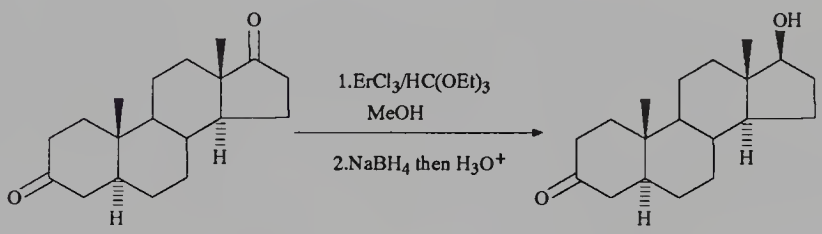


- $Na(OAr)_3BH/THF$ [YK1];
- $Li(OCEt_3)_3AlH$ or LBTA/THF [K4, M1];
- $BH_3{\bullet}Me_2S$ or $BH_3{\bullet}LiCl$ [HC1, YC1];
- amine-boranes/Et_2O at 0°C, *t*-$BuNH_2{\bullet}BH_3$ [A1] being the most effective; pyridineborane on Al_2O_3 [BS1];
- $NaBH_4$+$SnCl_2$/THF reduces aromatic aldehydes without affecting ketones [OH1].

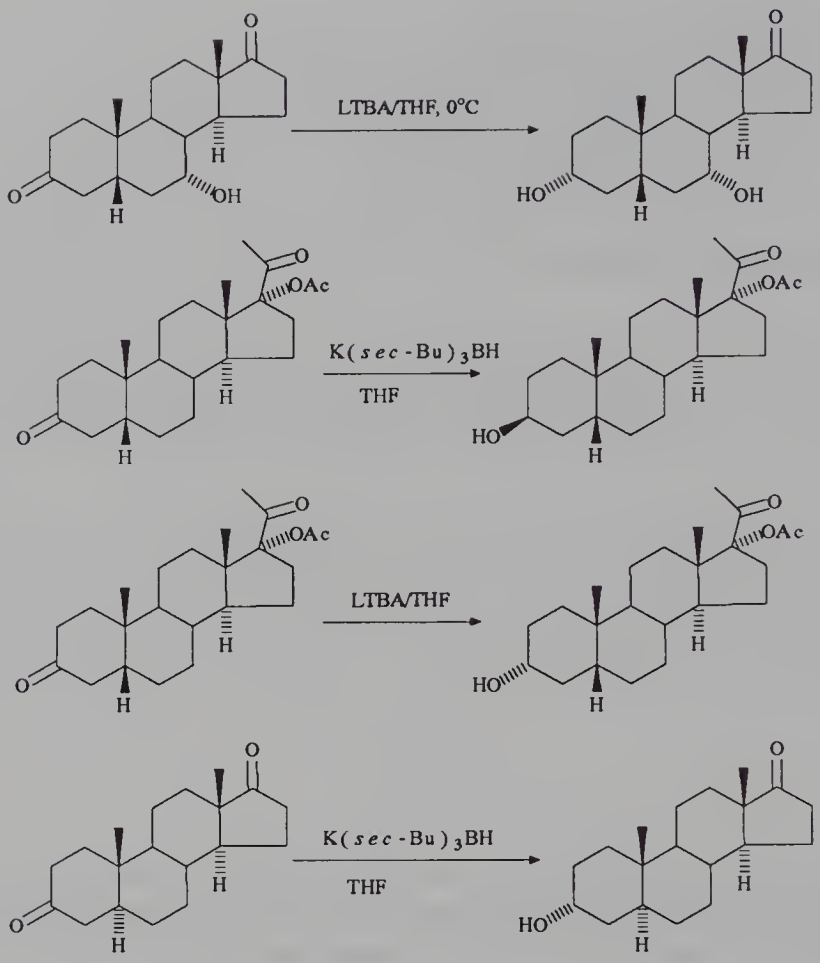
A noteworthy result is that ketones can be reduced without affecting aldehyde groups by using $NaBH_4/CeCl_3$ in aqueous MeOH or EtOH at –15°C [GL1, GL2]. This is due to a rapid transformation solely of aldehydes, under these conditions, to ketals or hemiketals, which are not reduced.



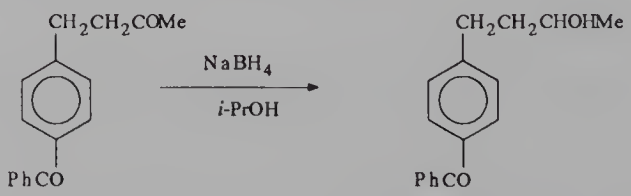
The same type of situation permits the relatively rapid formation of ketals of unhindered ketones, in the presence of $HC(OMe)_3$, whereby the selective reduction of the most hindered ketones is possible [GL1].



Because of the sensitivity of the reduction of some ketones to steric hindrance, it is possible, with a judicious choice of reducing reagents, to selectively reduce the least-hindered carbonyls in di- or triketones. The most effective reducing reagents in this regard are the complex $Zn(BH_4)_2{\bullet}1.5$ DMF in MeCN [HJ1], amine-boranes/Et_2O [A1], LTBA/THF [M1] or K(*sec*-Bu)$_3$BH, as shown by the following examples, chosen from steroid series, in which the ketone at the 3-position, the least hindered, is selectively reduced, in agreement with the stereochemical rules discussed later (§2.2.2) [WB1, GO1, TK1].



The different reactivities of aromatic ketones and aliphatic ketones can be exploited in the same way by carrying out selective reduction of the latter: $Zn(BH_4)_2$•1.5 DMF/MeCN or $Zn(CNBH_3)_2/Et_2O$ in the presence of trace amounts of water is a good route [HJ1, KK5], as is $NaBH_4$/*i*-PrOH or $LiBH_4$/diglyme [PS1].



In the presence of bulky groups on coordinating agents of the carbonyl group, such as methylaluminum bis (2,6-di-*t*-butyl-4-methylphenoxide) (MAD), the reverse reactivity is observed. Selective complexation of the most accessible carbonyl group takes place, so that this group is no longer able to be reduced.

Under these conditions, DIBAH or Br_2AlH reduces PhCO-*t*-Bu in the presence of PhCOMe or camphor [MA2].

However, discrimination between an aldehyde and a ketone is unsuccessful.

The competition between ketone and α-enone is examined later (§2.2.8).

2.2.2. Stereoselectivity of the Reduction of Aldehydes andKetones

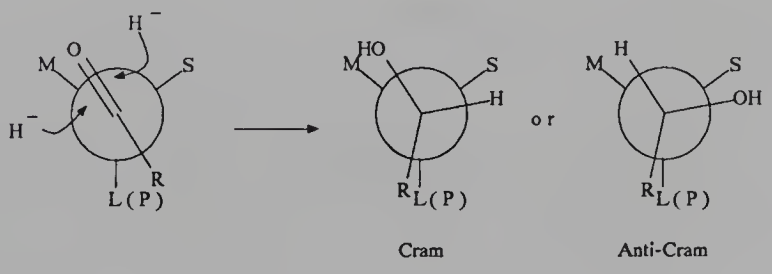
The stereoselectivity of the reductions of aldehydes and ketones has been the object of in-depth mechanistic and theoretical studies [N2, W2, CB1, ES1, HW1]. According to the Lewis acid strength of the reducing agent, two models can interpret the observed stereoselectivity:

- when the reduction is carried out with reagents whose central atom (Al or B) is tetracoordinated, the Felkin–Anh model is considered [N2, CP2, HW1, WH1, MW1, WH2]: it permits comparison of the interactions involved in the nucleophilic attack of the hydride on the C═O bond;
- when the reductions are carried out by means of reagents whose central atom is tricoordinated, Houk's model can explain the reaction path: it takes into account the predominant interactions during the coordination of the carbonyl oxygen with the Lewis acid before any hydride transfer [HW1, HP3].

Whether the reaction follows either of the two reaction pathways, it is possible to obtain selectively one isomer or the other by carrying out the reduction either with an alumino- or borohydride, or with DIBAH or a borane. The first to exploit this dichotomy was M. Midland [MK1].

The principal types of interaction to be taken into consideration are those of stereoelectronic origin: steric, torsional, and orbital interactions, and eventually the position of the transition state (early or late) along the reaction coordinates.

The Felkin–Anh Model [N2, CP2, WH1, WP2, WH2]. The attack of a hydride H^- on the prochiral carbonyl can be accomplished either on the *Re* or *Si* face of the carbonyl, leading to a pair of diastereomers, as the following scheme indicates:

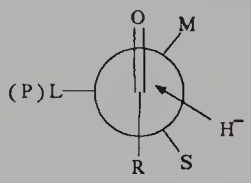


where L represents the most bulky group, P the most polar, and S the smallest group.

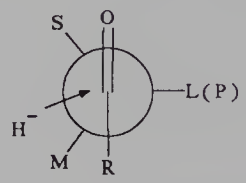
Initially Cram proposed a slightly different rule to interpret the formation of the major isomer, called "Cram" in the scheme, the other isomer being labeled "anti-Cram".

The model to which most authors actually refer is a modification of the 1952 Cram scheme. This transition state model, proposed by Felkin and Cherest and supported by calculations of Nguyen Trong Anh and Eisenstein, considers that the transition state most resembles the reagents ketones and hydrides.

The attack of the hydride takes place anti to the most bulky group L or polar group P. In agreement with the proposals of Dunitz and Burgi, this does not take place perpendicular to the plane of the carbonyl but with an attack angle of about 109°. To minimize steric interactions, the attack preferentially involves the C_1 conformer of the ketone and not C_2, as indicated in the Newman projections shown below.

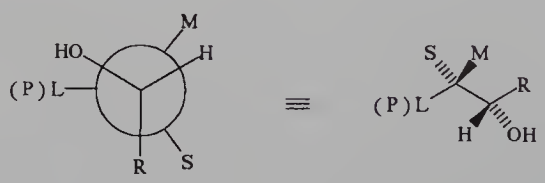


C_1

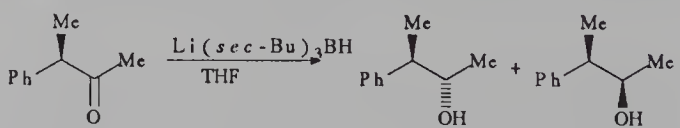


C_2

The favored attack on C_1 thus leads in a prevailing manner to the following stereoisomer, the "Cram" product:



In the absence of other steric constraints, this stereoisomer is the preponderant one when the reductions are performed on acyclic ketones, as the following results indicate [SK1]. The stereoselectivity of the reduction is improved as the reducing reagent becomes more bulky.



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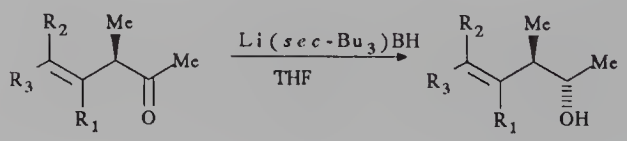
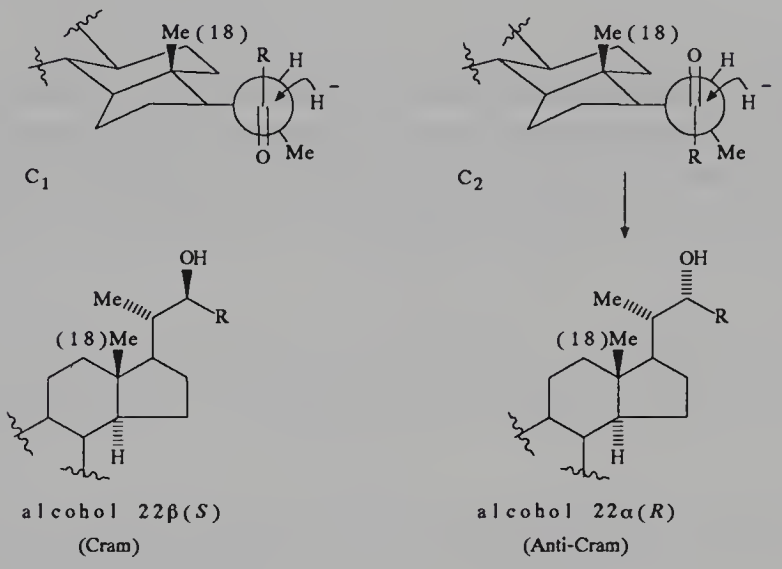


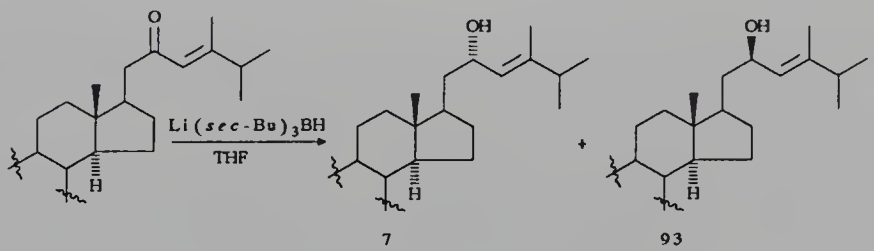
>99:1

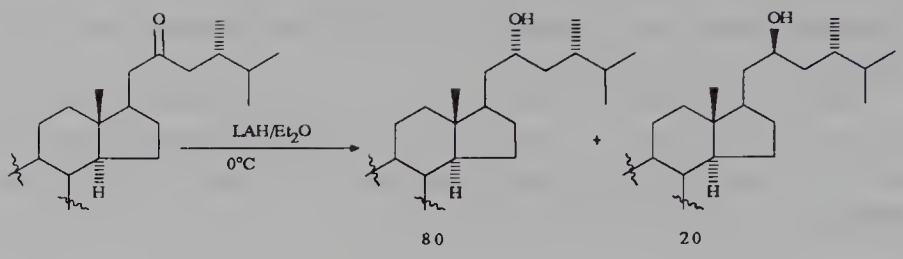
In the two preceding examples, the phenyl or unsaturated substituent plays the role of the bulky group L or polar group P, the methyl group being M group and hydrogen being S group.

However, if the carbon skeleton of the ketone to be reduced is substituted in such a manner that the C_1 conformer is very sterically hindered, the reduction takes place with the C_2 conformer and the stereoselectivity is reversed: an example is given here in steroid series:



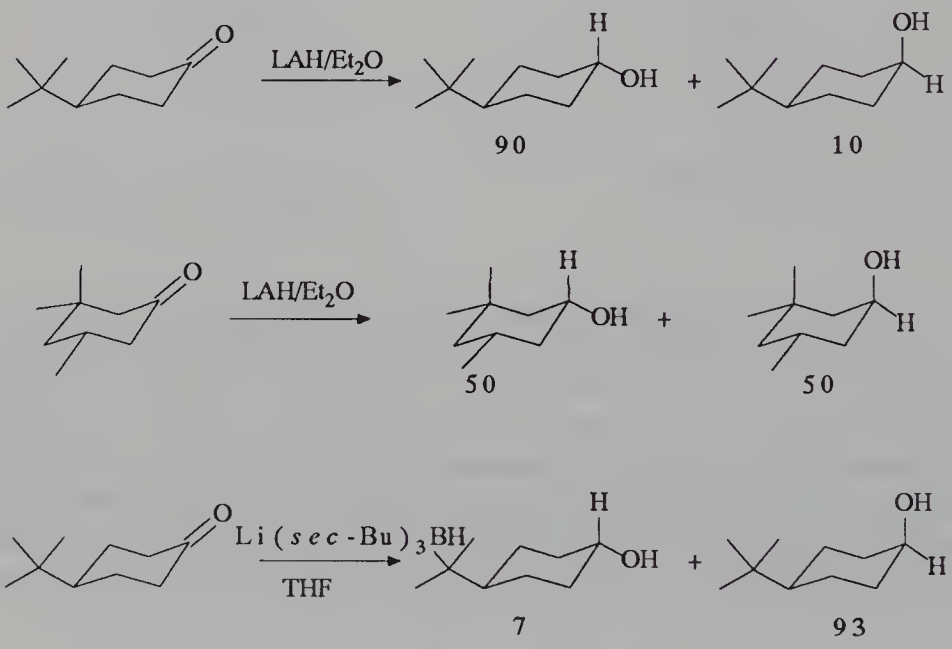
When R is an unsaturated group, the interaction between this grouping and the axial methyl at position 18 is not sufficient to disfavor the participation of conformer C_1 during the reduction: by using Li(*sec*-Bu)$_3$BH, one obtains preferentially the 22-β alcohol [TO1]. Nevertheless, when R is a branched saturated chain, a steric interaction between this chain and the 18-methyl group disfavors the C_1 conformer, and C_2 can participate. For example, the reduction by LAH of such carbonyl compounds give a mixture of 22-α and 22-β alcohols in a 4:1 ratio [PR3].





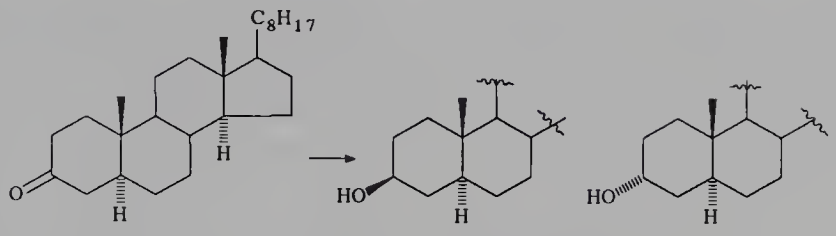
Some other examples are given by Cherest and Prudent [CP2].

The reduction of cyclic ketones can be explained by the same approach [W2, N2]. Stereoelectronic control favors axial attack on the rigid cyclohexanones; but steric interactions, as a result of either the substituent present on the molecule or the structure of the reactants can work against this pathway. From this fact, one observes the following results [HUD]:



Li(*sec*-Bu)$_3$BH, being very bulky, enters by the least-hindered face of the molecule and gives rise selectively to the axial alcohol.

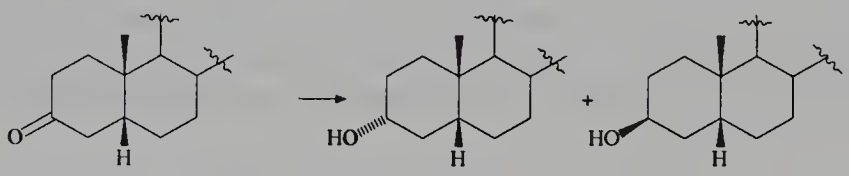
In the steroid series, LAH preferentially attacks the axial face of the ketones at the 3-position while Li(*sec*-Bu)$_3$BH does so at the equatorial face. One can thus obtain selectively the 3-β-cholestanol with equatorial OH or 3-α with an axial OH compound, depending on the reducing agent employed [DA1].



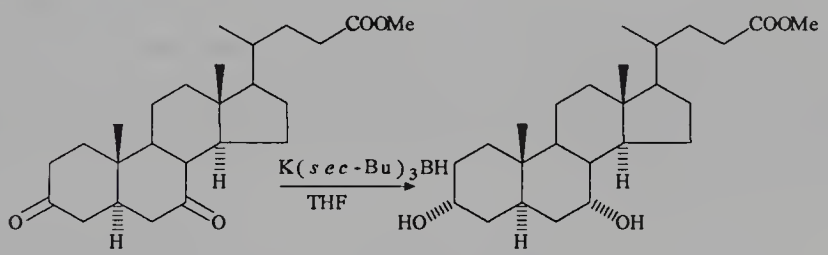
LAH/Et_2O	88	12
Li(*sec*-Bu)$_3$BH/THF	20	80

Some other examples are described by Ohloff et al. [OM2].

In the coprostane series, where the cyclic AB junction is cis-, the same reagents selectively give rise to either 3-α alcohols with an equatorial OH or 3-β alcohols with an axial OH [OM2].

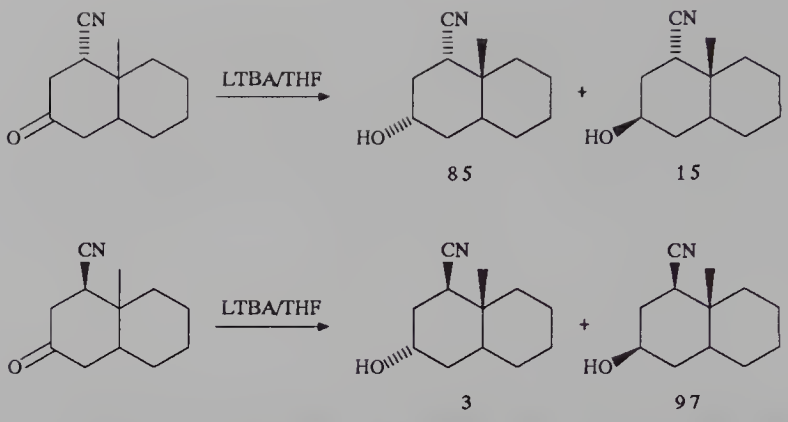


Similarly, K(*sec*-Bu)3BH allows for the strong stereoselection of the diaxial-3-α,7-α-diol from the starting corresponding dione, the ester functional group remaining unchanged [TF1].



The stereoselectivity of the reduction of polymer supported 6-ketosteroids by aqueous KBH_4 has been examined: it depends on the polymer used and on whether a phase transfer catalyst is added [BH4].

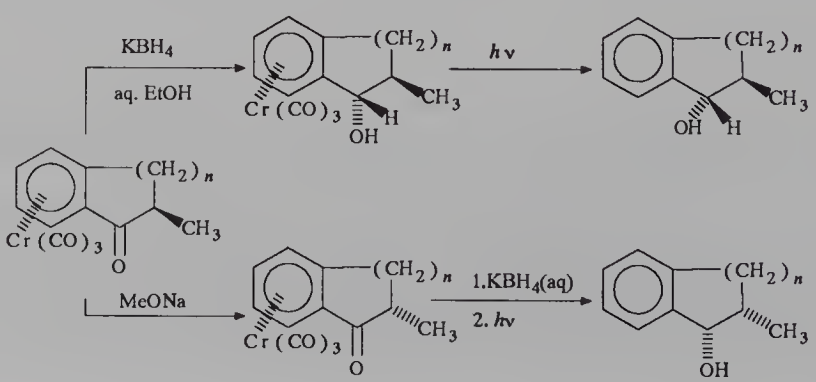
The cycle substituents, other than alkyl groups, can also influence the stereoselectivity of the reduction: the presence of a CN group at the β-position with respect to the carbonyl on either face of the molecule orients the reduction by LBTA/THF to the preferential generation of the axial or equatorial alcohol [CB1].



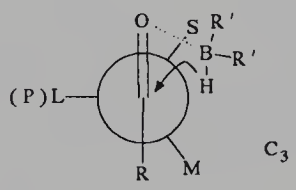
Some other examples have been gathered by Caro and coworkers [CB1].

In the norbornane series, the attack of LAH/Et_2O takes place on the exo face, leading to *endo*-norbornanols, the least thermodynamically stable ones, showing thus that the reductions performed by LAH, at least, do not follow "product development control" but essentially depend on stereoelectronic factors [AN1]. The same exo attack is observed in other strained bicyclic systems, Li(*sec*-Bu)$_3$BH/THF/–78°C being more stereoselective than LAH/THF [KG2].

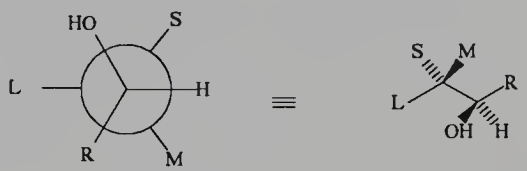
An interesting example is the reduction of the chromium tricarbonyl complexes of indanones and tetralones [JM1]. The hindered organometallic group opposes the attack of the hydride on the same face of the molecule. Because it is possible to obtain the corresponding ketones in optically active form, one has access, after decomplexation, to enantiomerically pure stereomers as shown in the following examples.



Houk's Model [HP3, HW1, PR1]. The presence of a favored conformation, by which the reduction occurs, depends on the stereoelectronic interactions between the Lewis acid–base complex formed between the carbonyl compound and the reducing agent (boranes, DIBAH). This is accomplished in a way that serves to minimize the different repulsive interactions, the transfer of the hydride taking place then in a second stage. The C_3 conformation of the ketone in this complex is accordingly more favored when the substituents on the boron or aluminum atom are bulkier. As previously, the hydride transfer takes place in anti position with regard to the most bulky (L) or polar (P) group.

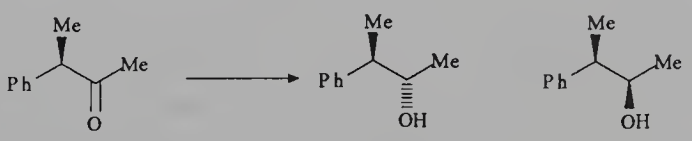


Under these conditions, the reduction leads to the "anti-Cram" diastereomer:

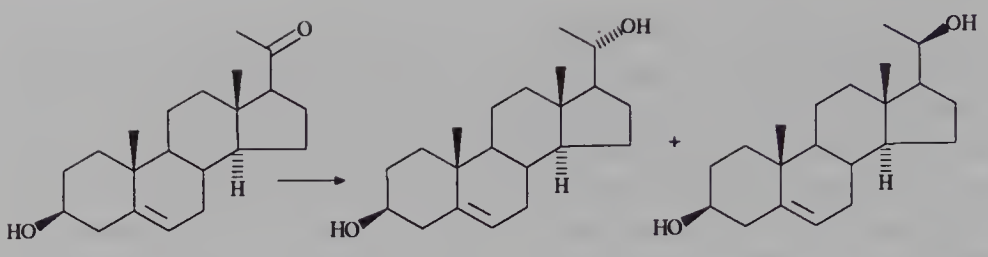


In addition to the pioneering work by Midland [MK1], a certain number of reports in the literature show an opposite stereoselectivity, as in the reduction of the prochiral ketones either by alumino- and borohydride or by boranes or DIBAH, enabling the process to be interpreted either by the Felkin–Anh model or by Houk's model.

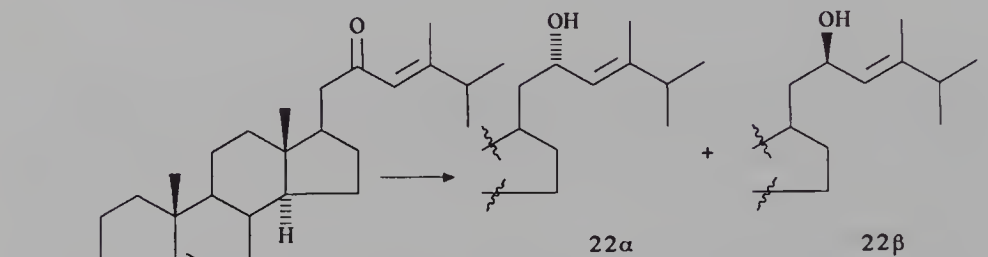
The following examples are illustrative [MK1, SK1, TO1, SH7].



Li(*sec*-Bu)$_3$BH/THF	96	4
Si a$_2$BH/THF	20	80

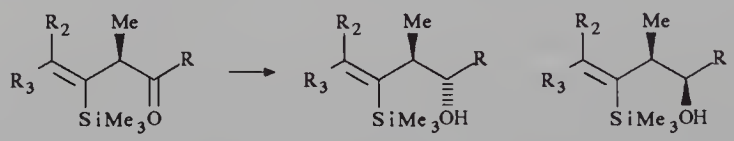


	20S	20R
Li(*sec*-Bu)$_3$BH/THF	1	99
Sia$_2$BH/THF	90	10



	22α	22β
Li(*sec*-Bu)$_3$BH/THF	7	93
DIBAH/toluene	97	3

However, in the following case, the size of the L substituent leads to a comparable selectivity, whatever the reducing agent employed.

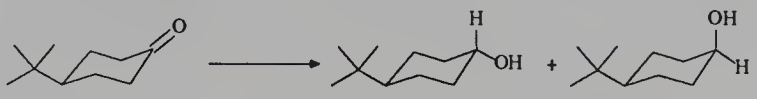


Li(*sec*-Bu)$_3$BH/THF	>99	<1
DIBAH/toluene	>90	<10

If the double bond does not carry an SiMe3 group, reduction by DIBAH gives a higher proportion of the other isomer.

In the examples discussed above, stereoselectivity is high, either because the structure of the ketone to be reduced means the two faces are sufficiently different in terms of steric hindrance or because of the size of the reducing reagent. In many cases, the stereoselectivity is reduced, since the different factors more or less compensate. Recall that it is necessary to consider the position of the transition state on the reaction coordinate — early with aluminohydrides and late with borohydrides in alcoholic media [CB1] — as well as the possibility of electrophilic assistance by the alkaline cation. The latter effect especially

facilitates the axial attack of cyclohexanones, as shown in the following examples, where the eventual effect of solvent on stereoselectivity can be observed [AK1].



LAH/THF	90	10
LAH/[2.1.1]/THF	70	30

It is also necessary to consider the size of the reducing agent, the structure of the ketone, and the possibilities of conformational equilibria [KW3].

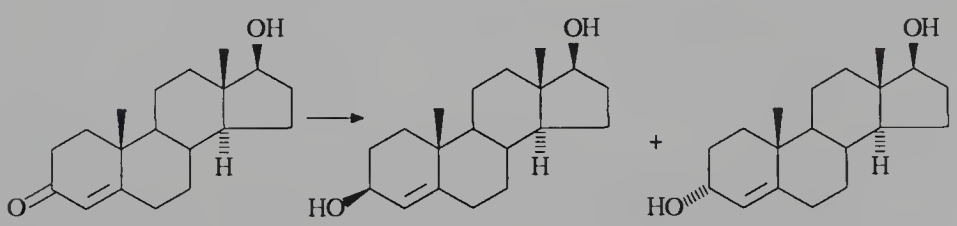
For example, Table 1 indicates the stereoselectivity of the reduction of two rigid ketones and a conformationally flexible ketone by different reagents.

Adsorption of the ketone on Montmorillonite clay enhances the axial attack of $NaBH_4$ reduction: > 99% for 4-*t*-butylcyclohexanone and 78% for 3,3,5-trimethylcyclohexanone [SR1]. Other hindered substituted borohydrides have also been proposed for that purpose [CY1].

From the numerous studies to date, it appears that torsional and mainly steric factors are nearly always predominant: such is the case, for instance, with the eight-membered cyclic taxane derivatives [SH7].

However, the stereoselectivity of the reduction of the 5-substituted adamantanones [CT2], of 1,2,3,4,-tetrahydro-1,4-methano and ethanonaphthalen-9-ones [OT1] as well as that of the 3-substituted cyclohexanones seems to be under electronic control: another model has been developed to interpret these results [C6, CT3].

Allylic alcohols can be obtained with a very high stereoselectivity, as below (the regioselectivity of the reduction is examined in §2.2.8) [T1, GL2, KA2, DD1, BB5, GM1, KY3].



$NaBH_4$/MeOH	90	10
$NaBH_4/CeCl_3$/MeOH	99	1

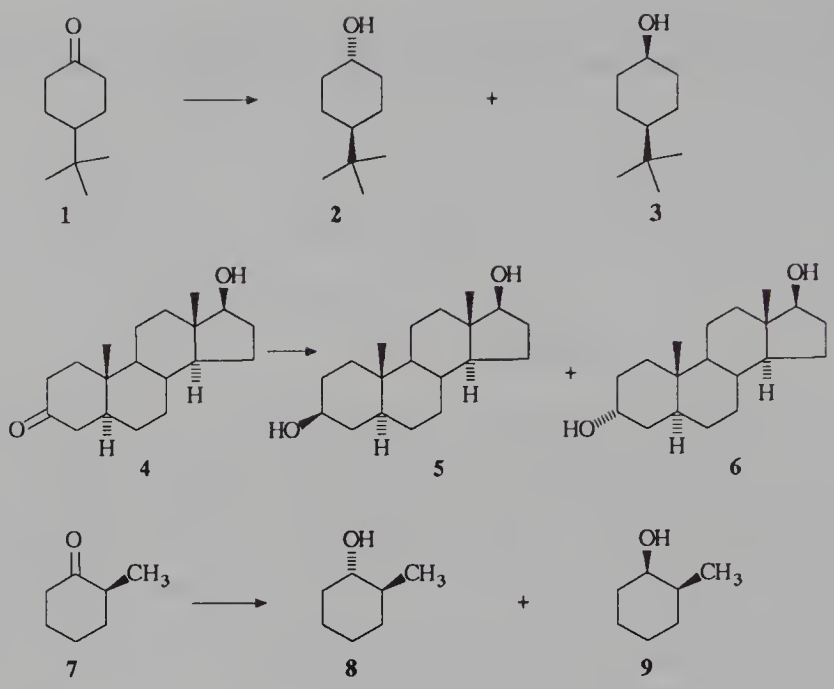


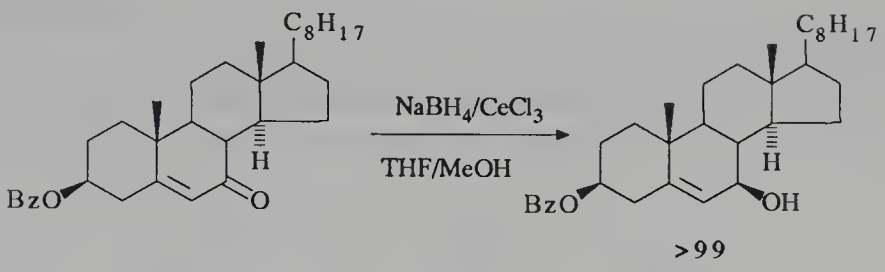
Table 1. Stereoselectivity of the Reduction of Ketones **1**, **4**, and **7** [CB1, GL2, M1, PS1]

Reducing Agent	% **2**[a]	% **5**[b]	% **8**[c]
LAH/THF	90	76	76
$NaBH_4$/MeOH	81	81	70
$NaBH_4/CeCl_3$/MeOH	94	>95	70
$LiBH_4$/THF	93	71	70
LTBA/THF	90	98.5	70
Li(*sec*-Bu)$_3$BH/THF	7		1
K(*sec*-Bu)$_3$BH/THF	1	20	8
9-BBN/THF	92		60
Thexyl BHCl•Me_2S	44		5.5

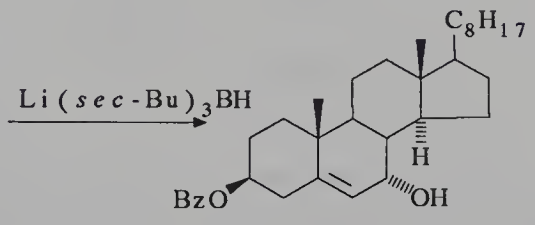
[a] The rest of the product is **3**.

[b] The rest of the product is **6**.

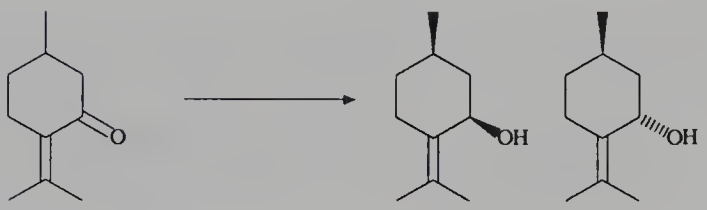
[c] The rest of the product is **2**.



>99



>99



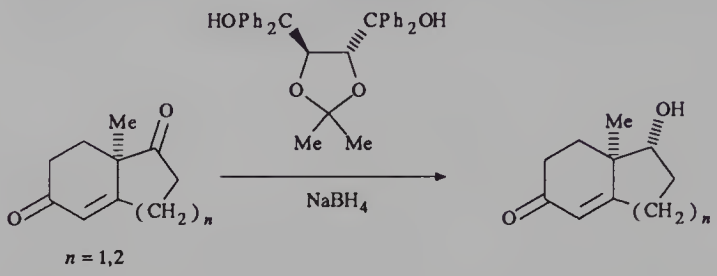
$NaBH_4$/MeOH	69	31
$NaBH_4/CeCl_3$/MeOH	97	3

The enantioselective reduction of ketones has been the purpose of numerous studies [M2, GH1, BP2]. The use of boranes modified by optically active groups [M2] or of chiral alkoxy- or aminoaluminohydrides [GH1, BP2] has been suggested for carrying out these reductions. High enantiomeric excesses have been obtained [AC1], especially by using alkoxy- or aminoaluminohydrides, derivatives of binaphthol (the two enantiomeric binaphthols being available, the reduction can give rise to the desired *R*- or *S*-alcohols), from the secondary diamines derived from proline, from amino alcohols of the ephedrine type, possibly in the presence of alkylphenol or alkylanilines [AC1, IS3], and from complexes of borane with proline or chiral amino alcohols [IN1] or chiral diols. Just recently some chiral alkoxyborohydrides, derivatives of 9-BBN [BP1] and $LiBH_4$ complexed to *N,N'*-dibenzoylcysteine [SY2], have been suggested, as well as chiral cyclic boranes [IT2] and chiral oxazaborolidines [CB2, CB3].

These chiral oxazaborolidines can be used in catalytic amounts, the reducing agent being BH_3•THF [CG6, CL2, CC3, RG2], BH_3•Me_2S [YL4], or catechol-

borane [CB4]. These reagents can also be used to reduce α-enones with a high enantiomeric excess (ee) [CB4].

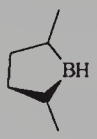
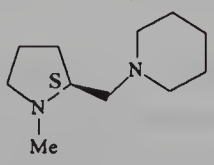
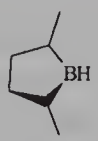
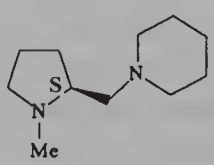
Inclusion of complexes of some enediones and $NaBH_4$ in a chiral dioxolane leads, without solvent, to a single enantiomerically pure alcohol [TK2].

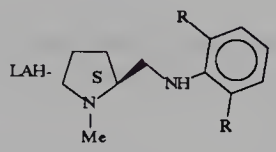
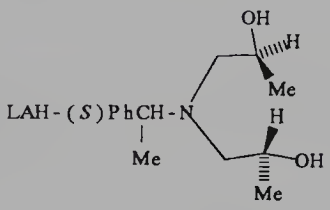
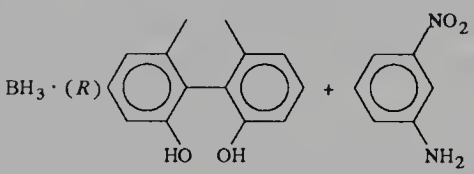
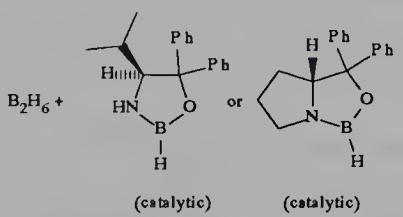
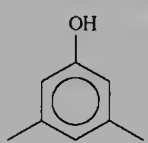
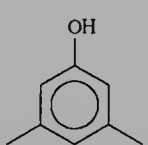


n = 1,2

Table 2 gives the observed enantiomeric excess in the reduction of aliphatic ketones, of acetophenone and α,β-acetylenic ketones by different reducing agents [IT2, AC1, CB2, CB3, MS5, IN1].

Table 2. Enantiomeric Excess Observed in Reductions by Different Agents

	ee(%)	Configuration
$PhCH_2COMe \longrightarrow PhCH_2{*}CHOHMe$		
	97	*R*
DIBAH/$SnCl_2$ + 	77	*R*
$C_6H_{13}COMe \longrightarrow C_6H_{13}{*}CHOHMe$		
	80	*R*
DIBAH/$SnCl_2$ + 	61	*R*
LAH-(*S*) Binaphthol	24	*R*
$BH_3{\cdot}Me_2CHCH(NH_2)C(OH)Ph_2$	58	*R*

	ee(%)	Configuration
PhCOMe ⟶ Ph*CHOHMe		
LAH-(*S*) Binaphthol	95	*S*
 R = H or Me	92	*S*
	82	*R*
	84	*R*
$BH_3 \cdot Me_2CHCH(NH_2)C(OH)Ph_2$	94	*R*
	97	*R*
LAH-(–)*N*-methylephedrine + 	83	*R*
HC≡CCOC$_5$H$_{11}$ ⟶ HC≡CCHOHC$_5$H$_{11}$		
LAH-(*S*) Binaphthol	84	*R*
LAH-(–)*N*-methylephedrine + 	84	*R*

A critical and comparative review of a number of examples has recently been published [BP2].

Acylstannanes ($RCOSnBu_3$) can also be asymmetrically reduced with a high ee by LAH-binaphthol [CC4] or a borane–chiral α,α-diphenyl-β-amino alcohol complex [BS4].

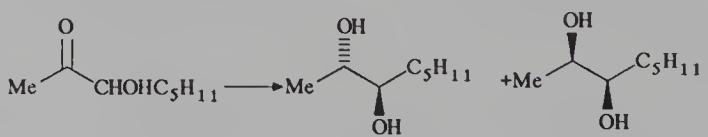
Other chiral boranes can also be used to carry out enantioselective reductions [AC1, M2, BP2], but the transferred hydride comes from the carbon skeleton and these reagents are not discussed in this book.

2.2.3. Functionalized Aldehydes and Ketones

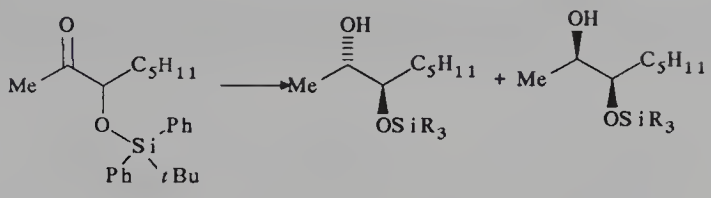
If heteroatoms are present in the neighborhood of the carbonyl, the formation of chelates around an alkali cation or the aluminum or boron atom, which plays the role of a Lewis acid, can interfere and influence the course of the reduction. The Lewis acid–base interaction can be quite energetic depending on the nature of the heteroatom and its substituents, of the ligands attached to boron and aluminum, and finally of the solvent. In this way, the stereoselectivity of the reduction can be modulated.

The reduction of aminoketones by LAH, LTBA, and borohydrides has been well studied [T2]. Highly stereoselective reductions have been observed in certain cases [T2, BL1, E1]. Recently, the stereoselectivity of the reduction of α-hydroxyketones [ON1, PR4], α-ketoethers [B2, MK2, E1, CN2, RO1, KT1], and α-epoxy ketones [B2, ON1, E1, BB6] has been reexamined, and conditions have been described that allow the highly stereoselective synthesis of each of the diastereomeric alcohols.

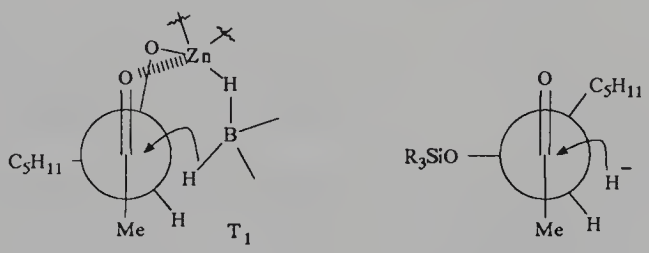
Thus the reduction of an α-ketoalcohol by $Zn(BH_4)_2/Et_2O$ leads to the *anti*-diol with good selectivity. When one uses LAH/Et_2O, this selectivity is lower. On the other hand, the reduction of the corresponding silyl ether by Red-Al/toluene gives essentially the silyl ether of the corresponding *syn*-diol [ON1], which, in the presence of $n\text{-}Bu_4N^+F^-$, regenerates the *syn*-diol. The following examples illustrate these possibilities:



	anti	*syn*
$Zn(BH_4)_2/Et_2O$, 0 °C	85	15
LAH/Et_2O	70	30

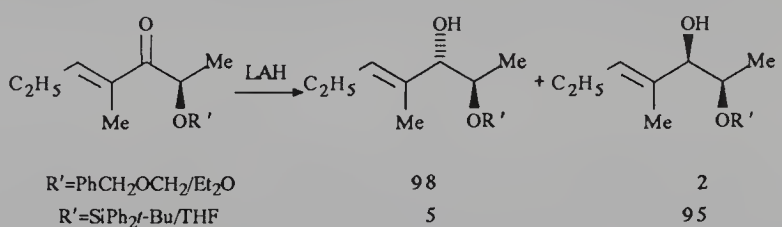


In the first case, chelation between carbonyl and the zinc alcoholate that is formed facilitates a cyclic transition state (T_1), the hydride being subsequently transferred to the side of the least bulky substituent (H). In the second case, one can propose a Felkin–Anh type of transition state, with the most polar group being $OSiR_3$ and H the smallest one:



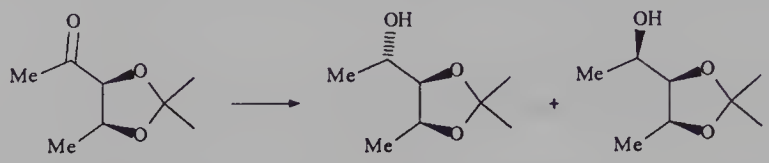
Again, according to steric hindrance and conformational effects, different levels of selectivity can be observed [see, e.g., SK4].

The possibility of chelation at transition state can also be envisaged during the reduction of the α-alkoxyketones RCOC(OR′)HR″: it depends above all on the nature of the R′ group. If this group is $PhCH_2OCH_2$ or CH_3OCH_2, the chelation may take place. On the other hand, as we have just seen when R′ = $SiPh_2$-*t*-Bu, chelation does not take place and the Felkin–Anh model applies. If R′ = alkyl, the reductions are slightly stereoselective. The following example illustrates some of these possibilities [OM1].



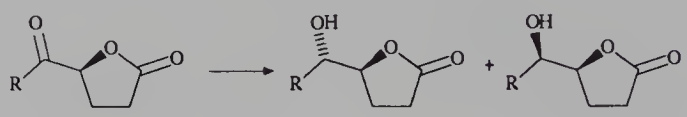
Similar results have been obtained starting from the alkynylketones [TM1].

In certain cases, the stereoselectivity is low in the presence of $Zn(BH_4)_2$: it can be enhanced by the use of DIBAH, a stronger Lewis acid, and a bulkier reagent.



$Zn(BH_4)_2$	47	53
DIBAH (2 eq)	8	92

Comparable results have been obtained with the optically active acyl-4-butanolides [LL2] or other chiral α-alkoxyketones [GB4].

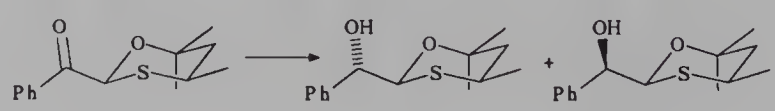


$NaBH_4$/EtOH	75	25
$Zn(BH_4)_2/Et_2O$	70	30
Red-Al/toluene	58	42
Li(*sec*-Bu)$_3$BH/THF	2	98

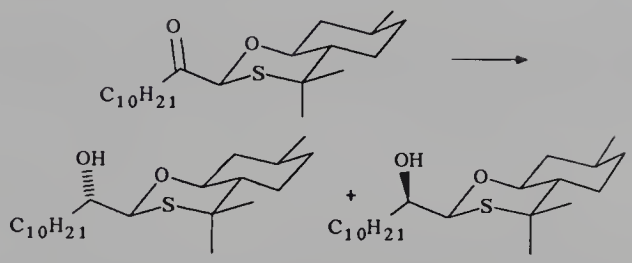
However, 2-methoxy-1,2-diphenylethanone is reduced to the *anti*-α-methoxy alcohol with good stereoselectivity, whatever the reducing agent (LAH, DIBAH, $NaBH_4$ or K(*sec*-Bu)$_3$BH) [FH4].

Cyclic epoxy ketones are also reduced highly stereoselectively by $NaBH_4/CeCl_3$ [BB6].

Similarly, the reduction of 2-acyl-1,3-oxathianes by LAH/Et_2O or Li(*sec*-Bu)$_3$BH/THF is very stereoselective because it promotes chelation by the oxygen atoms. It permits the synthesis of optically active α-hydroxyaldehydes or α-hydroxyesters from chiral oxathianes [E1, KE1, KF4].

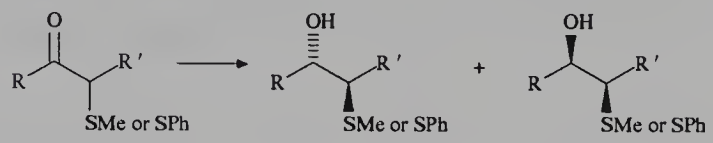


LAH/Et_2O,20°C	92	8
Li(*sec*-Bu)$_3$BH	98.5	1.5
toluene, -78°C		



Li(*sec*-Bu)$_3$BH	91	9
toluene, -78°C		
DIBAH	9	91
toluene, -78°C		

The method can also be applied to α-methylthio or α-phenylthioketones:

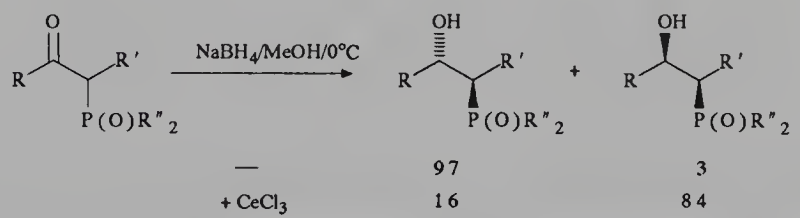


Their reduction by Li(*sec*-Bu)$_3$BH leads very selectively to the syn isomer, whereas $Zn(BH_4)_2$ preferentially gives the anti isomer with lower stereoselectivity.

The problem of the reduction of 2-methylthiolcyclohexanones has also been examined [CD1].

Additives can induce the formation of chelates: chiral α-ketosulfoxides can be reduced with high stereoselectivity by DIBAH/$ZnCl_2$/hexane/THF [BP4], via a cyclic chelated transition state.

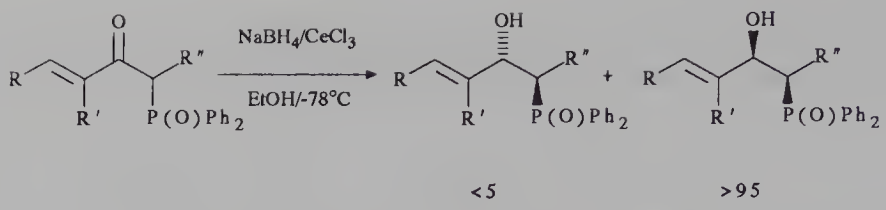
α-Phosphinyloxyketones also undergo a stereoselective reduction to *syn*-alcohols when using $NaBH_4/CeCl_3$/MeOH, while *anti*-alcohols are obtained without $CeCl_3$ [EW1].



—	97	3
+ $CeCl_3$	16	84

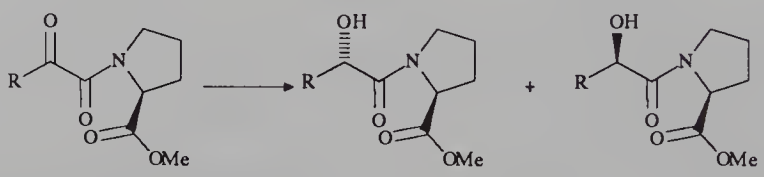
Hydroxy substituents on R′ can induce good stereoselectivity [GW2].

α-Phosphinyloxy α-enones do not suffer a stereoselective reduction by $NaBH_4/CeCl_3$ unless the R″ group is bulky enough (*i*-Pr, cyclohexyl): the syn isomer is thus predominant, in agreement with a chelated transition state [EH1].

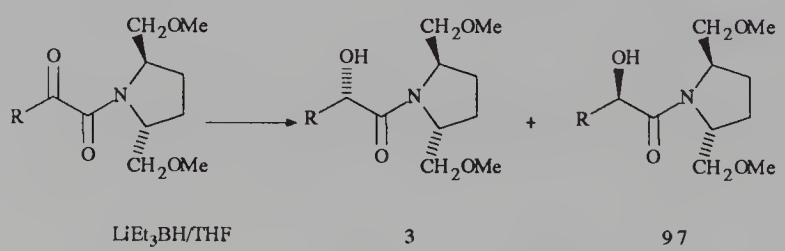


In the case of polysubstituted derivatives such as carbonyl α,β-dialkoxyl compounds, Li(*sec*-Bu)$_3$BH and Zn(BH$_4$)$_2$ lead each to a different isomer, but the stereoselectivity is lower than in the former cases because of competition among the different association sites [IY1, YK3, YK4, FK3]. Analogous problems also arise in the chemistry of sugars [MT2].

The stereoselective reduction of α-ketoesters and α-ketoamides can also be performed. For example, the reduction of the following chiral ketoamide by LiBH$_4$/THF in the presence of LiBr selectively leads to one of the enantiomerically pure diastereomers [SI1]; with DIBAH the reduction appears to be less selective.

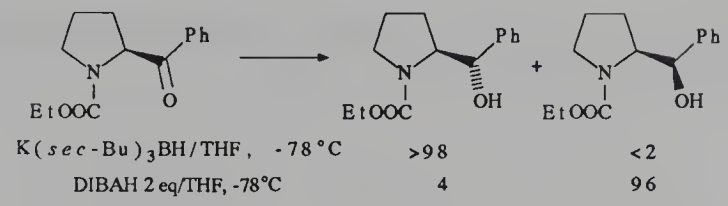


The most interesting results are obtained if the heterocycle carries two methoxymethyl groups [KF3] or CH$_2$OMEM [KF5].



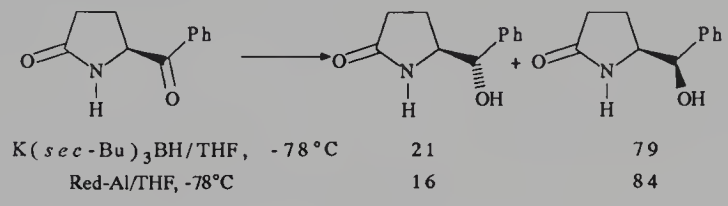
The reaction of Zn(BH$_4$)$_2$ is not stereoselective, whereas those of NaBH$_4$ or KBH$_4$/*i*-PrOH are clearly less than when LiEt$_3$BH is used.

The stereoselectivity is high if the ketone group is fixed on a five-membered ring as shown in the following examples [OS1], where carbamoylketones are reduced:



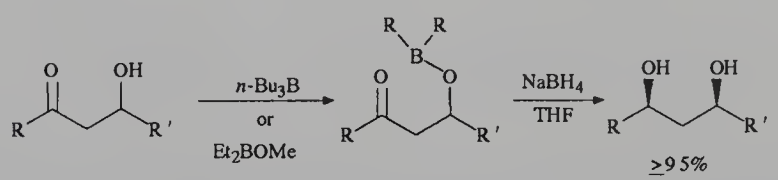
Other reducing agents appear to be less effective (Li(*sec*-Bu)3BH/THF, $NaBH_4$/THF-MeOH, LAH/THF, or BH_3•THF).

If one employs a secondary cyclic amide, the stereoselectivity is lower [OS1].



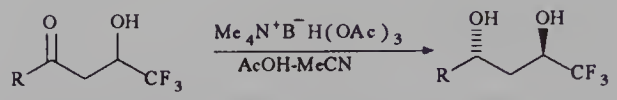
When the reduction is carried out at low temperature or at 0°C, the amides are not affected (§2.2.7).

Stereocontrolled aldolization reactions have been the object of many recent studies, and the reduction of β-hydroxyketones or of their ethers to 1,3-diols has been much studied. This reduction can be extremely stereoselective. Thus, from β-hydroxyketones, one obtains *syn*-diols very selectively either by the action of DIBAH in THF at low temperature [KK4], with $LiAlH_4$/LiI/Et_2O at –100°C [MK4], or after the preliminary formation of an alkyl borate by means of Bu_3B [NP1] or, better yet, of Et_2BOMe [CH1, CG4, HH4], by reaction with $NaBH_4$/THF.

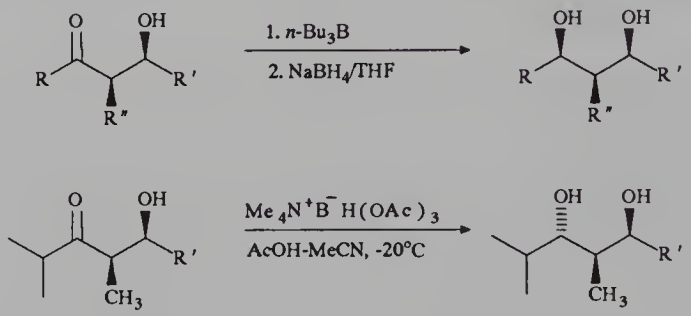


The reduction of trifluoro β-ketoalcohols by DIBAH leads very stereoselectively to *syn*-diols [LY1].

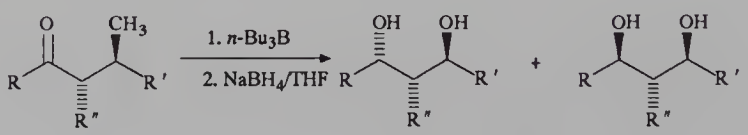
The *anti*-diols are obtained in a stereoselective manner by reaction with $Me_4N^+B^-H(OAc)_3$ [EC1, LY1, EC2].



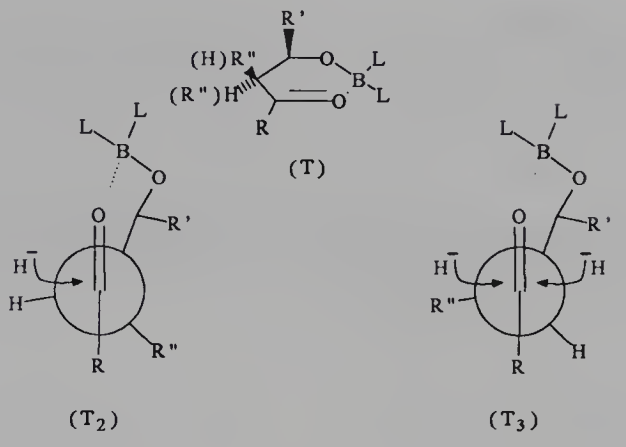
When the β-hydroxyketones carry an alkyl substituent in the α-position, the relative stereochemistry of the R″ group and the hydroxyl group defines the stereoselectivity [NP1]. If these two are in a syn relationship, one obtains selectively the *syn, syn*-diols by reaction with *n*-Bu_3B followed by $NaBH_4$/THF. The *syn, anti* isomers can be obtained by action of $Me_4N^+B^-H(OAc)_3$ in AcOH MeCN [EC1, EC2].



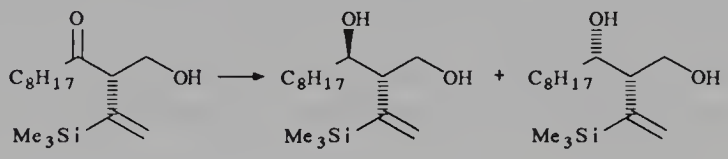
On the other hand, if the OH and R″ groups are in an anti relationship, one obtains a mixture of stereoisomers [NP1].



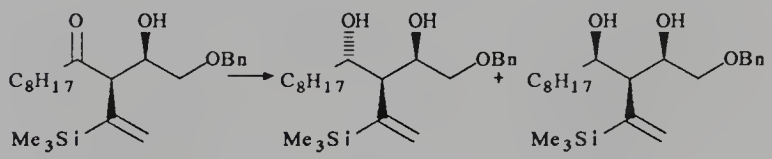
With regard to the reductions involving the intermediate alkylborates, the following transition states can be suggested. The course of the reduction depends on the relative stereochemistry of R″ and the hydroxyl. When R and R″ are on the same side of the plane of the chelate, the hydride approaches the carbonyl on the side opposite to the substituents and the reduction is stereoselective (T2). On the other hand, if R and R″ are on either side of this plane, the approach of the hydride is always constrained and one no longer observes any stereoselectivity (T3).



Nevertheless, when the R and R″ groups become too bulky, it is no longer possible to envision a chelation. Whatever the reducing agent may be [Li(*sec*-Bu)3BH or DIBAH], the reaction follows the course given by the Felkin–Anh rule [SS2] as shown in the following examples:

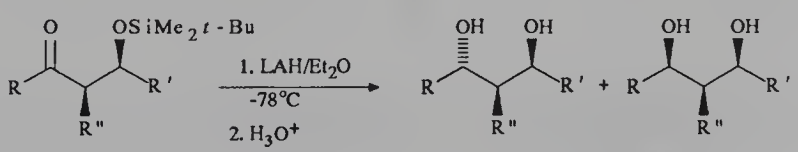


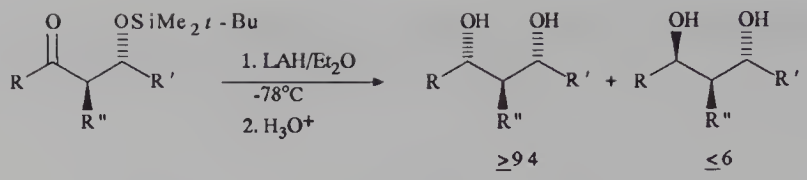
$LiBEt_3H$/THF	<1	>99
DIBAH/THF	20	80



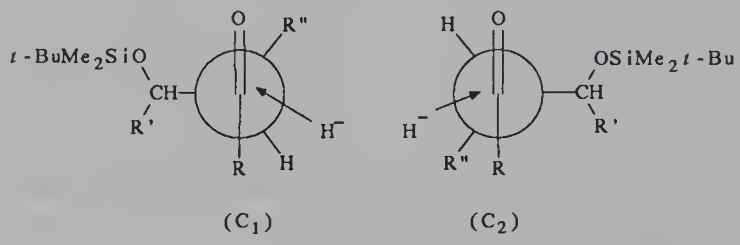
$LiBEt_3H$/THF	<1	>99
DIBAH/THF	<1	>99

Similarly, the application of the Felkin–Anh rule, when chelation is prevented by the formation of *t*-$BuMe_2Si$ ethers of β-hydroxyketones allows the access to *syn,anti* or *anti,anti*–α-alkylated diols, depending on the stereochemistry of the starting β-hydroxyketones [BG3].

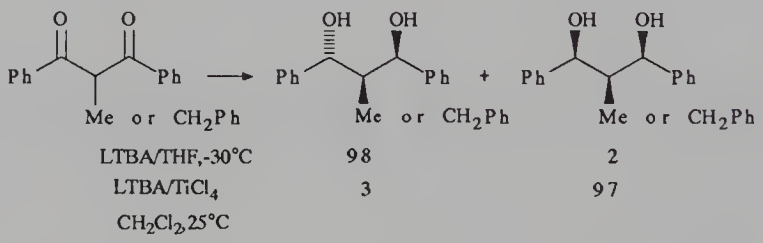


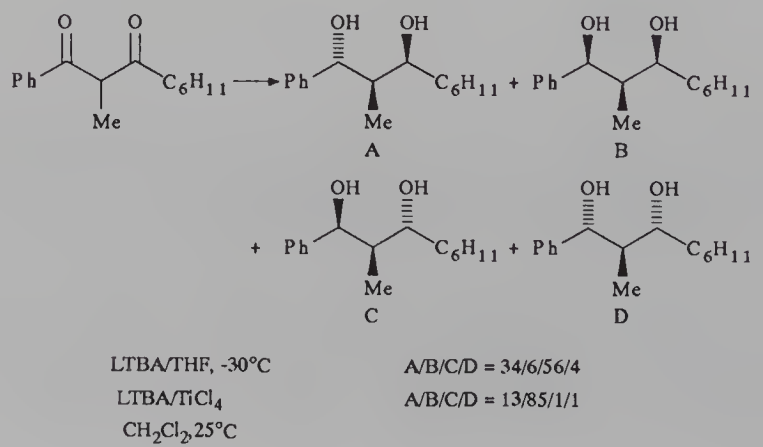


However, in the latter case, if R″ = H, the reduction is only slightly stereoselective, the two conformations C_1 and C_2 are equally populated. When R″ is not H however, C_1 is favored.



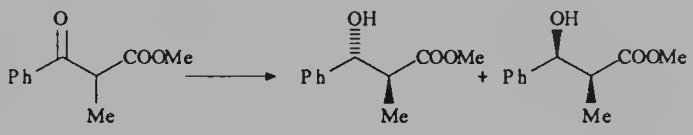
The reduction of the 1,3-diketones to diols can also be stereoselective and can lead to either *syn,syn*-diols or *syn,anti*-diols, depending on the possibility (or not) of intramolecular chelation after the formation of the alcoholate resulting from the initial reduction [BR2]. The selectivity is higher when the environment of the two carbonyl groups is similar, as shown in the following examples:



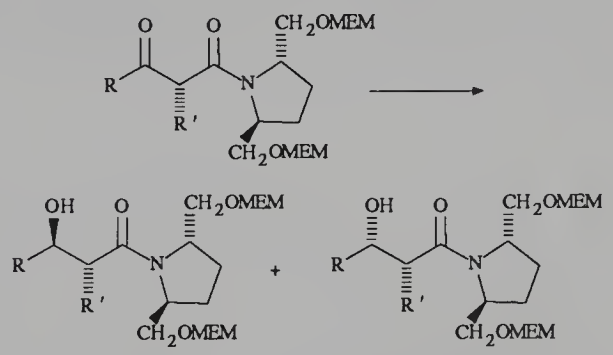


A very stereoselective reduction of a [3.1.0]bicyclic diketone by $NaBH_4/CeCl_3$ at low temperature has recently been described [KS6]. $LiBEt_3H$ gives the other stereoisomer while LAH and $LiBH_4$ are poorly stereoselective.

The reduction of β-ketoesters or β-ketoamides by $Zn(BH_4)_2$ is extremely stereoselective in favor of the *syn*-β-hydroxy isomer; KBH_4 or *n*-$Bu_4N^+BH_4^-$ in EtOH or, better, K(*sec*-Bu)$_3$BH, leads selectively to the anti isomer [ON1, IK1], as shown in the following examples, from a racemic or optically active series.

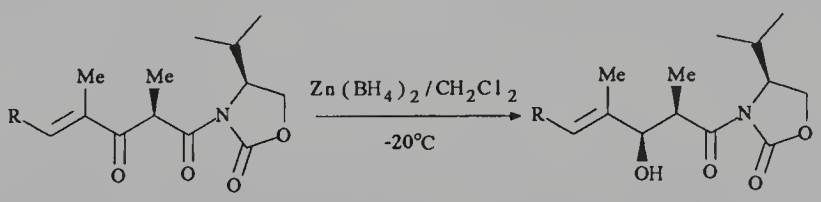


$Zn(BH_4)_2/Et_2O$	<1	>99
$LiBH_4/Et_2O$	10	90
KBH_4 or *n*-$Bu_4N^+\bar{B}H_4$/EtOH	70	30



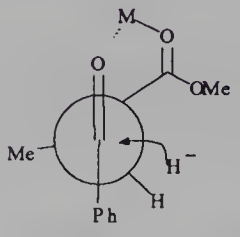
$Zn(BH_4)_2/Et_2O$	<2	>98
$KBEt_3H/Et_2O$	>98	<2
$LiBEt_3H/Et_2O$	66	33

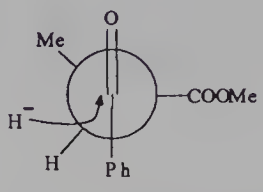
Similarly, β-keto*N*-acyloxazolidinones are stereoselectively reduced to *syn*-alcohols by $Zn(BH_4)_2/CH_2Cl_2$ [NF1].



As before, when the cation associated with the reducing agent or the reagent itself is a strong Lewis acid, one can consider a transition state of the chelate type

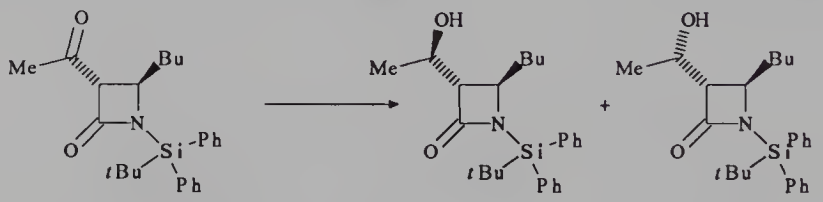
(T_1). When, in the other cases, a Felkin–Anh type of transition state is envisioned, the attack of the hydride will take place on the face opposite to the most polar groups — in this case, an ester or amide group.





(T_1)

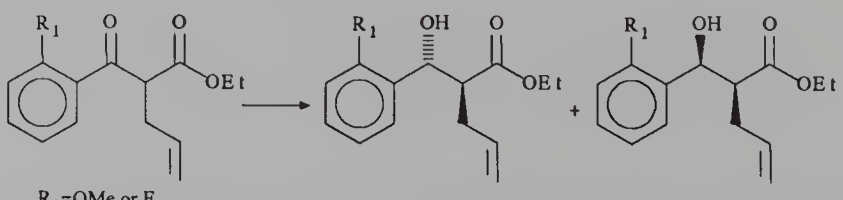
When the reduction is carried out with $LiEt_3BH$, the result obtained shows that two possible transition states are equally important. This behavior is dominant during the reduction of the cyclic ketoamides below by Li(*sec*-Bu)$_3$BH/THF at low temperature. The observed stereoselectivity then is opposite to that using K(*sec*-Bu)$_3$BH/Et_2O at 20°C. Chelation is certainly favored by entropic effects due to the lowering of the temperature [PA1]. Other reagents are less selective.



Li(*sec*-Bu)$_3$BH/THF, -78°C	14	86
K(*sec*-Bu)$_3$BH/Et_2O, 20°C	>98	<2

Other similar results have been obtained for related cases [SK2].

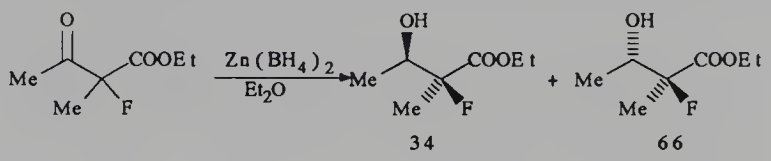
Other substituents in the vicinity of the ketone group can also influence the stereochemical course of the reduction. An OCH_3 group or a fluorine atom at the ortho position in an arylketo ester induces an opposite stereoselectivity depending on the reagent employed [BF1]:



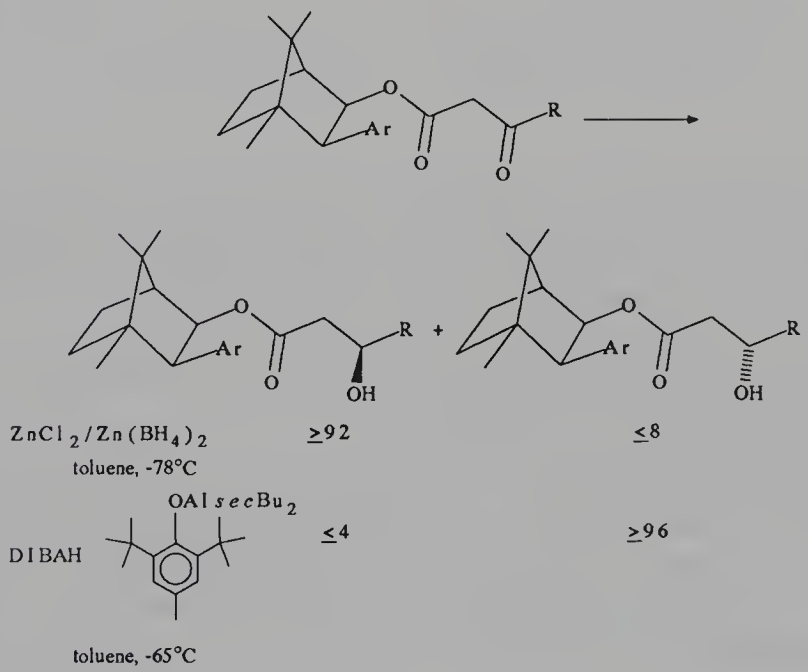
R_1=OMe or F

$Zn(BH_4)_2$/THF	6	94
KBH_4/MeOH	84	16

The presence of a fluorine atom on the α-alkylated carbon diminishes the stereoselectivity of the reduction of β-ketoesters by $Zn(BH_4)_2$ [KK7].

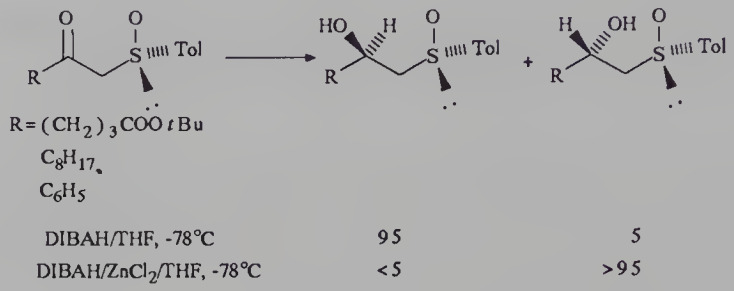


Finally, the introduction of additives may allow the stereoselectivity of the reductions to increase. Thus, the addition of $ZnCl_2$ to $Zn(BH_4)_2$ or the coordination of the carbonyl group by a bulky Lewis acid such as diisobutylaluminum-2,6-di-*t*-Bu-4-methylphenolate (BHT) induces high and opposite stereoselectivity from chiral β-ketoesters. In the first case, chelation is strengthened and the reduction involves a cyclic transition state. In the second case, chelation is disfavored and the reduction follows the Felkin–Anh rule, as shown in the following examples [TD1]:

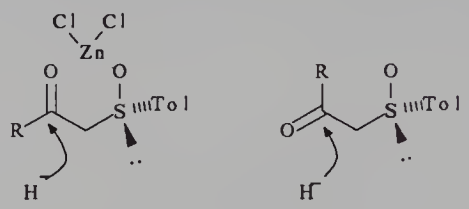


In the case of α-triazoylketones, which are β-aminoketones, while *n*-$Bu_4N^+BH_4^-/CH_2Cl_2$ reduction preferentially gives the Felkin–Anh isomer, the other is obtained in the presence of $TiCl_4$ [TS2]. Similarly, β-benzyloxyketones are stereoselectively reduced by Li(*sec*-Bu)$_3$BH/$MgBr_2$•OEt_2/CH_2Cl_2 [TC1].

β-Ketosulfoxides can also be reduced in a stereoselective fashion and, depending on the condition chosen, can lead to either of the two possible diastereomers [SD1, SG1, KK3, CD1, CG5].



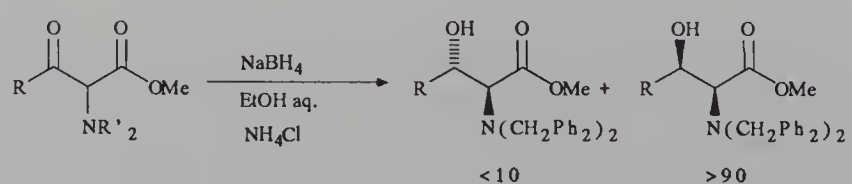
The transition states for this reduction imply either a chelated model or an open model, the hydride attacking the carbonyl from the least hindered side — that is, on the face opposite the tolyl group.



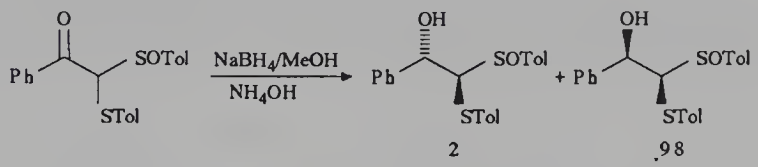
The interest in these reductions lies in access to chiral alcohols after the cleavage of the C—S bond by aluminum amalgam. Starting from this type of compound, one can also obtain chiral epoxides and lactones.

The reduction of these ketosulfoxides by BH_3•THF, $Zn(BH_4)_2/Et_2O$-THF, LTBA/Et_2O, or $NaBH_4$/EtOH is poorly stereoselective [KK3, GP1], as is the reduction of chiral ketosulfoximines [JS3].

When the ketones to be reduced are substituted by several groups capable of chelating the reducing agent or the associated cation, the reactions are only slightly stereoselective unless one introduces, on one of the groups, substituents that disfavor chelation. The reduction of the following aminoketoesters is poorly selective except if R′ = CH_2Ph and if the reduction is performed in a slightly acidic medium [GB1, GD3, RD1].

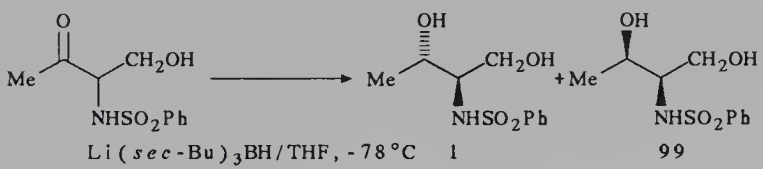


Chelation with protonated nitrogen is prevented, with the result that the reduction takes place preferentially on a rigid chelate system because of hydrogen bonding between the ketone and the ester. An analogous example is the case of the following compound, whose reduction is not stereoselective in neutral medium [OF1].

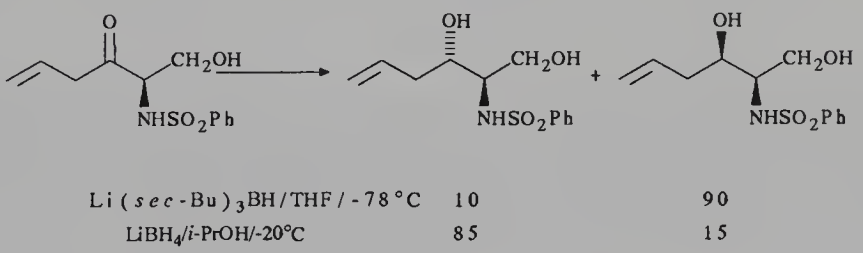


A similar stereoselectivity toward the syn isomer has been observed in the reduction of 2-methyl-2-thiophenyl-β-ketoesters by $Ca(BH_4)_2$/MeOH/THF [SS4].

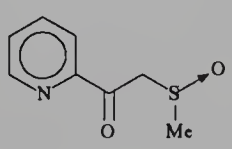
Similarly, only Li(*sec*-Bu)$_3$BH/THF selectively reduces the following multifunctional complex, wherein the transition state concerned is of the Felkin–Anh type [MT1].



Similar results are given for other aminoketones that lead predominantly to syn isomers with Li or K(*sec*-Bu)$_3$BH in THF and to anti ones with $LiBH_4$/*i*-PrOH [RR1].

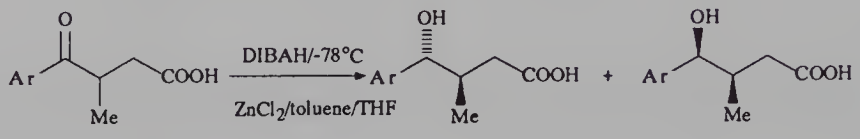


Similar observations could be made concerning the reduction of β-pyridyl-ketosulfoxides [GP1].



More or less stereoselective reductions have been performed when substituents able to induce chelation are located on each side of the carbonyl group [MS4, HJ4, MT3].

When the chelating group is located in the γ-position, stereoselective reduction can also be observed: such is the case for γ-oxo-γ-phenylbutanoic acids, which are reduced to *syn* γ-hydroxyacids by DIBAH/$ZnCl_2$. The other reducing agents are far less stereoselective [FK2]



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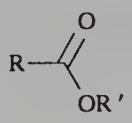
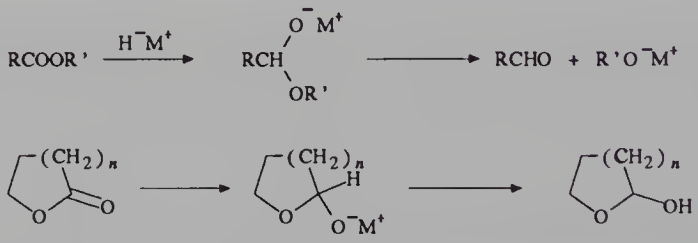
2.2.4. Esters and Lactones



The reduction of esters and lactones can be partial, and it can imply the participation of a single hydride. Starting with the esters, one thus obtains aldehydes via the corresponding hemiacetals, and starting with lactones one gets the lactols.



This reaction is still difficult to realize in practice: LTBA/THF at 0°C allows the phenyl esters to be transformed to aldehydes with some good yields, while the reaction of aliphatic esters is much slower [BK5, C5, M3].

$$\text{RCOOPh} \xrightarrow{\text{LTBA/THF,0°C}} \text{RCHO}$$

Aluminum bis(*N*-methylpiperazino)hydride/THF at 25°C allows this transformation to take place starting from alkyl esters [HUD, C5, M3]. However, the use of LAH in the presence of diethylamine in pentane seems to be of greater generality. AlH_3 formed after the transfer of the first hydride precipitates in the form of a complex with Et_2NH, used in excess [CK1]. α,β-Ethylenic esters are also reduced to corresponding aldehydes, just like the diesters, which lead to the

dialdehydes. More recently, it has been reported that the yields are not always as high as previously indicated [CK3]

$$\text{RCOO alkyl} \xrightarrow{\text{LAH–Et}_2\text{ NH/pentane}} \text{RCHO}$$

$$\text{CH}_3\text{CH}{=}\text{CH–COOEt} \xrightarrow{\text{LAH–Et}_2\text{NH/pentane}} \text{CH}_3\text{CH}{=}\text{CH–CHO}$$

DIBAH in toluene at low temperature is often recommended for carrying out the reduction of saturated esters to corresponding aldehydes [W1, K2, YG1, C5]. In the presence of *o*-anisidine, yields are improved [KK9].

$$\text{RCOOR}' \xrightarrow{\text{DIBAH/toluene,–78°C}} \text{RCHO} + \text{R}'\text{OH}$$

The reduction is compatible with an α-SePh substituent, whose absolute configuration as a chiral molecule is retained [DD1].

The reaction of DIBAH with ketones is, however, more rapid. The selective reductions of ketoesters (§2.2.3) have already been described.

Nevertheless, α,β-unsaturated esters give rise to allylic alcohols, even if one uses a less than stoichiometric amount of reagent (§2.2.8).

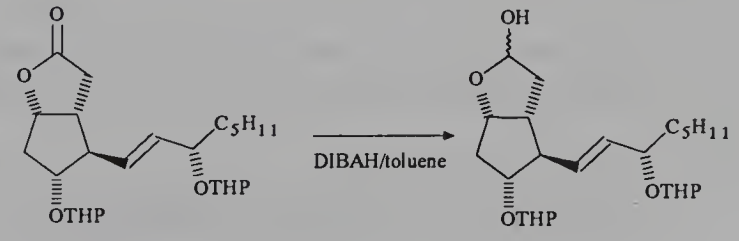
$$\text{RCH}{=}\text{CH–COOR}' \xrightarrow{\text{DIBAH/toluene, –78°C}} \text{RCH}{=}\text{CHCH}_2\text{OH}$$

Use of *i*-Bu_2AlD leads to deuterated aldehydes [KW1].

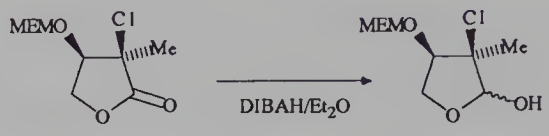
$$\text{RCOOEt} \xrightarrow{i\text{-Bu}_2\text{AlD/toluene, –78°C}} \text{RCDO}$$

Lactones, under the same conditions, or in Et_2O, lead to the corresponding lactols [W1, M3] as shown in the following two examples.

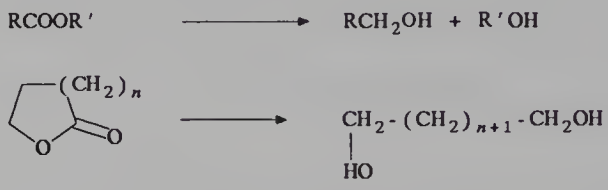
One of the early syntheses of prostaglandins, due to Corey, involves the reduction by DIBAH of the following lactone [W1], followed by a Wittig reaction, which can be carried out directly on the lactol.



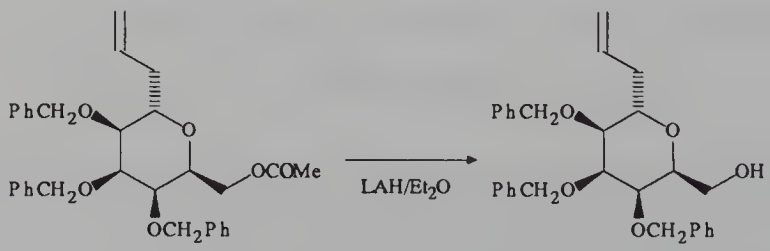
The reduction of the following multifunctional lactone respects the integrity of the other groups [WV1].



Esters and the lactones are respectively reduced to two alcohols or diols by numerous reagents:



LAH in ethers and on silica gel converts them to alcohols resulting from a second reduction, even at low temperature, where one obtains a mixture of aldehydes and alcohols [BK5, HUD, KH2, M3]. The reduction of esters by LAH may allow alcohols to be prepared from acetates, for example, under conditions that would permit hydrolysis to induce some side reactions, such as epimerizations (§1.2). The following example is an application [AK2]:



Since LTBA is often less reactive at low temperature toward esters, selective reduction of ketones can be performed [M3].

AlH_3 also reduces esters to alcohols [BK5] just as does $LiBH_4$/hot DME or $LiBH_4$/refluxing Et_2O [BS1, BK5]. The reduction requires electrophilic assistance since, with $LiBH_4$, it is faster when the solvent is not a good solvating agent of the cation:

$$Et_2O > THF \cong DME > i\text{-}PrOH \quad [BN1]$$

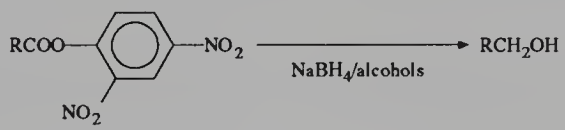
$LiBH_4$ can be generated in situ from $NaBH_4/LiCl/THF/EtOH$ [HS4, HI1]; with this system, chiral amino esters can be reduced to amino alcohols without epimerization [JF2]. $Ca(BH_4)_2$, formed from $CaCl_2 + NaBH_4$ in aqueous ethanol, can also be used for this purpose [BR3].

The selective reduction of an ester functionality in the presence of a secondary tosylate can be performed with $LiBH_4/LiBEt_3H/Et_2O/THF$ at 0°C [AS1].

The reaction can be accelerated by the addition of other Lewis acids such as Et_3B [YP2], $B(OMe)_3$ [BN3], or methanol [SO3]. In the last case the reduction is carried out under reflux in THF in the presence of 4 equivalents of MeOH. The selective reduction by $LiBH_4$ of the ketone group in ketoesters nevertheless can be accomplished (§2.2.3).

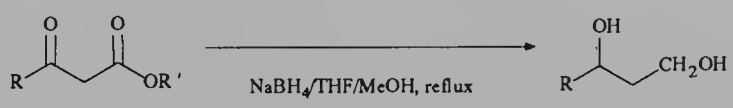
$LiBuBH_3/Et_2O$ at 0°C reduces esters but leaves them untouched in toluene-hexane at –78°C [KM2]. Lithium trialkylborohydrides/THF equivalently transform esters to alcohols and lactones to diols [BK5]. Steric hindrance around one ester moiety can allow the regioselective reduction of the least hindered functional group of a dissymetrically substituted diester by $LiBEt_3H/THF$ at 0°C [FR1]. $KBEt_3H/THF$ reduces esters quickly enough to leave epoxides, amides, and nitriles unchanged [YY1]. Moreover, $K(sec\text{-}Bu)_3H/THF$ at 0°C reduces lactones into diols faster than PhCOOEt or ethyl caproate [YH2].

$n\text{-}Bu_4N^+BH_4^-/CH_2Cl_2$ does not react with esters [RG1]; reductions by $NaBH_4$ in alcohols or on alumina are very slow except with 2,4-dinitrophenyl esters, which are easily reduced to alcohols [PS1].



The reduction takes place, however, in the presence of ethylene glycol oligomers at 80°C [SF1]

Nevertheless, reduction can be accomplished in the presence of additives: the action of $NaBH_4$ on esters in THF or refluxing *t*-BuOH in the presence of MeOH [SO1], or in refluxing EtOH [OS3] or even in water [BP3], leads to the corresponding alcohols. Under these conditions, primary amides, acids, and NO_2 groups remain inert. Thus, starting from ketoesters, one can obtain diols [SO2].



Moreover, α-cyano α-epoxy esters are easily reduced to α-cyano epoxy alcohols by $NaBH_4$/aqueous THF [MR4].

Ethanedithiol can also be an additive for the reduction of esters by $NaBH_4$, except *t*-butyl esters; the nitrile groups remain unperturbed under these conditions [GE1]. Methyl benzoate is reduced to benzylalcohol by $NaBH_4/ZrCl_4$/THF [IS1].

Esters are much less sensitive than ketones to $Zn(BH_4)_2$ or cyanoborohydrides [PS1]: the selective reduction of the ketone groups of α- and β-ketoesters can be accomplished without problems (§2.2.1, 2.2.3).

BH_3•THF or BH_3•SMe_2, at room temperature, reacts very slowly with esters in THF [BK5, L2, PS1]. Under reflux with THF, BH_3•SMe_2 reduces esters to alcohols [BC1]. Nevertheless, α-hydroxyesters can be reduced at room temperature by BH_3•SMe_2/THF in the presence of a catalytic quantity of $NaBH_4$, wherein the following selective reduction takes place [SH1].

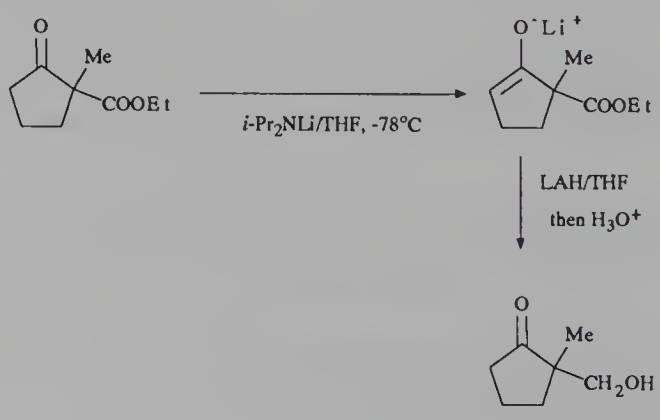
$$MeOCOCHOHCH_2COOMe \xrightarrow{BH_3\bullet SMe_2/THF} HOCH_2CHOHCH_2COOMe$$

γ-Carboxyesters also undergo reduction of the ester group by BH_3•SMe_2 [FC2]

Acyloxyboranes [MM1] and aminoboranes [A1] do not react either with esters or with lactones, except Ph_2NH•BH_3, which reduces aliphatic esters [CU1].

Substituted boranes are more efficient: 9-BBN reduces esters under reflux in THF [PS1], Sia_2BH transforms lactones to hydroxyaldehydes [BK5], ThexBHCl gives rise to alcohols under heating [BN5]. Finally, the -ate complex Li 9-BBNH reduces esters to alcohols and lactones to diols. Acids, amides, nitriles, and halogenated derivatives remain intact under these conditions [BM1].

It has been emphasized that ketones are reduced more rapidly than esters. It is nevertheless possible, in forming the corresponding lithium enolates in a first step, to reduce ketoesters to corresponding ketoalcohols, as shown in the following example [KF2, BH2]:



The limitation of the method is the stability of the enolates formed and the need for the absence of labile hydrogen at the α position of the ester group.

Competitive enolization decreases the yield for reduction of malonates to 1,3-diols: in this case, the best reagents for avoiding this side reaction are electrophilic hydrides such as AlH_3 or, better, DIBAH/THF [CE2].

In coupling the reduction of the esters by $LiBH_4$ and the condensation of the aldehydes formed with an organomagnesium reagent, it is possible to prepare secondary alcohols via a "one-flask" method from ethyl esters [CH2]:

$$\text{RCOOEt} + \text{R'MgX} + \text{LiBH}_4 \xrightarrow[\text{THF, } -20^\circ\text{C}]{} \text{RCHOHR'}$$

The reduction of bromoesters to bromoalcohols by AlH_3 in Et_2O leaves the carbon—halogen bonds unchanged [BK5, E2]:

$$\text{MeCHBrCH}_2\text{COOEt} \xrightarrow{\text{AlH}_3/\text{Et}_2\text{O},0^\circ\text{C}} \text{MeCHBrCH}_2\text{CH}_2\text{OH}$$

The thiolesters (RCOSEt) are reduced to alcohols by an excess of *n*-$Bu_4N^+BH_4^-$ in refluxing $CHCl_3$, but are inert in the presence of B_2H6 [LL4]. Dithioesters and thioxoesters are reduced to thiols by BH_3•Me_2S [JS4].

2.2.5. Carboxylic Acids and Acid Anhydrides: RCOOH, RCOOCOR'

Again, incomplete reduction can lead to aldehydes or alcohols: the choice of reducing reagent and reaction conditions can allow one to reach one or the other functional group.

The reduction of acids to aldehydes may be accomplished by aluminum bis(*N*-methylpiperazino)hydride in THF, starting from both aliphatic and aromatic acids with excellent yields [HUD, HE1, MM3, C5].

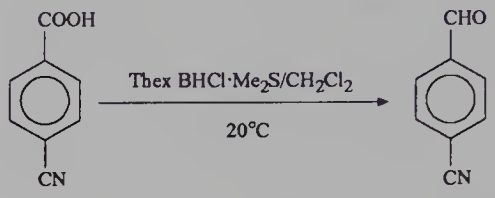
$$\text{RCOOH} \longrightarrow \text{RCHO}$$

$$\text{ArCOOH} \longrightarrow \text{ArCHO}$$

On the other hand, the use of DIBAH on a preparative scale does not appear to give satisfying results [YG1].

Likewise, ThexBHCl•Me_2S/CH_2Cl_2 as well as 9-BBN in excess lead to this

transformation [BC4, BC5, C5, CO1], which is compatible with halogenated substituents, even on aliphatic residues and with NO_2, CN, and ester groups.



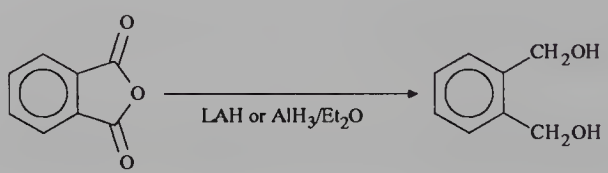
$$Br(CH_2)_5COOH \xrightarrow[20°C]{\text{Thex BHCl·Me}_2\text{S/CH}_2\text{Cl}_2} Br(CH_2)_5CHO$$

$$EtOCO(CH_2)_4COOH \xrightarrow[20°C]{\text{Thex BHCl·Me}_2\text{S/CH}_2\text{Cl}_2} EtOCO(CH_2)_5CHO$$

Another methodology consists of treating acylboranes obtained by the action of 9-BBN on acids with 1 equivalent of Li 9-BBNH [CK2], the reduction being compatible with the same groups as before.

LAH and AlH_3 in ethers, $Li(MeO)_3AlH$, or Red-Al/C_6H_6 at 80°C can be used to reduce acids and anhydrides to their corresponding alcohols [HUD, BK5, BY1, M3]: cyclic anhydrides are thus transformed into diols.

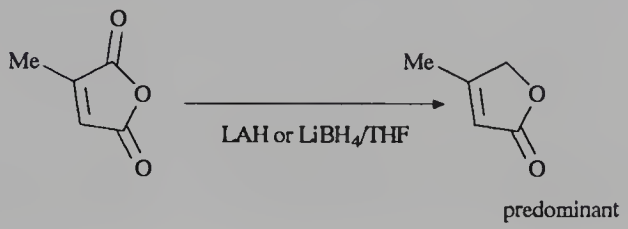
$$RCOOH \xrightarrow[\text{LAH or AlH}_3/\text{Et}_2\text{O}]{} RCH_2OH$$

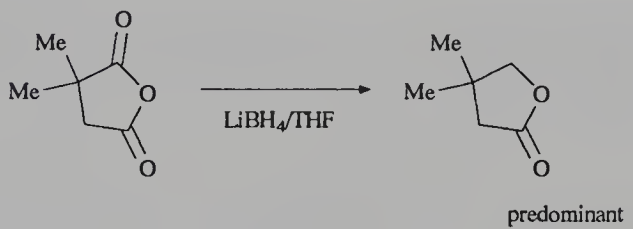


However, using a measured amount of LAH and when working at low temperature, cyclic anhydrides are reduced to lactones [M3]:

$LiBH_4$/THF at 25°C [N1], $NaBH_4$/THF at 25°C in the presence of methanol added dropwise, DIBAH in the presence of *n*-BuLi [KA1], or lithium trialkylborohydrides/THF [BK6] also will lead to lactones.

The reduction of the dissymetrical anhydrides is regioselective: hydride attack takes place on the carbonyl that is α to the most substituted carbon, as shown in the following examples [KM1, VN1, M3]:

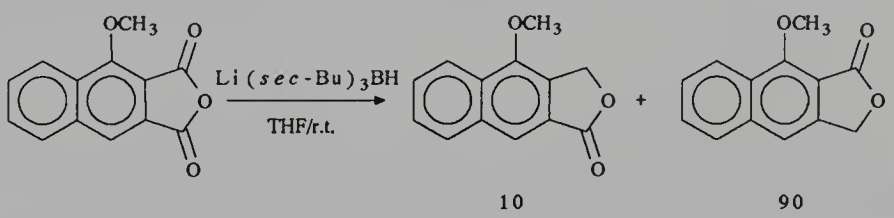




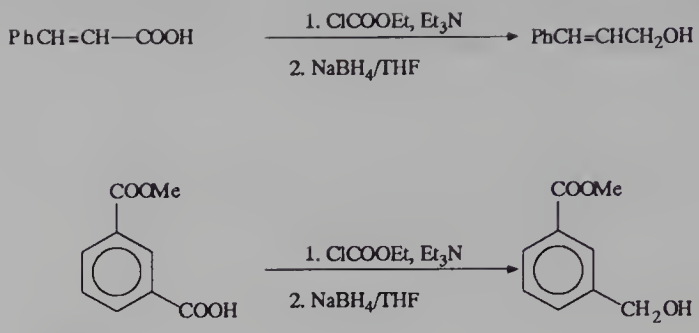
Similar results were also obtained with aspartic anhydride [MH4].

$NaBH_4$ in DMF may lead to the same reduction [BJ2].

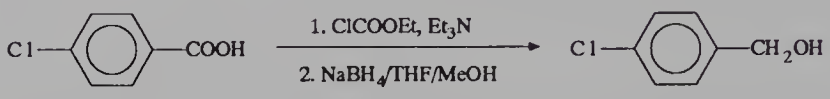
However, bulky complex metal hydrides such as K or Li(*sec*-Bu)$_3$BH lead to a complete reversal of regioselectivity [M3]. Such is the case with alkoxy-substituted phthalic anhydrides, which lead regioselectively to the lactone resulting from reduction of the carbonyl group that is away from the OCH_3. Contrary to another report [MM4], $NaBH_4$ and $LiBH_4$/THF are poorly regioselective in this case.



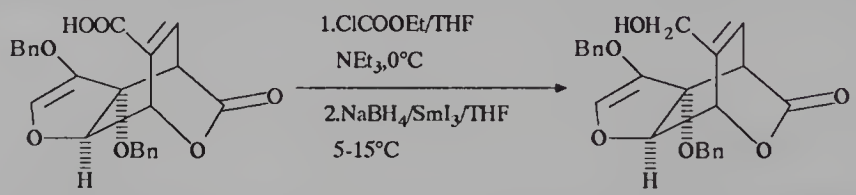
An easy and smooth method of reducing acids to alcohols consists of transforming them by reaction with ClCOOEt/Et_3N into mixed carboxylic–carbonic anhydrides, which are easily reduced by $NaBH_4$/THF, possibly in the presence of MeOH. This method does not affect double bonds and the NO_2, CN, $CONH_2$, and COOR groups, as shown in the following examples [SY1, IK2].



In the presence of MeOH, the reduction takes place at 10°C and the aromatic halides are not affected [SY1].



In certain cases, reduction by $NaBH_4$ of mixed anhydrides of unsaturated acid can be delicate [JU1]. $NaBH_4/CeCl_3/MeOH$ does not appear to be efficient, with the formation of the methyl ester hindering the reduction. The use of $NaBH_4/SmI_3/THF$ leads to the expected allylic alcohol.



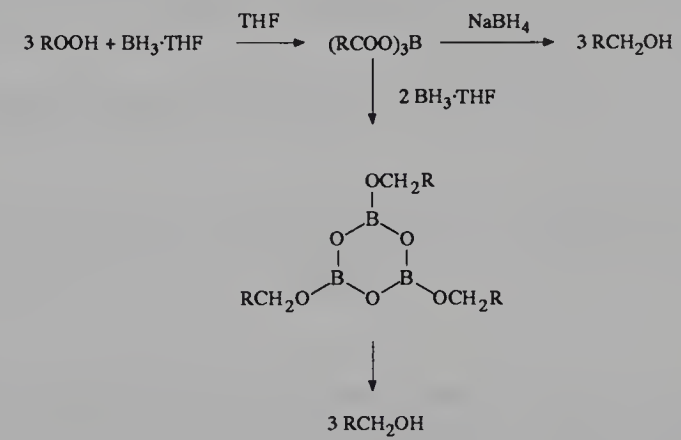
Some Japanese authors have recommended the use of mixed carboxylic–phosphoric anhydrides, but the yields are not so high [KY1].

Carboxylic acids are not reduced by alkaline borohydrides [BK5], trialkylborohydrides [BK5], 9-BBN, or Sia_2BH at room temperature [BK5], or by the acyloxyboranes [HM1, GN1]. The activation of $LiBH_4$ by MeOH in refluxing THF induces the reduction of carboxylic acids to alcohols [SO3], but in the presence of $B(OMe)_3$, the reduction is incomplete [BN3]. However, in the presence of $MeSi_3Cl$, $PhCH_2N^+Et_3BH_4^-$, $LiBH_4$, and $NaBH_4$/THF reduce acids

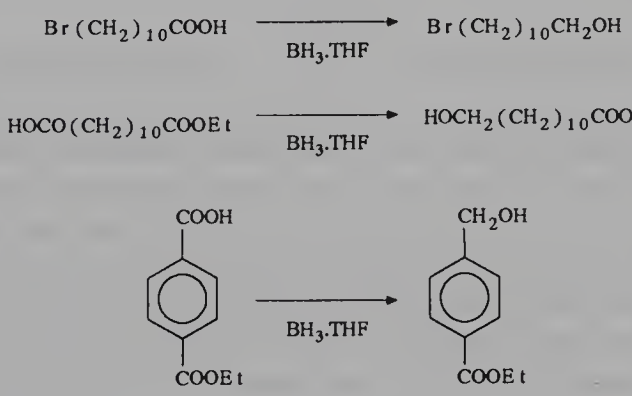
to alcohols [GS2, DC2]; this method can be applied to α-amino acids that are transformed into chiral α-amino alcohols without racemization.

$NaBH_4/ZrCl_4$/THF also reduces benzoic acids to benzyl alcohol [IS1].

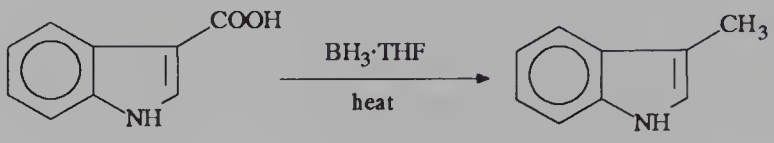
A selective method for performing the reduction of acids to their corresponding alcohols is the use of an excess of BH_3•THF [PS1, BK5]: this reagent reacts more rapidly with aliphatic acids than with aromatic ones. The reaction process implies the formation of a triacyloxyborane, reduced by excess of BH_3•THF to a cyclic borate, which is hydrolyzed to the corresponding alcohol; the intermediate triacyloxyborane, obtained by reaction of 3 equivalents of acid with BH_3•THF, can be equally well reduced to the corresponding alcohol by $NaBH_4$ in an alcoholic medium.



Under these conditions, esters, halogen derivatives, nitriles, amides, and nitro compounds are inert [YP1, HC1, BK5, HI1, BF2], which gives rise to the possibility of the following selective reductions:



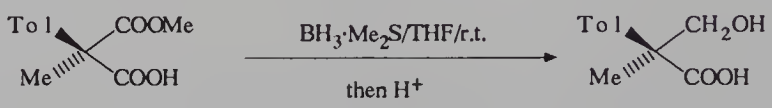
In some cases, the reduction may proceed directly to the hydrocarbon, as shown in the following example [PS1]:



Such is also the case of cyclane-substituted carboxylic acids, which, moreover, lead to ring-expanded cycloalkanes by action of $NaBH_4/HOTf/Et_2O/-78°C$ [OW2].

When starting from substituted malonic acids, BH_3/THF reduction does not give good yields because of side enolborate formation; this can be prevented if the reduction is run at –20°C [CE1].

However, reduction of a chiral malonic acid monoester by $BH_3 \cdot Me_2S$ takes place on the ester group [FC2].



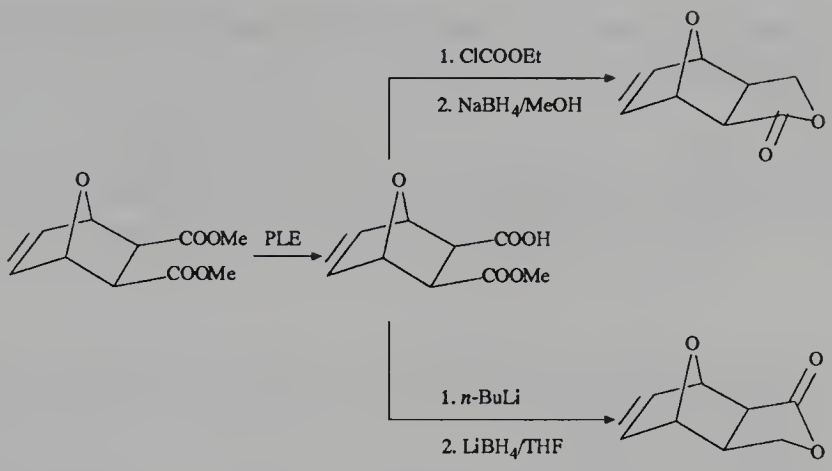
$BH_3 \cdot Me_2S$ or amine-boranes induce the same reductions of acids to alcohols; linear anhydrides are reduced by $Ph_2NH \cdot THF$ to alcohols, while succinic and phthalic anhydrides remain intact [CU1].

The special reactivity of carboxylic acids allows the following selective reductions given as examples:

- β-Chloropropionic acid is reduced by AlH_3/Et_2O to β-chloropropanol [BK5]:

$$ClCH_2CH_2COOH \xrightarrow{AlH_3/Et_2O} ClCH_2CH_2CH_2OH$$

- The following optically active hemiester, obtained by the action of pig liver esterase (PLE) on the corresponding methyl diester, may be transformed into two optically active enantiomeric lactones either through reduction of the methyl ester by $LiBH_4$, which leaves the carboxylic acid functional group unattacked, or else through action of $BH_3 \cdot THF$, or, better, via transformation to the mixed carboxylic–carbonic anhydride and reduction by $NaBH_4$, which does not reduce the ester [BG2].



Thioacids are also reduced to thiols by $BH_3 \cdot Me_2S$ [JS4].

2.2.6. Acid Chlorides: RCOCl

The reduction of acid chlorides is particularly easy, however by carefully adjusting the reaction conditions, the reduction process can be controlled.

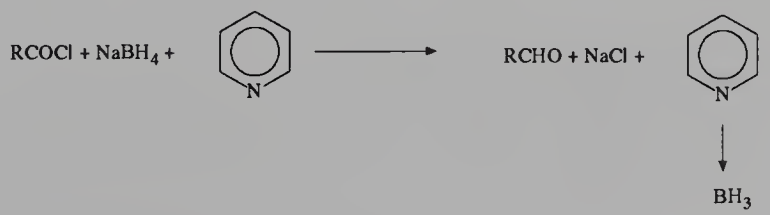
Starting from acid chlorides, aldehydes (RCHO) can be obtained by four different methods [CS, M3]:

- By action of LTBA/diglyme at –78°C: at this temperature, the aldehyde formed is not reduced. The yields are good if the aldehydes are not easily enolized, given the basicity of the reagent in this medium, that is, when starting from either aromatic or α,β-unsaturated acid chlorides [BK5], we can write:

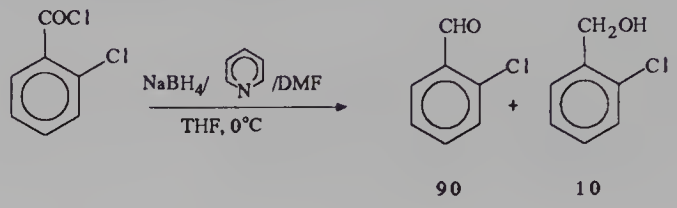
$$ArCOCl \xrightarrow{\text{LTBA/diglyme,–78°C}} ArCOH+LiCl+Al(Ot\text{–}Bu)_3$$

$$ArCH{=}CH\text{–}COCl \xrightarrow{\text{LTBA/diglyme,–78°C}} ArCH{=}CHCHO$$

  The method is compatible with ester, nitrile and nitro groups.
- By action of $NaBH_4$ in DMF/THF in the presence of pyridine at 0°C [B1]; the reduction generates borane, which coordinates to pyridine, forming a complex that precipitates under these conditions:



The reduction leaves the halide functional group intact, as shown in the following example:



90 10

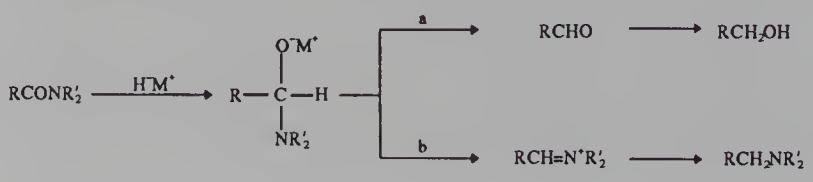
- By action of $NaBH_4$ in the presence of $CdCl_2$ in DMF: this method is compatible with aliphatic chlorides, esters, nitriles, NO_2 groups, and double bonds [EB3].
- Complex borohydrides $(Ph_3)_2CuBH_4$ [DF1, W4] or $(Ph_3)_2CuCNBH_3$ [HM2]: the reductions take place at room temperature in acetone; only the acid chlorides are sensitive under these conditions.

Other reducing reagents transform acid chlorides into corresponding alcohols: LAH/THF or on silica gel [BK5, KH2]; AlH_3/Et_2O [BK5], DIBAH [YG1]; $NaBH_4$ and $LiBH_4$ in THF, dioxane, DME, or on alumina or in the presence of polyethylene glycol [BK5, PS1, SF2]; n-$Bu_4N^+BH_4^-/CH_2Cl_2$; $Zn(BH_4)_2$/TMEDA/Et_2O [KU3]; cold 9-BBN [PS1]. The reductions by BH_3•THF and Sia_2BH are nevertheless relatively slow [BK5].

The selective reduction of acid chlorides in the presence of esters by 9-BBN in cold THF is thus possible, because esters are reduced only under reflux in THF [PS1]. $Zn(BH_4)_2$/TMEDA/Et_2O reduction leaves Cl, NO_2, ester, and conjugated double bonds unchanged [KU3].

2.2.7 Amides and Imides: $RCONR'_2$, $(RCO)_2NR'$

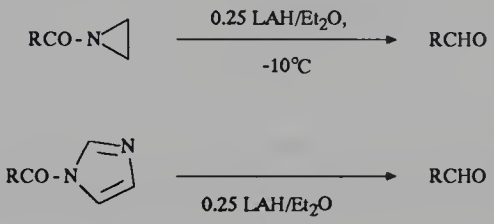
The attack of the amide carbonyl group by a hydride implies a tetracoordinated intermediate, which can proceed either (path a) by the breaking of the C—N bond, leading thus to an aldehyde, which can eventually be reduced to an alcohol, or (path b) by the breaking of the C—O bond, producing thus an iminium salt, the precursor of an amine.



Depending on the nature of the reducing agent and the nitrogen substituents, the reaction follows one pathway or the other.

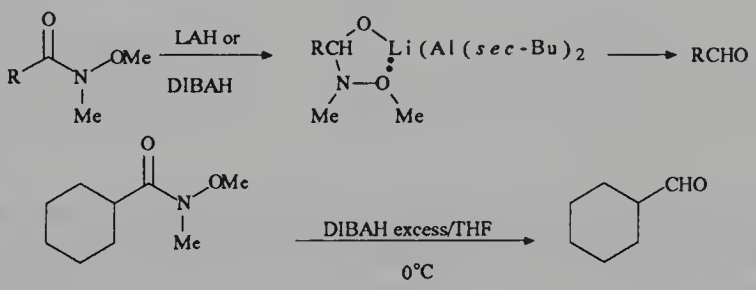
Path a: Access to aldehydes and alcohols.

The synthesis of aldehydes [C5] from tertiary amides can be accomplished by controlled reduction of acylaziridines [BK5] or of acylimidazoles [W3] by LAH/Et_2O at –10°C, by LTBA or by Red-Al/C_6H_6 [HUD, M3]:



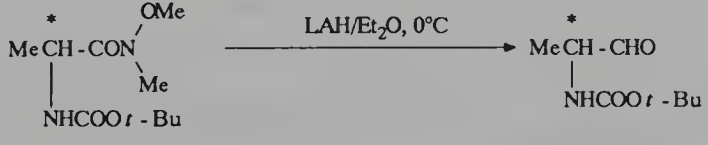
where R can be aliphatic or aromatic.

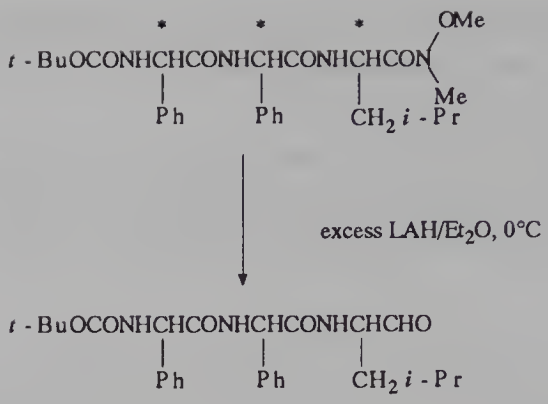
The *N*-methoxy *N*-methylcarboxamides are also well reduced to aldehydes by LAH/THF in excess at low temperature or by DIBAH/THF at 0°C. In numerous cases, the latter reagent does not lead, as before, to low yields of alcohols resulting from a subsequent reduction of the aldehyde [NW1]. This behavior can be understood by the stabilization through chelation of the lithium or aluminum intermediate:



α,β-Unsaturated aldehydes may also be prepared by this method, using DIBAH/THF [NB1]

The method can be applied to *N*-protected amino acid derivatives or to peptides [FC1, FH3], without racemization.

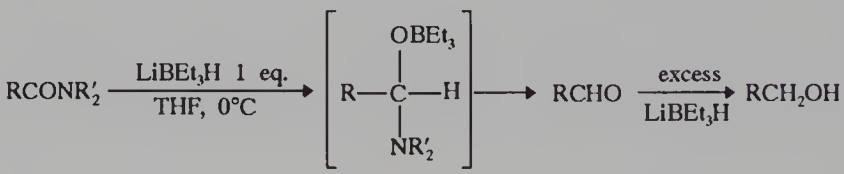




LTBA or, better, LTEA/Et_2O, reduces all tertiary amides to aldehydes at 0°C whenever the latter are less reactive than the tertiary amides, which coordinate the Li^+ cation better because their carbonyl is more basic [C5, M3].

$$RCONR'_2 \xrightarrow{\text{LTEA(1 equiv)/Et}_2\text{O,0°C}} RCHO$$

Treatment of tertiary amides by $LiEt_3BH$/THF at 0°C leads, via a triethylborate, to aldehydes, which can be reduced to alcohols by an excess of reagent [BK3, BK5].



N-Dimethylamides react with EtOTf, thus leading to immonium salts, which can be selectively reduced to aldehydes by Li(*sec*-Bu)$_3$BH/THF at –78°C [TR2]: this method can be applied to α,β-unsaturated amides and is compatible with isolated double bonds, nitriles, and esters.

The other alkylborohydrides, 9-BBN and Sia_2BH, also transform tertiary amides to alcohols [BK5, PS1].

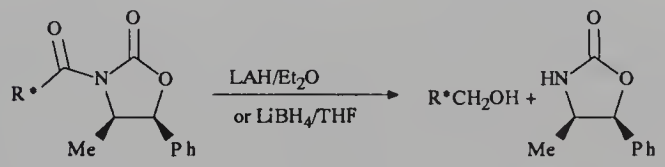
Alcohols are, likewise, obtained via action of $LiBH_4$/MeOH/hot diglyme on tertiary amides [SO3]:

$$PhCONMe_2 \xrightarrow{LiBH_4/\text{diglyme/MeOH}} PhCH_2OH$$

$$PhCH_2CONMe_2 \xrightarrow{LiBH_4/\text{diglyme/MeOH}} PhCH_2CH_2OH$$

Secondary amides remain inert under these conditions [SO3], while at lower temperature or in the absence of MeOH, reduction of tertiary amides seldom takes place. An exception has, however, been found with fused xanthines [CK4].

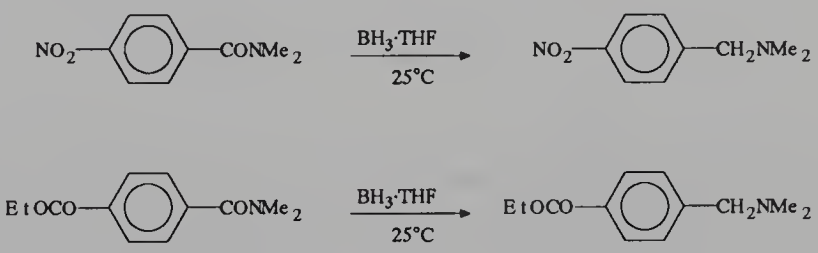
The cleavage of chiral acyloxazolidinones, used to carry out some asymmetrical aldolization reactions, to produce chiral primary alcohols and oxazolidinone, can be accomplished by LAH/Et_2O or $LiBH_4$/THF [ES2, EB2] or $LiBH_4/Et_2O$ in the presence of 1 equivalent of H_2O [PD1].



Chiral sultams may also be cleaved in the same way [OB2].

Path b: Access to amines.

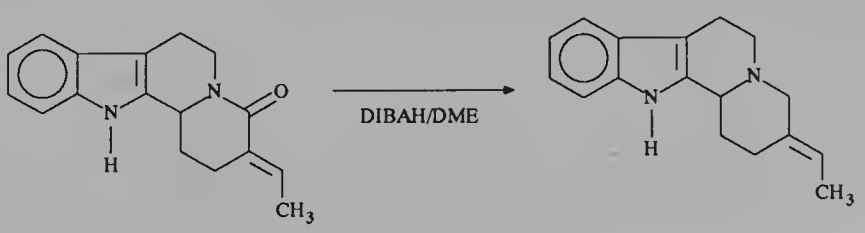
LAH in ethers (Et_2O, THF), Red-Al/C_6H_6, AlH_3/Et_2O, BH_3•THF, or BH_3•SMe_2 reduces most of the amides to amines at room temperature; primary amides, however, are reduced by BH_3•THF only under reflux in THF [BH1, L2, PS1, BK5, BN2, M3]. Since BH_3•THF reduces neither esters, nitro derivatives, nor nitriles under these conditions, the following selective reductions can be run [BK5]:



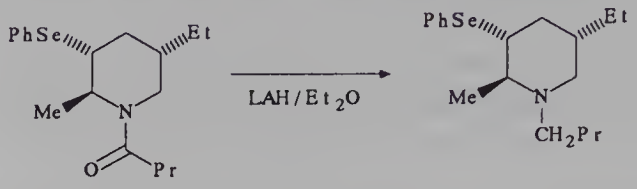
Selective reduction of tertiary amides to amines in the presence of secondary ones can be carried out, provided the secondary amides are protected as lactim ethers [WB2].

Sulfonamides are reduced by BH_3•Me_2S in refluxing THF only [BF2].

DIBAH reduces tertiary amides well and appears to be more selective than LAH with α,β-unsaturated derivatives, LAH/Et_2O inducing the partial reduction of the double bond in the following case [W1] (§2.2.8).

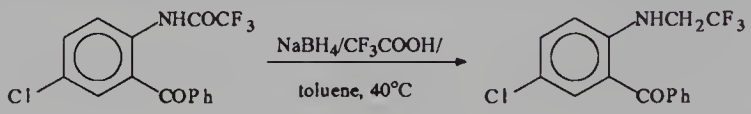


The reduction of amides by LAH/Et_2O is compatible with the presence of an SePh group in the molecule, as shown in the following example [TT1]:



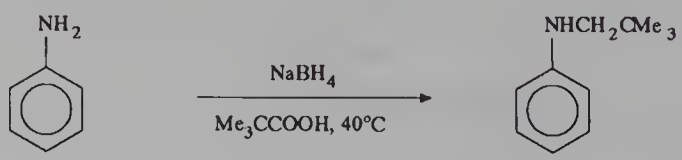
The alkali borohydrides in an ether medium do not reduce amides at room temperature [BK5], but under reflux of THF, secondary and tertiary amides are reduced to amines [PS1]. $LiBH_4$ or $NaBH_4$/THF in the presence of Me_3SiCl also reduces primary, secondary, or tertiary amides to the corresponding amines [GS2]. $NaBH_4/ZrCl_4$ reduces $PhCONMe_2$ to the corresponding amine [IS1]. Tertiary amides are transformed to the corresponding amines by *n*-$Bu_4N^+BH_4^-$ in refluxing CH_2Cl_2 [WI1]. In the presence of an organic acid and under reflux, $NaBH_4$ reduces all amides to amines [UI1, GN1].

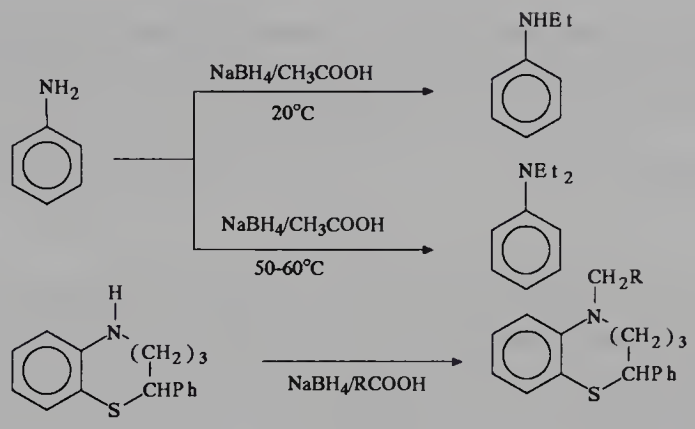
Under these conditions, a diarylketone can remain unaffected, as shown in the following example:



The activation of $NaBH_4$ by ethanedithiol allows access to primary amines, with the nitriles remaining intact [GE1]. The same reduction can be accomplished either by $LiBH_4$/diglyme/hot MeOH starting from primary aliphatic and aromatic amides [SO3] or by $NaBH_4$ in an alcohol medium in the presence of $CuCl_2$, for aromatic amides only [W4]. $(CF_3COO)_2BH$ leaves the amides unchanged [MM1].

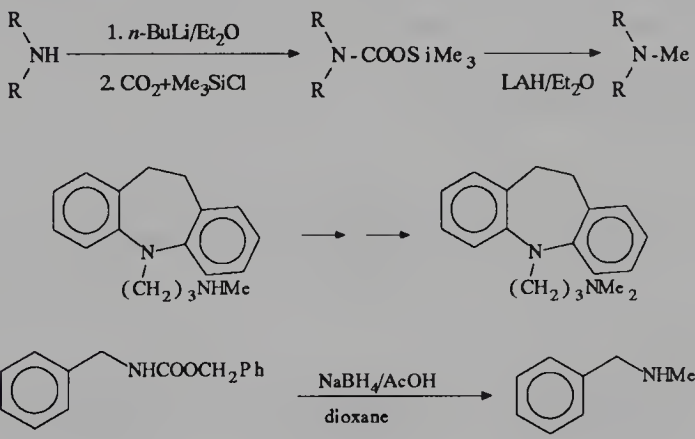
An alkylation method involving primary and secondary amines consists of treating them with $NaBH_4$ in an organic acid medium. In the cold, one observes the monoalkylation of primary amines, while at high temperature, the secondary amines are in turn alkylated. The mechanism of this reaction has not been elucidated [GN1]. The reaction takes place better when starting from aromatic amines and is compatible with OH, COOEt and $CONR_2$ groups, and heterocycles, as shown in the following examples:



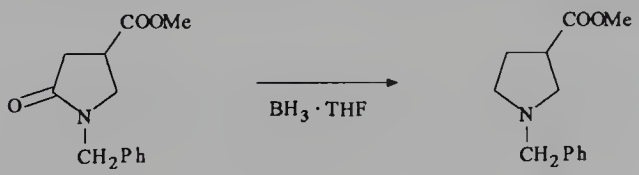


With formic acid, the reaction is not always easy to run; in the presence of CF_3COOH, or if $NaBH_4$ is replaced by $NaCNBH_3$, this alkylation does not take place (§2.3.1).

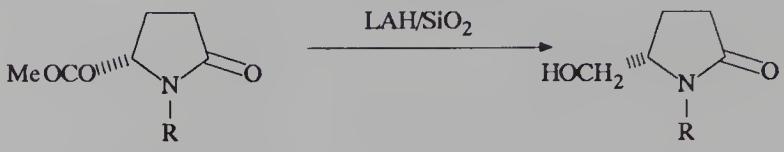
Another facile method of methylation of amines consists of their transformation into carbamates, which are reduced in situ either by LAH [RE1] or by $NaBH_4$ in the presence of AcOH or of CF_3COOH in dioxane or in THF [GN1]. However, under the latter conditions, the *t*-butyl carbamate reacts poorly.



Lactams are reduced under the same conditions as the linear amides, as shown in the following example [BK5]:

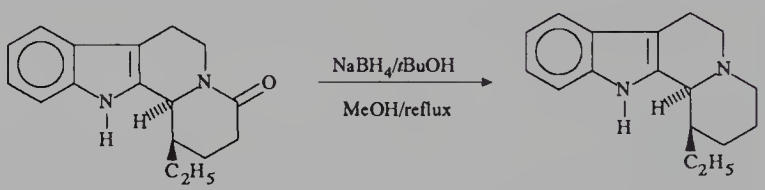


However, LAH on silica gel does not reduce lactams while it reduces esters [BK5].

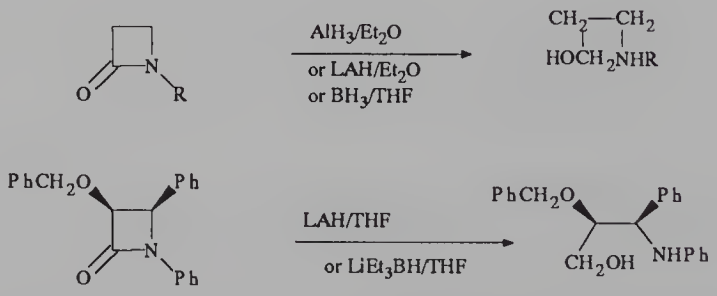


Under suitable conditions, with LAH, it is possible to selectively reduce a lactam bearing a sulfone group that remains unchanged [TG1].

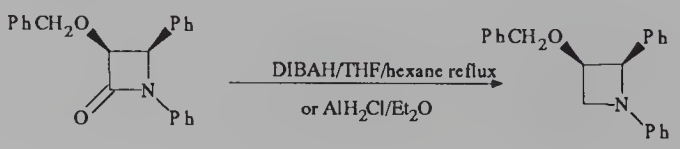
The reduction of the lactams to tertiary cyclic amines has been recently accomplished through reaction with $NaBH_4$ in refluxing *t*-BuOH in the presence of MeOH added dropwise [MG1, MG2]



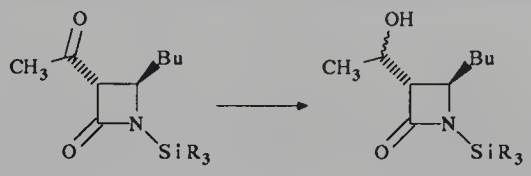
A problem that has received some attention, in relation to the chemistry of β-lactamic antibiotics, is the reduction of the azetidin-2-ones [YO2]. While AlH_3 or LAH/Et_2O and BH_3•THF cleave the *N*-alkylazetidinones to 3-amino-propanols, the 3-benzyloxy-1,4-diphenylazetidinone is cleaved only by LAH or lithium trialkylborohydrides/THF.



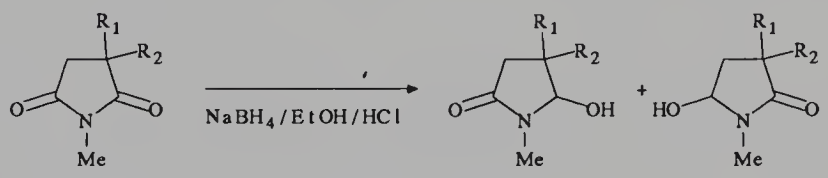
The reduction by DIBAH in a hexane-THF mixture under reflux or by AlH_2Cl or $AlHCl_2/Et_2O$ preserves the heterocycle and allows one to obtain selectively the substituted azetidine:



Let us recall that when the β-lactam carries a methyl ketone functional group at the 3-position, the selective reduction of the ketone group by $NaBH_4$/THF, $Zn(BH_4)_2/Et_2O$, or Li and K(*sec*-Bu)$_3$BH/THF leaves the β-lactam unchanged [PA1] (§2.2.2).

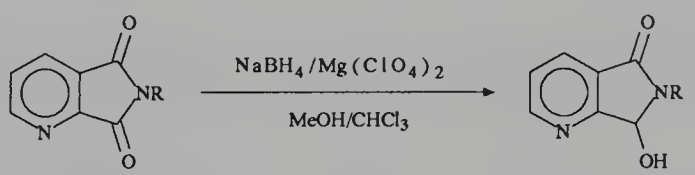


Cyclic imides undergo a reduction whose regioselectivity is comparable to that of cyclic anhydrides (§2.2.5): $NaBH_4$/EtOH in the presence of HCl or in MeOH reduces the imides partially to α′-hydroxyamides, the carbonyl adjacent to the most substituted carbon being preferentially reduced, as shown in the following examples [PS 1, SH2]:

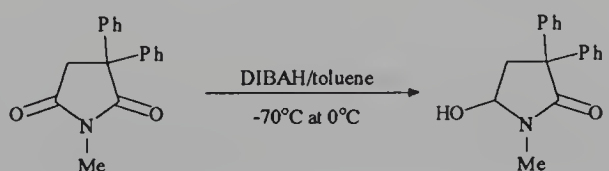


$R_1 = R_2 =$ Me	79	21
$R_1 = R_2 =$ Ph	>95	<5
R_1 = Me, R_2 = H	59	41

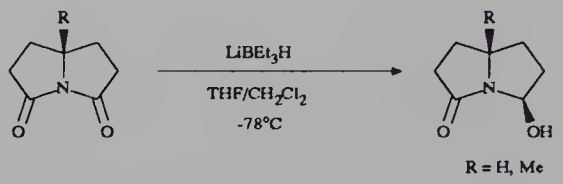
However, chelation can direct the reduction of one carbonyl, as in the following case [GK2].



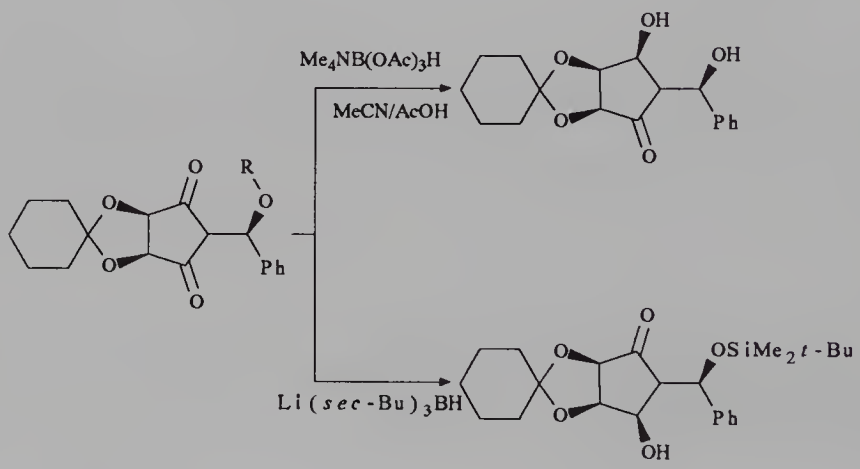
DIBAH in toluene at low temperature also brings about this reduction [SH2, HT2, W1], but the regioselectivity is inverted.



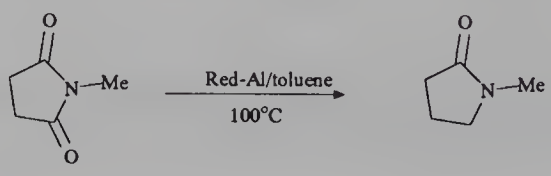
The reduction of *N*-methylglutarimide to the corresponding lactamol by DIBAH gives very poor yields; this transformation can easily be performed with $LiBEt_3H/CH_2Cl_2$ at low temperature [TR1]. This reagent is also the best one to reduce pyrrolizinediones to the corresponding lactamols [TR1] because $NaBH_4$ in acidic conditions induces ring cleavage and $Zn(BH_4)_2$ gives lower yields.



The highly stereoselective formation of cis-substituted α′-hydroxylactams via the auxiliary controlled reduction of imides has been carried out from chiral imides [MC3]: reduction of the free alcohol by $Me_4NB(OAc)_3H$ or of the related *t*-$BuMe_2$ silyl ether by L-selectride gives selectively each cis enantiomer:



Red-Al reduces *N*-methylsuccinimide to *N*-methylpyrrolidone [HUD].



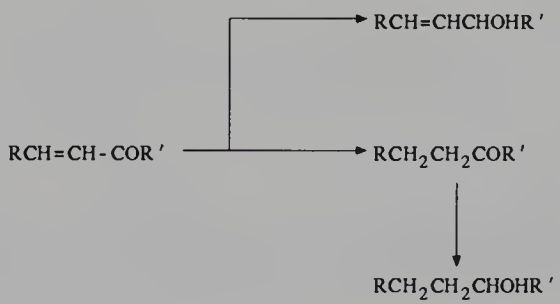
Reduction of succinimides to pyrrolidines can be carried out by $NaBH_4/BF_3{\cdot}Et_2O$/diglyme [MS2].

Thioamides are reduced to amines by $BH_3{\cdot}Me_2S$ [JS4]

2.2.8. α,β-Ethylenic Carbonyl Compounds: α,β-Ethylenic Aldehydes, Ketones, Esters, and Amides: RCH=CHCOY(Y = H, R′, OR′, NR′R″)

α,β-Ethylenic aldehydes and ketones can, with a reducing agent, lead to three compounds:

- allylic alcohols resulting from attack on the carbonyl;
- saturated aldehydes and ketones resulting from attack on the double bond;
- saturated alcohols resulting from the subsequent reduction of saturated aldehydes and ketones, generally observed in the presence of proton donors (most frequently the solvent).



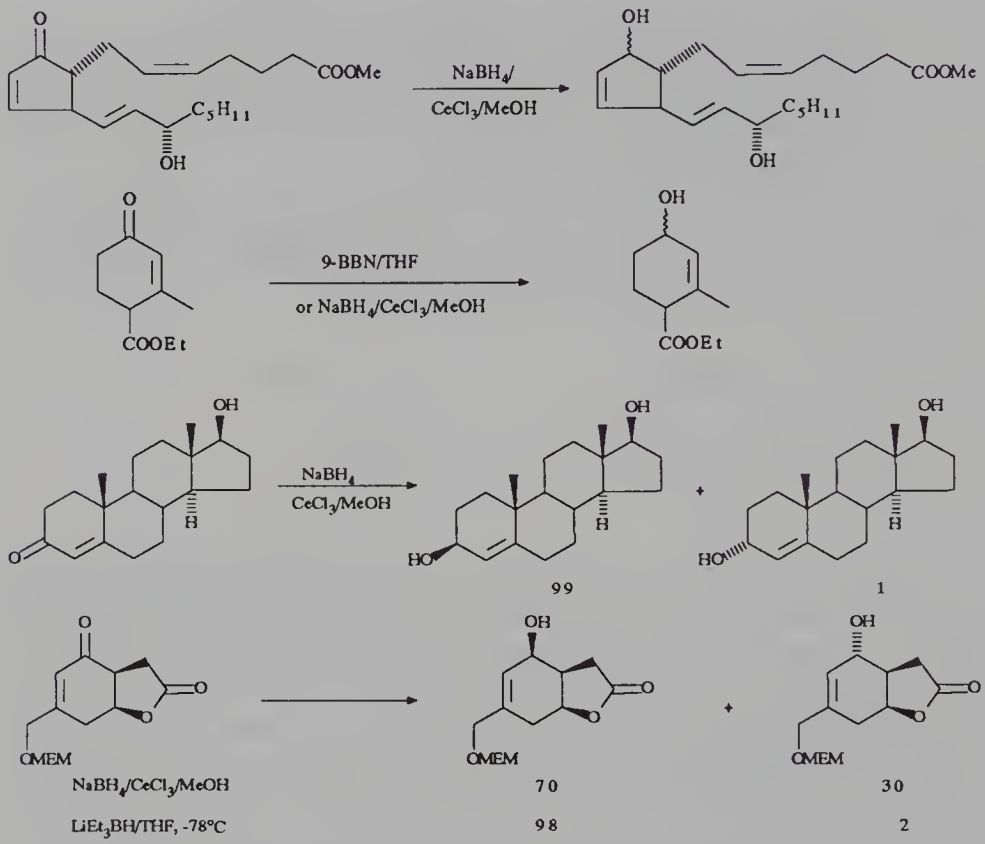
Regioselectivity of these reductions depends on the structure of the starting compound: aldehydes are more sensitive to the attack of the carbonyl than ketones. All things being equal, when the double bond is sterically hindered, the reduction of the carbonyl becomes predominant. The reduction depends also on the type of reducing agent and the medium: the more important the electrophilic assistance by a protic solvent, by the cation associated with the reagent, by the reagent itself, or by an added Lewis acid, the easier the attack on the carbonyl [LL3, LS1]. In contrast, the reduction of the double bond is observed to be more important if the reducing agent is bulkier, or if it is associated with a cation such as ammonium, adept in inducing electrophilic assistance, or with a transition metal such as copper, and if the reduction is run in aprotic media, which strongly solvate alkaline cations.

These trends are found in the reduction of α,β-ethylenic esters and lactones either to allylic alcohols or to saturated esters and lactones.

Thus, the attack on the carbonyl of α-enones or α,β-ethylenic aldehydes is preferred when one uses LAH/Et_2O [LS1, PR5], AlH_3/Et_2O [M1, E2], DIBAH/hexane [W1, CG3, PR5], $LiAlH(OMe)_3$/Et_2O [M1, M3], Red-Al/C_6H_6 [M1], $Zn(BH_4)_2$ or $NaCNBH_3$/$ZnCl_2$/Et_2O [YL1, VM1, IL1, KO1], BH_3•Me_2S [HC1], $LiBuBH_3$/Et_2O [KM1], 9-BBN/THF [BK5, KB2, PS1],

$Na(OAc)BH_3/THF$ [NB3], and $NaBH_4/CeCl_3/MeOH$ [GL1, W4, EH1]. This latter reduction can also be carried out in $CH_2Cl_2/EtOH$ and is compatible with SePh groups [DD1]

With the last two reagents, the ester, nitrile, and NO_2 groups are unchanged and the reduction of the ketone group can be very stereoselective (§2.2.2). Examples in sugar systems are given by Jarosz [J1].



Steric hindrance of the double bond induces the regio- and stereoselective attack of the carbonyl by $LiEt_3BH$ via the least hindered face (see below).

α,β-Unsaturated aldehydes can be selectively reduced to primary allylic alcohols by $NaBH_4/MeOH/CH_2Cl_2$ at –78°C, leaving α-enones unchanged [WR1].

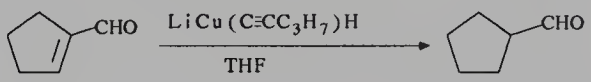
Moreover, benzalacetone $PhCH{=}CHCOCH_3$ is overreduced by AlH_3 to 1-phenyl-1-butene $PhCH{=}CHCH_2CH_3$ [E2].

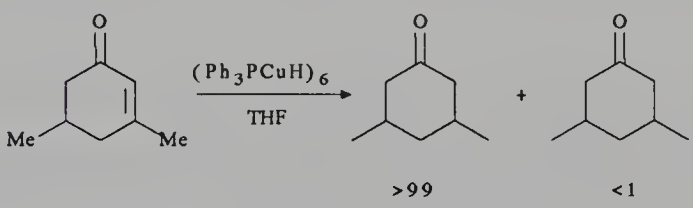
In the presence of nickelocene, LAH reduces the C=C bond of α-enones [CC2].

BH_3•THF generally attacks the carbonyl and the double bond [PS1].

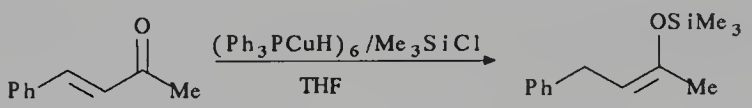
In contrast, in the presence of copper salts, $LiAl(OMe)_3H$ or Red-Al/THF [SS1, M1, CL3, M3], various complexes of CuH with organolithiums [BM4, MB1], the complex $(Ph_3PCuH)_6$ [MB2, MS6], DIBAH/THF-HMPT possibly in the presence of MeCu [TH1], LAH in the presence of cuprates [AL1], *n*-$Bu_4N^+BH_4^-$/THF [IL2], and Li and K(*sec*-Bu)$_3$BH/THF [G1, OM2, CR1, KH3] or KPh_3BH [KP2] favor the reduction of the double bond.

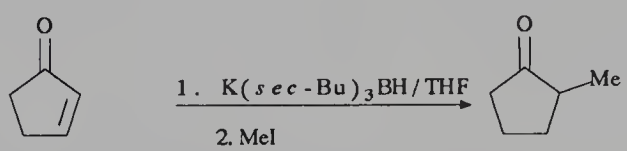
The 1,4-reduction by $LiAl(OMe)_2H_2$•CuBr in the presence of BH_3•Et_2O is compatible with the >N—COO*t*-Bu group [CL3].

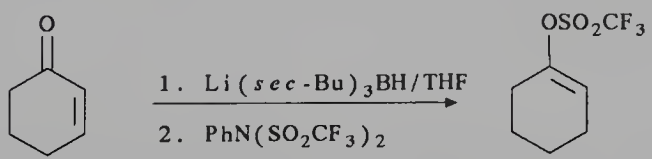




The mechanism of the reduction is a conjugate addition of hydride: the enolate formed can then be trapped by an electrophile [OM2, G1, CN1, CS1, KS1, MB2].

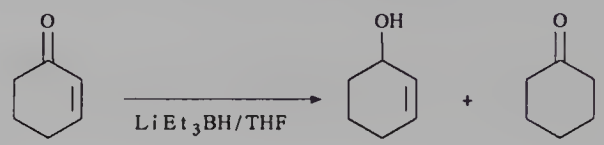






The reduction of α,β-unsaturated aldehydes to saturated ones can be carried out by $(Ph_3PCuH)_6/Me_3SiCl/C_6H_6$. When the reaction is run in wet THF without Me_3SiCl, saturated alcohols are formed [BS3].

The conjugate addition of Li and K(*sec*-Bu)$_3$BH/THF to α-enones is sensitive to the steric hindrance of the double bond; the 3-methylcyclohexenone gives a mixture of ketone and allylic alcohol [G1]. LTBA/THF [M1] or $LiEt_3BH$ [G1, BK6, CL3], although less bulky, often give rise to mixtures.

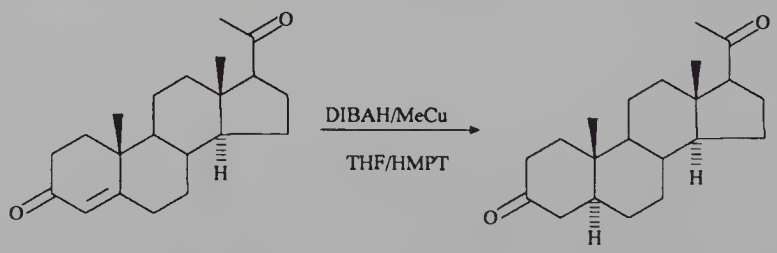


Similarly, 2α-fluoro-Δ-4-androsten-3,17-dione is reduced by K(*sec*-Bu)$_3$BH to the 3 α-ol [GM1].

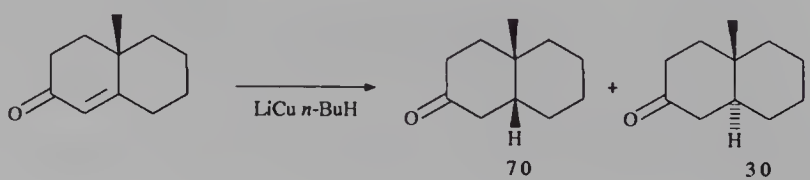
However, in the presence of MAD [aluminum bis (2,6-di*t*-butyl-4-methylphenoxide), Li(*n*-Bu)(*i*-Bu)$_2$AlH [NM2], $LiEt_3BH$, or Li(*sec*-Bu)$_3$BH [CL3] give 1,4-reduction of sterically hindered α-enones.

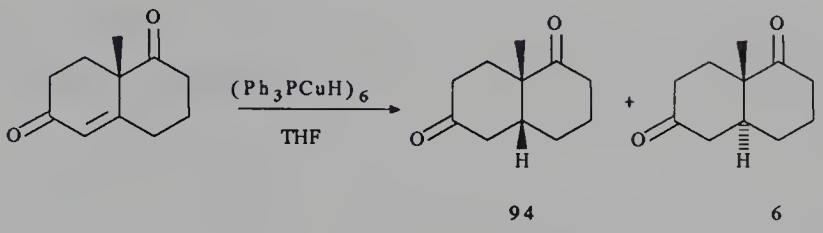
Cyclopentenones, which are particularly able to undergo conjugate addition, are reduced by LTBA to the corresponding cyclopentanones [M1], since the 3-substituted cyclohexenones give mainly allylic alcohols [BG1, G1] (see above).

The complexes of copper hydrides or DIBAH-MeCu are much less sensitive to steric hindrance [TH1, MB1, MB2, LU1]: in fact, progesterone is selectively reduced to progestanone under these conditions.

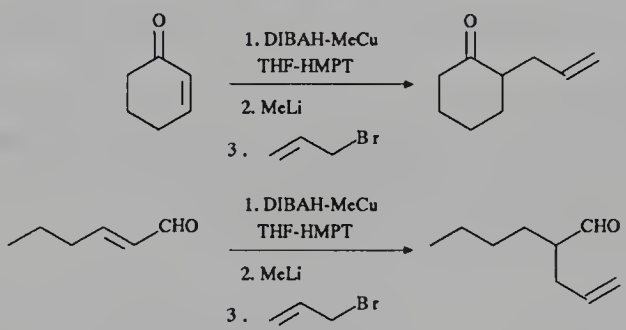


Likewise, the following bicyclic ketones are reduced at the ring junction in a stereoselective fashion:

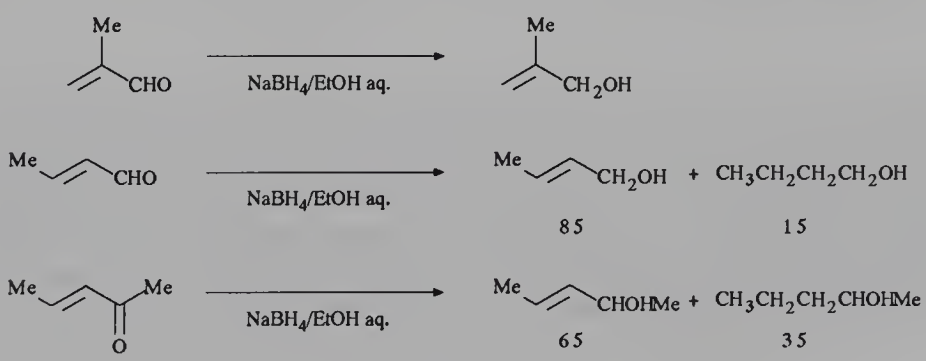


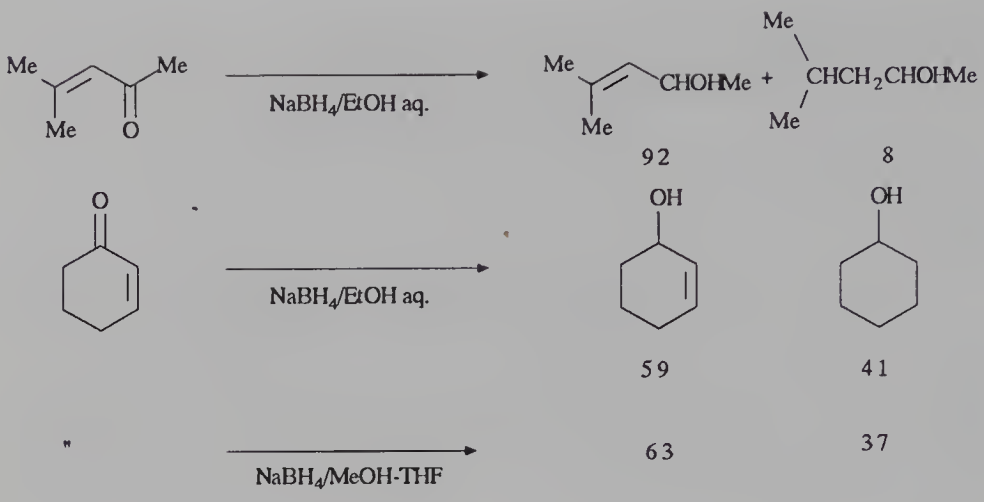


With regard to the reactions with DIBAH/MeCu, trapping of the aluminum enolates obtained from alkyl halides requires their transformation into an -ate complex by reaction with MeLi [TS1] or *t*-BuLi [DK1]: in the latter case, trapping of the Al enolate can be carried out with aldehydes or acyl chlorides; ketones, esters, methyl vinyl ketone or methylacrylate, MeI, tosylates and methylchloroformates do not react. The reactions of polyalkylation are thus avoided.



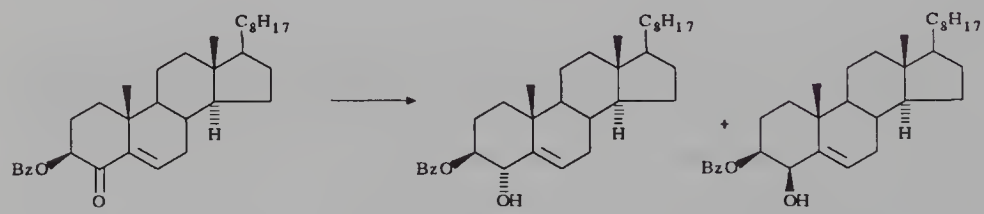
The reduction of α-enones by the alkaline borohydrides in alcohols or THF in the presence of a protic solvent most often gives mixtures in proportions that depend on the solvent and on the structure of the substrate [VK1, PS1, EH1]. Aldehydes principally lead to allylic alcohols and so do some linear ketones. When starting from cyclic α-enones, one obtains saturated alcohols, the intermediate enolate being protonated to give a saturated ketone, which is then reduced:





Vinyl ketones are reduced to saturated ketones by $NaBH_4$ on resin in dioxane, but α,β-unsaturated aldehydes under the same conditions give saturated alcohols [NS1].

Cyanoborohydrides in acid media in MeOH or HMPT most often lead to allylic alcohols from linear α-enones or α,β-unsaturated aldehydes and to mixtures from cyclic α-enones [HK2], even though some of the steroid ketones could have been reduced to allylic alcohols [VM1].



1.	$NaBH_4$/THF/MeOH	94	6
2.	$NaCNBH_3$/THF/HCl	>99	<1
3.	$Zn(BH_4)_2/Et_2O$	>99	<1
4.	$NaBH_4$/dioxane	mixture of 1,2 and 1,4	

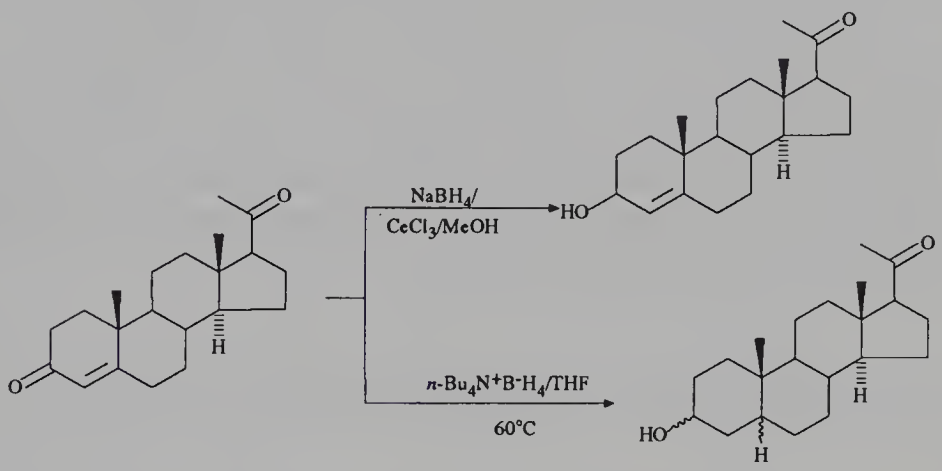
The relative reactivity of α-enones and ketones related to different reducing agents has been examined. When electrophilic assistance is important, the more basic saturated ketone is selectively reduced: this is the case of LTBA/THF [M1], $Zn(BH_4)_2$•1.5 DMF/MeCN [HJ1] $NaBH_4$ or BH_3•NH_3/MeOH [A1, IL1, TK2].

Provided steric hindrance does not intervene, the reactivity order with $NaBH_4$/MeOH/CH_2Cl_2 at –78°C is as follows [WR1, WR4]:

α-enones < ketones < α,β-unsaturated aldehydes < aldehydes

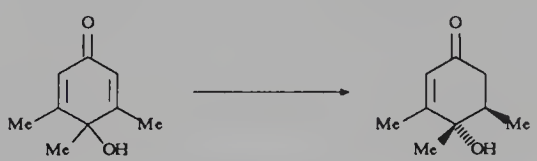
It is therefore possible, using this reagent/solvent mixture, to selectively reduce ketones in the presence of α-enones.

Curiously, $Zn(BH_4)_2/Et_2O$ does not appear to be not very selective toward progesterone [IL1], whereas $NaBH_4/CeCl_3/MeOH$ [GL1] reduces the α-enone moiety to allylic alcohol while $n\text{-}Bu_4N^+BH_4^-$/THF leads to 20-keto-3-ols [IL1].

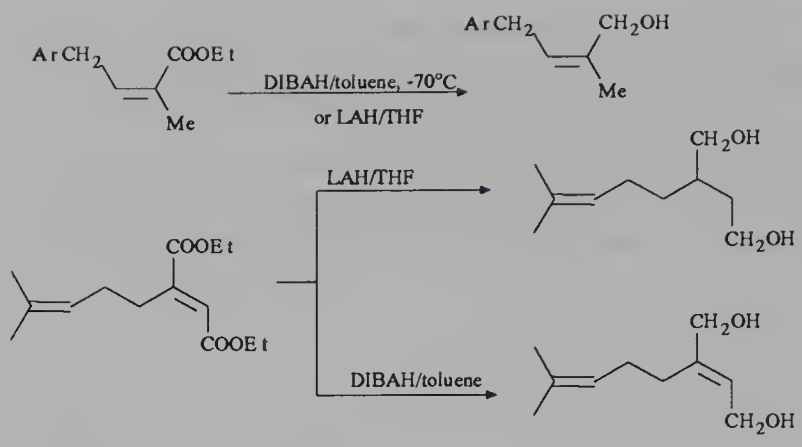


Enaminones $RCOC(R')=\!=CHNMe_2$ are reduced by LAH/Et_2O to β-aminoketones $RCOCH(R')CH_2NMe_2$ [SE1].

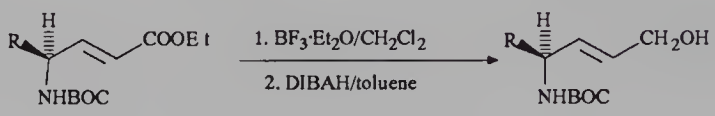
The presence of a hydroxy group at the α position may direct the double bond reduction to the face where this group is lying, as in the following case [SJ2].



In the case of α,β-ethylenic esters, DIBAH in toluene at –70°C is the reagent of choice to access to allylic alcohols [YG1], the *E* or *Z* configuration of the double bond being retained [MT4, DD2]. $LiBEt_3H$ may also be used: with this reagent, isolated benzoate esters may be preserved in sugar derivatives, while they are reduced by DIBAH [DD2]. LAH/THF or /Et_2O or /C_6H_6 can also induce this reduction, above all when one adds the ester to a cold solution of LAH, but the results are often unsatisfying, as shown in the following examples:

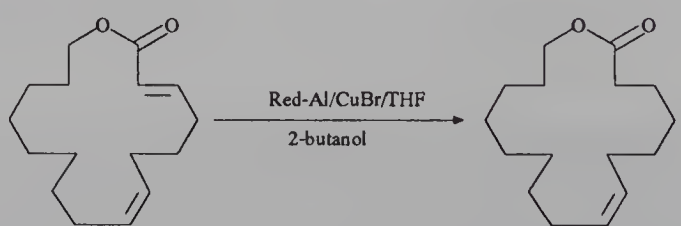


When the α,β-unsaturated ester bears an acylamino group, the yield of the reduction is higher if one begins by adding BF_3•Et_2O to prevent the complexation of the reagent to the nitrogen site [MH3].

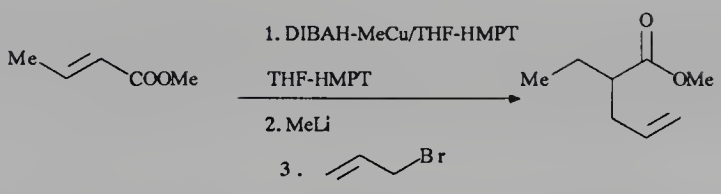


A stoichiometric amount of Red-Al/C_6H_6 can give access to allylic alcohols [HAJ].

Red-Al or $LiAl(OMe)_3H$ in the presence of CuBr in THF-2-butanol leads to saturated esters [SS1, M3] just as $LiEt_3BH$ in THF-*t*-BuOH [G1] does. The role of the alcohol here consists in the protonation of the enolate formed thus avoiding side condensations. As shown in the following example, the nonconjugated double bonds are not touched [BS2]:

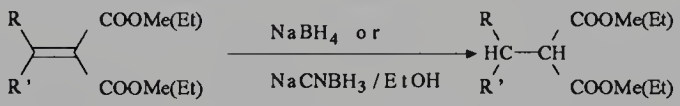


DIBAH/MeCu also gives access to saturated esters [TH1]. Just as in the case of α-enones, trapping of the enolates formed by reaction with an alkyl halide requires going through an intermediate -ate complex [TS1].

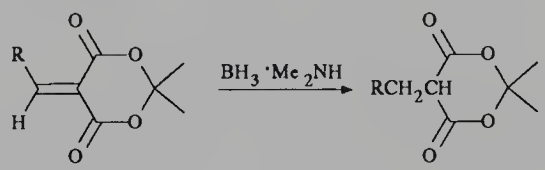


In dioxane solution, $NaBH_4$ on a resin reduces α,β-ethylenic esters to saturated esters [NS1] as well as $NaBH_4/Cu_2Cl_2/MeOH$ at 0°C [NH1]; with the latter system, disubstituted isolated double bonds remain unchanged [NH1].

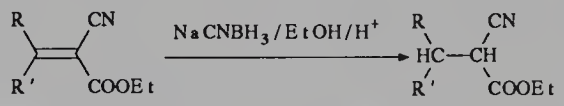
Alkaline borohydrides in alcoholic media or in THF-MeOH [SO3] most often give mixtures, while $NaBH_4$/LiCl/THF/EtOH leads to saturated alcohols [JD1]. However, *gem*-diesters or α,β-unsaturated lactone-esters are reduced to saturated esters by $NaBH_4$ or $NaCNBH_3$ in alcoholic media [PS1, SS3, HR1].



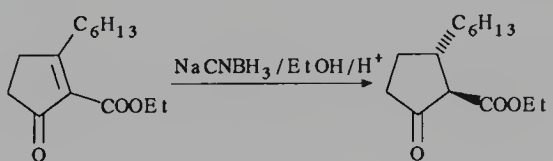
In some cases, BH_3•Me_2NH may be preferred, as shown in the following example [HS2]:



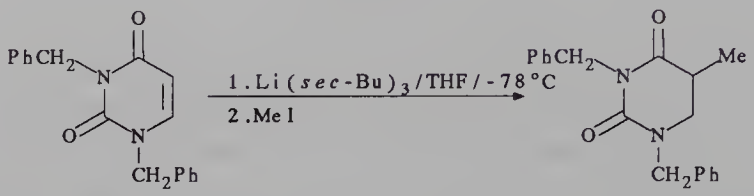
$NaCNBH_3$ in an alcoholic medium and at pH 3–4 reduces unsaturated *gem*-ketoesters or the nitrile-esters to saturated derivatives without modifying other functional groups [HR1], while $NaBH_4$ reduces the nitrile-esters to alcohols in the same medium [MR4], unless $NaBH_4$ is fixed on a resin [NS1].



The reduction can be stereoselective, as shown below [BJ3].



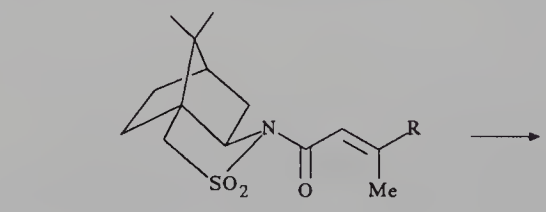
α,β-Unsaturated amides are reduced to saturated amides by Li or K(*sec*-Bu)$_3$BH [G1]: trapping by alkyl halides has been described in many analogous cases, as exemplified by the following [KS1]:

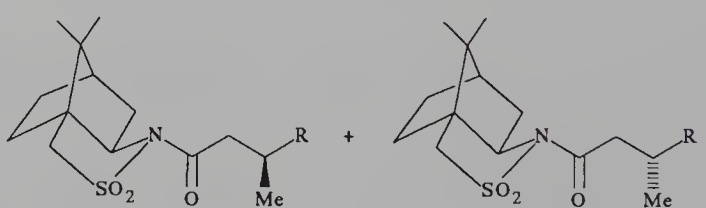


$NaCNBH_4$ also reduces α,β-ethylenic amides, geminally substituted by another electron-withdrawing group, to saturated compounds [HR1].

α,β-Unsaturated lactams can be reduced to saturated cyclic amines by LAH or alkoxyaluminohydrides in ether media, but the results are often disappointing [HUD].

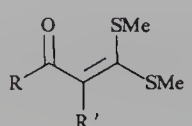
Chiral α,β-unsaturated sultams are reduced by LAH/$CoCl_2$ in suspension in THF or Et_2O to saturated derivatives, precursors to chiral alcohols [OM3]: the stereoselectivity is inverted depending on the nature of the solvent.



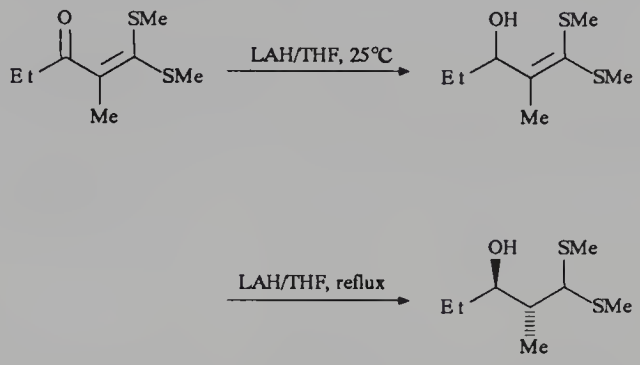


LAH/$CoCl_2$/THF	92	8
LAH/$CoCl_2$/Et_2O	16	84

A particular case worth pointing out is that of the α-oxoketene dithioketals of



whose reduction by LAH/THF at room temperature leads to allylic alcohols, while under reflux, the hydroalumination of the double bond takes place: the reaction can be stereoselective as shown in the following example [GB2, RC1]:

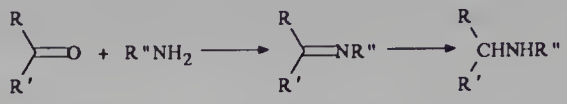


2.3. CARBON–NITROGEN DOUBLE BONDS: >C=N—

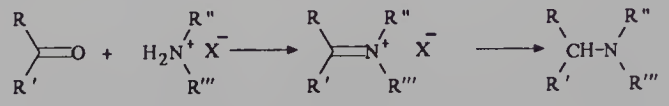
2.3.1. Imines and Iminium Salts

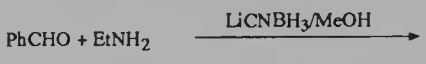
The imines and iminium salts are easily reduced to amines by LAH/THF or Et_2O, Red-Al/C_6H_6 at room temperature [PS1, HUD, M3], alkaline borohydrides in alcoholic medium, in AcOH [GN1], or in the presence of Co or $NiCl_2$ in THF/MeOH [PD2], $Zn(BH_4)_2/Et_2O$ [KY2], $NaBH_4/ZrCl_4$/THF [IS1], alkyl borohydrides/THF [WG1], BH_3•THF [L2], $(CF_3COO)_2BH$•THF [NM1], or amine-boranes in acid media in CH_2Cl_2 [PS1]. In the case of *N*-triphenylmethyl-imines, because LAH induces unwanted bond cleavage, $NaBH_4$/AcOH must be used [PR6]. Nevertheless, the most interesting reductions are those run with the cyanoborohydrides at pH 6–8 [L1], $NaCNBH_3/ZnCl_2/Et_2O$/MeOH [KO1] or even $NaBH_4$ or $NaCNBH_3$ in the presence of organic acid [GN1]. Indeed, under these conditions, ketones and aldehydes are reduced much more slowly. It is then possible to carry out "one-flask" reductive amination of carbonyl compounds by reaction of a primary or secondary amine in the presence of cyanoborohydrides in aqueous MeCN or in MeOH at controlled pH [L1, PS1, KO1] or of $NaBH_4$ or cyanoborohydrides in MeCOOH or CF_3COOH [GN1], or of preformed $Na(OAc)_3BH$ [AM1] or else $NaCNBH_3$/EtOH in the presence of Ti(O*i*-Pr)$_4$ at room temperature [MP1]. When using $NaBH_4$/MeCOOH, one can still observe the side reaction of alkylation (§ 2.2.7) [GN1]. This reaction can also be carried out on a phase transfer catalyst [HM1] or in the presence of pyridine-borane [PR2].

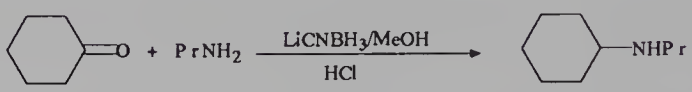
Primary amines or NH_3 give imines, which are then reduced [HUD].



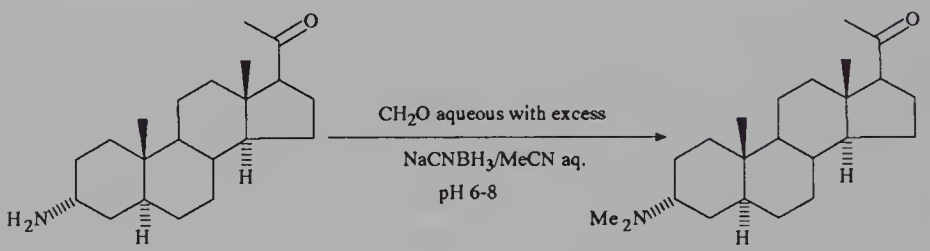
In acid media, secondary amines are converted to iminium salts, which also undergo reduction:

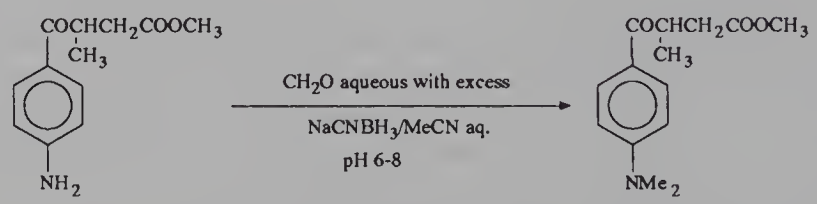






The following examples show the compatibility of the reaction with the presence of various functional groups [L1].



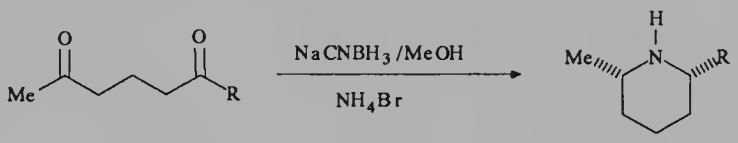


The methodology involving Ti(O*i*-Pr)$_4$ and $NaCNBH_3$ [MP1] leaves acid-sensitive groups such as acetals, carbamates, ureas, esters, and amides unchanged.

The application in the *N*-methylation of alkaloids has been the topic of a recent article [SH3]. The *N*-methylation of amines by paraformal-

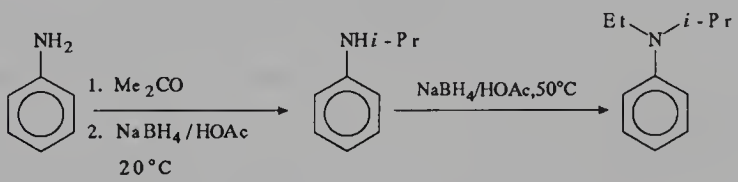
dehyde/$NaBH_4$/CF_3COOH in the presence or absence of THF or by CH_2O/$NaCNBH_3$/AcOH has also been recommended [GN3]: the limitation of this method lies in the impossibility of access to monomethylated amines from primary amines, since the transformation of the intermediate secondary amine to tertiary amine is very rapid. The best way to get to monomethylated amines is then via the carbamates (§2.2.7).

Reductive amination can also be well accomplished in an intramolecular fashion [VO1], as shown in the following reaction, which leads to one predominant stereoisomer [AO1].

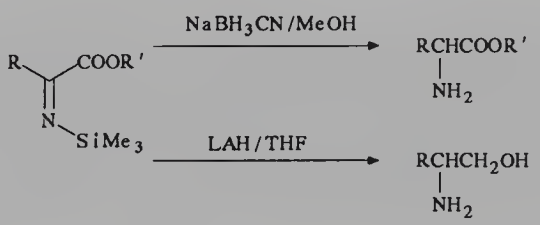


It is possible to obtain amino acids from ketoacids, although with average yields, using $LiCNBH_3$/MeOH under a careful control of the reaction pH [BB1].

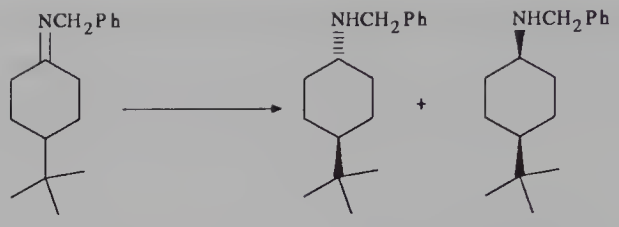
Finally, one can couple the reductive amination and the alkylation process by an acid (§2.2.7) by varying the conditions of temperature [GN1].



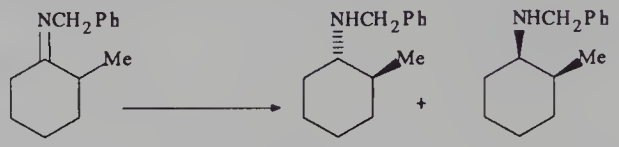
α-Amino esters can easily be obtained from *N*-silylimino esters by $NaCNBH_3$/MeOH, $NaBH_4$/MeOH, or $Me_2NH{\bullet}BH_3$/MeOH [MT5], while LAH converts them to amino alcohols [MT5].



The stereoselectivity of the reduction of the cyclic imines has been examined [WG1, HS1, PD2, M3]: the results are comparable to those obtained with the cyclic ketones, as shown in the following examples:



$NaCNBH_3/MeOH/H^+$	65	35
Li(*sec*-Bu)$_3$BH/THF	2	98

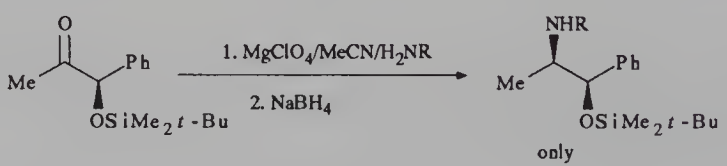


$NaCNBH_3/MeOH/H^+$	36	64
$LiBEt_3BH/THF$	3	97

One nevertheless observes less axial attack by slightly hindered reagents than with the corresponding ketones [HS1].

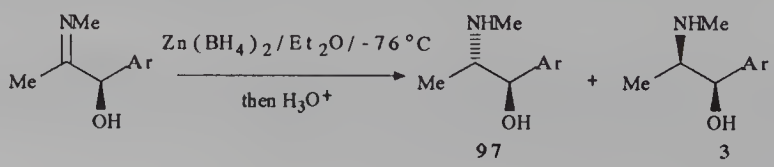
A recently suggested variant involving *N*-diphenylphosphinylimines allows the preparation of axial primary amines with an excellent stereoselectivity [HR2], by action of Li(*sec*-Bu)3BH followed by treatment in an acid medium.

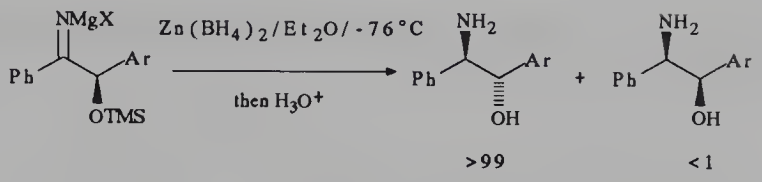
Asymmetric reductive amination can be carried out on chiral ketones able to form an intermediate imine, which can generate a chelate in the presence of a Lewis acid [BW1].



Using $NaCNBH_3$ as reducing agent gives a lower stereoselectivity.

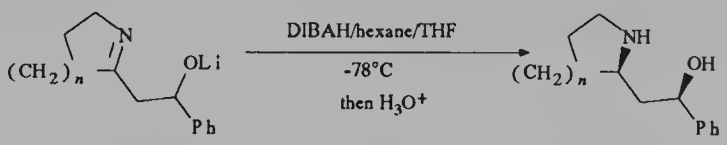
Another way to obtain stereoselectively achiral or chiral β-amino alcohol derivatives is to use $NaBH_4$ or $Zn(BH_4)_2$ reduction of hydroxyimines or trimethylsilyloxy *N*-magnesioimines, formed by a Grignard reaction with the corresponding protected cyanohydrin [JJ1, KJ1].



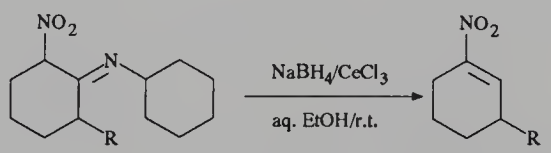


$NaBH_4$ gives a poorer stereoselectivity except when using $OSiMe_2t$-Bu ethers, which are subsequently cleaved by HF to avoid racemization: syn isomers are predominant in this case [BD1].

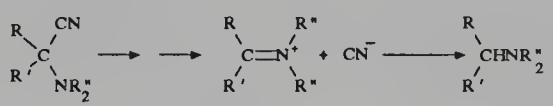
γ-Amino alcohols have also been obtained in a stereoselective fashion by DIBAH reduction of iminoalcoholates [TV1].



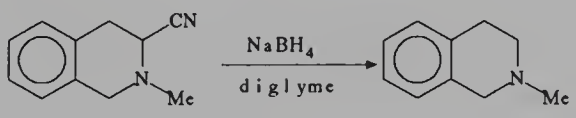
A peculiar reaction has been observed when reacting 2-nitroimines with $NaBH_4/CeCl_3$, thus leading to nitroalkenes [DS3].



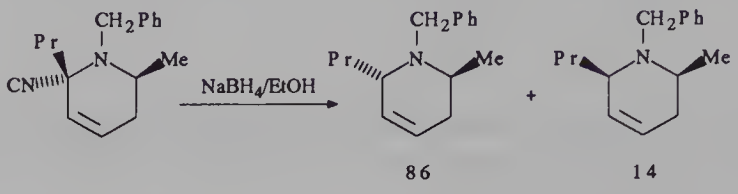
Iminium salts can also be formed by cleavage of the C—CN bond of amino nitriles either in alcoholic media or in the presence of a cation having sufficient Lewis acid properties. The intermediates are then transformed in situ into amines.



Amino nitriles are thus reduced to amines by LAH/Et_2O [CT1], AlH_3/Et_2O [E2], $NaBH_4$ in alcoholic medium [GR1, MR2] or in diglyme [YA1], $Zn(BH_4)_2$ in ether medium, possibly in the presence of $AgBF_4$ [GR1, GR2]. The reduction is still inhibited if the carbon is too sterically hindered [BM2].



This reductive decyanation can be stereoselective in cyclic systems, as shown in the following example [BR1]:



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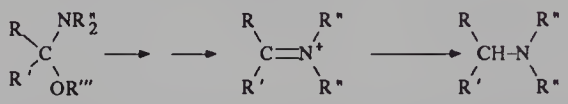
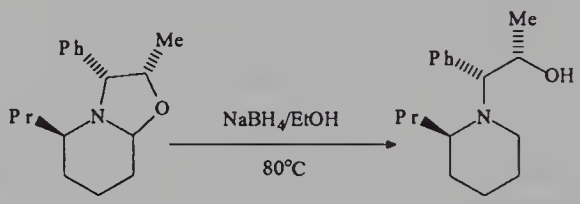
In noncyclic molecules, the stereoselectivity is lower [MR2].

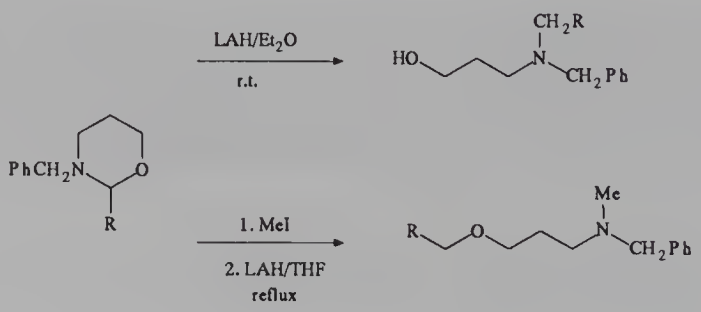
Another way to produce iminium salts is to treat aminals in alcoholic media: they can be reduced to amines by LAH, AlH_3, DIBAH or $NaCNBH_3$/AcOH [WR3, GR1, MR2], or $NaBH_4$/EtOH:



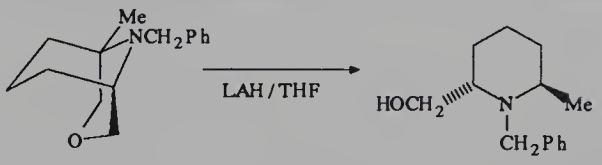
Cyclic aminals thus are converted to amino alcohols [GR1, MR2].



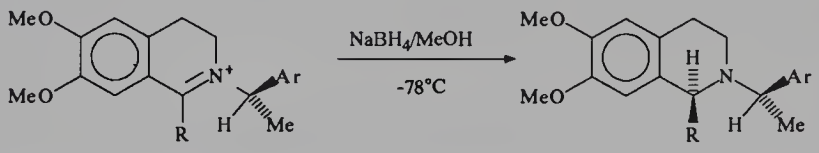
However, six-membered tetrahydro-1,3-oxazines are not reduced by $NaBH_4$. LAH/Et_2O converts them by C—O bond cleavage to γ-amino alcohols, and their corresponding methiodides by C—N bond cleavage to alkyl *N*-methyl-3-aminopropyl ethers [AA1].



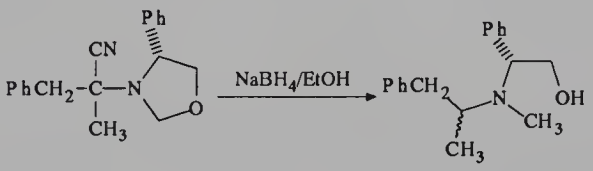
Stereoselective reductions can be observed:



Similarly, chiral iminium salts can be reduced in a diastereoselective fashion by $NaBH_4$/MeOH/–78°C [PK1].

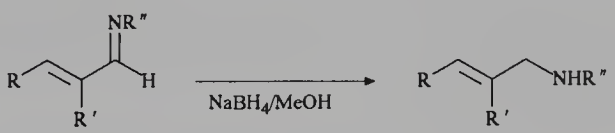


The highest stereoselectivity is observed when the aryl group is 2, 6-dichlorophenyl. The bifunctional derivatives can undergo two successive reductions [MR2].

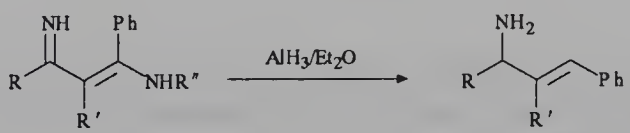


65/35 mixture of
2 diastereoisomers

α,β-Unsaturated imines are converted into secondary amines by $NaBH_4$/MeOH or EtOH [DS2].



Allylic amines can be obtained from 4-aminoazadienes and AlH_3 or DIBAH [BA2].

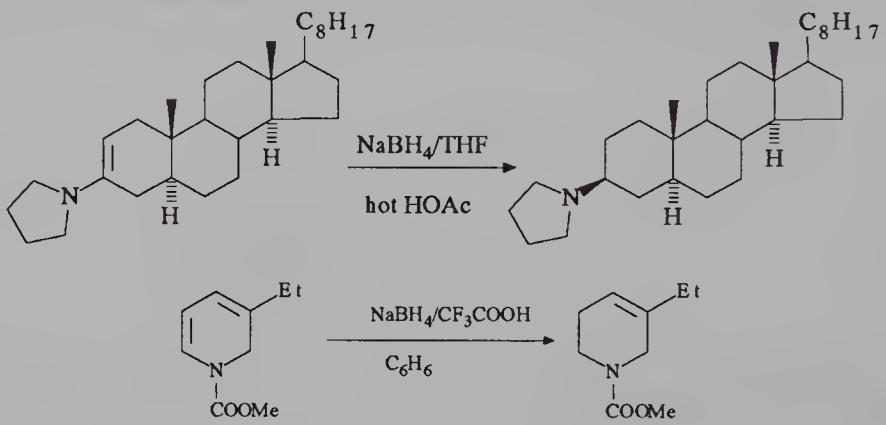


If R′ is too bulky (allyl or benzyl), saturated imines are predominantly formed, but sequential treatment of these azadienes by DIBAH or $NaBH_4$/MeOH leads to allylic amines.

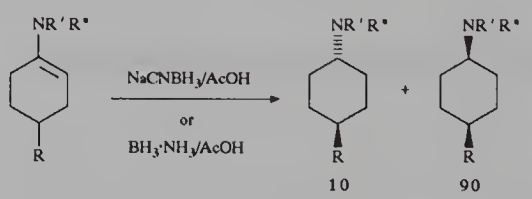
2.3.2. Enamines

Since the mechanism of the reduction of enamines implies the protonation of the enamines and the tautomerism, protonated enamine ↔ iminium salt, the phenomenon is important in this context. The substrates will be accordingly reduced only in the presence of sufficiently strong acids or in protic media.

LAH/THF does not reduce enamines. On the other hand, enamines are transformed into saturated amines by AlH_3/Et_2O [HUD] and by $NaBH_4$ in alcoholic media [BB1], or in THF-MeCOOH [GN1] or in the presence of CF_3COOH [GN1] or, better yet, $Zn(CNBH_3)_2$/MeOH [KO1] and $NaCNBH_3$/THF-MeOH [BB1].



The stereoselectivity of the reduction of cyclic enamines has been examined. By reaction with $NaCNBH_3$ in AcOH or BH_3•NH_3 in AcOH, the axial amines are obtained predominantly [HS1]:

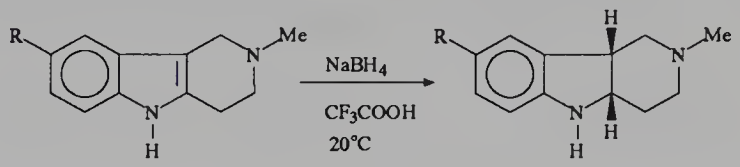


In heterocyclic systems, such as alkaloids, highly stereoselective reductions can be observed; however, they are highly dependent on both substituent and conformation [WF1].

2.3.3. Nitrogen Heterocycles

Indoles. The indoles may be considered to be just like cyclic enamines. Therefore, they are reduced to indolines in acid medium by BH_3•THF/CF_3COOH [MM1], BH_3•pyridine/CF_3COOH [K3], $NaCNBH_3/CF_3COOH$ [GN1, GN2, KL2]. The use of $NaBH_4$/MeCOOH or CF_3COOH is unsuitable, because there may be concurrent *N*-acylations [GN1, GN2, GJ1]. However, if the indoles carry a COMe or COEt substituent, it is reduced by $NaCNBH_3/CF_3COOH$ to CH_2Me or CH_2Et groups [KL2]. It is interesting to note that $NaBH_4/CF_3COOH$ does not lead to indolines with NSO_2Ph derivatives [KL1], while $NaCNBH_3/CF_3COOH$ does [KL2]. These reductions are compatible with ester and nitrile substituents, which remain unchanged.

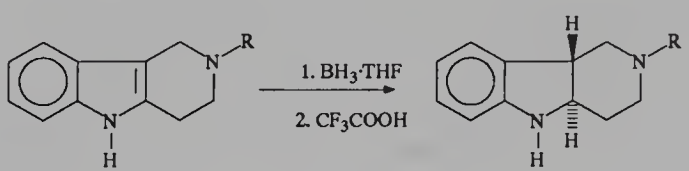
The reduction by $NaBH_4/CF_3COOH$ is compatible with halides and ester groups and it can be stereoselective, as shown below [GN1]:



R = Cl, F, Br, COOEt

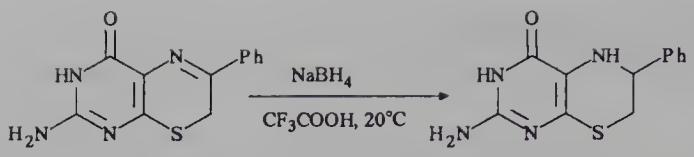
The reduction by BH_3•pyridine/CF_3COOH [K3] or BH_3•THF/CF_3COOH [MM1] is compatible with amide, nitrile, or ester groups. It is interesting to emphasize that LAH in ether media reduces these groups without affecting the indole heterocyclic double bond.

The formation of a compound with a trans ring junction can be realized starting from an indole conjugated to a nitrogen heterocycle, preforming the corresponding amine-borane, which leads to the *trans*-indoline in an intramolecular fashion [EG1]:

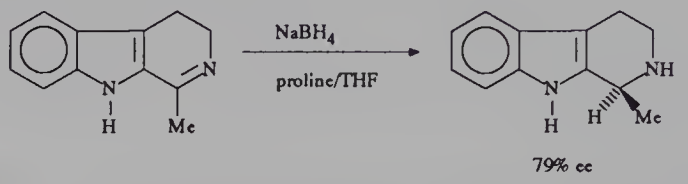


R = H or Me

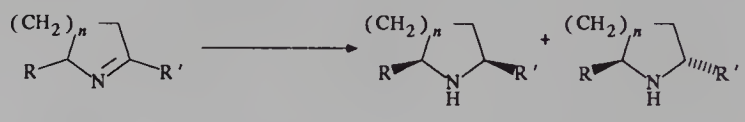
Heterocyclic Imines and Iminium Salts. Heterocyclic imines are reduced under the same conditions as linear imines: this reduction is compatible with the same functional groups, as shown in the following example [GN1]:



If the acid used is chiral, one can observe an asymmetric induction [GN1]. In the following example, the presence of the secondary amine in the six-membered ring prevents the subsequent reduction of the indole, which is not protonated under these conditions.

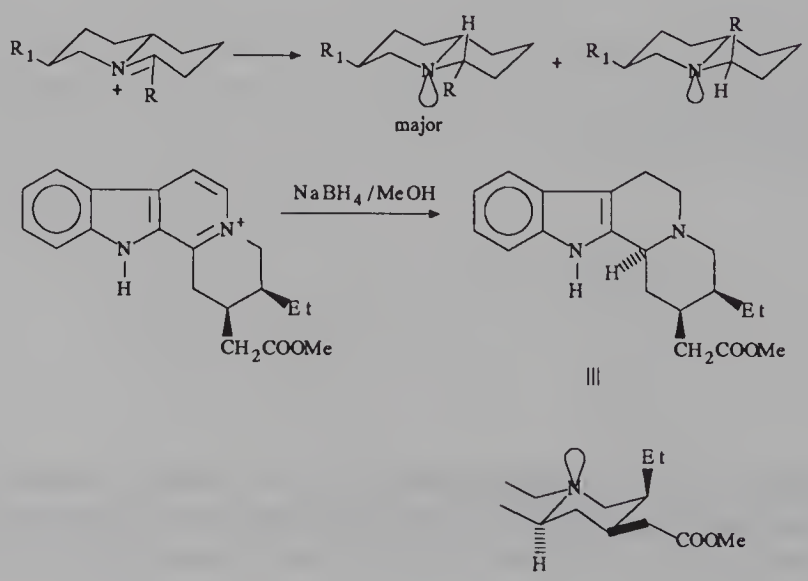


2,6-Dialkylpiperideines or 2,5-dialkylpyrrolines can be stereoselectively reduced to cis- or trans-disubstituted piperidines or pyrrolidines using either DIBAH or LAH/Me3Al [MM5, BC8], the other reagents being less stereoselective.



DIBAH/CH_2Cl_2	>99	<1
LAH/Me_3Al/THF	5	95

The reduction of the bicyclic iminium salts having the nitrogen at the ring junction is very stereoselective:

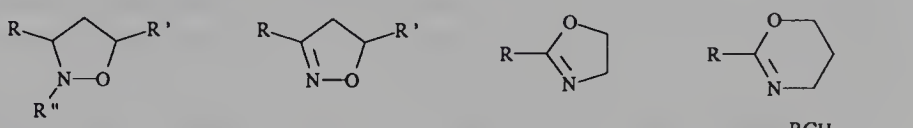


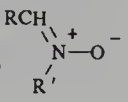
The hydride enters preferentially on the axial face in antiperiplanar position to the lone pair, which is developing on the nitrogen [D2, NS3, M3].

LTBA can be more stereoselective than $NaBH_4$ [M3].

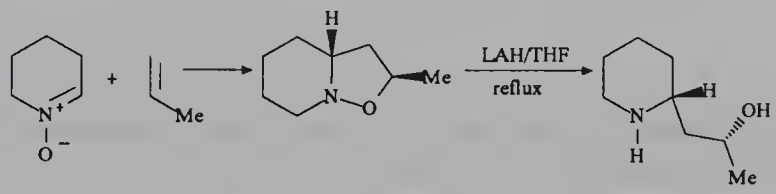
However, when the nitrogen atom is not at the ring junction, the reduction is often less stereoselective [BB4, SM5].

Isoxazolidines, Isoxazolines, Oxazolines, and Oxazines

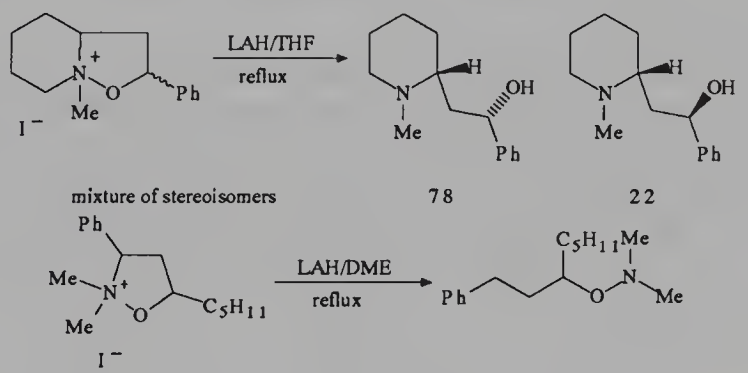


The isoxazolidines, easily obtained by cycloaddition of nitrones 

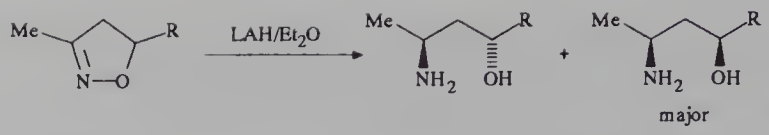
to olefins, are reduced to 1,3-amino alcohols by reaction with LAH in ether media. The synthesis of racemic sedridine is illustrative [TA2]:



The quaternary ammonium salts derived from isoxazolidines are also reduced by LAH but, depending on the nature of the substituents, hydride attack takes place α to the oxygen, as previously, or α to the nitrogen. One can then obtain either a 1 ,3-amino alcohol [TA2] or a substituted hydroxylamine [LS3], as shown below:



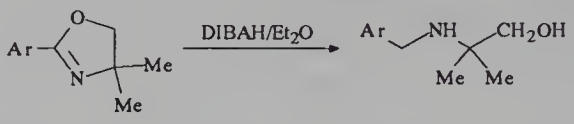
Isoxazolines are obtained by cycloaddition of nitrile-oxides on olefins: their reduction by LAH/Et_2O leads to 1,3-amino alcohol, the syn isomer in general being largely predominant [JS2, WP1]. This constitutes an interesting synthetic method.



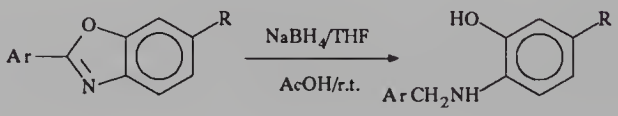
When R is a latent carboxyl group such as *p*-anisyl or α-furyl, α-hydroxy-amino acids can be obtained in a highly stereoselective fashion [JG1]. Such methodology can also be applied to the synthesis of amino sugars [JG1, JM2].

However, $NaCNBH_3$ in the presence of HCl reduces only the C=N bond and converts the isoxazolines to the corresponding isoxazolidines [JB1], which can still be reduced by $LAH/NiCl_2$ [GO2].

The reduction of aryloxazolines to 1,3-amino alcohols is carried out by $DIBAH/Et_2O$ or /hexane at 0°C [MH1]: this is compatible with a halogen substituent on the aromatic nucleus:

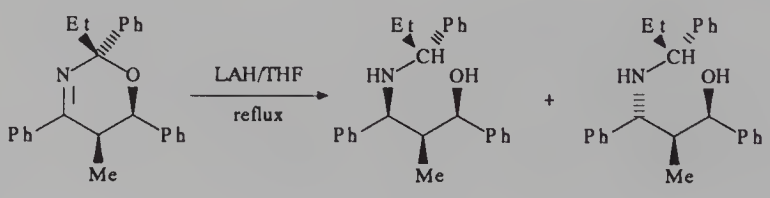


2-Amino-substituted phenols can also be prepared by reduction of the right oxazoline by $NaBH_4/THF$ in the presence of AcOH [YL3].



This method leaves the ester groups unchanged, while nitriles suffer some reduction to amines.

The stereoselective synthesis of 1,3-amino alcohols having three or four chiral centers can be carried out by LAH reduction of 1,3-oxazines [BJ4].



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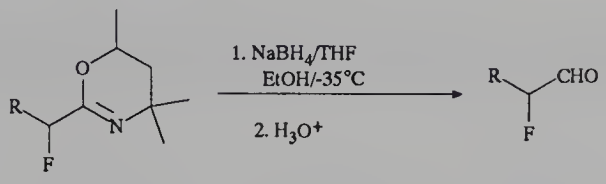
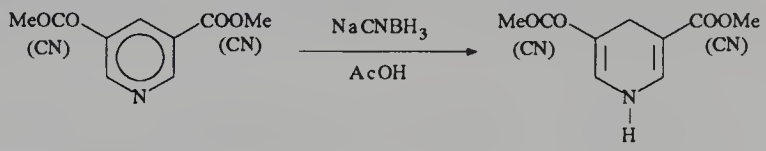
However, $NaBH_4/THF/EtOH$ only can reduce the C=N bond, leading thus to aminals, which are hydrolyzed under acidic conditions to aldehydes [PH1].



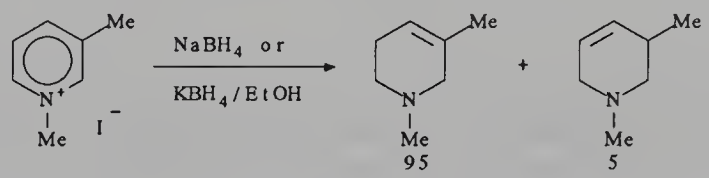
The reduction of cyclic aminals is described in §2.3.1.

Pyridines, Quinolines, and Analogues. Pyridines are not reduced by the alumino- and borohydrides unless they carry electron-withdrawing groups at 3- and 5-positions. In this case, they are converted into the corresponding 1,4-dihydropyridines by $NaCNBH_3$/MeCOOH [GN1]; the use of $NaBH_4$ leads to mixtures.

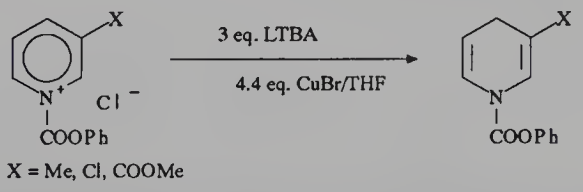


LAH in pyridine is a reducing agent [LL1].

Pyridinium quaternary salts are, on the other hand, easily reduced by AlH_3 or LAH in ether media, Red-Al/C_6H_6, or alkaline borohydrides in alcoholic media, leading thus to the 1,2,3,4-tetrahydro-*N*-alkylpyridines. If the pyridinium salt bears a substituent at the 3-position, one of the regioisomers is selectively formed.

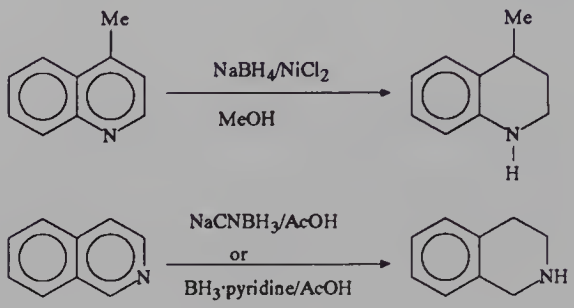


Acylpyridinium salts are converted to mixtures by reaction with $NaBH_4$ or $NaCNBH_3$, or with LBTA or Red-Al/CuBr under usual conditions [SS1]. A specific methodology allows one to obtain, through the reaction with LTBA/CuBr in THF, *N*-acyl-1,4-dihydropyridines. Under these conditions, chlorides and esters remain intact [CA1].

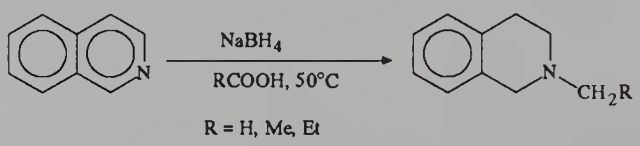


The quinolines and isoquinolines are more easily reduced than pyridines: aluminohydrides or BH_3•THF/CF_3COOH [MM1] leave them intact, but $NaBH_4$

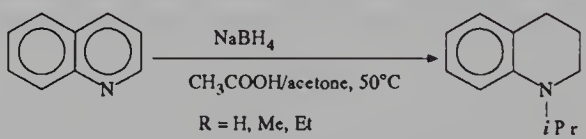
or $NaCNBH_3$/AcOH [GN1], BH_3-pyridine/AcOH [HUD] and $NaBH_4/NiCl_2$ in MeOH [GO2] reduce them to tetrahydroquinolines or isoquinolines.



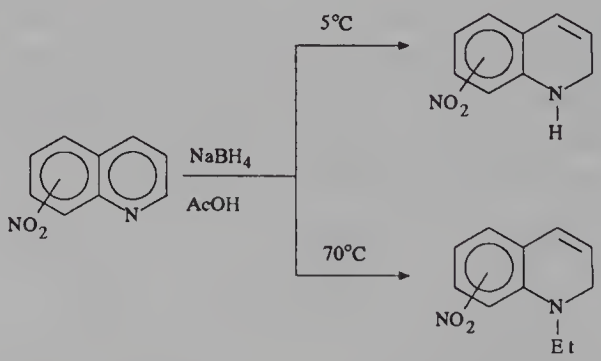
With $NaBH_4$ in a hot organic acid medium, one can carry out a subsequent *N*-alkylation (§2.2.7) [GN1]. However, $NaBH_4/CF_3COOH$ leads to mixtures.



In the presence of a ketone, it is possible to form an *N*-alkylated amine by reduction followed by reductive amination (§2.3.1) [GN1].

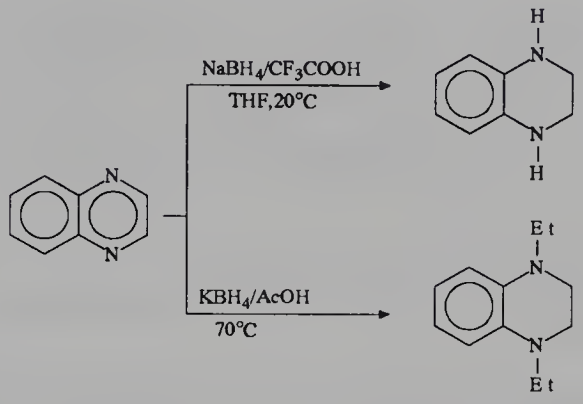


The reduction of the nitroquinolines by $NaBH_4$/AcOH at 5°C leads to the dihydrogen compounds, the NO_2 functional group being kept [GN1]. On heating, one obtains the corresponding *N*-ethylamine (§2.2.7) [GN1].



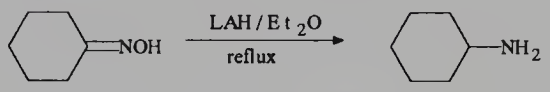
Quinoxalines and quinazolines or acridine show the same kind of reactivity: $NaBH_4$/AcOH or CF_3COOH in the cold leads to cyclic secondary diamines,

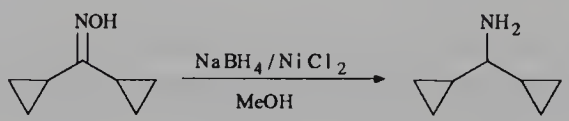
while in hot AcOH, one obtains the corresponding bis-*N*-ethylamines (§2.2.7) [GN1].



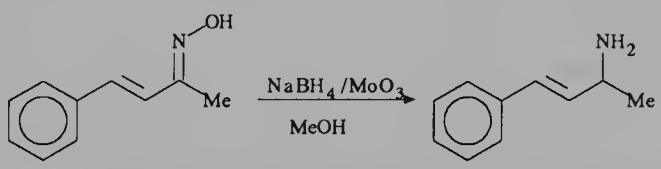
2.3.4. Oximes and Hydrazones

Oximes are reduced to amines by LAH/THF or /Et_2O [HUD] but are inert in the presence of LTBA or $NaBH_4$, unless one adds to the latter $NiCl_2$ in MeOH [GO2] or $ZrCl_4$ in THF [IS1].



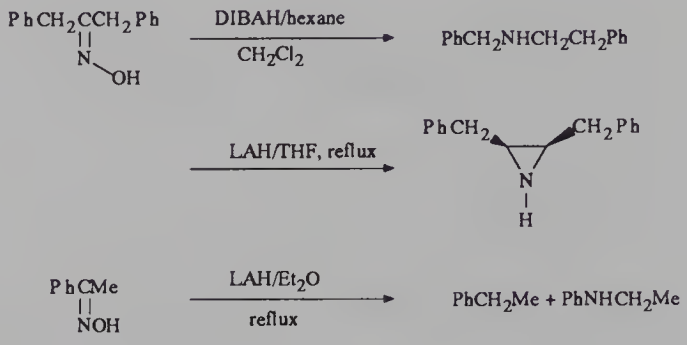


Under these conditions α,β-ethylenic oximes are reduced to saturated amines. However, in the presence of MoO_3, the double bond is preserved [GO2].

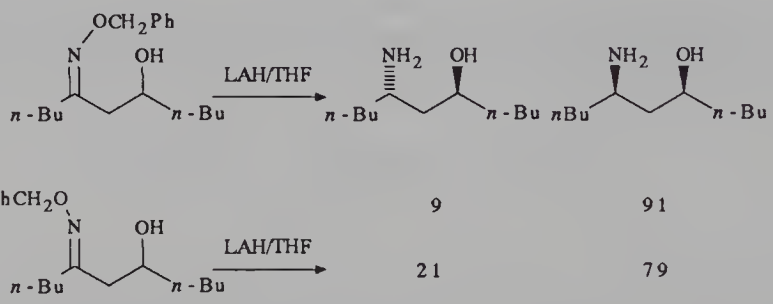


The reduction by DIBAH induces some rearrangements [SM4] while, in some cases, reductions by LAH/Et_2O or Red-Al in C_6H_6 can give mixtures of

primary and secondary amines, or even aziridines. as shown in the following examples [GW1, PP1, M3]:

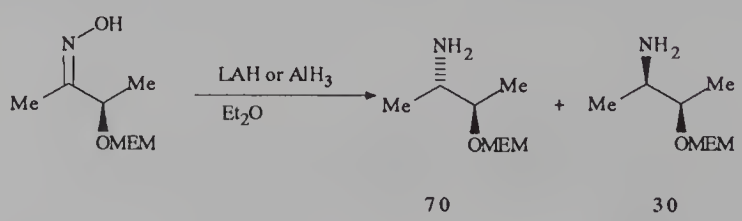


The reduction of *syn*-β-hydroxyoximes by LAH/THF is stereoselective, while that of the anti isomer is less so [NU1]. In both cases, the *syn*-amino alcohol is the predominant isomer:



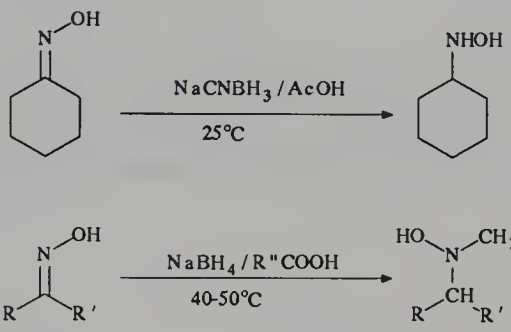
If the reduction is carried out in the presence of MeONa, the *anti*-oxime is reduced more selectively to the *syn*-β-amino alcohol (≥ 96%) [NY1].

On the other hand, the reduction of α-alkoxyoximes by LAH or AlH_3 is poorly stereoselective [IY2].

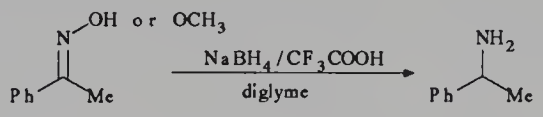


Oximes are reduced to the corresponding hydroxylamines by BH_3•THF, BH_3/CF_3COOH, amine-boranes [KK11], $NaBH_4$, or $NaCNBH_3$/AcOH in the

cold. On warming, $NaBH_4$ in organic acids leads to *N*-alkylhydroxylamines [GN1, MM1].

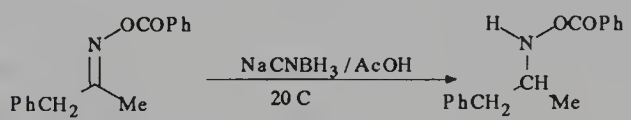


In the presence of CF_3COOH, under heating, one obtains primary amines [GN1].



Asymmetric reduction of ketoxime *O*-alkylethers to chiral primary amines can be carried out with a high enantiomeric excess by $NaBH_4/ZrCl_4$/THF in the presence of a chiral amino alcohol [IS2].

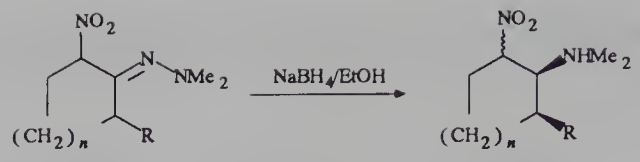
Oxime esters can be reduced to acyloxyamines by $NaCNBH_3$/AcOH [GN1, SJ1].



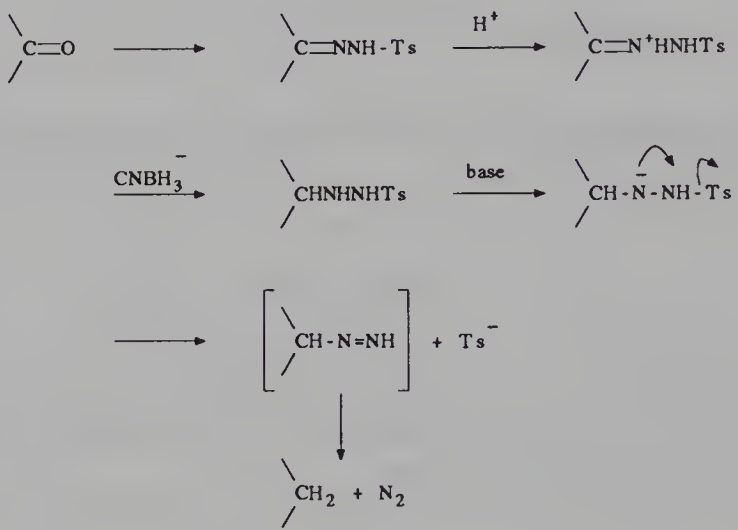
On the other hand, BH_3•THF converts them to amines and to the corresponding alcohols [HUD]. $NaCNBH_3/TiCl_4$/aq MeOH converts oximes into amines: this reduction is compatible with ketones, esters, acetals, and isolated double bonds [LK2].

Moreover, α-oximinoesters can be reduced to α-amino acid esters by $NaCNBH_3/TiCl_4$/aq. MeOH in buffered conditions: tartaric acid is the best buffer, although no asymmetric induction is observed [HT3].

Hydrazones are reduced to hydrazines by LAH in ether or BH_3•THF. Whereas dialkylhydrazones are resistant to reduction with $NaBH_4$, α-nitrohydrazones are reduced extremely rapidly in EtOH [DS2].

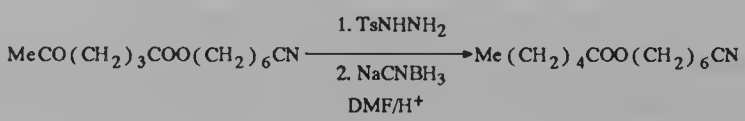


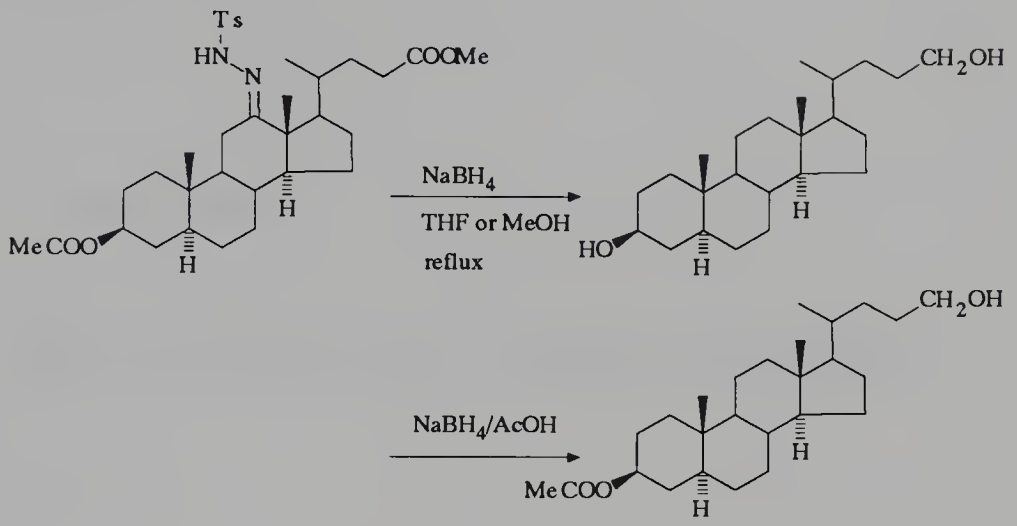
But the most interesting reduction is that of the tosylhydrazones, due to the presence of the leaving group which, in a basic medium, converts the tosylhydrazine that is formed into saturated hydrocarbons and nitrogen:



This reduction can be accomplished with $NaBH_4$/EtOH [PS1], BH_3/PhCOOH, or BH_3/CF_3COOH in THF [KB4, MM1] but, above all, by $NaCNBH_3$ in DMF in the presence of acid or $NaBH_4$ in organic acid media [L1, HN1, MY1]. $NaCNBH_3/ZnCl_2$ in refluxing MeOH has also been used: under these conditions, epimerization of the carbon α to the tosylhydrazone moiety is avoided [SH5].

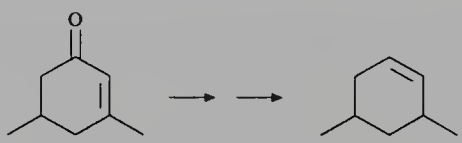
The reaction can be run in "one-flask" fashion starting from the ketone: it is thus a modification of the Wolff–Kishner reaction and is compatible with ester and nitrile functional groups, as shown in the following examples [L1, IT1].



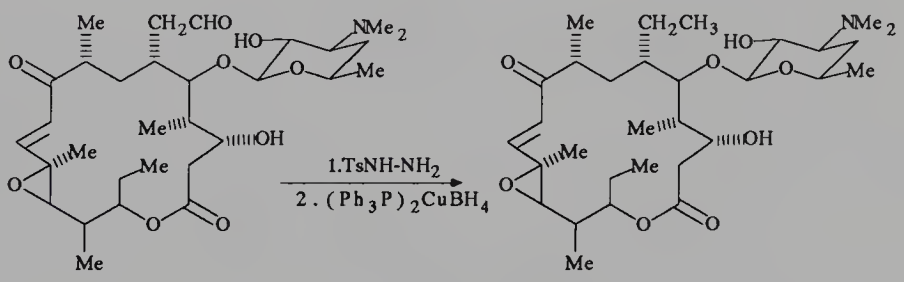


However, when starting from tosylhydrazones derived from arylketones, the transformation to hydrocarbons requires warming in the presence of base.

The limitation of the method is the migration of the double bond during the reduction of tosylhydrazones of α-enones [L1].



$(Ph_3P)_2CuBH_4$ in hot $CHCl_3$ reduces tosylhydrazones of aldehydes, or, of aliphatic or alicyclic ketones to hydrocarbons [FH2], but leaves the tosylhydrazones of aromatic or α,β-unsaturated ketones and aldehydes unperturbed. This method has been applied to the selective reduction of the tosylhydrazone of a multifunctional aldehyde [GL3], carrying an α-enone, an epoxide, and a lactone, all of which remain unchanged.



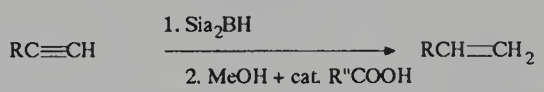
Finally, BH_3•pyridine reduces tosylhydrazones to tosylhydrazines, even in the aromatic series [KK8]. In the presence of the base and with heating, these tosylhydrazines can be converted to the corresponding hydrocarbons.

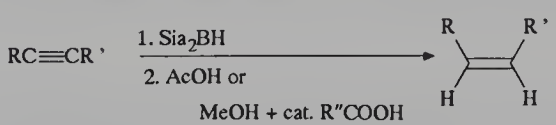
CHAPTER 3

REDUCTION OF TRIPLE BONDS

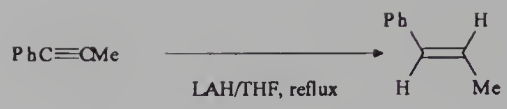
3.1. CARBON–CARBON TRIPLE BONDS

C≡C bonds undergo facile hydroboration [PS1, HH1] and hydroalumination [HH1, W1, HH3] at room temperature. Therefore the boranes and DIBAH must not be used, except for special cases, in the selective reduction of other functional groups. Still, it is good to point out that the alkynes can undergo monohydroboration by using relatively bulky boranes such as Sia_2BH or $(cyclohexyl)_2BH$. The stereospecific cleavage of the C—B bond of the *cis*- alkenylboranes thus formed by an organic acid or by MeOH in the presence of catalytic quantities of organic acid [BM3] is an often used methodology for the synthesis of terminal or disubstituted (*Z*) alkenes. There are numerous applications in the synthesis of pheromones.



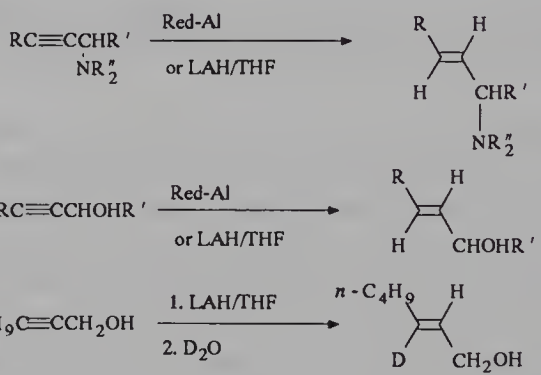


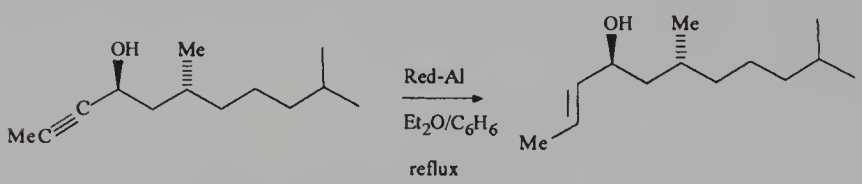
LAH in THF or hot diglyme converts disubstituted alkynes to *trans*-alkenes [HH1, DM1, HUD].



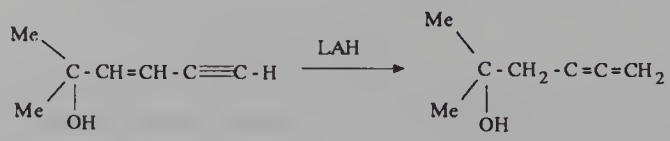
However, at room temperature, the isolated triple bonds are not attacked by LAH, LTBA, AlH_3, or Red-Al [HH1] or by the alkaline borohydrides except in the presence of Lewis acids, which induce the formation of diborane. In the presence of transition metal salts ($PdCl_2$, Co^{2+}, Ni^{2+}), $NaBH_4$ in alcoholic media reduces alkynes to alkenes or to saturated hydrocarbons, depending on the conditions [GO2, W4, SK3].

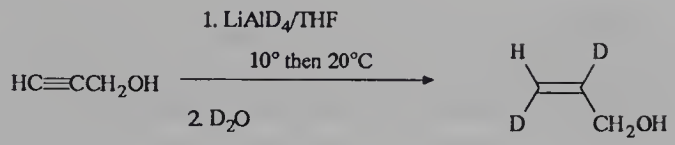
Propargylic amines and alcohols are reduced to allylic amines and alcohols by LAH in ether media or Red-Al in ether or toluene [HH1, M1, HH3]. With LAH, the reduction is stereoselective only if the solvent is basic enough (THF or DME) [DJ1, M1, DM1]: one obtains the (*E*) isomers, the reduction implying an intramolecular regioselective transfer of hydride as shown by trapping of the adduct by D_2O.



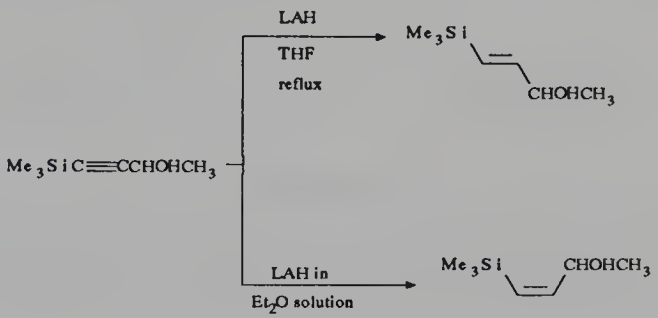


Although some authors have pointed out that the reaction leads to allenes if R = H [HH3], propargylic alcohol has been selectively reduced to *trans*-dideuterated alcohol by precisely mastering the experimental conditions [BB2].





Starting from silyl derivatives, it is possible to obtain selectively the (*E*) or (*Z*) allylic alcohol [MH2].

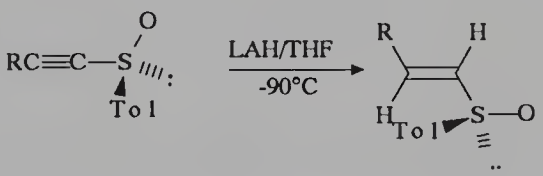


LAH in suspension in Et_2O gives a mixture of (*E*) and (*Z*) isomers.

The presence of a leaving group α′ to the triple bond induces the formation of α-allenic alcohols [HH3].

1-Alkynylsulfides are also reduced to 1-alkenylsulfides: according to the reagent, (*E*) or (*Z*) isomers are formed: $Li(MeO)_3AlH$ or LAH leads to (*E*) isomers, while $Li(MeO)_3AlH/CuBr$ gives the (*Z*) form [M3].

Chiral α-acetylenic sulfoxides are converted to (*E*)-α,β-unsaturated analogues by DIBAH or, better, LAH/THF at low temperature [KK10].

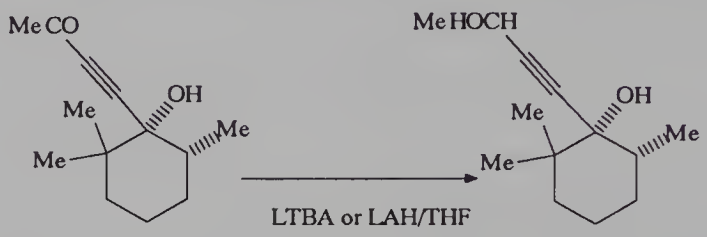


3.2. α,β-ACETYLENIC KETONES AND ESTERS

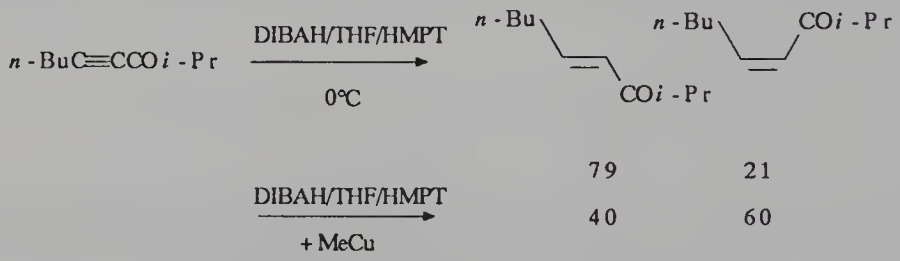
The alkoxyaluminohydrides, LAH, modified by amines or amino alcohols [M1, GH1], DIBAH, and cyanoborohydrides in acid media [HK2], reduce the α-ynones to propargylic alcohols. Use of chiral ligands can give a highly asymmetric induction [M1, GH1, MS5] (§2.2.2). Asymmetric reduction of α-ynones

to optically active propargylic alcohols can also be carried out via acetals formed from chiral 1,3-diols (§ 1.4).

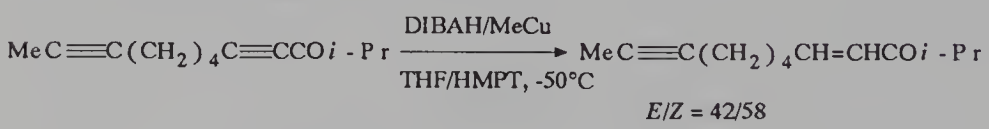
The following example shows that, in spite of the presence of the alcoholic functional group, LTBA selectively reduces the ketone and leaves the triple bond alone [SA1].



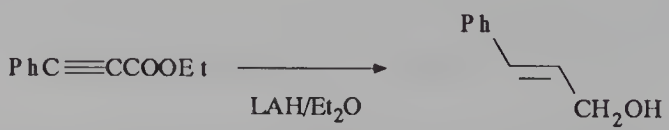
The selective reduction of the α,β-acetylenic ketones to α,β-ethylenic ketones is accomplished by reaction with DIBAH in THF/HMPT [TY2]. In the presence of a catalytic quantity of MeCu, the reduction is faster and the stereoselectivity is modified. Nevertheless, the stereoselectivity is not very high, as indicated in the following example [TY2].



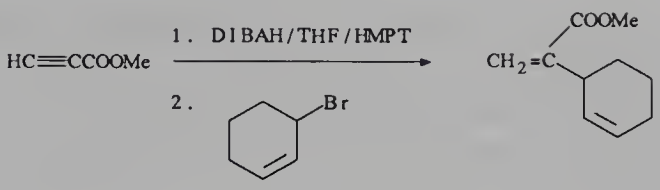
The reagent does not reduce an isolated triple bond:



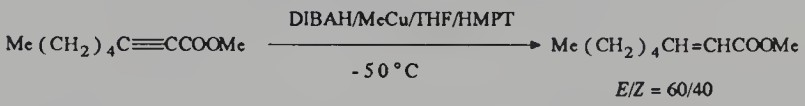
α,β-Acetylenic esters are reduced to (*E*)-allylic alcohols by LAH/Et_2O [DM1].



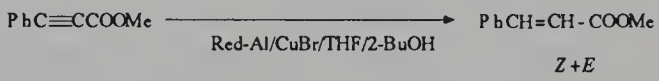
Reduction of the same esters by DIBAH in THF-HMPT takes place only if the alkyne contains HC≡C moiety; the adduct thus formed may then be trapped by an allylic bromide [TY1].



Substituted α,β-acetylenic esters are reduced only in the presence of MeCu:

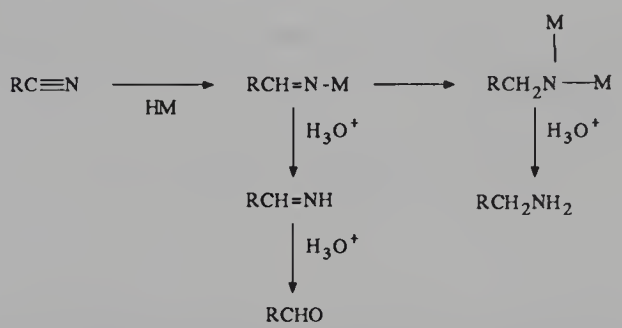


They are also reduced to α,β-ethylenic esters by Red-Al/CuBr in the presence of 2-butanol: the reaction leads to a mixture of (*Z*- and *E*-) α,β-unsaturated esters and gives good results only if the triple bond is disubstituted [SS1]



3.3. CARBON–NITROGEN TRIPLE BONDS: NITRILES

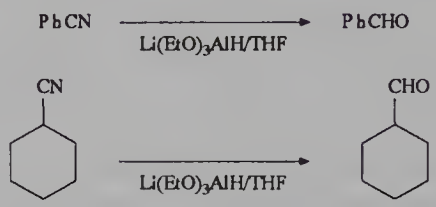
The reduction of nitriles can take place in two steps: (1) formation of an imine, which can be hydrolyzed to an aldehyde, and (2) double reduction to amine. Depending on the reagents and experimental conditions, one may observe either process [HH3, C5].



Nitriles are not reduced by LAH/SiO_2 [KH2], alkaline borohydrides in alcohol media or in ethers at room temperature [PS1, BK5], $(CF_3COO)_2BH$ [MM1], or cyanoborohydrides, whatever the medium may be [L1, GN1]. Never-

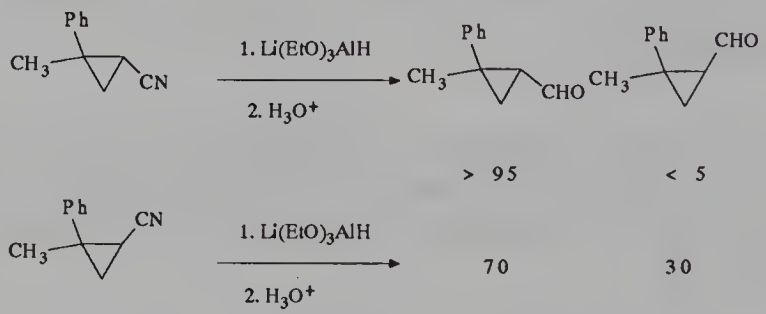
theless, the 2-cyano- or 4-cyanopyridines are reduced to amines by $NaBH_4$/EtOH under reflux [KK2, HH3].

Two reducing agents lead to the imine and, after hydrolysis, to the aldehyde: trialkoxyaluminohydrides and DIBAH/toluene at –78°C; among the first set of reagents $Li(EtO)_3AlH$/THF proves to be the best, while LTBA is unreactive [BK5, HUD, C5, M3].

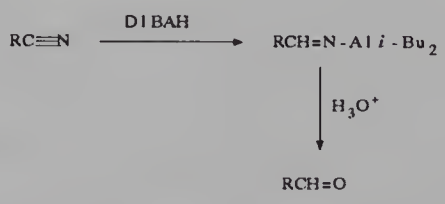


The intermediate $RCH{=}NAl(OEt)_2$ can be trapped by Me_3SiCl and leads thus to *N*-trimethylsilylimines [AC2].

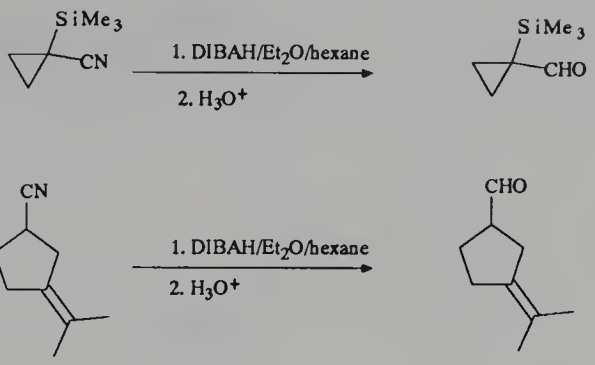
However, the initial stereochemistry of the nitriles that are not substituted at α-position is not retained: starting with a pure nitrile, one can obtain a mixture of stereoisomeric aldehydes as shown in the following examples [PS2]:



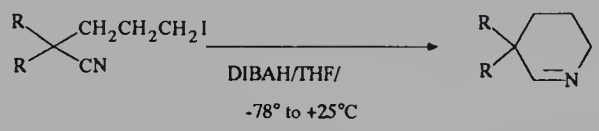
If employed in the cold and in stoichiometric quantities, DIBAH leads to the iminoaluminate, which is hydrolyzed to aldehyde [W1, K2, YG1].



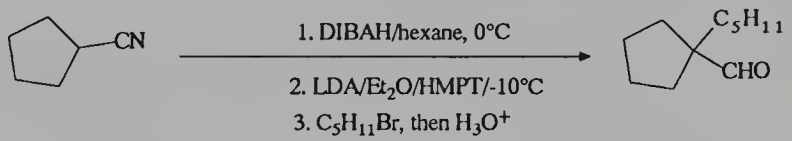
The reaction proceeds with aliphatic, aromatic, α,β-unsaturated (see §3.4), or cyclopropanic nitriles [WY1, HH3]:



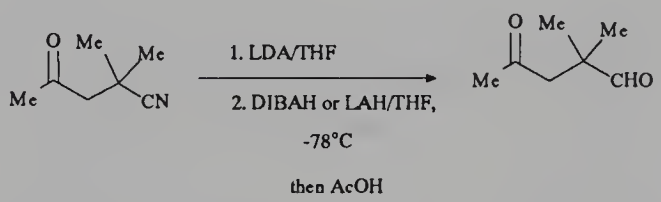
The iminoaluminate thus formed can undergo an intramolecular alkylation, as shown in the following example [OB1]:



The deprotonation at α-position of the iminoaluminate, by reaction with LDA then followed by alkylation, allows access to the branched aldehydes [GT1].

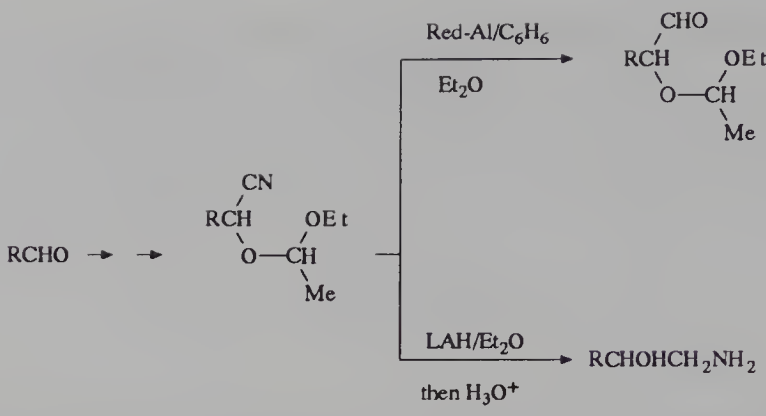


As in the case of ketoesters, selective reduction of the ketonitriles, in which the CN is located on a tertiary carbon, can be carried out, provided the ketone enolate is preformed [KF2].



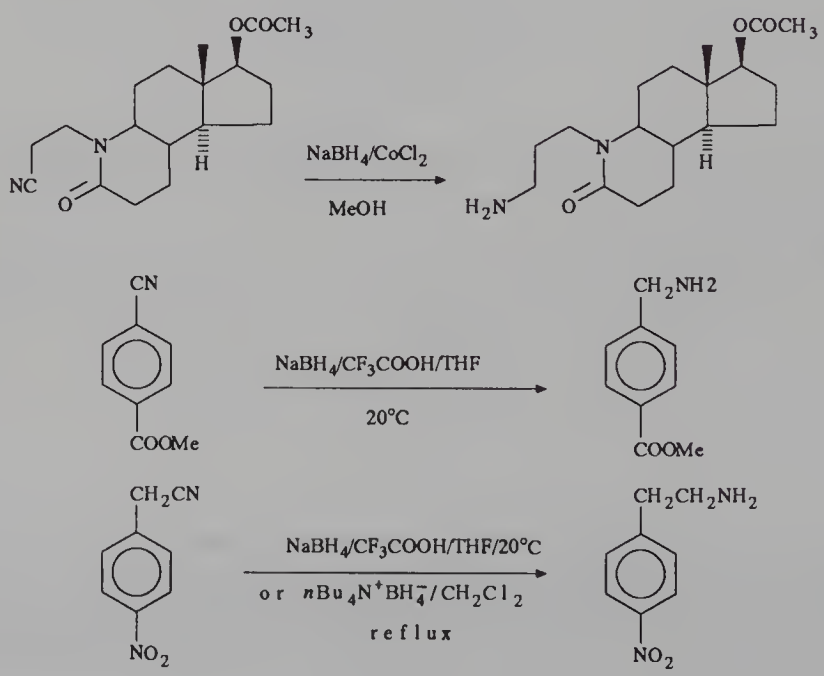
The use of $NaEt_2AlH_2$ in the presence of a Lewis acid for converting aliphatic nitriles to aldehydes has been described recently [YK2].

Starting with the aldehydes, converted into cyanohydrins whose hydroxyl group is protected as an acetal, one can obtain α-hydroxyaldehydes by reaction with Red-Al or α-hydroxyamines via reduction by LAH [SB1].

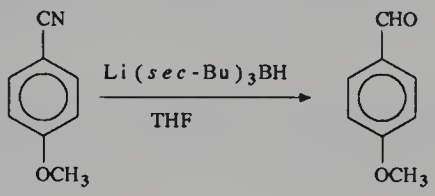


The reduction of the nitriles to amines can be carried out by LAH in an ether medium, AlH_3/Et_2O, $Li(MeO)_3AlH$ [M3], or Red-Al at 80°C in the case of aromatic nitriles [M3], BH_3•THF or aminoboranes under warming [HUD, BK5, E2, L2, PS1], Na or $LiBH_4/Me_3SiCl$/THF [GS2], $NaBH_4/ZrCl_4$/THF [IS1], $NaBH_4$/ $CoCl_2$/MeOH [W4, GO2], $NaBH_4/CF_3COOH$/THF [GN1], *n*-$Bu_4N^+BH_4^-$ under reflux of CH_2Cl_2 [WI1], or $LiBH_4$/diglyme/hot MeOH [SO3], $LiBH_4/(MeO)_3B$/ Et_2O at 25°C [BN3]; with the last reagent, the sulfones, sulfoxides, the NO_2 group, and the pyridine moiety remain unchanged.

Therefore, it is possible to perform a number of selective reductions, some examples of which appear below [GO2, GN1]:



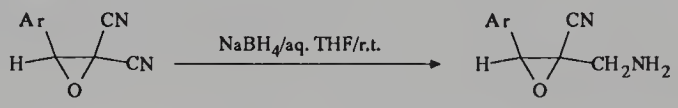
Trialkylborohydrides also reduce nitriles to amines [BK5], except for Li(*sec*-Bu)$_3$BH, which leaves aliphatic and aromatic nitriles intact unless the latter are parasubstituted by an electron-donating group [SM1]. An aldehyde is then obtained.



Under reflux in toluene, Red-Al reduces aromatic nitriles to amines but leaves the aliphatic nitriles intact [MC1].

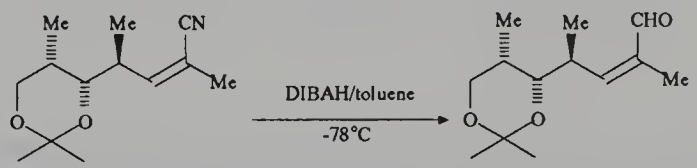
Whereas thexylborane and 9-BBN hardly react with nitriles [PS1], thexylchloroborane reduces aliphatic nitriles into corresponding amines [BN5].

Surprisingly, *gem*-dicyanoepoxides are reduced to α-cyano α-epoxymethyl amines by $NaBH_4$/aq THF [MR4].

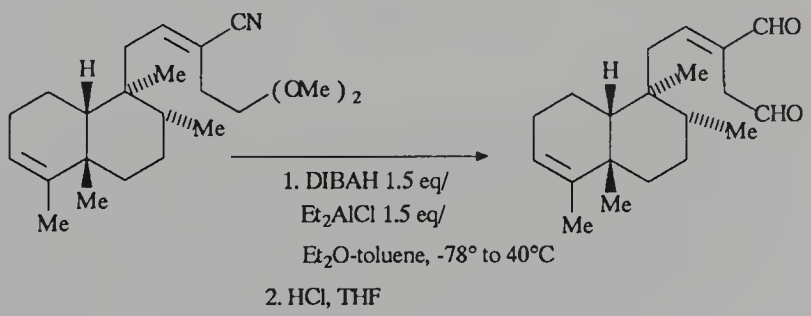


3.4. α,β-UNSATURATED NITRILES

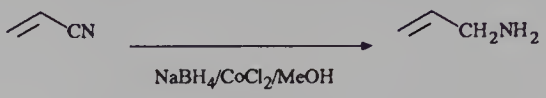
α,β-Ethylenic nitriles are reduced to α,β-unsaturated aldehydes by DIBAH/toluene at low temperature [K2], as shown below:



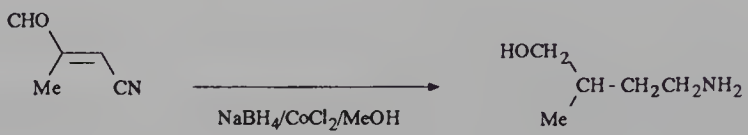
The presence of an acetal group that can coordinate to DIBAH leads to a decrease in the extent of the reduction in the case shown below: the addition of a Lewis acid, here Et_2AlCl, solves the problem, and the formation of the aldehyde is carried out with a satisfying yield [TT2].



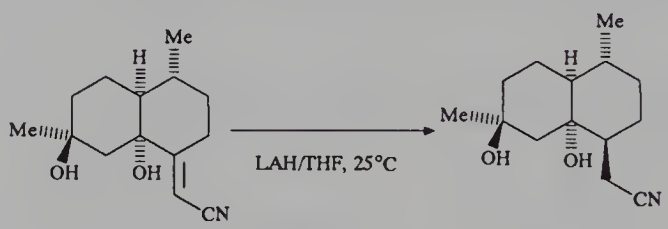
$NaBH_4/CoCl_2/MeOH$ also reduces α,β-unsaturated nitriles without affecting the double bond, but one obtains an α,β-ethylenic amine [GO2].



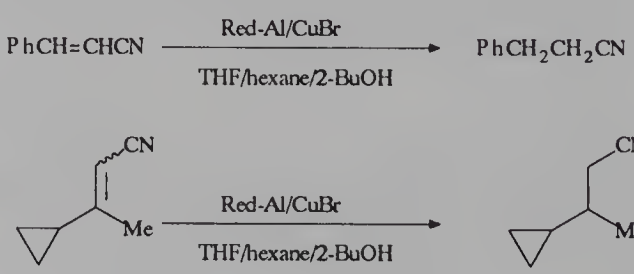
However, if the double bond is conjugated either to another double bond or to an aldehyde, the totally reduced product is obtained [GO2].



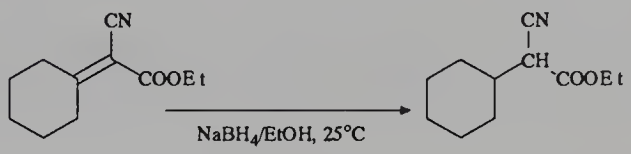
LAH reduces α,β-unsaturated nitriles to saturated amines [HUD]. However, the formation of an alcoholate in a suitable position, followed by an intramolecular hydride transfer, allows the selective reduction of an α,β--unsaturated nitrile to a saturated nitrile by reaction with LAH [LM1, LV1] or even by $LiBH_4$/THF under reflux [LV1].



Reduction of α,β-unsaturated nitriles to saturated nitriles is generally carried out with Semmelhack's system [SS1, M3]; Red-Al in the presence of CuBr/THF/hexane/2-BuOH proceeds as shown in the following examples [OP1]:



Alkaline borohydrides in alcoholic media do not reduce the α,β-ethylenic nitriles, except $NaBH_4$/MeOH/pyridine under reflux [RB2] and $NaBH_4$/EtOH in some cases [KS6, UC1]. On the other hand, if the double bond is activated by another electron-withdrawing group, reduction to the saturated compound takes place [MC2, MR4]. If the experimental conditions are appropriate, the functional groups remain unchanged:



The reduction of α,β-acetylenic nitriles to (*E*)-a,β-ethylenic nitriles by 0.5 equivalent of LAH/Et_2O under reflux [VK4] or $NaBH_4$/EtOH [KS6] has been described.

CHAPTER 4

OTHER DERIVATIVES

4.1. NITRO AND NITROSO DERIVATIVES: RNO_2, RNO

The RNO_2 and RNO compounds are among the most difficult to reduce using alumino- and borohydrides.

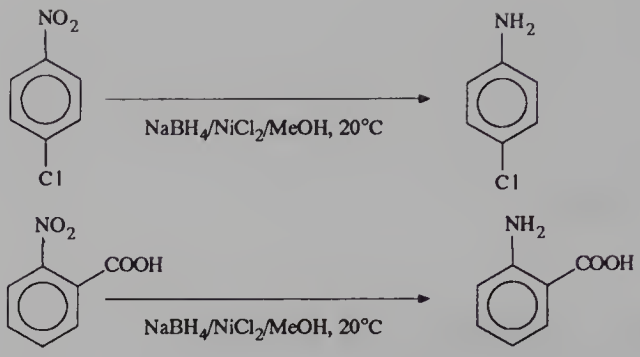
LAH in an ether medium and $Li(MeO)_3AlH$ reduce the nitro and aromatic nitroso derivatives to the azo derivative ArN=NAr, as well as Red-Al [HUD, M3]. On the other hand, nitro derivatives are untouched by AlH_3/Et_2O [BK5, E2] or by LAH/SiO_2 [KH2]. Borohydrides and boranes leave them unchanged under the usual conditions (ether or alcohol solvent) [PS1, L2] or in acid media [MM1].

$LiBH_4$/diglyme/MeOH under reflux allows the reduction of aliphatic and aromatic nitro derivatives to the corresponding amines [SO3].

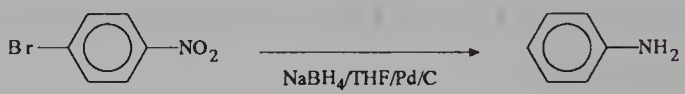
$$RNO_2 \xrightarrow[LiBH_4/diglyme/MeOH,\ reflux]{} RNH_2$$

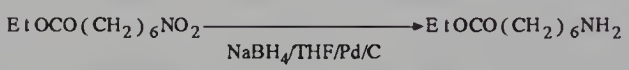
$$ArNO_2 \xrightarrow[LiBH_4/diglyme/MeOH,\ reflux]{} ArNH_2$$

In the presence of transition metal derivatives [$SnCl_2$, $Cu(acac)_2$, $(Ph_3P)_4Ni$, $NiCl_2$, $CoCl_2$], reduction of aromatic nitro derivatives to amines by $NaBH_4$ takes place, in ether or dioxane [W4, GO2]. Under these conditions, halogen or acid groups remain unchanged. In the presence of $SnCl_2$ or $Cu(acac)_2$, reduction is also compatible with ketone, ester, amide, and nitrile groups [W4, C4]. Similarly, reduction of aromatic nitro compounds to amines by $KBH_4/Cu_2Cl_2/MeOH$ is compatible with Br and ester substituents, but I is reduced [HZ1].

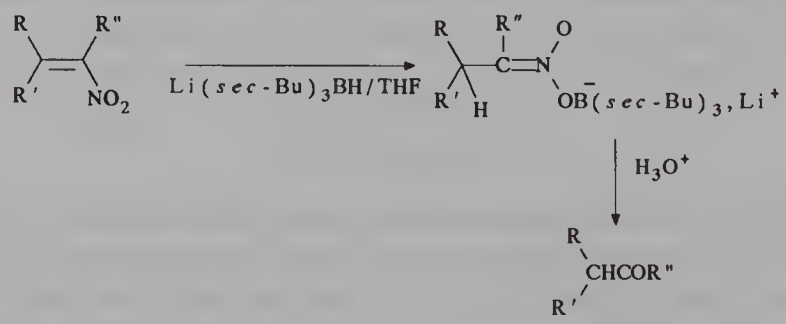


Primary and secondary aliphatic or aromatic nitro derivatives can also be reduced to amines by $NaBH_4$/THF in the presence of palladium on charcoal [PB1]. The reduction is compatible with ester and nitrile groups and also with chloride derivatives, but bromo aromatic derivatives are reduced under these conditions:





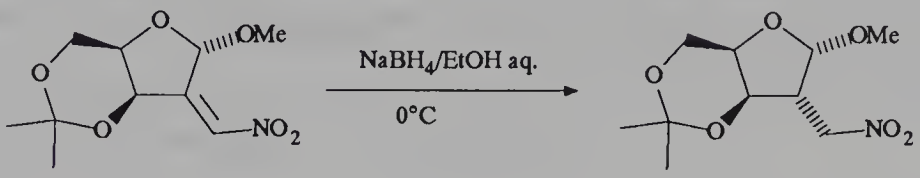
α,β-Ethylenic nitro derivatives are converted to saturated nitro ones by reaction with $NaBH_4$ or $NaCNBH_3$ in alcohol media or in THF-MeOH [VK3] or even with Li(*sec*-Bu)$_3$BH or LiEt$_3$BH/THF [MV1]. Treatment in an acid medium allows access to the corresponding ketones.



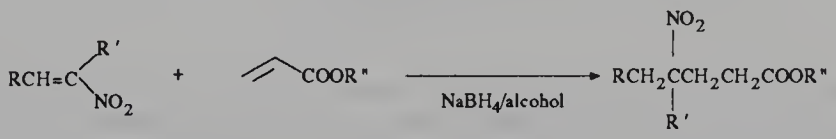
In the case of nitrostyrenes, one also obtains polymeric products: the formation of these by-products is avoided if the reaction is carried out on SiO_2 in $CHCl_3$/*i*-PrOH [SB2].

$$PhCH{=}CHNO_2 \xrightarrow[NaBH_4/SiO_2/CHCl_3/i\text{-}PrOH]{} PhCH_2CH_2NO_2$$

The reduction can be stereoselective as shown in the following example [NS2]:



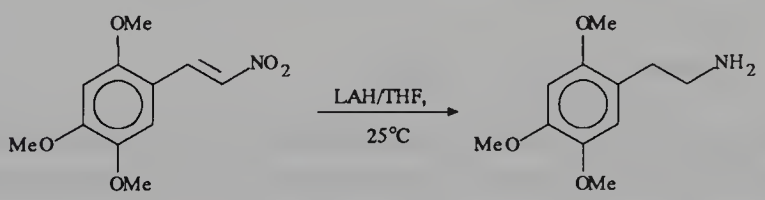
Finally, it is possible to trap in situ the carbanion formed during the reduction of α,β-ethylenic nitro derivatives by an acrylate: γ-nitroesters are thus obtained.



Reduction of the same compounds by LAH or BH_3/THF in the presence of catalytic amounts of $NaBH_4$ leads, on the other hand, to saturated primary amines [VK2, MV2].

$$RCH{=}CHNO_2 \xrightarrow[NaBH_4\ cat.]{LAH\ or\ BH_3/THF,} RCH_2CH_2NH_2$$

Similarly, LAH/THF [KS4] or $NaBH_4$/Me_3SiCl/THF [GS2] allows the reduction of an α,β-ethylenic aromatic nitro derivative to saturated amine.



4.2. AZIDES : RN_3, ArN_3

The RN_3 and ArN_3 derivatives are reduced to amines by LAH in ether media [S1]:

$$RN_3 \xrightarrow[LAH]{} RNH_2$$

$$ArN_3 \xrightarrow[LAH]{} ArNH_2$$

$NaBH_4$ in alcohol or in THF reduces the azides with difficulty except for certain sugars [S1] and $ArOSO_2N_3$, which give sulfoxamides ($ArOSO_2NH_2$) [HG1]. Nevertheless, under phase transfer conditions, reduction of the aryl derivatives by $NaBH_4$ takes place at room temperature, and that of alkyl azides at 80°C [R1]. Such a reduction can be carried out with borohydride supported on an ion-exchange resin [KW2]. In a similar fashion, arylsulfonylazides are converted into arylsulfonamides [KW2].

$$ArN_3 \xrightarrow[25°C]{NaBH_4\,(aq)/toluene/PTC} ArNH_2$$

$$RN_3 \xrightarrow[80°C]{NaBH_4\,(aq)/toluene/PTC} RNH_2$$

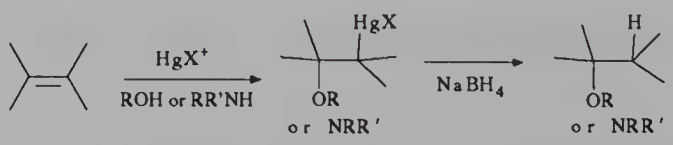
$NaBH_4$/THF under reflux in the presence of MeOH also reduces the primary aliphatic or aromatic azides to amines. The reduction is compatible with Cl and NO_2 substituents on the aromatic ring, which remain unchanged [SY3]. Aliphatic secondary azides are not reduced under these conditions.

4.3. ORGANOMETALLICS

Reduction by hydrides of two types of organometallic has received some synthetic applications: this is why only these cases are discussed.

4.3.1. Organomercurials: RHgX

Solvomercuration and aminomercuration reactions from unsaturated compounds have been the topic of many studies. Organomercurials thus formed, when treated by alkali borohydrides in alcoholic media or by LAH in ether, are reduced to saturated functionalized compounds [WS, R2].



The mechanism of the reduction implies the formation of an intermediate metal hydride, which undergoes homolytic cleavage and starts a chain reaction:

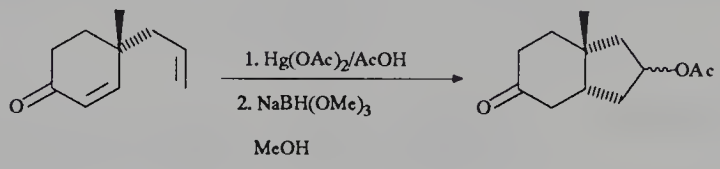
$$RHgX \xrightarrow{NaBH_4} RHgH$$

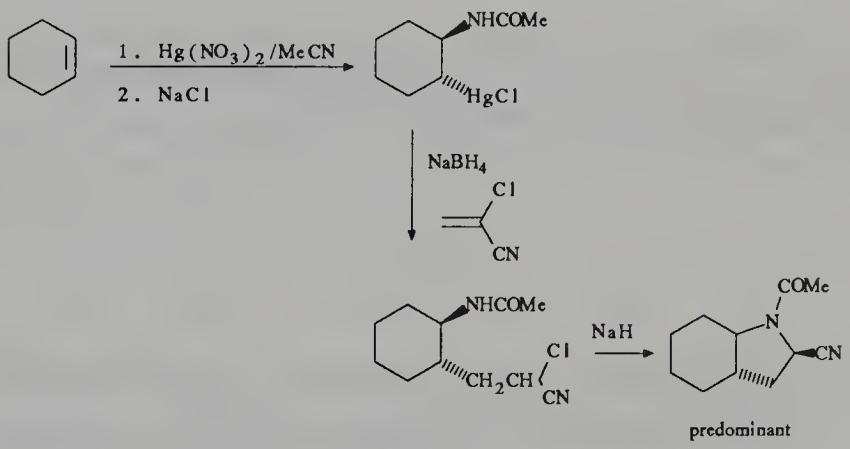
$$RHgH \longrightarrow RHg^{\bullet} + H^{\bullet}$$

$$RHg^{\bullet} \longrightarrow R^{\bullet} + Hg^{0}$$

$$R^{\bullet} + RHgH \longrightarrow RH + RHg^{\bullet}$$

The radicals formed during reductions can also be trapped by α,β-unsaturated compounds [G2]:





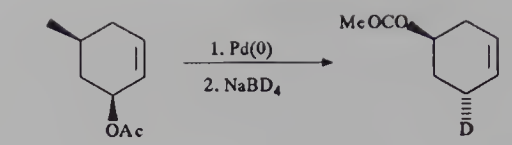
Alkylmercurials can also be generated from cyclopropanes.

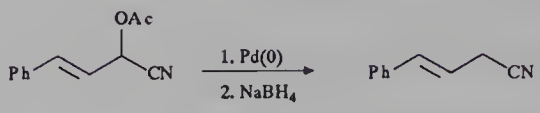
These reductions are compatible with $P(O)(OEt)_2$, COOEt, CN, SO_2Ph, and $SiPh_3$ groups [RJ1].

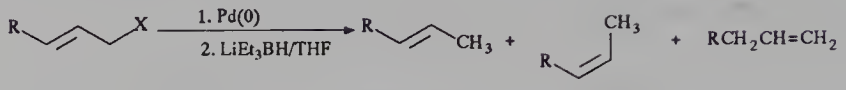
Vinylmercurials can be reduced to alkenes, but a mixture of (*Z*) and (*E*) isomers is obtained [RJ1].

4.3.2. Palladium Complexes

Complexes of π-allylpalladium formed by reaction with Pd (0) complexes on allylic derivatives can be reduced in a regio- and stereoselective fashion by $NaBH_4$ or $LiEt_3BH$/THF to the corresponding alkene derivatives, as shown in the following examples [KR1, HL1, ME1].



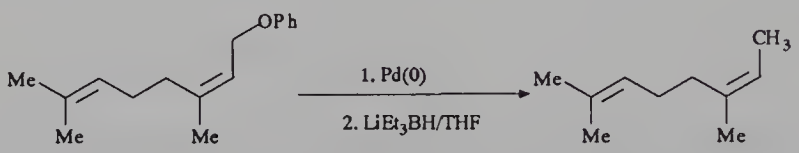




X =			
OPh	97	3	<1
OCH_3	94	3	3
SPh	94	5	1
SO_2Ph	86	13	1
$OSiMe_2t$-Bu	98	1	1

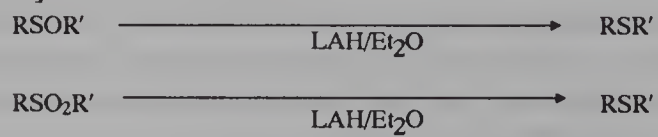
Reductions in which X is a different group (halogen, OCOR′, etc.) are less selective; the same is true of reactions performed with LAH or NaCNBH3 [HL1].

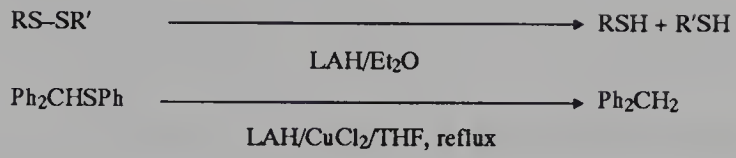
The method preserves the isolated double bonds:



4.4. SULFIDES, THIOETHERS, SULFOXIDES, AND SULFONES: RSR′, RSOR′ or RSO_2R'

LAH or AlH_3 in an ether medium, as well as $NaBH_4/Me_3SiCl$/THF [GS2], reduces the sulfoxides and sulfones to sulfides and the disulfides to thiols [HUD, BY1, M4], just as DIBAH/hot toluene [HUD, YG1, M3, M4] or nickelocene-LAH do [CC2]. Diaryl or dialkyldisulfides are converted to thiols by LTBA/THF at room temperature [KA3, M3]; the reduction is faster with diaryl compounds and is compatible with MeO, Cl, and CN substituents. In the presence of copper salts, desulfurization takes place under heating, and the corresponding hydrocarbons are obtained [GO2]. In the presence of $NiBr_2$, such total reduction also takes place [HL2].





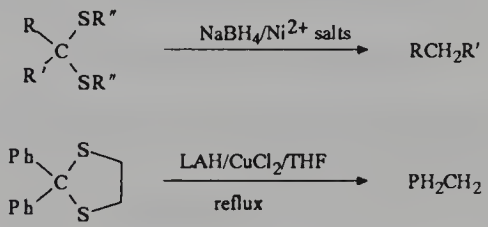
Sulfones and sulfoxides are not affected by borohydrides in alcohol media [RJ1] except in the presence of transition metal salts such as $FeCl_2$, $CoCl_2$, or $TiCl_4$ [CH3, W4, LZ1, GO2]. The sulfides obtained are not reduced under these conditions but are desulfurized in the presence of the Ni^{2+} salts [GO2].

$$RSOR' \xrightarrow[Fe^{3+},\ Co^{2+},\ or\ Ti^{4+}salts]{NaBH_4/EtOH} RSR'$$

Another possibility is to treat the sulfones with $NaCNBH_3$/MeOH. Such a reduction takes place via the sulfoxonium salt [PS1].

$$RSOR' \xrightarrow[NaCNBH_3/MeOH,\ 0°C]{} RS^+(OMe)R' \longrightarrow RSR'$$

Reductive desulfurization of the dithioketals is performed under the same conditions as those for thioethers [GO2]: LAH in the presence of copper salts or borohydrides in the presence of nickel salts.

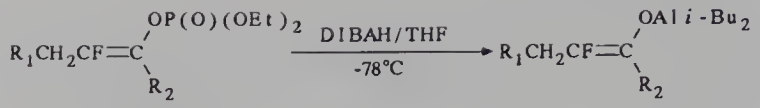


4.5. PHOSPHINE OXIDES AND PHOSPHATES: R_3PO and $\geq C—O—P\leq$

Phosphine oxides are reduced to corresponding phosphines by LAH/$CeCl_3$/THF [GO2].

$$RR'R''PO \rightarrow RR'R''P$$

Phosphates are cleaved by LAH/THF to corresponding alcohols [JF1], while enol phosphates are converted into carbonyl compounds. However, when using LAH-$CuBr_2$ or DIBAH [IK3], it is possible to generate the corresponding aluminum enolates:



4.6. SILYL DERIVATIVES: $\rangle$Si—X[†]

The silicon–halogen, silicon–oxygen, and silicon–sulfur bonds of the halogenosilanes, silyl ethers, and silyl thioethers are cleaved by reaction with LAH, AlH_3, or DIBAH: the corresponding silyl hydrides are obtained. Ultrasound activation can be applied [LG2].

$$\rangle\text{Si—X} \xrightarrow[\text{X = F, Cl, Br, I, OR, SR}]{\text{LAH, AlH}_3\text{ or DIBAH}} \rangle\text{Si—H}$$

Anionic pentacoordinated silicon compounds are reduced to hydrogenosilanes by LAH or DIBAH [BC6].

A study focusing on the stereochemistry of reduction has been carried out on molecules chiral at silicon. Depending on the Lewis acid character of the reducing agent and the nature of the X group, one observes more or less retention or inversion of configuration at the silicon atom. For the same leaving group, the amount of retention increases as the Lewis acid character of the reducing reagent increases:

DIBAH/hexane > DIBAH/Et_2O > DIBAH/THF > AlH_3/Et_2O > LAH/Et_2O

> LAH/THF > LAH/THF/[2.1.1]

For the same reducing agent, the degree of configuration retention becomes higher as the X group becomes harder:

RO > F, SR > Cl,Br

A theoretical interpretation of these results has been suggested [CG1,CG2].

4.7. BORON DERIVATIVES

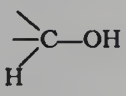
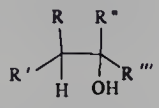
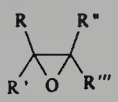
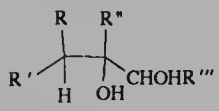
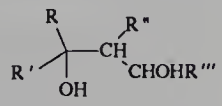
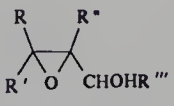
B—Cl and B—Br bonds are converted to B—H bonds by LAH in stoichiometric amounts or K(*i*-PrO)$_3$BH [BC3]. LAH also converts boronates RB(OR')$_2$ into -ate complexes $Li^+RBH_3^-$, which are cleaved into corresponding alkylboranes by Me_3SiCl [BJ5].

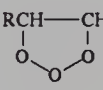
If the R alkyl group is chiral, its configuration is retained.

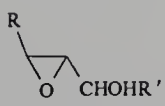
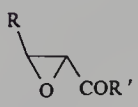
[†][CG1, CG2]

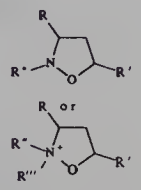
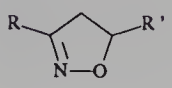
PART III

SYNOPTIC TABLES

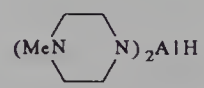
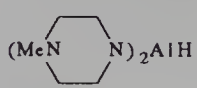
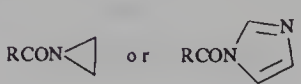
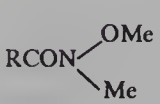
Products	Substrates	Reference (Part II)	Reagents
	ALCOHOLS: 		
		§1.3	LAH; AlH_3; DIBAH; $NaCNBH_3/BF_3$; $LiBH_4/BEt_3$; BH_3/BF_3; $LiBEt_3BH$; Li 9-BBNH
 and/or			
		§1.3	Red-Al; LAH; DIBAH; $LiBH_4$/Ti salt
ROH	$ROSiMe_3$	§1.4.2	LAH; $LiAl(OR)_{4-n}H_n$; MBH_4
RCH_2OH	RCHO	§2.2.1 §2.2.2	LAH; $LiAl(OR)_{4-n}H_n$; AlH_3; Red-Al; R_3BH; $BH_3{\cdot}R_3N$, THF or Me_2S; $MCNBH_3$/acid; MBH_4; $(Ph_3)_2CuBH_4$/acid
$RCH{=}CHCH_2OH$	$RCH{=}CHCHO$	§2.2.8	$NaBH_4$/alcohols; LAH; $MCNBH_4$/acid; AlH_3; DIBAH; Red-Al; $BH_3{\cdot}Me_2S$
RCH_2OH	RCOOR′ or lactones	§2.2.4	LAH; AlH_3; $LiBH_4$ (under heating); LiR_3BH; $NaBH_4$/MeOH or other additives; $BH_3{\cdot}Me_2S$ (under warming); 9-BBN and ThexBHCl (under warming); Li 9-BBNH; $Ca(BH_4)_2$

Products	Substrates	Reference (Part II)	Reagents
RCH=CHCH$_2$OH	RCH=CHCOOR′	§2.2.8	DIBAH; LAH/Et$_2$O; AlH$_3$
RCH=CHCH$_2$OH	RC≡COOR′	§3.2	Red-Al/CuBr
RCHOHCHOHR′		§1.4.4	LAH; NaBH$_4$; BH$_3$•Me$_2$S
RCH$_2$-CH$_2$CH$_2$OH	RCH=CHCOOR′	§2.2.8	LAH/THF
RCH$_2$OH	RCOOH or (RCO)$_2$O	§2.2.5	LAH; AlH$_3$; Red-Al (under heating); LiBH$_4$/hot MeOH; BH$_3$•THF or NR$_3$; LiBH$_4$ + Me$_3$SiCl
RCH$_2$OH	RCOOCOOEt	§2.2.5	NaBH$_4$
RCH=CHCH$_2$OH	RCH=CH-COOCOOEt	§2.2.5	NaBH$_4$/SmI$_3$/THF
RCH$_2$OH	RCOCl	§2.2.6	LAH; AlH$_3$; DIBAH; MBH$_4$; 9-BBN; Zn(BH$_4$)$_2$
RCH$_2$OH	RCONR′$_2$	§2.2.7	LiR$_3$BH; 9-BBN; Sia$_2$BH; LiBH$_4$/hot MeOH
RCHOHR′	RCOR′	§2.2.1 §2.2.2 (stereo-selectivity)	LAH; LiAl(OR)$_{4-n}$H$_n$; AlH$_3$; Red-Al; MBH$_4$; BH$_3$•THF, R$_3$N or Me$_2$S; MR$_3$BH; MCNBH$_3$/acid; NaBH$_4$/CeCl$_3$/MeOH
RCH=CH-CHOHR′	RCH=CH-COR′	§2.2.8	LAH/Et$_2$O; AlH$_3$; DIBAH; LiAlH(OMe)$_3$; Red-Al; Zn(BH$_4$)$_2$; NaCNBH$_3$/ZnCl$_2$; BH$_3$•Me$_2$S; 9-BBN; NaBH$_4$/CeCl$_3$/MeOH

Products	Substrates	Reference (Part II)	Reagents
$RCH{\equiv}C\text{-}CHOHR'$	$RC{\equiv}C\text{-}COR'$	§2.2.2 (stereo-selectivity) §3.2	LAH; $LiAl(OR)_{4-n}H_n$; DIBAH; $MCNBH_3$/ acid; LAH + ligand
$RCHOHCO\begin{vmatrix}OR'\\NR'_2\end{vmatrix}$ and $RCHOHCHCO\begin{vmatrix}OR'\\NR'_2\end{vmatrix}$ (R'')	$RCOCO\begin{vmatrix}OR'\\NR'_2\end{vmatrix}$ and $RCOCHCO\begin{vmatrix}OR'\\NR'_2\end{vmatrix}$ (R'')	§2.2.2 §2.2.3 (stereo selectivity)	BH_3*t*-$BuNH_2$; DIBAH; M(*sec*-Bu)$_3$BH; Red-Al; LAH; $Zn(BH_4)_2$ $LiEt_3BH$
		§2.2.2 §2.2.3 (stereo-selectivity)	$Zn(BH_4)_2$; MBH_4; $NaBH_4/CeCl_3$
$R'CHCHOHR''$ RO; $R'CHCHCHOHR''$ RO R''	$R'CHCOR''$ RO; $R'CHCHCOR''$ RO R''	§2.2.3 (stereo-selectivity)	$Zn(BH_4)_2$; LAH; Red-Al; DIBAH; M(*sec*-Bu)$_3$BH; $NaBH_4$ (+$RBEt_2$); $R_4N^+B^-H(OAc)_3$
$RCHOHCHCHOHR'$ R''	$RCOCHCOR'$ R''	§2.2.3 (stereo-selectivity)	LTBA (with or without $TiCl_4$); $NaBH_4/CeCl_3$; $LiEt_3BH$
$RCHOHCH_2SOTol$	$RCOCH_2SOTol$	§2.2.3 (stereo-selectivity)	DIBAH (with or without $ZnCl_2$); LAH
$RCHOHCH_2P(O)Ph_2$	$RCOCH_2P(O)Ph_2$	§2.2.3 (stereo-selectivity)	$NaBH_4$ (with or without $CeCl_3$)
$RCHCHOHR'$ $R_2'N$; $RCHCHOHR'$ $R_2'N$ R'''	$RCHCOR'$ $R_2'N$; $RCHCHOHR'$ $R_2'N$ R'''	§2.2.3 (stereo-selectivity)	LAH; LTBA; MBH_4
$RCHCH_2OH$ NH_2	$RCHCOOR'$ $NSiMe_3$	§2.3.1	LAH

Products	Substrates	Reference (Part II)	Reagents
RCHCHOHAr NHR′	RCCHOHAr NR′	§2.3.1 (stereo-selectivity)	$Zn(BH_4)_2$
RCHCH$_2$CHOHR′ R″$_2$N		§2.2.3	LAH; LAH/$NiCl_2$
RCHCH$_2$CHOHR′ NH$_2$		§2.2.3	LAH

ALDEHYDES RCHO

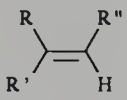
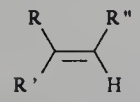
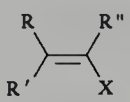
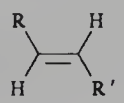
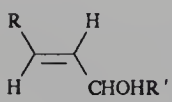
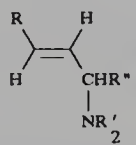
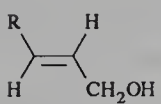
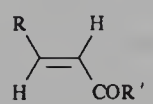
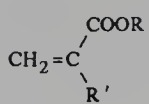
RCHO	RCOOPh	§2.2.4	LTBA
RCHO	RCOOEt	§2.2.4	LAH/Et_2NH/pentane or  DIBAH
RCH═CH-CHO	RCH═CH-COOEt	§2.2.4	LAH/Et_2NH/pentane
RCHO	RCOOH	§2.2.5	 ThexBHCl
RCHO	RCOCl	§2.2.6	LTBA; DIBAH; $NaBH_4$/DMF/pyridine; $NaBH_4/CdCl_2$/DMF; $(Ph_3P)_2CuBH_4$; $(Ph_3P)_2CuCNBH_3$
RCHO		§2.2.7	LAH; Red-Al
RCHO		§2.2.7	LAH; DIBAH
RCH═CHCHO		§2.2.7	DIBAH
RCHO	RCONR′$_2$	§2.2.7	LTEA; LiR3BH

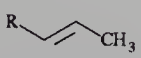
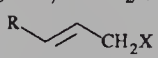
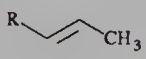
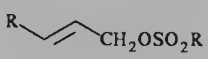
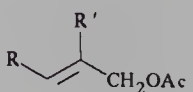
Products	Substrates	Reference (Part II)	Reagents
RCH_2CH_2CHO	$RCH{=}CHCHO$	§2.2.8	DIBAH/MeCu
$RCH_2\underset{\displaystyle R'}{\underset{\vert}{C}}HCHO$	$RCH{=}CH\text{-}CHO$	§2.2.8	DIBAH/MeCu/R'X
RCHO	RCN	§3.3	LTEA; DIBAH; $NaEt_2AlH_2$/Lewis acid
RR'R"CCHO	RR'CHCN	§3.3	DIBAH/LDA/R"X
$RCH{=}CH\text{-}CHO$	$RCH{=}CH\text{-}CN$	§3.4	DIBAH
AMINES (Amino Alcohols: see Alcohols) Primary: $R\text{-}NH_2$			
RCH_2NH_2	$RCONH_2$	§ 2.2.7	LAH; AlH_3; Red-Al; BH_3•THF;$NaBH_4$/hot acid; $LiBH_4$/diglyme/ MeOH; MBH_4/Me_3SiCl
$RR'CHNH_2$	R'C=NOH	§2.3.4	LAH; $NaBH_4/NiCl_2$ or $ZrCl_4$; $NaBH_4/CF_3COOH$/ diglyme (under heating); $NaCNBH_3/TiCl_4$
$RCHNH_2$ COOR'	$RCH{=}NOH$ COOR'	§2.3.4	$NaCNBH_3/TiCl_4$
$RCH{=}CH\text{-}CHR'$ NH_2	$RCH{=}CH\text{-}C\text{-}R'$ NOH	§2.3.4	$NaBH_4/MoO_3$
RCH_2NH_2	RCN	§3.3	LAH; AlH_3; BH_3; $NaBH_4/CoCl_2$;$NaBH_4$/ acid; RedAl (under heating);$LiBH_4$/diglyme/ MeOH; $LiBEt_3H$
$RCH{=}CHCH_2NH_2$	$RCH{=}CHCN$	§3.4	$NaBH_4/CoCl_2$
$RCH_2CH_2CH_2NH_2$	RCH=CHCN	§3.4	LAH
$RCHNH_2$ COOR'	$RC{=}NSiMe_3$ COOR'	§2.3.1	$NaCNBH_3$/MeOH; $NaBH_4$/MeOH; $Me_2NH{\bullet}BH_3$/MeOH

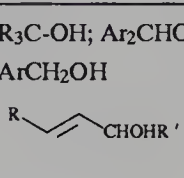
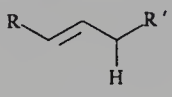
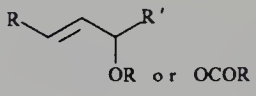
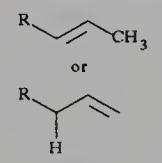
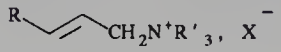
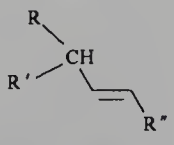
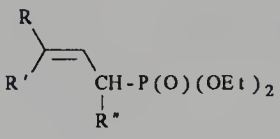
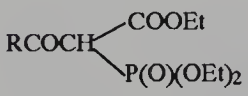
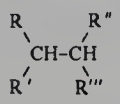
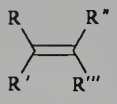
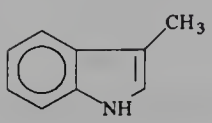
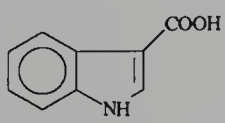
Products	Substrates	Reference (Part II)	Reagents
$RCH{=}CHCHR'$ NH_2	$RC{\equiv}CCHR'$ NH_2	§3.1	LAH; Red-Al
$RCHCH_2CHOHR'$ NH_2	$RCCH2CHOHR'$ $\|\|$ $NOCH_2Ph$	§2.3.4 (stereo-selectivity)	LAH
RNH_2	RNO_2	§4.1	$LiBH_4$/diglyme/hot MeOH; $NaBH_4$/transition metal salts or Pd/C
$RCH_2CH_2NH_2$	$RCH{=}CHNO_2$	§4.1	LAH; BH_3; $NaBH_4/Me_3SiCl$
RNH_2	RN_3	§4.2	LAH; $NaBH_4$/THF/hot MeOH; $NaBH_4$/PTC

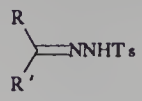
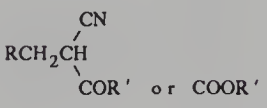
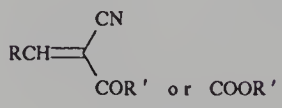
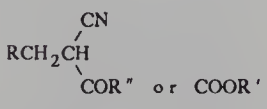
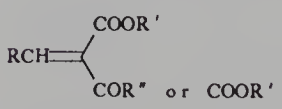
Secondary and Tertiary: RNHR′ and RNR′R″

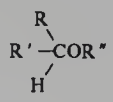
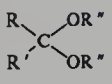
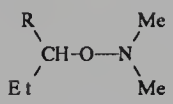
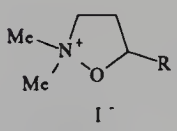
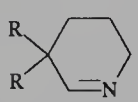
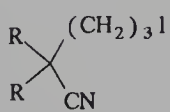
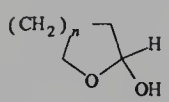
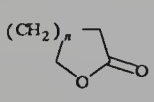
Products	Substrates	Reference (Part II)	Reagents
$RCH_2NR'R''$	$RCONR'R''$	§2.2.7	LAH; AlH_3; Red-Al; DIBAH; $LiBH_4$ (under heating); MBH_4/hot acid; $BH_3{\cdot}THF$; $NaBH_4/Me_3SiCl$
$RCH{=}CHCH_2NR'R''$	$RCH{=}CHCONR'R''$	§2.2.7 §2.2.8	DIBAH
RCH_2NHR'	$RCH{=}NR'$	§2.3.1 (stereo-selectivity)	LAH; Red-Al; MBH_4/acid; MR_3BH; BH_3; $MCNBH_3$
$RCH{=}CHCH_2NHR'$	$RCH{=}CH\text{-}CH{=}NR'$	§2.3.1	$NaBH_4$/MeOH
$RCH_2CH_2NR'R''$	$RCH{=}CH\text{-}NR'R''$	§2.3.2	AlH_3; MBH_4/acid; $MCNBH_3$/acid; BH_3/acid
$RCH_2NR'R''$	$RCHO + HNR'R''$	§2.3.1	$MCNBH_3$; $NaBH_4$/acid
RNR'_2	RNH_2	§2.2.7	$NaBH_4$/acid
$RN(R')CH_3$	$RN(R')COOR''$	§2.2.7	LAH; $NaBH_4$/acid
$RR''CHNR''_2$	$RR'C(CN)(NR''_2)$	§2.3.1	LAH; $NaBH_4$; $Zn(BH_4)_2$; AlH_3
$RCH{=}CHCHR'$ NR''_2	$RC{\equiv}CCHR'$ NR''_2	§3.1	LAH; Red-Al

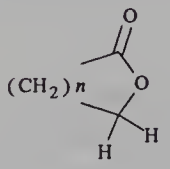
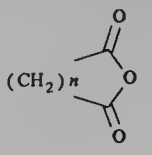
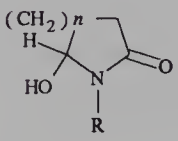
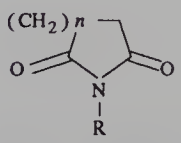
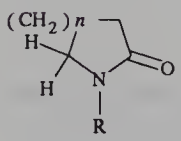
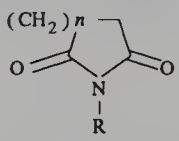
Products	Substrates	Reference (Part II)	Reagents
RR′R″N	RR′R″N$^+$MeX$^-$	§1.5	LAH; $LiEt_3BH$
Nitrogen Heterocycles: see §2.3.3			
UNSATURATED DERIVATIVES:  or RC≡CH or ArH			
		§1.1	LAH; $NaBH_4$/transition metal salt; LAH + $CeCl_3$
	RC≡CR′	§3.1	LAH (under heating)
	RC≡C-CHOHR′	§3.1	LAH; Red-Al
	RC≡C-CHR″ 	§3.1	LAH, Red-Al
	RC≡C-COOEt	§3.2	LAH
	RC≡C-COR′	§3.2	DIBAH/MeCu; DIBAH/HMPT if R = H
	HC≡CCOOR	§3.2	DIBAH + R′X
RCH═CHCOOR′	RC≡C-COOR′	§3.2	DIBAH/MeCu; Red-Al/CuBr
RCH═CH-CN	RC≡CCN	§3.3	LAH; $NaBH_4$/MeOH
RCH═CHS(O)R′	RC≡CS(O)R′	§3.1	DIBAH; LAH/THF
RC≡C-H	RC≡C-X	§1.1	Red-Al; LAH + $CeCl_3$

Products	Substrates	Reference (Part II)	Reagents
Ar-H	Ar-X	§1.1	LAH; Red-Al; $NaBH_4$/DMF/*hν*; $NaBH_4$;/transition metal salts
		§1.1	LAH; Red-Al; $NaBH_4$;/DMF (X = Br)
SATURATED DERIVATIVES: —C—H			
RCH_3 or RCH_2R'	RCH_2Cl or $RR'CHCl$	§1.1	LAH; Red-Al; $LiEt_3BH$; $NaCNBH_3$
RCH_3 or RCH_2R'	RCH_2OSO_2R or $RR'CHOSO_2R$	§1.2	LAH; $LiBH_4$; $LiEt_3BH$; DIBAH; $NaBH_4$/hot DMSO
RCH_3 or RCH_2R'	RCH_2Br or $RR'CHBr$	§1.1	LAH; Red-Al; LTBA; $NaBH_4$/hot DMSO or DME; $LiEt_3BH$; $NaCNBH_3$; *n*-$Bu_4N^+CNB^-H_3$
RCH_3 or RCH_2R'	RCH_2I or $RR'CHI$	§1.1	LAH; Red-Al; LTBA; $LiEt_3BH$; $NaCNBH_3$; *n*-$Bu_4N^+CNB^-H_3$
R_3CH $ArCH_3$ 	R_3C-X; $ArCH_2X$ 	§1.1	LAH; $NaBH_4$/alcohols; BH_3/CF_3COOH; $Zn(BH_4)_2$; $NaCNBH_3/ZnI_2$ or $SnCl_2$; 9-BBN•BuLi
$RC{\equiv}CCH_3$	$RC{\equiv}CCH_2X$	§1.1	Li 9-BBNH
$R_2C{=}C{=}CH_2$	$R_2C(Cl)C{\equiv}CH$	§1.1	LAH
		§1.2	LAH; AlH_3
RCH_2CHCH_3 R′		§1.2	$NaBH_4/NiCl_2$

Products	Substrates	Reference (Part II)	Reagents
R_3CH; Ar_2CH_2 $ArCH_3$ $RCH{=}CHCH_2R'$	R_3C-OH; Ar_2CHOH $ArCH_2OH$ 	§1.4.1	$NaBH_4/CF_3COOH$ or CF_3SO_3H; AlH_3; $NaBH_4/AlCl_3$; $NaBH_4/ZnI_2$
		§1.4.2 §4.3.2	$NaBH_4/NiCl_2$; Pd(0)/$NaBH_4$ or $LiEt_3BH$
$ArCH_3$	$ArCH_2N^+Me_3$, X^-	§1.5	$NaCNBH_3$
		§1.5	LAH; Red-Al; $NaBH_4$/alcohols
		§1.6	LAH
$RCOCH_2COOEt$		§1.6	LTBA
$PhCH_3$	$PhCH_2P^+R_3$, X^-	§1.6	LAH
		§2.1	$NaBH_4/CoCl_2$; $LiEt_3BH$
$ArCH_2R$	$ArCOR$	§2.2.1	$NaBH_4$/acid; $LAH/AlCl_3$; $NaBH_4/AlCl_3$; $NaBH_4/ZnI_2$; $NaBH_4/PdCl_2$; t-$BuNH_2{\cdot}BH_3/AlCl_3$
		§2.2.5	$BH_3{\cdot}THF$

Products	Substrates	Reference (Part II)	Reagents
RCH_2R'		§2.3.4	$NaBH_4$/RCOOH; BH_3/RCOOH; $NaCNBH_3$/RCOOH or $ZnCl_2$; $NaBH_4$/alcohol; $(Ph_3P)_2CuBH_4$ in a few cases
RCH_2CH_2R'	$RC{\equiv}CR'$	§3.1	$NaBH_4$/transition metal salts
RCH_2CH_2COR'	$RCH{=}CHCOR'$	§2.2.8	Red-Al/CuBr; DIBAH/MeCu; Li and K(*sec*-Bu)$_3$BH; LTBA; $NaBH_4$/resin; LAH/nickelocene
RCH_2CH_2COOR'	$RCH{=}CHCOOR'$	§2.2.8	Red-Al/CuBr; LiAl-$(OMe)_3H$/CuBr; $LiEt_3BH$; DIBAH/MeCu; $NaBH_4$/resin; $NaBH_4/Cu_2Cl_2$
$RCH_2CH_2CONR'_2$	$RCH{=}CHCONR'_2$	§2.2.8	Li and K(*sec*-Bu)$_3$BH
RCH_2CH_2CN	$RCH{=}CHCN$	§3.4	LAH in a few cases; Red-Al/CuBr
		§3.4	$NaBH_4$
		§2.2.8	$NaBH_4$; $NaBH_3CN$
$RCH_2CH_2NO_2$	$RCH{=}CHNO_2$	§4.1	$NaBH_4$/alcohol; $NaCNBH_3$/alcohol; $LiEt_3BH$
RH	RSH	§4.4	LAH/Cu^{2+} salts MBH_4/ Ni salts
RH	RHgX	§4.3.1	$NaBH_4$; $NaB(OMe)_3H$

Products	Substrates	Reference (Part II)	Reagents
ETHERS			
		§1.4	LAH/$TiCl_4$; DIBAH under heating; AlH_3; BH_3; $AlBr_2H$; $AlCl_2H$; $ClBH_2{\cdot}Me_2S$; $NaBH_4$ or $NaCNBH_3$/acid; $Zn(BH_4)_2/Me_3SiCl$ or $TiCl_4$
HYDROXYLAMINES: RNHOH			
RCH_2NHOH	RCH═NOH	§2.3.4	BH_3; $NaBH_4$/RCOOH; $NaCNBH_3$/RCOOH
		§2.3.3	LAH
HYDRAZINES			
RCH_2NHNHR'	RCH═N-NHR'	§2.3.4	LAH; BH_3
$RCH_2NHNHTs$	RCH═NNHTs	§2.3.4	BH_3/pyridine
IMINES			
$RCH{=}NSiMe_3$	RCN	§3.3	$Li(OEt)_3AlH$, then Me_3SiCl
		§3.3	DIBAH/THF
LACTOLS, LACTONES; LACTAMS			
		§2.2.4	DIBAH

Products	Substrates	Reference (Part II)	Reagents
		§ 2.2.5	LAH in calc. amounts; $LiBH_4$; $NaBH_4$/THF/MeOH or DMF; MR_3BH; DIBAH/*n*-BuLi
		§ 2.2.7	$NaBH_4/H^+$; DIBAH
		§ 2.2.7	Red-Al
	PHENOLS		
ArOH	ArOMe	§ 1.4.2	DIBAH

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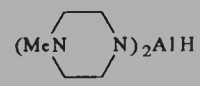
INDEX

Reductions by the principal reagents are listed (the case involved and compatibility with other functional groups are shown in parentheses).

AMINE-BORANES

BIS(METHOXYETHOXY)ALUMINO HYDRIDE, SODIUM: Red-Al

BIS(*N*-METHYL-PIPERAZINO)HYDRIDE, ALUMINUM:



9-BORABICYCLO [3.3.1] NONANE: 9-BBN

9-BORABICYCLO [3.3.1] NONANE, LITHIUM: Li 9-BBNH

BORANE: BH_3

in ethers

BORANE IN THE PRESENCE OF ORGANIC ACID AND ACYL-BORANES

BOROHYDRIDE, BISTRIPHENYL-PHOSPHINE, CUPROUS: $(Ph_3P)_2CuBH_4$

BOROHYDRIDE, LITHIUM: $LiBH_4$

in ethers

in ether + methanol

TRI(*sec*-BUTYL)BOROHYDRIDE, POTASSIUM: K(*sec*-Bu)$_3$BH

TRI(*t*-BUTOXY)ALUMINO-HYDRIDE, LITHIUM: LTBA

Reductions by the Alumino- and Borohydrides in Organic Synthesis

J. Seyden-Penne
Université de Paris-Sud

Prompted by the interest of researchers confronted with reduction problems, this easy-to-use guide allows the reader to select, given the synthetic goal, the right reagent for the desired reduction employed in organic synthesis.

Initiated by a preparatory Ph.D. course given at Orsay for many years, topics given special emphasis in this work include: • the compatibility between the reduction of the group in question and the other functional groups which are present in the molecule • the possibility of partial reduction • the regio- and stereo selectivity of reductions included in particular by other neighboring groups. It also includes a foreword by Nobel Laureate H.C. Brown.

Three convenient sections cover: • the enumeration of the most useful reagents, indicating the stability and solubility characteristics as well as their principal applications • reactivity of the functional groups towards reducing reagents with special reference to problems of stereochemistry and compatibility • access by hydride reduction of the main functions groups of organic chemistry in the form of synoptic tables. This practical new book will be and important reference for those involved in organic, medicinal and pharmaceutical chemistry.

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