

1.4

Reduction of C=X to CHXH by Dissolving Metals and Related Methods

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1.4.1 INTRODUCTION

Dissolving metals have been used as reducing agents in organic synthesis for well over a century and for many years metal–alcohol or metal amalgam–water systems were the principal methods employed for the reduction of aldehydes and ketones to primary and secondary alcohols, respectively. The same reagents were employed for the reduction of imines and oximes to the corresponding amines. Catalytic hy-

drogenation was the only viable alternative to dissolving metal reductions until the development of the Meerwein–Ponndorf–Verley reduction in the mid 1920s and the introduction of complex metal hydrides in the years following World War II.

Although complex metal hydrides have, to a large extent, replaced dissolving metal systems for the reduction of carbonyl compounds and their derivatives, dissolving metal reductions frequently offer advantages for the control of stereochemistry. In particular, the dissolving metal reduction of hindered cyclic ketones provides a highly stereoselective method for the preparation of equatorial alcohols, which are difficult to prepare by other methods. The prototype for this synthetic methodology was the nearly simultaneous observation that $Li-NH_3$ -alcohol¹ or Na -propanol² reduction of 11-keto steroids gives exclusively the equatorial 11 α -alcohol, while metal hydride reduction of these hindered ketones gives the axial 11 β -alcohol.

The stereochemical course of these, and other similar reductions, led Barton to suggest that dissolving metal reductions of ketones and oximes to secondary alcohols and primary amines would lead to mixtures of products rich in the thermodynamically more stable product.³ However, in the early 1960s a number of reports appeared in which the reduction of ketones gave primarily the thermodynamically less stable epimeric alcohol. These observations have prompted a continuing series of investigations into the mechanism of these reductions.

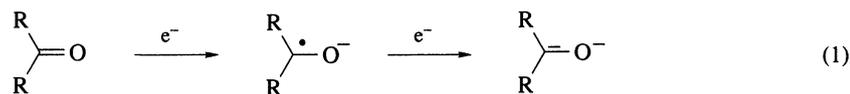
In contemporary organic synthesis, dissolving metal reductions still provide the most effective method for reducing hindered cyclic ketones stereoselectively to the more stable secondary alcohol, and in many cases are more stereoselective than complex metal hydrides for the reduction of unhindered cyclic ketones. These procedures also continue to be useful for the reduction of oximes and imines to the corresponding amines. Although many of the dissolving metal reductions employed in organic synthesis are carried out using either active metals (Li, Na, K) in liquid NH_3 , or the same metals in alcohols, a number of variations on these procedures have been developed, and several low-valent metal ions, most notably Sm^{2+} , have been found to give improved chemoselectivity. However, all of these reactions are mechanistically similar in that they proceed by initial addition of a single electron to the substrate to form a radical anion, the fate of which is determined by a complex set of variables. Among the more important of these variables are the structure of the substrate, the metal or metal ion used as reducing agent, and the solvent system.

1.4.2 MECHANISM OF CARBONYL REDUCTION

1.4.2.1 Early Mechanistic Studies

The overall transformation effected in the reduction of an aldehyde or a ketone to the corresponding alcohol by a dissolving metal is conceptually simple; however, the reaction is actually quite complex, and an evolving series of mechanisms has been suggested to explain the experimental observations. Historically, the reducing properties of dissolving metals were attributed to 'nascent hydrogen', but it is now recognized that these reactions proceed *via* single electron transfer (SET) reaction paths.

It was suggested in the 1950s that the reduction of aliphatic ketones by dissolving metals proceeded by two sequential one-electron additions to provide a dianion (equation 1). This mechanism was based on the observation that benzophenone affords a dianion on reaction with excess Na in liquid NH_3 , and it was inferred that aliphatic ketones would behave similarly. A number of workers presented mechanistic rationalizations for the stereochemical course of the dissolving metal reductions of cyclic aliphatic ketones based on this dianion concept. However, in a 1972 review, it was noted that the reduction potentials of alkali metals were not sufficient to effect the addition of two electrons to an aliphatic carbonyl group, and an alternative mechanism was suggested which with some modification is now generally accepted.⁴



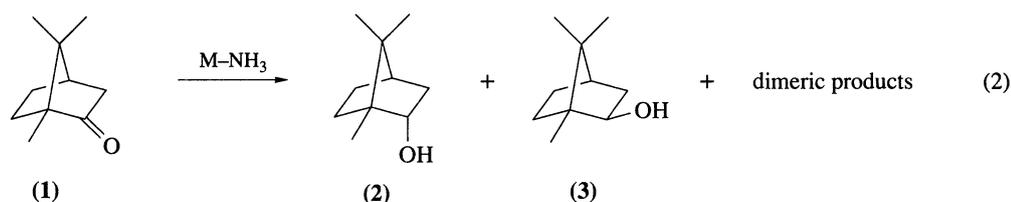
The contemporary view of these reductions recognizes that the reactions of carbonyl compounds with dissolving metals follow one of two general reaction paths. One of these prevails in reductions carried out in the absence of proton donors, the other in reductions in the presence of an alcohol or other proton source, frequently NH_4Cl . Two recent reviews present rather different mechanistic explanations for these reactions, particularly those in liquid NH_3 in the absence of added proton donors.^{5,6}

1.4.2.2 Reduction in the Absence of Proton Donors

For reductions carried out in the absence of an added proton donor the usual solvents are liquid NH₃, usually with an ethereal cosolvent, or less commonly an ether (THF, DME or diethyl ether). The reducing agent is usually one of the common alkali metals (Li, Na, K), although Rb, Cs and alkaline earth metals have also been used.⁴⁻⁶ At least in the case of camphor both types of solvent systems give similar ratios of epimeric alcohols; however, product ratios may vary as a function of the metal used as reducing agent.⁴⁻⁷ In reductions carried out in ethereal solvents the use of ultrasound increases the rate of the reaction, but does not affect the product distribution.⁷

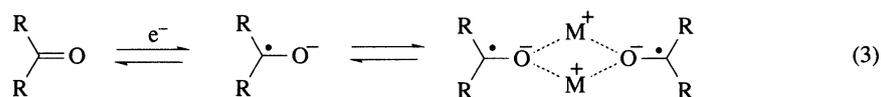
A number of experimental details have contributed to an understanding of the mechanism of reductions carried out under these conditions. Among the more important observations are the facts that ketones react with one and only one equivalent of alkali metal in NH₃; enolizable ketones afford equal amounts of enolate and alcohol, while nonenolizable ketones give metal ketyls which are stable at low temperature.^{5,7-9} Also, pinacol formation is a major reaction path with Li, but K affords little or no pinacol.^{5,10} Finally, α -deuterio ketones afford product alcohols in which deuterium has been transferred to the carbinol carbon of the product alcohol or alcohols.^{9,10}

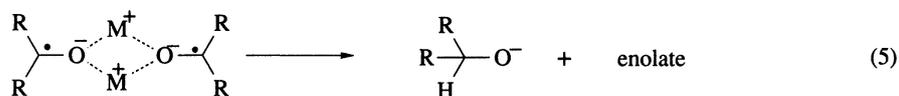
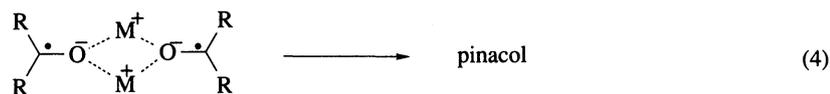
The substrate ketone which has been investigated most extensively is camphor (**1**; equation 2), both as one optical antipode (usually the (+)-enantiomer) and as the racemate. In addition to borneol (**2**) and isoborneol (**3**), reduction using Li-NH₃ or Li-THF gives up to 70% yield of dimeric reduction products, while Na-NH₃ gives 20%.¹¹ Pinacols are not usually obtained when K is used as the reducing agent. Although (+)-camphor can, in theory, afford three pinacols, only two, which correspond to *exo*-*endo* and *endo*-*endo* coupling have been isolated.^{10,12,13} A third dimeric reduction product which apparently arises by β -cleavage of an intermediate alkoxy radical has also been observed.¹³ Although the relative proportions of isomeric pinacols varies as a function of reaction conditions, the ratios of epimeric alcohols are apparently independent of the composition of the pinacol mixtures.¹³ For a detailed discussion of pinacol formation see Volume 3, Chapter 2.6.



It has been long known that different ratios of product alcohols (**2** and **3**) are obtained in the reduction of (+)-camphor with various metals in liquid ammonia. On the other hand, reduction of (\pm)-camphor with Li, Na or K in liquid NH₃ affords, within experimental error, the same 82:18 ratio of (**2**):(**3**). An explanation in terms of diastereomeric bimolecular reactions has been presented.¹⁴

On the basis of these observations and a variety of other experimental data, a mechanism has been suggested which in modified form is presented in equations (3) to (5).⁵ The first step (equation 3) is the reversible transfer of an electron to a carbonyl group, generating a metal ketyl, which may be in equilibrium with a dimer or higher aggregate, although not necessarily of the structure depicted. The position of the equilibrium for the addition of an electron to a carbonyl group is a function of the difference in reduction potential of the carbonyl group and the oxidation potential of the metal. Unfortunately the reduction potentials of aldehydes and ketones in liquid NH₃ are not known, but for the reaction of camphor with an alkali metal K_{eq} has been estimated, using reduction potentials in other solvents, to be 3.4×10^2 based on $\Delta V = 0.15$ V.⁷ The intervention of ketyl aggregates in these reactions was inferred from studies carried out on aromatic and nonenolizable aliphatic ketones.⁵ Regardless of the exact nature of the intermediate at this stage, it must be formed at a considerably greater rate than its subsequent irreversible conversion to products, because it has been observed that in reductions of (+)-camphor carried out with mixtures of alkali metals and the salt of a second metal, the products reflect a weighted average of that predicted assuming a mixture of metals.¹¹





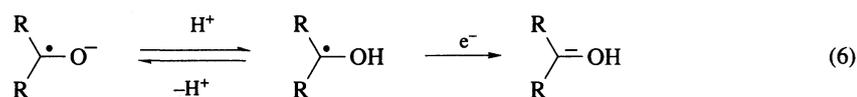
Pinacol formation (equation 4) is considered to occur *via* coupling of two ketyl units, either within a higher aggregate as depicted or by direct coupling of two ketyls. Production of alcohols by hydrogen transfer (equation 5) probably occurs either within a ketyl aggregate or by the direct interaction of two metal ketyls.^{5,9,10}

In a recent review it was once again suggested that these reductions proceed by way of the vicinal dianion path.⁶ This argument has again been refuted on the basis of reduction potentials and stoichiometry⁷ and most convincingly by a consideration of the relative acidities of the various species present in the reaction medium.¹⁵

1.4.2.3 Reduction in the Presence of Proton Donors

In terms of synthetic utility, the reduction of carbonyl compounds by a dissolving metal in liquid NH_3 in the presence of an alcohol, water or NH_4Cl is far more common and usually far more efficient than reduction in the absence of a proton donor. Historically these reductions were carried out using active metals, usually Na, in alcohols and the experimental results are similar in both systems.⁴⁻⁶

Although reductions under these conditions are more common than those carried out in the absence of a proton donor, relatively few mechanistic studies have been carried out. It is known that in the presence of NH_4Cl the reduction of (+)-[3,3- $^2\text{H}_2$]camphor by Li, Na or K in liquid NH_3 gives very little product resulting from deuterium transfer.¹⁰ In the presence of water or ethanol-water mixtures some deuterium transfer occurs, but to a lesser extent than is observed in the absence of an added proton donor, which indicates that the disproportionation path presented in equation (5) is attenuated in the presence of strongly acidic proton donors.¹⁰ The generally accepted alternative mechanism is that suggested by House,⁴ in which a ketyl is protonated to give a carbon radical which is subsequently reduced to a carbanion (equation 6) which on protonation provides the product alcohol. Although the details of the mechanism are not certain, it appears that the stereochemical course of the reaction is relatively insensitive to the nature of the metal used for reduction since (+)-camphor gives a borneol:isborneol ratio of 9.0-9.5:1 using Li, Na or K in NH_3 with NH_4Cl present.¹⁰ With less acidic proton donors there is competition by reduction *via* protonation and hydrogen transfer.^{5,10}



Although it was once believed that reductions by dissolving metals in alcohols or liquid NH_3 would invariably provide the thermodynamically more stable alcohol as the major product,³ it has been known for many years that the thermodynamically less stable epimeric alcohol is sometimes the major product on either metal-alcohol or metal- NH_3 -proton donor reduction.⁴⁻⁶ A detailed explanation for the stereochemistry of these reductions based on a combination of steric and frontier molecular orbital interactions has been presented.⁶

It must be emphasized that reduction of carbonyl compounds by dissolving metals, either in the presence or absence of an added proton donor is a kinetically controlled process. This was tacitly stated in 1972,⁴ and has been repeated or implied in more recent reviews of this topic.^{5,6} A recent study of the reduction of several bicyclo[2.2.1]heptanones using alkali metal- NH_3 - NH_4Cl systems emphasizes that these reductions are kinetically controlled.¹⁶

A variety of other less common reaction conditions, which employ a variety of either dissolving metals or low-valence metal cations, have been used to effect the reduction of carbonyl groups to primary or secondary alcohols. Although the mechanisms of these reactions have not been explored in detail, they almost certainly proceed by mechanisms similar to those outlined above.

1.4.3 SYNTHETIC UTILITY OF CARBONYL REDUCTION

1.4.3.1 Reaction Medium

1.4.3.1.1 Alcohols and water

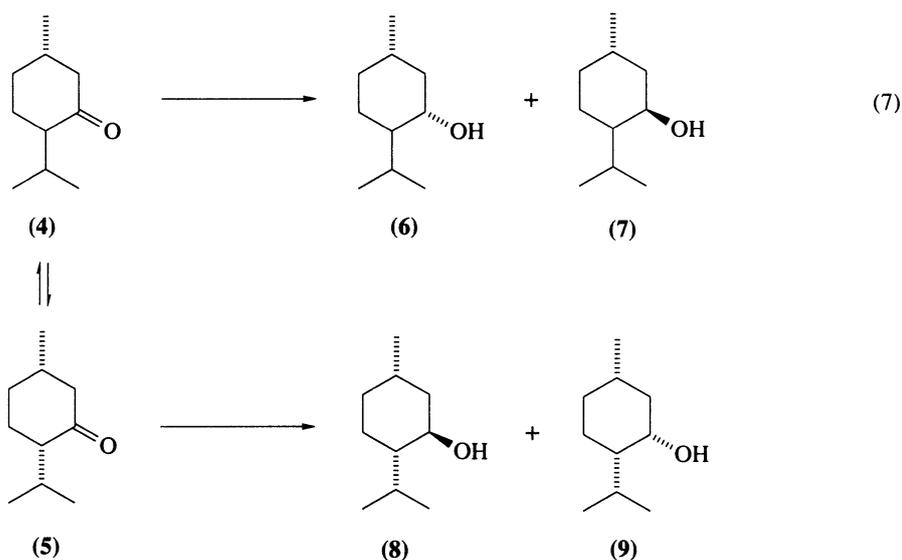
The reduction of various substrates by dissolving metals in alcoholic and aqueous media is a very old procedure in synthetic organic chemistry. In addition to aldehydes, ketones, imines and other unsaturated nitrogen compounds, many other functional groups are reduced under these conditions. Historically, the most common reduction conditions were Na in ethanol, and the reductions were carried out by adding the metal to a solution of the substrate in alcohol and the reaction mixture was heated at reflux for varying periods of time. Other reduction systems included Na–Hg amalgam in water or alcohols and, for easily reduced compounds such as aldehydes and aromatic ketones, Zn–NaOH or Fe–acetic acid have been used.⁴

Although reductions of ketones by active metals in alcohols have been largely supplanted by other procedures in modern synthetic chemistry, these methods still find occasional use. A modification employing K in *t*-butyl or *t*-pentyl alcohol has been used for the stereoselective reduction of 7-keto steroids in high yield,^{17,18} and the Li–ethanol and Na–ethanol reductions of 16-keto steroids have been investigated.¹⁹ Both traditional Na–ethanol^{20–22} reductions and a variation using Na–propan-2-ol in toluene^{4,23} have also been used recently in selected systems.

In terms of product distribution, reductions in these protic media are similar to those obtained using metal–NH₃–proton donor systems and it is generally accepted that they proceed by similar mechanisms.^{4–6} However, in terms of synthetic utility, metal/alcohol systems suffer from two inherent liabilities. The first, which has been commented upon in various reviews, is the possibility of equilibration of epimeric product alcohols as their alkoxide *via* a Meerwein–Ponndorf–Verley-type mechanism.^{4,6} Thus, although the initial product distribution is the result of a kinetically controlled reduction, prolonged heating of the reaction mixture will lead to mixtures approaching the composition predicted on the basis of thermodynamic control. It has been suggested that equilibration *via* hydrogen transfer from the solvent alcohol may be alleviated by carrying out metal–alcohol reductions in *t*-butyl alcohol,⁶ other tertiary alcohols appear to be equally effective.¹⁸

The second inherent problem is encountered in the reduction of ketones with a proton-bearing chiral center adjacent to the carbonyl group. In this case, enolate formation may lead to equilibration before reduction. For example, reduction of a 98.6:1.4 mixture of menthone (4) and its epimer isomenthone (5) with Na or K in ethanol gave approximately 15% of a mixture of alcohols (8) and (9), in addition to 82% of menthol (6) and a small amount of neomenthol (7),²² because of partial isomerization.

Enolization is an inherent problem with any metal–alcohol reducing system, and cannot be avoided due to the inevitable formation of metal alkoxides. This side reaction also occurs, although to a somewhat lesser extent, in the reduction of (4) with Na in moist ether.²²



1.4.3.1.2 Ammonia, added proton source

In terms of mechanism and stereochemical consequences, reductions by dissolving metals in liquid NH_3 are very similar to reductions by the same metals in alcoholic media.⁴⁻⁶ However, reductions carried out in liquid ammonia do not suffer from the same inherent problems as those by metals in alcohols. There is no evidence for equilibration of the product alcohols, and ketones which undergo epimerization prior to reduction with metals in alcohols are reduced cleanly by metals in NH_3 . For example, menthone (4) on reduction with $Li-NH_3$ -ethanol gives a mixture of alcohols (6) and (7), with no trace of alcohols (8) and (9).²²

The conventional method for carrying out reductions under these conditions consists of adding the appropriate metal to a solution of the compound to be reduced in a mixture of liquid NH_3 and an ethereal cosolvent, usually ether or THF, plus the proton donor, commonly NH_4Cl or an alcohol. The use of NH_4Cl has been advocated due to the observation that reduction by hydrogen transfer (Section 1.4.2.2) is effectively suppressed under these conditions.¹⁰ However, NH_4Cl is a very strong acid which is only sparingly soluble in NH_3 -ether mixtures and in preparative scale work a large excess of metal must be used to ensure complete reduction.²⁴ A suitable alternative is the use of an excess of a primary alcohol (methanol or ethanol) which affords little of the product obtained by hydrogen transfer.²⁵ This procedure results in a homogeneous reaction mixture, and complete reduction is obtained with only a modest excess of metal.²² Tertiary alcohols and relatively small amounts of primary alcohols lead to product mixtures resulting from reduction by a combination of hydrogen transfer and protonation.^{5,26}

Reductions carried out under these procedures do not lead to bimolecular products and usually afford excellent yields of reduction products. Dissolving metal reductions in liquid NH_3 in the presence of a proton donor are usually the method of choice for effecting the reduction of a substrate by a dissolving metal.

1.4.3.1.3 Ammonia, no added proton source

As noted above (Section 1.4.2.2) reduction of carbonyl compounds under these conditions proceeds with hydrogen transfer to afford an equimolar mixture of alkoxide and enolate, plus varying quantities of dimeric reduction products. As a consequence, at least in theory, this procedure should afford an equimolar mixture of recovered ketone and reduction product. This appears to be the case if less than one equivalent of metal is used; however, with excess metal, camphor,^{10,11} some 12-keto steroids²⁵ and several 1-decalones²⁴ afforded 70-99% yields of secondary alcohols. The explanation which has been offered is that the product enolate is protonated by NH_3 to regenerate the starting ketone, which is recycled through the reduction process.¹⁰

The usual experimental procedure for carrying out reductions in the absence of an added proton donor entails the addition of a metal (Li, Na, K) to a solution of the substrate ketone in a mixture of NH_3 and an ethereal cosolvent, usually ether or THF at the reflux temperature of liquid NH_3 . The metal is added until a permanent blue color is obtained and the reaction is stirred for 10 to 30 min. The excess Li is decomposed, traditionally with NH_4Cl or an alcohol; however, sodium benzoate is probably superior.⁶

Reductions by dissolving metals in liquid NH_3 in the absence of proton donors, are, in general, inferior in terms of general synthetic utility to reductions carried out under other conditions. In many cases, particularly when Li is used as a reducing agent, bimolecular reduction is difficult to predict and the ratios of epimeric alcohols may vary as a function of the metal used as the reducing agent.⁴⁻⁶

1.4.3.1.4 Other solvents

The vast majority of the dissolving metal reductions of carbonyl compounds which have been carried out synthetically have used either alcohols or liquid NH_3 as the solvent.⁴⁻⁶ However, a variety of other solvents have been employed, frequently in connection with studies of the mechanism of the reductions or in exploratory synthetic studies.

Ethereal solvents, principally THF, either with or without sonication, have been reported to give results similar to those obtained on reductions in NH_3 with no added proton donor, and pinacol formation as a major reaction path.^{7,27} A potentially useful selective reduction of unhindered cyclohexanones in the presence of other ketones using Al amalgam in aqueous THF has been described and will be discussed in detail subsequently (Section 1.4.3.3.2).²⁸ In this procedure aliphatic ketones give no pinacols; however, aromatic ketones give only the corresponding pinacol.²⁸

A number of steroidal and triterpenoid ketones have been reduced with Li-ethylenediamine to give results consistent with those anticipated by analogy with NH₃.²⁹⁻³¹ In addition to NH₃ and aliphatic amines, a number of other solvents provide relatively stable solutions of solvated electrons, usually using Na as the metal. These solvents, which include HMPA, *N,N*-diethylacetamide and *N*-ethylpyrrolidone, provide a medium for producing Na ketyls, which have been reacted with alkenes both inter- and intramolecularly.³² In these reactions, secondary alcohols are by-products, and presumably conditions could be found which would provide a viable synthetic method for the reduction of ketones to secondary alcohols. These solvents, however, would appear to offer no advantages compared to NH₃.

The reduction of a number of ketones by alkali metals in HMPA has been carried out, both in the presence and absence of added proton donors.^{27,33} The results are qualitatively similar to those obtained using the corresponding metal in NH₃ under similar conditions. If deuterated *t*-butyl alcohol is used as the proton donor, high levels of deuterium incorporation at the carbinol position are obtained.²⁷ Due to the carcinogenicity of HMPA it cannot be considered as a viable solvent for preparative chemistry and it also offers no advantage over other solvents.

1.4.3.2 Metal

In reductions carried out by dissolving metals in alcohols, Na in primary alcohols or K in tertiary alcohols are the most common systems. Somewhat different epimeric mixtures are occasionally obtained with these systems¹⁸ and it has been reported that Li-ethanol does not reduce a menthone/isomenthone mixture.²²

All five Group I metals (Li, Na, K, Rb and Cs) and three Group II metals (Ca, Sr, Ba) have been used in NH₃ to effect the reduction of ketones to secondary alcohols.^{4-6,11} In addition, it has been reported that Yb-NH₃ reduction of α,β -unsaturated ketones affords the saturated alcohol as the major product, which presumably arises *via* reduction of the intermediate saturated ketone.³⁴ Reduction of (+)-camphor with Yb-NH₃ both in the absence and presence of NH₄Cl affords the same 86:14 ratio of borneol (2) to isoborneol (3). In the presence of NH₄Cl, the ketone is completely consumed and dimeric reduction products are not observed.³⁵ Excess Yb-THF-HMPA effects bimolecular reduction of aromatic ketones,³⁶ but aliphatic ketones are apparently inert to Yb-THF.^{35,36}

A variety of other electron transfer reagents have been employed in reactions which appear to be mechanistically similar to the more common metal-NH₃ or metal-alcohol systems. These include K-graphite,^{37,38} Zn-KOH-DMSO³⁹ and both Li⁴⁰ and Al²⁸ amalgams. The amalgams from Zn, Mg, Ni, Cu, Sn and Pb have been found not to be effective in the reduction of cyclohexanone in aqueous THF.⁴¹ Also, several low-valent metal cations have been employed in the reduction of carbonyl compounds to alcohols. Among these reagents are low-valence salts of Ti,⁴²⁻⁴⁶ Ce⁴⁷ and Sm.^{48,49}

Some of these procedures have considerable potential as chemoselective reagents for the reduction of different types of carbonyl groups as will be discussed below. However, others, in particular CeI₂⁴⁵ and low-valence Ti salts,⁴²⁻⁴⁵ are primarily of interest as reagents for dimeric reduction and are of little synthetic utility in reductions to form alcohols (see Volume 3, Chapter 2.6).

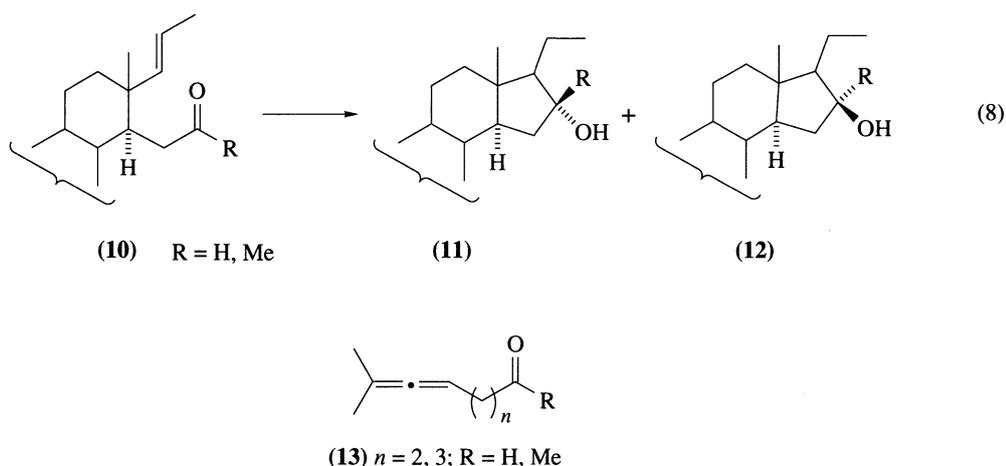
1.4.3.3 Chemoselectivity

1.4.3.3.1 Metal-ammonia and metal-alcohol systems

Under the usual reaction conditions alkali metal-NH₃ and alkali metal-alcohol systems are very powerful reducing systems. As noted above (Section 1.4.2.2) the reduction potentials of various functional groups in liquid NH₃ are not known. However, if it is assumed that the same relative order of reduction potentials is maintained in aqueous and nonaqueous systems, then it is apparent that in polyfunctional molecules the functional group with the least negative reduction potential should be reduced most readily. The reduction potentials (*versus* saturated calomel electrode) for aliphatic ketones range from -2.3 to -2.7 V and aromatic carbonyl compounds are considerably less negative (approximately -1.5 V).⁵⁰ Many common functional groups, including conjugated dienes, aromatic hydrocarbons, unsaturated carbonyl, halo, nitro and nitroso compounds all have reduction potentials less negative than those of aliphatic ketones and do not survive dissolving metal reductions using alkali metals in NH₃ or alcohols. Although carboxylic acids are stable to metal-NH₃ reductions,^{4,5} they are reduced to alde-

hydres by Li in methylamine (see Chapter 1.12, this volume).⁴ The reduction of esters to primary alcohols with Na in alcohol is the classical Bouveault–Blanc reduction (see Chapter 1.10, this volume).⁴

Both disubstituted alkynes (Chapter 3.3, this volume) and isolated terminal double bonds may be reduced by alkali metals in NH_3 , but isolated double bonds are usually stable to these conditions. However, 16,17-secopregnanes (**10**; equation 8) afford mixtures of cyclization products (**11**) and (**12**) in 61% to 80% yield with Na naphthalenide–THF, Na– NH_3 –THF, Na–THF or Li– NH_3 –THF. With Na– NH_3 –THF–*t*-butyl alcohol, a 91% yield of a 72:28 mixture of (**11**):(**12**) ($R = Me$) is obtained.⁵¹ This type of radical cyclization of alkenes and alkynes under dissolving metal reduction conditions to form cyclopentanols in the absence of added proton donors is a general reaction, and in other cases it competes with reduction of the carbonyl group.^{6,51,52} Under the conditions of these reactions which involve brief reaction times, neither competitive reduction of a terminal double bond nor an alkyne was observed.^{51,52} However, allenic aldehydes and ketones (**13**) with Li– NH_3 –*t*-butyl alcohol afford no reduction products in which the diene system survives.⁵³

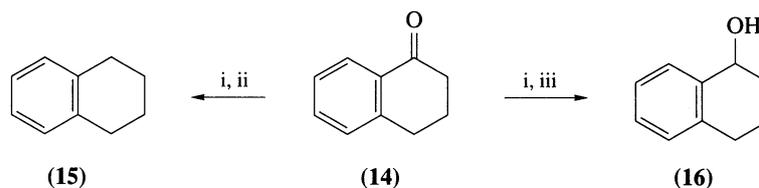


In addition to the inherent problems associated with easily reduced functional groups in dissolving metal reductions, ketones with an α -hetero substituent suffer removal of the α -substituent rather than reduction of the carbonyl group (Chapter 4.8, this volume). Cyclopropyl ketones constitute a special example of reduction of α -substituted ketones in which the ketyl formed by addition of one electron to the carbonyl group behaves as a cyclopropyl carbinyl radical, providing ketonic products arising from cleavage of the cyclopropane ring.^{54–56}

The metal– NH_3 reductions of carbonyl groups are exceedingly fast reactions; for the reaction of acetone with an ammoniated electron the rate is $9 \times 10^7 M^{-1} s^{-1}$.⁵⁷ Although many, particularly older, published experimental procedures for the metal– NH_3 reduction of ketones employ prolonged reaction times with excess metal, these conditions are unnecessarily harsh. The reactions of carbonyl compounds with metals in NH_3 are effectively instantaneous and by using short reaction times it appears that reduction of terminal alkenes and disubstituted alkynes can be avoided.⁵² In addition to the functional groups mentioned above, alcohols, amines and ethers, other than epoxides, are usually stable to reductions of aldehydes and ketones by dissolving metals.^{4–6}

Aromatic ketones represent a rather special case in dissolving metal reductions. Under many conditions pinacol formation is the predominant reaction path (see Volume 3, Chapter 2.6). Also, the reduction potentials of aromatic carbonyl compounds are approximately 1 V less negative than their aliphatic counterparts.⁵⁰ The reductions of aromatic ketones by metals in ammonia are further complicated by the fact that hydrogenolysis of the carbon–oxygen bond can take place (Chapter 1.13, this volume) and Birch reduction may intervene (Chapter 3.4, this volume).

The course of reductions of aromatic ketones is far more dependent on the exact reaction conditions than those of aliphatic ketones. A series of aromatic ketones, of which 1-tetralone (**14**; Scheme 1) is typical, on reduction with excess Li– NH_3 in the presence of a trace of Co or Al and quenching with NH_4Cl gave almost exclusively tetralin (**15**).^{58,59} However, quenching with sodium benzoate⁵⁸ or inverse quenching into aqueous NH_4Cl gave 1-tetralol (**16**) as the major product.⁵⁹ Reduction at $-78^\circ C$ with Li gave significant amounts of dimeric reduction products. Up to 31% of a Birch reduction product was obtained when Li or Na was added to a solution of (**14**) in THF– NH_3 .⁵⁹



i, Li-NH₃-THF, -33 °C; ii, NH₄Cl; iii, NaOBz

Scheme 1

The metal-NH₃ and metal-amine reductions of acetophenone and acetyl derivatives of polycyclic aromatics are complex and afford primarily mixtures of Birch reduction products. In some cases a ketonic carbonyl survives the reduction, and in some cases it is reduced to the corresponding alcohol.⁶⁰⁻⁶³

1.4.3.3.2 Other systems

Reduction of aromatic ketones using dissolving metal systems other than alkali metals-NH₃ in the absence of proton donors usually provide good yields of pinacols (see Volume 3, Chapter 2.6) with only small amounts of the secondary alcohol as by-product. A detailed study of the reduction of acetophenone by Li amalgam in several solvents using a variety of proton donors has been carried out.⁴⁰ In benzene the ratio of carbinol to pinacol was found not to vary in a regular way with the pK_a of the proton donor. Using ethanol as a proton donor and a variety of solvents the carbinol:pinacol ratio was greatest in solvents which coordinate poorly with Li (cyclohexane, benzene, ether). In polar solvents which coordinate well with Li ions (propan-2-ol, acetonitrile, THF) the pinacol was the major product. In the presence of optically active quaternary ammonium salts some asymmetric induction was observed, but the optical purity of the 1-phenylethanol did not exceed 8.9%.⁴⁰

A potentially useful chemoselective dissolving metal reagent for the reduction of aromatic ketones in the presence of other functional groups is the combination Zn-DMSO and aqueous potassium hydroxide.³⁹ In three examples (benzophenone, fluorenone and 4-benzoylpyridine), the yields of secondary alcohols were over 90%. Two other ketones (xanthone and thioxanthone) gave mixtures of alcohol and the hydrocarbon obtained by hydrogenolysis of a carbon-oxygen bond.³⁹

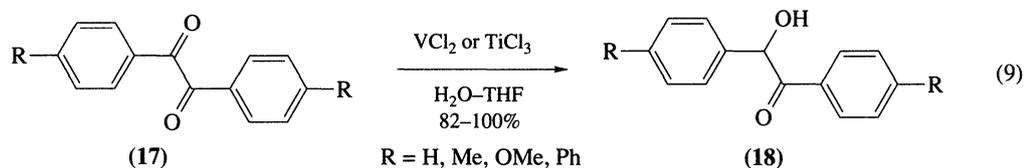
In general, the reduction of aromatic carbonyl compounds to the corresponding alcohols by dissolving metals is not a particularly valuable synthetic procedure. Better yields and chemoselectivity are usually obtained using complex metal hydrides.

In contrast to traditional dissolving metal systems, low-valence metal cations, particularly Sm²⁺, show considerable chemoselectivity in carbonyl reductions. In some cases these reagents can effect transformations which are difficult using metal hydrides or other traditional reducing agents. It has been suggested, and is almost certain, that these reductions are mechanistically similar to alkali metal reductions.⁴⁹

Samarium diiodide is usually prepared *in situ* by the reaction of Sm metal with 1,2-diiodoethane in THF,^{48,64} but a more convenient method appears to be the direct interaction of a slight excess of the metal with iodine in THF.⁶⁵ Although this reagent has found its principal utility as a reagent for effecting Barbier-type coupling reactions, in the presence of a proton donor it is an effective reagent for the reduction of aldehydes and ketones to the corresponding alcohols.^{48,49} With methanol as a proton donor, aldehydes and aromatic ketones are reduced efficiently to the corresponding alcohol. Aliphatic ketones are, however, only partially reduced at room temperatures in THF solution. This provides an effective and experimentally simple method of effecting the selective reduction of an aldehyde in the presence of an aliphatic ketone.⁴⁸ This procedure appears to be at least as efficient as other procedures for the selective reduction of aldehydes.⁶⁶ With water as the proton donor, 2-octanone is reduced to the corresponding alcohol in 64% yield; in the absence of proton donors pinacols are the major product in the reaction of carbonyl compounds with SmI₂.⁶⁴ Ytterbium diiodide behaves similarly, but is not as effective a reducing agent.⁴⁸

Although SmI₂ is more chemoselective than traditional dissolving metal reagents, it does react with sulfoxides, epoxides, the conjugated double bonds of unsaturated ketones, aldehydes and esters, alkyl bromides, iodides and *p*-toluenesulfonates.⁴⁸ It does not, however, reduce carboxylic acids, esters, phosphine oxides or alkyl chlorides.⁴⁸ In common with most dissolving metal systems, ketones with an α -hetero substituent suffer loss of the substituent rather than reduction of the carbonyl group.⁶⁷

Other low-valence metal ions which can effect selective reductions are VCl_2 and $TiCl_3$, both in aqueous THF, which selectively reduce benzils (**17**; equation 9) to the corresponding benzoin (**18**).⁴⁶ A similar chemo- and enantio-selective reduction of benzil employs the combination Sml_2 -HMPA-quinidine, which affords the (*R*)-enantiomer of benzoin (56% *ee*). Other chiral reagents are not as effective.⁶⁸ In basic media (methanol- NH_4OH or $NaOH$), $TiCl_3$ reduces both benzil (**17**) and benzoin (**18**) to the corresponding diol in 98% yield, with a (\pm):*meso* ratio of approximately 3:1.⁴³ Acetophenones and substituted acetophenones with alkaline $TiCl_3$ usually give pinacols; however, *p*-amino- and *p*-hydroxy-acetophenone afford the corresponding alcohols in good yield.⁴³



Aluminum amalgam in aqueous THF is a reagent which shows some promise for the selective reduction of unhindered cyclohexanones in the presence of a variety of other aliphatic ketones.^{28,41} Reduction of cyclohexanone and 3- and 4-methylcyclohexanone gave, respectively, 94%, 71% and 70% yields (GLC) of the corresponding secondary alcohols; however, cyclooctanone, cyclononanone, cyclododecanone, norcamphor, menthone, and 2-, 3- and 4-heptanone gave at most traces of reduction products. Cyclobutanone, cyclopentanone and cycloheptanone gave 12-33% yields of the corresponding alcohols.²⁸ Aromatic ketones gave good yields of pinacol under these conditions.²⁸ Based on preliminary competitive rate studies cyclohexanones are reduced approximately 10 times faster than cyclopentanones by Al amalgam-aqueous THF.⁴¹

1.4.3.4 Stereoselectivity

1.4.3.4.1 Generalizations

It was originally believed that the dissolving metal reduction of cyclic ketones would invariably afford the more stable of a pair of epimeric ketones as the major product.³ Although it has since been established beyond reasonable doubt that these reactions are kinetically controlled and that the less stable epimeric alcohol frequently predominates,^{4-6,16} the belief persists that these reductions are under thermodynamic control.^{29,69}

Reductions of cyclic ketones by dissolving metals are frequently highly stereoselective and these reductions have been used to obtain secondary alcohols which are difficult or impossible to prepare by metal hydride reduction. In terms of yield, the best results are usually obtained either by reductions with alkali metals (commonly Li) in liquid NH_3 in the presence of proton donors^{4-6,10} or with active metals in an alcohol.^{4,6} Although a number of explanations have been advanced for the stereoselectivity of these reductions, they are all rationalizations with dubious predictive value.⁴⁻⁶ There are, however, a number of empirical generalizations which are based on a considerable body of experimental data, specifically: (i) cyclohexanones with one or no α -alkyl substituents afford almost exclusively the equatorial alcohol; (ii) very hindered cyclic ketones afford almost exclusively the thermodynamically more stable alcohol; (iii) 2,2- or 2,6-disubstituted cyclohexanones may afford the less stable epimeric alcohol as the major product; and (iv) bicyclo[2.2.1]heptanones afford the *endo*-alcohol without regard to the relative stability of the *exo*- and *endo*-alcohols.

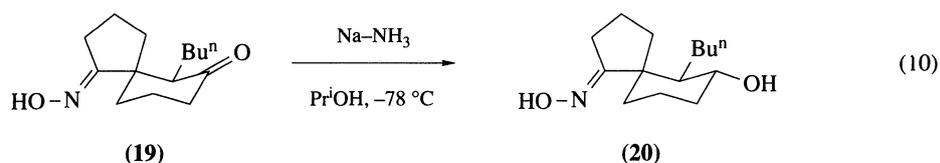
In reductions carried out in the absence of an added proton donor, it is difficult to predict the stereochemical consequences of a given reduction. The details of reductions under various conditions are discussed in Sections 1.4.3.4.2 through 1.4.3.4.6.

1.4.3.4.2 Cyclohexanones with one or no α -substituents

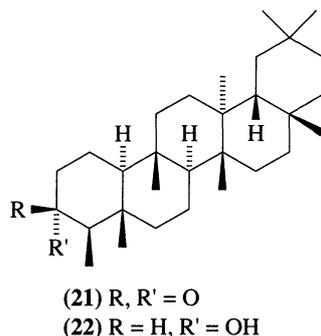
Reduction of a series of cyclohexanones (2- and 4-methyl, 4-isopropyl, 4-*t*-butyl and 3,3,5-trimethyl), both in the presence and absence of proton donors gave a 99:1 ratio of equatorial to axial alcohol. For 3-methylcyclohexanone the ratio was 94:6.⁷⁰ Also, reduction of menthone (**4**) affords a 97:3 ratio of equa-

torial alcohol to axial alcohol at $-30\text{ }^{\circ}\text{C}$.²² These are somewhat larger ratios of equatorial to axial alcohol than can be obtained by equilibration and considerably greater than can be obtained by conventional complex metal hydride reduction. Although LAH reduction of 4-*t*-butylcyclohexanone affords an equatorial:axial ratio (90:10) which is comparable to that obtained using dissolving metals, reduction of 3,3,5-trimethylcyclohexanone by either LAH or sodium borohydride gives the axial alcohol as the major product.⁷¹

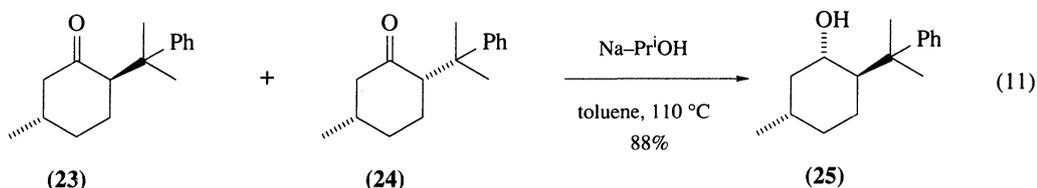
Although the metal-NH₃ reduction of unhindered cyclohexanones usually affords equatorial alcohols with greater stereoselectivity than metal hydride reductions, this method has not been used frequently in synthesis. An exception is the highly stereoselective reduction of ketoxime (**19**; equation 10), an intermediate in the synthesis of (\pm)-perhydrohistrionicotoxin, which gave an excellent yield of equatorial alcohol (**20**) on reduction with Na-NH₃. This reduction is noteworthy in that the oxime survives the reduction, which was carried out below the boiling point of liquid NH₃ for a relatively short period of time (30 min).⁷²



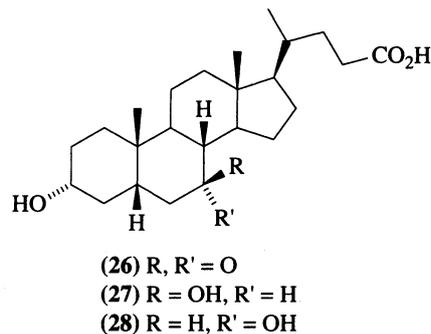
An unhindered keto triterpene, friedelan-3-one (**21**), with a large excess of Li in refluxing ethylenediamine has been reported to give a good (85–90%) yield of equatorial alcohol (**22**).^{29,30} Reduction of a second 3-ketofriedelane which also contained a sterically hindered lactone afforded the 3 α -ol with concomitant hydrogenolysis of the lactone.⁷³ The hydrogenolysis of esters by alkali metals in amines is a general method for the conversion of alcohols to the corresponding alkane.⁷⁴



Although metal-alcohol reductions of ketones suffer from possible epimerization of the product alcohol as well as isomerization of the substrate ketone (see Section 1.4.3.1.1), it was found possible to employ the latter type of epimerization to advantage in the preparation of an alcohol used as a chiral director in asymmetric synthesis.²³ In this preparation an 85:15 mixture of ketones (**23**) and (**24**; equation 11) was reduced with Na-isopropyl alcohol in toluene to afford alcohol (**25**) as the only isolated product in good yield.²³

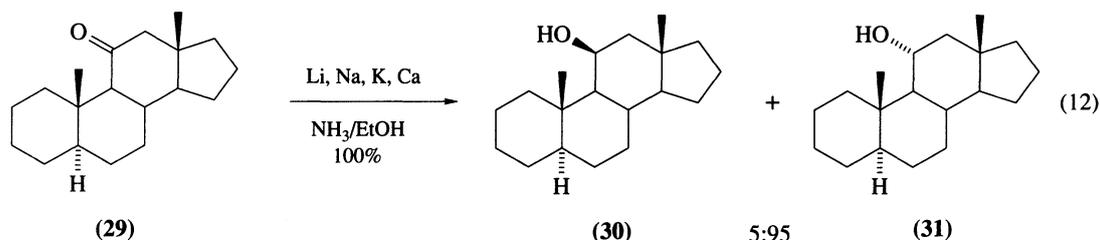


Metal-alcohol reductions have also been used in the stereoselective reduction of 3 α -hydroxy-7-ketocholanic acid (**26**) to the commercially important equatorial 7 β -ol (**27**).^{17,18} These reductions have been carried out with several alkali metals in secondary and tertiary alcohols, where reduction with K in tertiary alcohols is more stereoselective than Na-isopropyl alcohol.^{17,18} These reductions afford the equatorial alcohol as the major product in good yield, in contrast to sodium borohydride reduction, which provides the axial alcohol (**28**) almost exclusively.

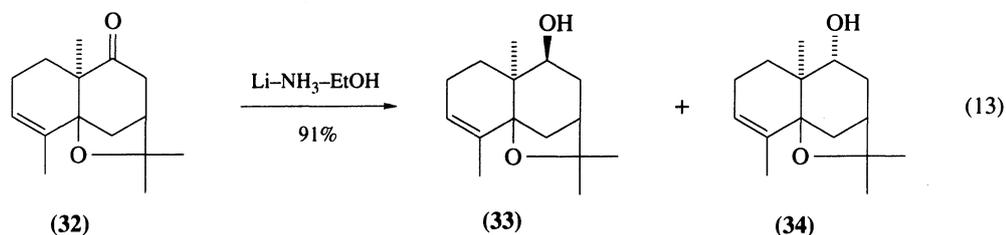


1.4.3.4.3 Sterically hindered cyclohexanones

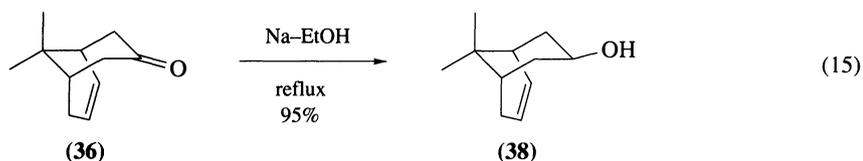
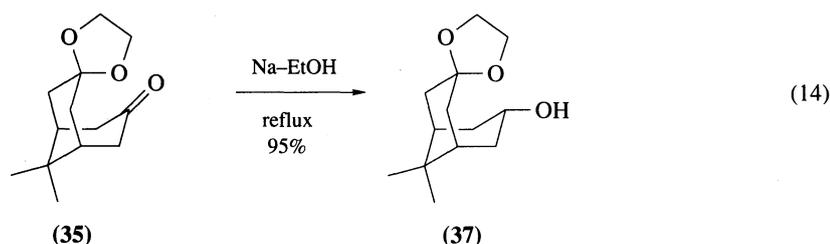
Dissolving metal reductions remain the method of choice, and are frequently the only viable method, for the reduction of sterically hindered cyclohexanones to equatorial alcohols. In the early 1950s it was found that reduction of 11-keto steroids using either Na–propan-1-ol² or Li–NH₃–dioxane–ethanol¹ gave good yields of the equatorial 11 α -alcohol. 11-Keto steroids, such as androstan-11-one (**29**; equation 12) have two axial methyl groups in a 1,3-relationship to the carbonyl group and afford exclusively the axial 11 β -ol (**30**) on reduction with metal hydrides.



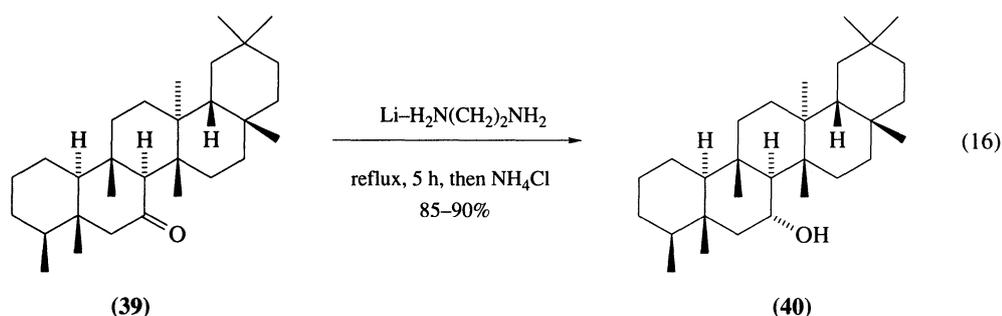
Reduction of the ketone (**29**) in NH₃–ethanol gave a quantitative yield of a mixture in which the equatorial 11 α -ol (**31**) predominated.⁷⁵ With Li–NH₃–NH₄Cl a quantitative yield of alcohols was also obtained, but quite surprisingly the ratio of (**31**):(**30**) was 55:45, which is similar to that obtained using alkali and alkaline earth metals (Li, Na, K, Cs, Sr) in the absence of a proton donor. Under these conditions Ca and Ba gave 79:21 and 65:35 ratios of (**31**):(**30**), respectively. In none of these reductions is there any evidence for pinacol formation.⁷⁵ Reduction of 19-keto- α -agarofuran (**32**; equation 13) using excess Li–NH₃–ethanol gave almost exclusively the equatorial 9 α -ol (**34**), while LAH gave the axial 9 β -ol (**33**) as the only isolable product.²⁶ As expected with a severely hindered ketone, no pinacols were obtained with any alkali metal–proton donor combination.²⁶



Although alkali metal–NH₃ reductions are usually preferable to Na–alcohol reductions in terms of yield and convenience, the stereochemical consequences of both systems are similar, at least for all sterically hindered systems studied thus far. Illustrative examples are the reductions of bicyclo[3.3.1]nonanones (**35**; equation 14) and (**36**; equation 15).²⁰ In both cases the equatorial alcohols (**37**) and (**38**) were obtained in excellent yield and with complete stereoselectivity. LAH reduction of ketone (**35**) gave only the epimeric axial alcohol, while (**36**) gave a mixture of (**38**) and its epimer.²⁰



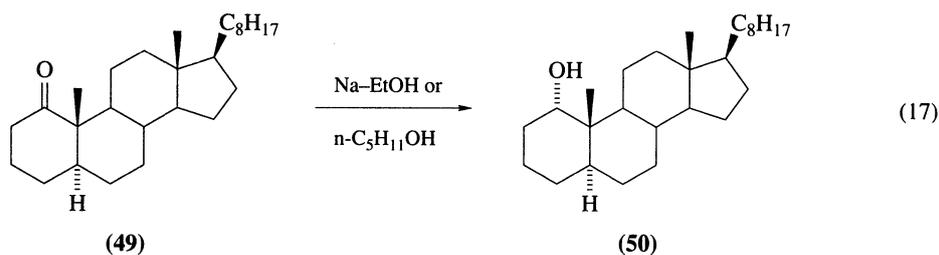
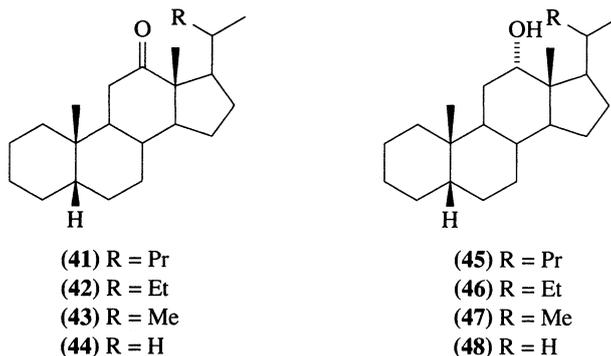
Several sterically hindered keto triterpenes, including friedelan-7-one (**39**; equation 16), were reduced with a large excess of Li in refluxing ethylenediamine.²⁹ This exceedingly hindered ketone (three axial methyl groups with a 1,3-diaxial relationship to the carbonyl) affords only the equatorial 7α -ol (**40**) in good yield. Other ketones which were reduced under these conditions are considerably less hindered than ketone (**39**), but all gave the equatorial alcohol in good yield.²⁹



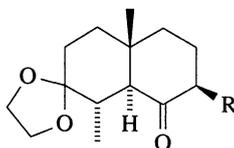
1.4.3.4.4 Moderately hindered cyclohexanones

A group of moderately hindered cyclohexanones which has been thoroughly studied is the 12-keto steroids, in which the stereochemical course of the reduction is governed by the structure of the C-17 alkyl group.^{5,6,25} Reduction of 12-keto steroids which have a secondary substituent on C-17, (**41**), (**42**) and (**43**), gave mixtures of alcohols with Li-NH₃-methanol in which the axial 12 α -ol, (**45**), (**46**) and (**47**), was the major product (70–80%).^{5,25} However, reduction of 5 β -pregnan-12-one (**44**) under the same conditions gave a mixture containing only 11% of the axial alcohol. Similar results were obtained using Na-propan-1-ol.⁶ Reduction of ketones (**41**) and (**42**) with Li-NH₃ in the absence of an added proton donor gave mixtures of epimeric alcohols containing from 10–20% of axial alcohols (**45**) and (**46**). Considerable quantities of pinacol were obtained under these conditions and pinacol was the major product from the reduction of ketone (**44**) in the absence of a proton donor.²⁵ Sodium borohydride reductions of ketones (**41**), (**42**) and (**43**) were comparable in terms of yield and stereoselectivity to reduction by Li-NH₃-alcohol. However, borohydride reduction of ketone (**44**) gave an approximately 1:1 mixture of alcohol (**48**) and the equatorial 12 β -ol.²⁵

Although they have apparently not been studied in detail, dissolving metal reductions of 1-keto steroids appear similar to those of the 12-keto steroids. In one report, cholestan-1-one (**49**; equation 17) on reduction with Na in either ethanol or 1-pentanol gave the axial alcohol, cholestan-1 α -ol (**50**), as the major reduction product in unspecified yield.⁷⁶ The equatorial 1 β -ol was detected by TLC, but could not be isolated.



The other group of moderately hindered cyclohexanones which has been examined in detailed is a group of substituted 1-decalones, which gave results similar to those of the 12-keto steroids on Li-NH_3 reduction.²⁴ These decalones were all derived from protected diketone (51) and included two different 2-monosubstituted derivatives (52) and (53). These decalones were reduced both in the presence of a proton donor (NH_4Cl) and under anhydrous conditions in yields of 69–99%. The axial alcohol was the major product in the presence of a proton donor, while the equatorial alcohol was predominant in its absence.²⁴



- (51) R = H
 (52) R = $\text{CH}_2\text{CH}=\text{CMe}_2$
 (53) R = $\text{CH}_2\text{CO}_2\text{H}$

The reductions of 1- and 12-keto steroids and their 1-decalone derivatives graphically illustrate the fact that dissolving metal reductions of ketones do not necessarily afford the more stable of a pair of epimeric alcohols. As a corollary, while the reduction of cyclic ketones is a synthetically useful procedure for the stereoselective preparation of secondary alcohols, it cannot be assumed that the thermodynamically stable alcohol will be the product which is obtained stereoselectively.

1.4.3.4.5 Bicyclo[2.2.1]heptan-2-ones

The dissolving metal reductions of bicyclo[2.2.1]heptanones have been studied extensively, and it has been established that both metal–alcohol and metal– NH_3 –proton donor systems provide the *endo*-alcohol regardless of its stability relative to the *exo* isomer.^{4–6,10,16,70} In the case of camphor (1) which has been studied in the most detail, the ratio of *endo*-alcohol (borneol; 2) to *exo*-alcohol (isoborneol; 3) is very close to 90:10 for all metal– NH_3 conditions employed. The variables include temperature (-33 and -78 °C),¹⁶ cosolvent (ether and THF),¹⁶ metal (Li, Na, K, Rb)^{16,70} and proton donor (NH_4Cl and ethanol).^{16,70} The same results are obtained with both (+)- and (±)-camphor.¹⁶ These results are, coincidentally, almost identical to the equilibrium ratio for alcohols (2) and (3).¹⁶

In addition to camphor (**1**), the metal-NH₃-proton donor reduction of four other bicyclo[2.2.1]heptan-2-ones and bicyclo[2.2.1]hept-5-en-2-one (**54**) have been studied systematically.^{16,70} The other ketones include the parent bicyclo[2.2.1]heptan-2-one (**55**), fenchone (**56**), 1-methylbicyclo[2.2.1]heptan-2-one (**57**) and 7,7-dimethylbicycloheptan-2-one (**58**). The results of these reductions and, where known, the equilibrium ratio of the alcohols are summarized in Table 1. In all cases and under the conditions noted, the *endo*-alcohol is produced stereoselectively.

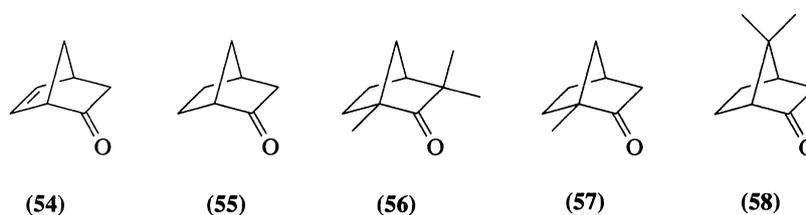
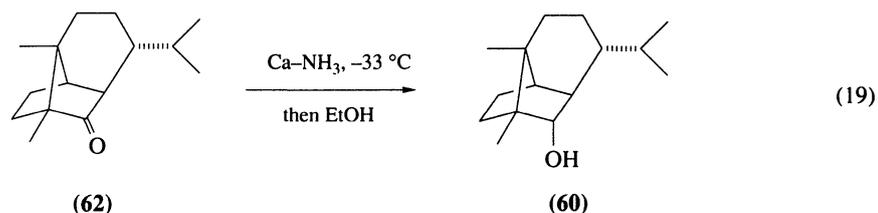
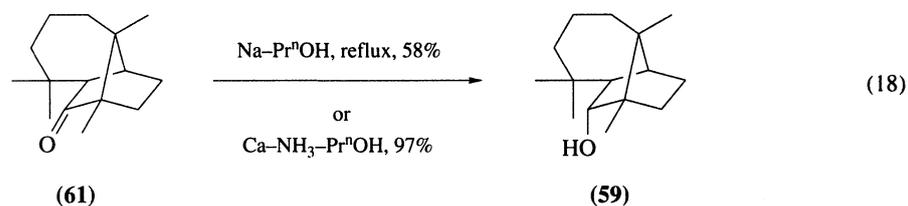


Table 1 Metal-Ammonia Reductions of Bicyclo[2.2.1]heptanones and Equilibrium Ratios of the Corresponding Alcohols

Ketone	Metal	Cosolvent	Proton donor	<i>Endo:exo</i> (reduction)	<i>Endo:exo</i> (equilibrium)	Ref.
(54)	Li	THF	NH ₄ Cl	99:1	50:50	16
(55)	Li	Et ₂ O	NH ₄ Cl	89:11	5:95	16, 70
(55)	Li	Et ₂ O	EtOH	85:15	—	69
(55)	Na	Et ₂ O	NH ₄ Cl	89:11	—	16, 70
(55)	Na	Et ₂ O	EtOH	85:15	—	69
(55)	K	Et ₂ O	NH ₄ Cl	90:10	—	16, 70
(55)	K	Et ₂ O	EtOH	90:10	—	70
(56)	Li	THF	NH ₄ Cl	>99:1	72:28	16
(57)	Li	Et ₂ O	NH ₄ Cl	91:9	40:60	16
(58)	Li	Et ₂ O	NH ₄ Cl	83:17	Unknown	16

The reduction of bicycloheptanones, particularly camphor (**1**) in the absence of added proton donors has been studied extensively in connection with the mechanism of the dissolving metal reductions and are discussed in Section 1.4.2.2. As previously noted, reductions under these conditions are of considerably less utility in synthesis than those carried out in the presence of a relatively acidic proton donor (NH₄Cl or ethanol).

The stereoselective dissolving metal reduction of bicycloheptanones has been applied to the synthesis of two tricyclic sesquiterpenes, longiborneol (**59**; equation 18) and ylangoborneol (**60**; equation 19). Alcohol (**59**) was originally prepared by metal-alcohol reduction of longicamphor (**61**)⁷⁷ and in improved yield using a metal-NH₃-alcohol procedure.⁷⁸ Using a similar procedure, ylangocamphor (**62**) gave alcohol (**60**) in excellent yield.⁷⁹ Reduction of ketone (**62**) using LAH afforded exclusively the *exo* isomer of alcohol (**60**).



1.4.3.4.6 Cyclopentanones

The stereochemistry of the reduction of substituted cyclopentanones has not been studied in great detail and it is not possible to make detailed generalizations regarding their course. Based on limited experimental data, it appears that metal-alcohol and metal-NH₃-proton donor reductions of alkyl-substituted cyclopentanones will usually afford a greater than equilibrium ratio of the thermodynamically more stable alcohol. In the absence of an added proton donor, pinacol formation may be a problem and different metals may give different ratios of epimeric alcohols.

The reductions of two steroidal ketones, androstan-17-one (**63**)⁷⁵ and androst-5-en-16-one (**64**)¹⁹ under various conditions have been studied in some detail. In the case of 17-ketone (**63**) the β -ol (**65**) is the stable epimer and for the 16-ol (**66**), the α -isomer is more stable. Dissolving metal reductions of both ketones in the presence of proton donors gave the more stable alcohol as the major product; however, reduction of 17-keto steroid (**63**) is considerably more stereoselective as noted in Table 2. Although pinacols are not usually obtained in dissolving metal reductions carried out in the presence of proton donors, ketone (**63**) gave from 6 to 34% of dimeric products under these conditions (Li, 6%; Na, 34%; K, 13%).⁷⁵

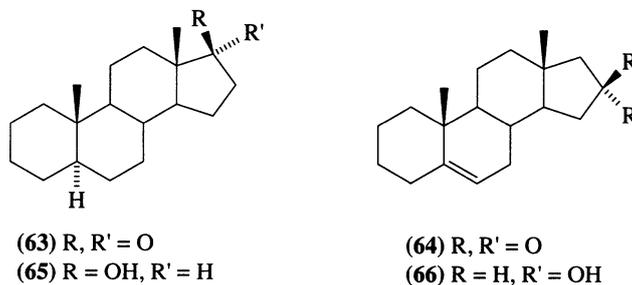
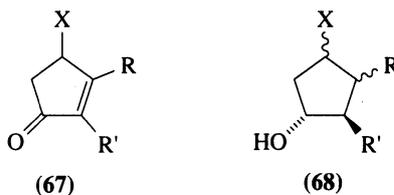


Table 2 Dissolving Metal Reductions of Androstan-17-one (**63**) and Androst-5-en-16-one (**64**)

Ketone	Reduction conditions	α -ol: β -ol (Reduction)	α -ol: β -ol (Equilibrium)	Ref.
(63)	Li-NH ₃ -EtOH	3:97	42:58	75
(63)	Na-NH ₃ -EtOH	0:100	—	75
(63)	K-NH ₃ -EtOH	0:100	—	75
(64)	Li-EtOH	63:37	82:18	19
(64)	Na-EtOH	85:15	—	19
(64)	Li-NH ₃ -THF	55:45	—	19
(64)	Na-NH ₃ -THF	42:58	—	19
(64)	K-NH ₃ -THF	22:78	—	19

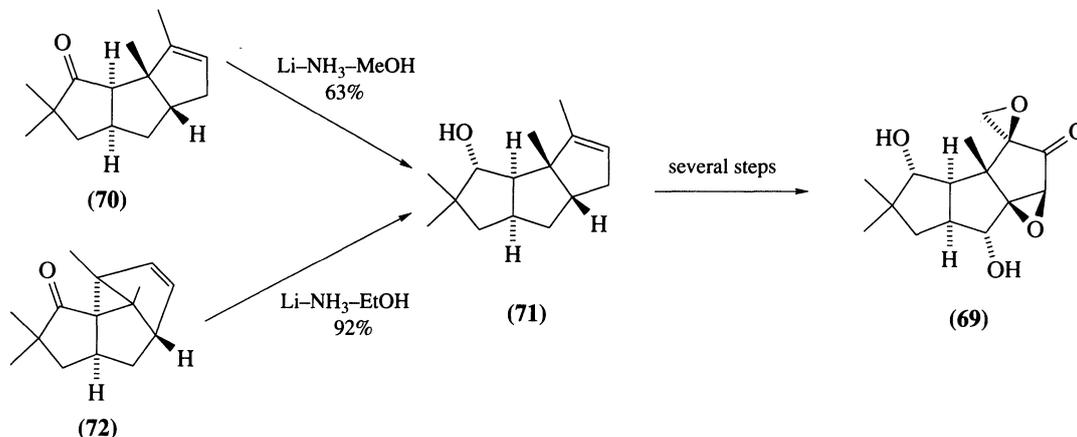
In the absence of an added proton donor, the 17-keto steroid again gave the 17 β -ol (**65**) as the predominant or exclusive product with seven metals (Li, Na, K, Cs, Ca, Ba, Sr) in NH₃. All the alkali metals gave the 17 β -ol (**65**) exclusively and the alkaline earth metals gave only 2–5% of the α -ol. With the exception of Ca, all of the metals gave pinacols in yields of 3% (Cs) to 28% (Li).⁷⁵ Reduction of 16-keto steroid (**64**) with alkali metals-NH₃ in the absence of an added proton donor gave less 16 α -ol with Na than with Li and still less with K (Table 2).¹⁹ Pinacols were not reported in the reductions of ketone (**64**).

A series of dialkylcyclopentenones (**67**) has been reduced with Li-NH₃ in the presence of various proton donors (phenol and methyl, ethyl, isopropyl and *t*-butyl alcohols).⁸⁰ These reductions gave complex mixtures of products, most of which were cyclopentanols (**68**), arising from sequential conjugate reduction to the cyclopentanone followed by reduction to the saturated secondary alcohol. In all cases, and regardless of the relative stereochemistry of R, R' and X, the major product was a secondary alcohol in which the hydroxy group was *trans* to the adjacent alkyl group (**68**).⁸⁰



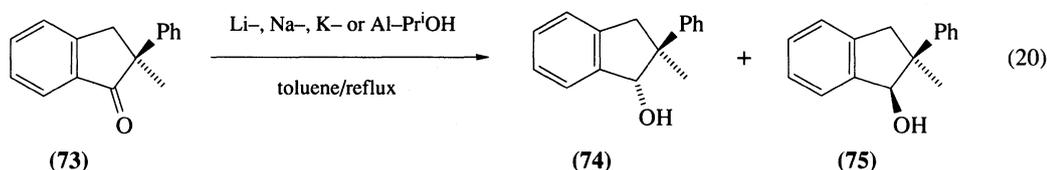
X = H or OH; R = R' = Me; R = Me, R' = Bu^t; R = Me, R' = Prⁱ

A stereoselective Li-NH₃ reduction of a cyclopentenone has been employed in two different syntheses of the cytotoxic sesquiterpene coriolin (**69**; Scheme 2). In one synthesis, tricyclic ketone (**70**) was reduced stereoselectively to alcohol (**71**) using Li-NH₃-methanol.⁸¹ In the second synthesis, tetracyclic enone (**72**) was converted in a single step to (**71**).⁸² This reduction proceeds by initial cleavage of the cyclopropyl ketone unit of (**72**) to give ketone (**70**), which is then reduced to (**71**).



Scheme 2

Metal-alcohol reductions of substituted indanone (**73**; equation 20) which afford mixtures of alcohols (**74**) and (**75**) have been described.²¹ Although alcohol (**75**) is the more stable isomer, Li and Na both afford alcohol (**74**) as the major reduction product (**74**:**75** = 60:40). Aluminum gives a (**74**):(**75**) ratio of 90:10, but with K it is 30:70. Prolonged (12 h) heating of the Al and K reactions changes the ratios to (**70**):(**30**) and (**10**):(**90**), respectively.²¹ It is apparent that some equilibration is occurring under these conditions, but it is not clear if the results after 3 h represent partial equilibration or if they are truly the result of kinetically controlled reductions.

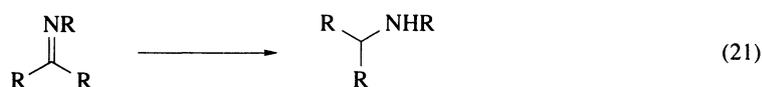


1.4.4 REDUCTION OF C=N AND C=S

1.4.4.1 Reduction of Imines and Oximes

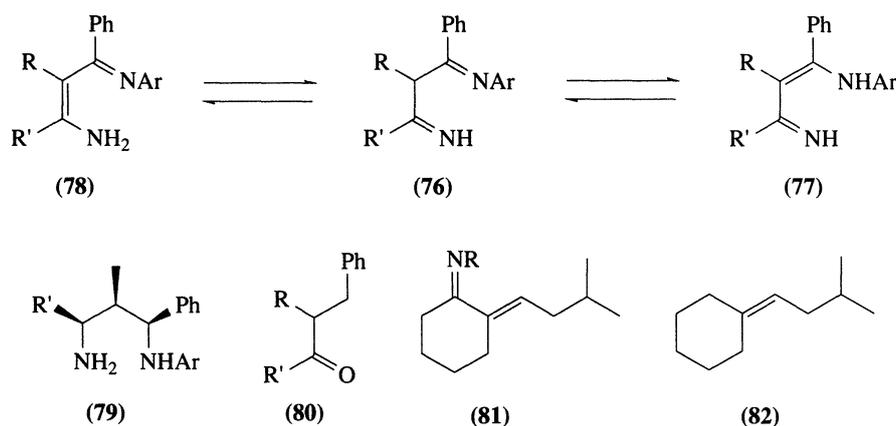
1.4.4.1.1 Reduction of imines

The reduction of imines to amines (equation 21) by dissolving metals is usually carried out using active metals in a protic solvent, typically Na-alcohol, Zn-NaOH and Al or Mg in alcohols.⁸³⁻⁸⁵ Although the mechanism of these reductions has not been investigated in detail it is almost certainly analogous to that of the reduction of ketones (Section 1.4.2). It has been established that radical anions are intermediates in these reductions and in the absence of a proton donor reductive dimerization is the principal reaction path.⁸⁶

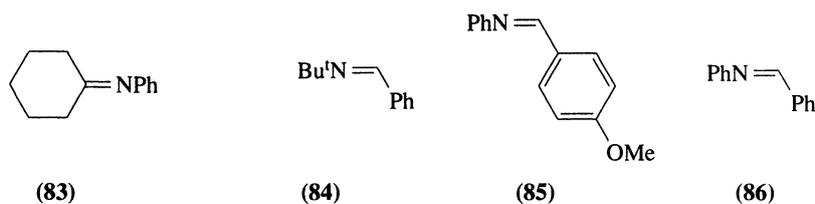


The reduction of a series of 1,3-diimines (**76**) has been investigated in which the dissolving metal reductions have been carried out both in the presence⁸⁷ and absence⁸⁸ of proton donors. These compounds exist as a tautomeric mixture of two enaminoimines (**77**) and (**78**) and the diimine (**76**). Reduction by Na-propan-2-ol of five examples (Ar = Ph, β -tolyl; R = Me; R' = Ph, β -tolyl, cyclohexyl) gave excellent (90–99%) yields of diastereomeric mixtures of three of the four possible fully reduced diamines in which no isomer comprised more than 50% of the reaction mixture. Diamines (**79**) were not observed, and their absence was attributed to steric factors.⁸⁷ On reduction with Li-THF for several hours, followed by quenching with methanol, ethanol or water a number of these tautomeric mixtures (**76**, Ar = Ph, β -tolyl; R = H, Me, PhCH₂, CH₂=CH-CH₂; R' = Ph, β -tolyl, Me, cyclohexyl) gave saturated ketones, (**80**) in 70 to 93% yield.⁸⁸

The metal-alcohol reduction of imines usually produces the reduced amine in good yield; however, the reduction of some allylic imines (**81**, R = Prⁿ, Buⁿ) with Na-alcohol proceeds with hydrogenolysis to give alkene (**82**).⁸⁹



Although by far the most usual method for the dissolving metal reduction of imines is metal-alcohols, a few other systems have been explored with mixed results. In one of these, the reduction of three imines (**83**)–(**85**) with potassium graphite (C₈K) in anhydrous THF gave the corresponding amines in 83–90% yields at room temperature in 30 min.⁹⁰ Much less favorable results were found in the reduction of benzalaniline (**86**) with SmI₂ in methanolic THF which gave *N*-benzylaniline in 50% yield, with much recovered starting material. An attempted Barbier-type coupling reaction employing (**86**), 1-iodobutane and SmI₂-THF gave a mixture of products of which *N*-benzylaniline constituted 60%.⁶⁴



1.4.4.1.2 Reduction of oximes

The reduction of oximes to primary amines by dissolving metals, usually Na-alcohol, is an established synthetic procedure which has been employed for many years.^{83,84} Although in some cases LAH reduction is superior, the reduction of many oximes with LAH leads either to aziridines or Beckman-type rearrangements.⁹¹

The reduction of a series of bicyclic and tricyclic ketoximes using both Na-ethanol and LAH has been carried out and the product mixtures analyzed in detail.⁹² In this investigation it was found that reduction of the oximes derived from two tricyclo[2.2.1.0^{2,6}]heptan-3-ones (**87**) and (**88**) with either LAH-THF or Na-ethanol gave mixtures of *exo* (**89**) and (**90**) and *endo* (**91**) and (**92**) amines. Neither method of reduction was particularly stereoselective and the yields were somewhat better with LAH (**87**; 76% versus 67% and **88**; 67% versus 44%). In contrast, reduction of the oximes of three bicyclo[2.2.1]heptan-2-ones (**93**)–(**95**) with LAH-THF gave significant quantities of azabicyclo[3.2.1]octanes (**96**)–(**98**) in addition

to mixtures of *exo* and *endo* primary amines. Reduction of oximes (**93**)–(**95**) with Na–alcohol gave only mixtures of epimeric amines.⁹² These results, outlined in Table 3, show that the *endo*-amine is the major stereoisomer, although the unsubstituted oxime (**93**) had previously been reported to give an *exo:endo* ratio of 75:25 on Na–alcohol reduction and exclusively the *endo*-amine on LAH reduction.⁹³

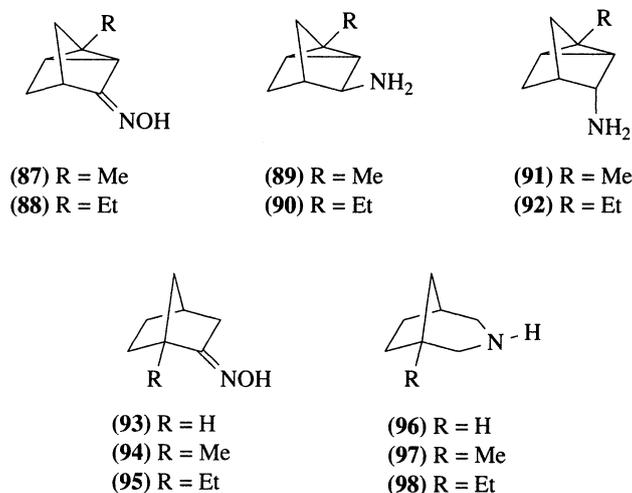
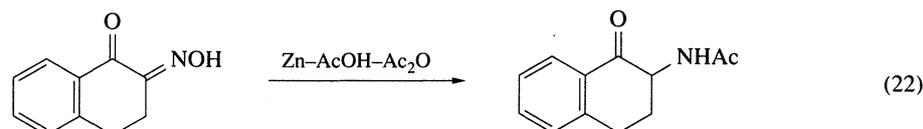


Table 3 Reduction of Oximes of Bicyclo[2.2.1]heptan-2-ones⁹¹

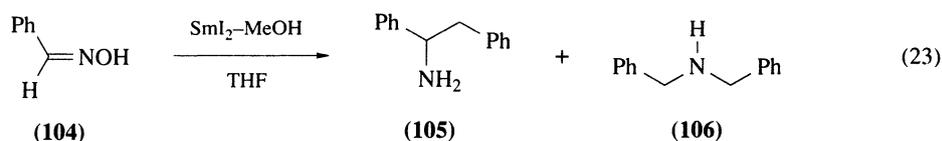
Oxime	Conditions	Yield (%)	Rearrangement (rel. %)	Amine (rel. %)	Exo:endo
(93)	Na–EtOH, 80 °C	67	0	100	27:73
(93)	LAH–THF, 65 °C	79	36	64	36:64
(94)	Na–EtOH, 80 °C	52	0	100	32:68
(94)	LAH–THF, 65 °C	87	60	40	10:90
(95)	Na–EtOH, 80 °C	50	0	100	14:86
(95)	LAH–THF, 65 °C	59	52	48	10:90

The chemoselective reduction of a series of 2-oximo-1-tetralones (**99**–**103**; equation 22) to the corresponding aminotetralones has been carried out using Zn–HOAc–Ac₂O in 55–65% yield. The amino group is acetylated under these conditions and the 2-acetamidotetralone is the product which is isolated.⁹⁴



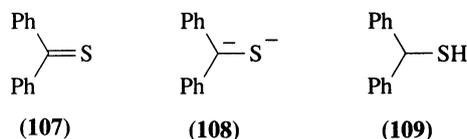
- (99) unsubstituted; 65%
 (100) 5-OMe; 62%
 (101) 6-OBn; 65%
 (102) 7-OBn; 60%
 (103) 5,8-di-OMe; 55%

The reduction of oximes by SmI₂ has been attempted, but complex mixtures of products are obtained.⁶⁴ In the case of benzaldehyde oxime (**104**; equation 23) two dimeric reduction products (**105**) and (**106**) were isolated, apparently in good yield.⁶⁴



1.4.4.2 Reduction of Thioketones

There is apparently only one report of the dissolving metal reduction of thioketones; thiobenzophenone (**107**) has been reduced with excess Na-THF to give dianion (**108**), which on acidification gave thiol (**109**). The thiol was not isolated, but was oxidized with iodine to give the corresponding disulfide in 65% overall yield.⁹⁵ The mechanism of the reduction is suggested to be the sequential addition of two electrons to the thiocarbonyl, which was confirmed by electron spin resonance spectroscopy studies of the intermediate thioketyl, and trapping dianion (**108**) with a variety of electrophiles.⁹⁵



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