Reduction of Organic Compounds with Diborane

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I. Introduction

Diborane, B_2H_6, was first isolated and characterized by Stock in 1912.[1] His process involved the preparation and hydrolysis of magnesium boride to give a mixture of higher boron hydrides. Thermal decomposition of the higher boron hydrides then gave B_2H_6 along with other boron hydrides. Although this pioneering work by Stock must be considered truly remarkable,[2,3] the process developed by Stock was extremely tedious and gave exceedingly low yields of diborane.

In 1931, Schlesinger and Burg reported an improved method for the preparation of diborane which involved passing hydrogen and boron trichloride through a silent electric discharge.[4] The major product was chlorodiborane, B_2H_5Cl, which disproportionated upon fractional distillation to yield diborane and boron trichloride. This procedure was satisfactory for the preparation of micro quantities of diborane, which was all that was required for the studies carried out by Schlesinger and co-workers on the Stock high-vacuum apparatus.

Schlesinger and his students were attracted to the boron hydrides because their formulas, which had been established without a doubt by Stock, did not conform to the then accepted theories of valence and molecular structure. As part of their investigation, the reaction of diborane with the carbonyl group in certain organic compounds was studied by Brown as part of his Ph.D. research.[5] This is the first report on the use of B_2H_6 for the reduction of an organic compound. The reactions were studied on the high-vacuum line in the absence of a solvent using micro amounts of reactants. Furthermore, relatively complex equipment was required to prepare the diborane. Consequently, although the results are now considered of fundamental importance, at the time the results of this study were of negligible importance to synthetic organic chemistry.

Fortunately, in 1940 a National Defense Project, initiated at the University of Chicago under the direction of Schlesinger and Brown, ultimately resulted in the development of large-scale processes for the preparation of both sodium borohydride and diborane.[6] With only minor modifications these processes are now used commercially in the United States to prepare both sodium borohydride and diborane. Unfortunately, the results of these projects carried out at the University of Chicago during the war were not made public until a series of eleven articles appeared in 1953.[8] While preparing these articles for publication, Brown again became interested in the use of diborane as a reducing agent for organic compounds. Also, since sodium borohydride had become commercially available and provided a ready source for diborane, it was apparent that diborane should be of utility as a reducing agent for applications in synthetic organic chemistry. A preliminary communication appeared in 1957[9] which was followed by a full paper.[10]

This investigation of the reduction of organic compounds by Brown and Subba Rao was responsible for the discovery of the hydroboration reaction which kindled vigorous activity in the study of organoboranes as intermediates in organic syntheses. Both the hydroboration reaction and the chemistry of organoboranes have been reviewed by Brown and others.[7,11-18] In these reviews, the use of diborane for the reduction of organic compounds is either barely mentioned or only briefly discussed.[19,20]

The molecular structure, molecular properties, physical properties, and preparation of diborane are covered in a recent review.[21] Also, the reaction chemistry of diborane has been reviewed with the emphasis being on the reaction of diborane with inorganic elements and inorganic compounds.[22] However, a comprehensive review devoted exclusively to the selective reduction of organic compounds with diborane and related borane complexes has not appeared.[23] In view of the increasing importance of selective reducing agents in synthetic organic chemistry, it was felt that such a review is both warranted and necessary.

In this review the literature is covered through 1974 with several references from early in 1975. Originally, it was hoped that every reference which describes a reduction using a borane reagent could be included in this review. However, early in the literature searching it became apparent that such a comprehensive coverage would not only be extremely difficult to obtain but would also probably not be appropriate for a journal review article. Thus, a number of limiting factors have, by necessity, been introduced. The review deals exclusively with the use of diborane and borane–Lewis base complexes for the reduction of organic compounds. The substituted boranes, such as bis(3-methyl-2-butyl)borane,[25] 2,3-dimethyl-2-butylborane,[26] and 9-borabicyclo[3.3.1]nonane,[27] which are also useful reducing agents, are not covered in this review. To be consistent and objective it was decided that a publication must meet at least one of the following criteria before it would be cited in the review: (1) the reference must illustrate the selectivity of the reagent, (2) the reference must provide some insight into the mechanism by which the reagent operates, or (3) the reference must contain a detailed experimental section.

A large number of borane reductions involve the use the borane–tetrahydrofuran reagent, which will be abbreviated as BH_3–THF. It should be understood that in all cases where BH_3–THF is discussed, the reagent is actually a solution of the borane–tetrahydrofuran complex in tetrahydrofuran. Other abbreviations used in this article are as follows.

Ac	Acyl
Ar	Aryl
BMS	Borane-methyl sulfide complex
Diglyme	Diethylene glycol dimethyl ether
Et	Ethyl
Me	Methyl
N:	Nucleophile
Ts	Tosyl

II. The Reagent

A. Preparation

Diborane, BH_3–THF, BMS, and various borane–amine complexes are all available commercially. A comprehensive coverage of the preparative chemistry of diborane is included in a recent review by Long.[21] Thus, only a short discussion of the more convenient methods of preparation will be given here along with some recent results.

Since sodium borohydride is available commercially at a reasonable price, this chemical is the starting material of choice for the preparation of diborane. For the vacuum-line preparation of small quantities of high-purity diborane, the Schlesinger-Burg process has been replaced by several more convenient procedures. Diborane can be prepared in a vacuum line in good yield from the reaction of sodium borohydride and concentrated sulfuric acid.[28] Sulfur dioxide, which is formed as a by-product, can be eliminated by the use of methanesulfonic acid in place of sulfuric acid.[28] To obtain a purer sample, phosphoric acid is also recommended in place of sulfuric acid.[29] A detailed literature procedure is available for the reaction of potassium borohydride with 85% orthophosphoric acid (eq 1).[30] The yield is only

$$2KBH_4 + 2H_3PO_4 \longrightarrow B_2H_6 + 2H_2 + 2KH_2PO_4 \qquad (1)$$

40–50%, but the purity of the diborane prepared by this method is excellent, only a trace amount of carbon dioxide (<0.1%) is observed in some cases.

Another potentially useful vacuum-line preparation of diborane involves the reaction of sodium borohydride in diglyme with either mercurous chloride (eq 2) or iodine (eq 3).[31] The yield by either

$$2NaBH_4 + Hg_2Cl_2 \xrightarrow{\text{diglyme}} 2Hg + 2NaCl + B_2H_6 + H_2 \qquad (2)$$

$$2NaBH_4 + I_2 \xrightarrow{\text{diglyme}} 2NaI + B_2H_6 + H_2 \qquad (3)$$

of these methods is very good (88–90%) and the purity of the diborane is excellent (no detectable impurities). Unfortunately, a detailed experimental procedure is not available and there is no indication if these methods are useful on a preparative scale.

Although diborane is available commercially in steel cylinders and can be handled safely by adequately trained personnel, it must be considered a very hazardous material. When large amounts of diborane are required for a preparative scale organic transformation, it is generally much safer to generate the diborane as needed and pass it directly into a reaction mixture. Alternatively, the reagent can be purchased in the form of a borane–Lewis base complex, such as BH_3–THF or BMS. Both of these reagents are stable but still reactive and can be safely and easily handled.

The reaction of sodium borohydride with boron trifluoride (eq 4), as developed by Brown and coworkers, is probably the most

$$3NaBH_4 + 4Et_2O{\cdot}BF_3 \xrightarrow[25\ ^\circ C]{\text{diglyme}} 2B_2H_6\uparrow + 3NaBF_4 + 4Et_2O \qquad (4)$$

convenient method available for the preparative scale generation of diborane. The reaction was studied extensively by Brown and Tierney[32] and experimental procedures for generating diborane have been reported.[32,33] Further refinements in the process were later introduced,[34] and a detailed experimental procedure is now available.[35]

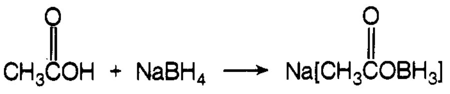
In addition to the use of externally generated diborane or the use of preformed borane–Lewis base complexes for organic reactions, these reducing agents can also be prepared in situ in the presence of a reactive compound. A variety of procedures for the in situ generation of diborane were developed for use in the hydroboration reaction,[36] and many of these procedures can be used for organic reductions. However, the presence of strong Lewis acids, such as boron trifluoride or aluminum chloride, can sometimes result in the formation of unexpected by-products (vide infra). Also, the starting material may react with the basic alkali metal borohydride (vide infra). Consequently, for exploratory work on a given reduction, it is usually wise to first use either externally generated diborane or preformed BH_3–THF. Almost invariably this results in fewer side reactions and a higher purity product.

A recent report of a simple in situ hydroboration procedure is interesting and deserves mention. By this procedure a mixture of an alkene and sodium borohydride in THF is treated with glacial acetic acid to give an organoborane.[37] Alkaline peroxide oxidation then gives a good yield of the corresponding alcohol (eq 5). It is unlikely that diborane is involved in this reaction. The in

$$n\text{-}C_4H_9CH{=}CH_2 \xrightarrow[2.\ NaOH,\ H_2O_2]{1.\ NaBH_4,\ AcOH} n\text{-}C_4H_9CH_2CH_2OH \qquad (5)$$

82%

situ presence of alkene is probably required. In the absence of alkene, sodium borohydride reacts with acetic acid and forms the relatively unreactive complex **1** (eq 6).[38] This mixture of



$$CH_3\overset{O}{\overset{\|}{C}}OH + NaBH_4 \longrightarrow Na[CH_3\overset{O}{\overset{\|}{C}}OBH_3] \qquad (6)$$

1

sodium borohydride plus acetic acid is currently under investigation as an interesting new reducing agent.[39,40]

B. Physical and Chemical Properties

The physical, chemical, and molecular properties of diborane were summarized in two recent reviews.[21,22] Also, a complete compilation of the major physical and thermodynamic properties of diborane is available in a concise graphical format.[41] The property data covered include critical constants, vapor pressure, heat of vaporization, heat capacity, density, viscosity, surface tension, thermal conductivity, heat of formation, and free energy of formation. The properties of BH_3–THF and BMS are discussed in the present review in the section dealing with borane–Lewis base complexes.

Sodium borohydride[42] and $LiAlH_4$[43] are both widely utilized for the selective reductions of organic compounds. These reagents react principally by nucleophilic attack on an electron-deficient center. Conversely, diborane, which is already electron-deficient, is believed to function through attack on an electron-rich center in the functional group.[5,44] Thus, diborane is an acidic-type reducing agent which exhibits markedly different selectivity than the basic-type reducing agents, sodium borohydride and $LiAlH_4$.[9] This interesting difference in the reducing activity of diborane and sodium borohydride prompted an extensive study of the reduction of organic compounds with diborane.[10,24]

In addition to the Lewis acid character of borane, other important chemical properties have enhanced the utility of borane complexes as reducing agents. Many reactions involving borane complexes have unusually low activation energies. Consequently, most reactions occur readily at room temperature or below. These low temperatures favor clean reaction mixtures with a minimum of side products. The solubility of diborane in ether solvents means that the reactions are usually homogeneous, proceed without induction periods, and are easily controlled. Finally, the inorganic by-product of a borane reduction is usually an inert, water-soluble borate salt, which can be washed away over a broad pH range. All of these chemical and physical properties combine to make diborane one of the most chemically versatile compounds known.

C. Reaction with Acidic Hydrogens

Boron hydrides and other metal hydrides react rapidly and quantitatively with various acidic hydrogens (H-Y), liberating one mole of hydrogen per equivalent of hydride (eq 7). Both the

$$\rangle B{-}H + H{-}Y \longrightarrow \rangle B{-}Y + H_2 \qquad (7)$$

$$Y = O,\ S,\ \text{or}\ N$$

acidity of the hydrogen and the ability of the donor atom Y to share a pair of electrons influences the rate of these reactions.[24]

The direct measurement of the volume of hydrogen gas produced upon hydrolysis of a boron hydride provides a convenient and accurate method for the determination of either the purity of a boron hydride or the concentration of a boron hydride in an appropriate solvent.[45] Also, a simple, rapid, and quantitative procedure for determining acidic hydrogens in organic materials has been developed based upon hydrogen evolution from a large excess of BH_3-THF.[46] The method is especially valuable for hydroxyl group determinations, and a precision of about 1% is possible.

In reactions of diborane with compounds containing acidic hydrogens, hydrogenolysis of the C–Y bond is usually not observed. Upon hydrolysis the alcohol, amine, thiol, or related functional group is regenerated unchanged. However, in a few specialized cases those benzylic alcohols which can readily form carbonium ions are transformed by diborane into the corresponding hydrocarbons (vide infra; section III.D). Even though the alcohol, thiol, and amine groups are normally recovered unchanged following a diborane reduction, their presence and reactivity must be considered when carrying out a diborane reduction; i.e., sufficient diborane must be added to compensate for loss of hydride activity upon reaction with acidic hydrogens. Consequently, an understanding of the reactivity of diborane toward alcohols, thiols, and amines is important.

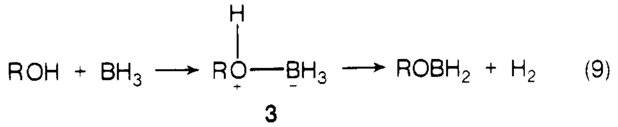
1. Alcohols

The hydrolysis of borane with simple alcohols proceeds in stages. The first two hydrides react rapidly, but the third is so slowly hydrolyzed that the intermediate dialkoxyborane can be isolated. Using this reaction, dimethoxyborane (**2**) was first isolated and characterized by Burg and Schlesinger (eq 8).[47] No

$$4CH_3OH + B_2H_6 \longrightarrow \underset{\mathbf{2}}{2(CH_3O)_2BH} + 4H_2 \qquad (8)$$

evidence was found for dimerization of **2**. Even in the presence of excess diborane, there was no indication of the formation of monomethoxyborane. Later investigations by Shapiro and coworkers, on the preparation of dimethoxyborane,[48] diethoxyborane,[49] and diisopropoxyborane,[50] substantiated the earlier results. For example, Shapiro found that when ethanol is added to a large excess of diborane, there is no detectable formation of $EtOBH_2$ by ir analysis.[49] Also, the diborane is quantitatively converted into diethoxyborane before there is any detectable formation of triethoxyborane. Even with excess ethanol, the rate of formation of triethoxyborane (triethyl borate) from diethoxyborane is slow at room temperature.[51] Stoichiometric evidence is also available which indicates that $HB(OH)_2$ is formed as an intermediate in the hydrolysis of diborane in aqueous solutions at temperatures around −70 °C.[52] Upon warming to room temperature, the remaining hydrogen is rapidly evolved.

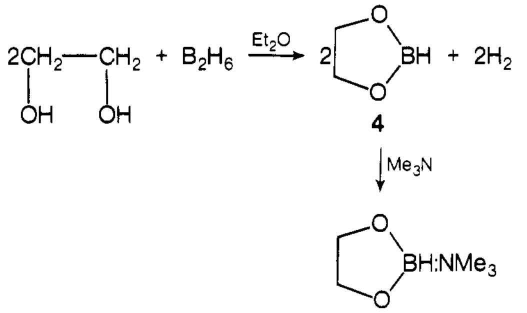
In the presence of excess BH_3-THF, the rate of hydrogen evolution for alcohols decreases in the order: primary > secondary > tertiary.[24] The acidity of the hydroxylic hydrogen also decreases in this order. A factor, in addition to the acidity of the hydrogen, must be involved in these reactions because diborane reacts relatively slowly with phenol. The results can be rationalized by prior coordination of BH_3 with the alkoxy oxygen to give the intermediate **3** which decomposes with evolution of hydrogen (eq 9). Mass spectrometric evidence is now available for the



$$ROH + BH_3 \longrightarrow \underset{\mathbf{3}}{R\overset{H}{\underset{+}{O}}{-}\underset{-}{B}H_3} \longrightarrow ROBH_2 + H_2 \qquad (9)$$

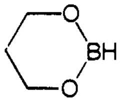
existence of an intermediate donor-acceptor adduct **3** in the reaction of borane with 2-propanol.[53] Also, stoichiometric evidence points to the formation of a dihydrate of diborane (empirical formula $B_2H_6{\cdot}2H_2O$) in the reaction of diborane with water at −130 °C.[54]

Cyclic dialkoxyboranes are formed by the reaction of diborane with 1,2- and 1,3-diols. For example, 1,3,2-dioxaborolane (**4**)



(10)

can be prepared through the reaction of ethylene glycol with diborane in diethyl ether and can be isolated as the trimethylamine adduct (eq 10).[55] The corresponding 1,3,2-dioxaborinane (**5**) can also be prepared from 1,3-propanediol.[56]



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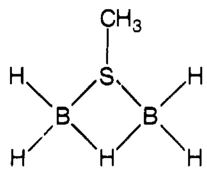
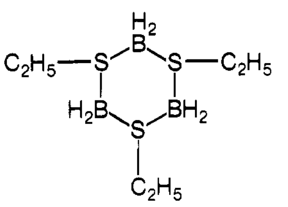
The reaction of borane with polyalcohols apparently results in a chelation which must enhance the reactivity of the boron hydride. Thus, hydrolysis of all three hydrides occurs very rapidly in the presence of a polyglycol, such as glycerol or mannitol.[45]

2. Thiols

The ability of sulfur to bring d orbitals into hybridization with s and p orbitals to form multiple bonds apparently exerts a pronounced effect on the products obtained through the reaction of diborane with alkanethiols. Thus, the first reported alkylthio derivative of diborane, methylthiodiborane,[57] has the structure **6** based on NMR data.[58] In this and other alkylthio derivatives of diborane, the alkylthio group occupies exclusively a bridging position, e.g., structure **7**.[58]



6



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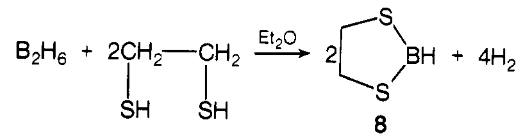
The reaction of diborane with excess ethanethiol in diethyl ether at 25 °C yields a viscous polymer, which on standing is converted into a mixture of the trimer **7** plus $(EtS)_3B$.[58,59] The initially formed polymer is sensitive to atmospheric oxygen and is rapidly hydrolyzed with water, while the trimer **7** is stable in air and extremely resistant to hydrolysis.[59] Interestingly, the reaction of diborane and ethanethiol in a 1:2 mole ratio gives **7** directly.[58] With the proper mole ratio of reactants, diborane and ethanedithiol react at room temperature to form 1,3,2-dithiaborolane (**8**) (eq 11).[60]



8 (11)

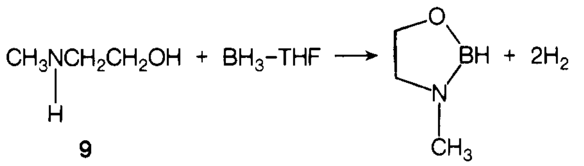
3. Amines

Primary and secondary amines react with BH_3-THF at 0 °C with the slow evolution of hydrogen.[24] With phenol, the slow evolution of hydrogen is presumably due to its weakly basic character which opposes formation of the prior addition complex **3**. On the other hand, amines readily form such addition complexes. Thus, the slow evolution of hydrogen must be caused by the low acidity of the hydrogen atoms attached to nitrogen.

At higher temperatures an increased rate of hydrogen evolution is observed. Primary or secondary amines react with BH_3-THF in refluxing THF to give monoaminoboranes (eq 12).[61]

$$R_2NH + BH_3\text{-THF} \xrightarrow{\Delta} R_2N\text{-}BH_2 + H_2 \qquad (12)$$

Even in the presence of a large excess of amine, no additional hydrogen evolution is observed. However, the amino alcohol **9** reacts with BH_3-THF under otherwise identical conditions to give the heterocyclic compound **10** (eq 13).[61]



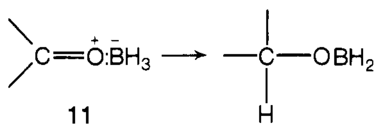
9 **10** (13)

Other functional groups, which contain acidic hydrogens, such as carboxylic acids and primary and secondary amides, react with borane with evolution of hydrogen. However, since these groups react further with borane, they will be discussed in later sections dealing with the reduction of these functional groups.

D. Borane-Lewis Base Complexes

The high reactivity of diborane is presumably due to its ready dissociation into borane (BH_3).[62] The borane molecule behaves as a strong electron pair acceptor (Lewis acid) forming coordination complexes with suitable electron donors (Lewis bases). Of the various known complexes, the borane-amine, borane-ether, and borane-alkyl sulfide complexes are all particularly interesting because of their wide range of physical and chemical properties.

These borane-Lewis base complexes provide a convenient source of borane for use as a reducing agent. Another reason for discussing these complexes is that all organic reductions with borane probably involve the initial formation of a donor-acceptor adduct between borane and the functional group undergoing reduction. Thus, a borane-carbonyl complex (**11**) was proposed



$$>C{=}\overset{+}{O}{:}\overset{-}{B}H_3 \longrightarrow -\underset{H}{\overset{|}{C}}-OBH_2 \qquad (14)$$

11

as an intermediate in the first report of a borane reduction.[5] This complex **11**, once formed, is presumed to undergo a rapid rearrangement (eq 14). Recently, convincing evidence was reported which shows that the first formed intermediate in the reaction of diborane with acetone is the donor-acceptor adduct.[53] Arguments were also presented which suggest that the formation of this adduct (**11**) is not a "dead-end" reaction in the overall process; i.e., the adduct is the first formed intermediate and it subsequently reacts to give product via a hydride rearrangement.[53]

1. Borane-Amine Complexes

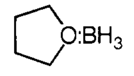
The borane-amine complexes are very useful reagents which have many important laboratory and industrial applications. A comprehensive review is available covering the physical and chemical properties of the borane-amine complexes along with their use as hydroboration reagents and as reducing agents.[63]

2. Borane-Ether Complexes

Schlesinger and Burg found that 2 mol of dimethyl ether reacts with 1 mol of diborane, at temperatures below −80 °C to form a new solid substance which is fairly stable at −80 °C.[64] The complex **12** was proposed for this new material. A later Raman

$(CH_3)_2O{:}BH_3$

12



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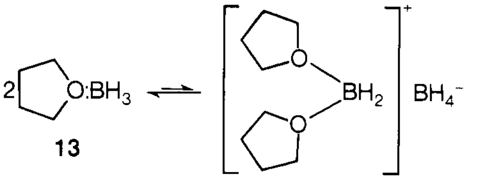
spectroscopic investigation of the liquid systems diborane-THF, diborane-dimethyl ether, and diborane-diethyl ether provides evidence for the formation of an $R_2O{:}BH_3$ addition complex in each system.[65] Also, a study of the solid-liquid equilibrium for diborane-THF clearly indicates the formation of the compound tetrahydrofuran-borane (**13**).[66] On the basis of these two studies, the stability of borane-ether complexes is believed to decrease in the order: **13** > **12** ≫ $Et_2O{:}BH_3$. Additional evidence is available for the existence of **13** in a THF solution of diborane. In THF the solubility of diborane is much greater than perfect solution predictions; i.e., the solubility increases as the square root of diborane pressures increases.[67] Also, a phase diagram study[68] and two ^{11}B plus ^1H NMR studies[69,70] provide convincing evidence for the existence of **13** in excess THF. When all of this evidence is taken as a whole, it is apparent that diborane must be present in THF solution as the complex **13**.

The stability of **13** is quite unique and is mainly responsible for the interest and utility of BH_3-THF as a convenient reducing agent.[24] Diborane has been shown to be a useful reducing agent in other ether solvents. However, in most of the previously cited investigations, which provide evidence for the formation of **13**, there is very little evidence for the formation of $Et_2O{:}BH_3$ in Et_2O solutions of diborane.[66,67,70] Diglyme is a particularly useful solvent for reactions involving the in situ generation of diborane.[10] Two solubility studies seem to indicate that a BH_3–diglyme complex is of negligible importance in this system.[71,72] At very dilute concentrations of diborane in diglyme, arguments were presented for a minor amount of complex formation.[71] However, this result was later disputed and was suggested to be due to the use of slightly impure diglyme.[72]

Even if there is no definite evidence for a borane–ether complex in the case of either diglyme or diethyl ether, it is well established that the reactivity of diborane is influenced by the presence of these ethers. Thus, the hydroboration of alkenes with diborane is greatly enhanced in diglyme.[73] Also, the ^{11}B NMR spectrum of liquid or gaseous diborane consists of a triplet of triplets while the spectrum of diborane dissolved in diglyme is collapsed to a seven-line multiplet.[74] This collapse is probably due to intramolecular proton exchange brought about by ether displacement of bridge protons.

A final factor which may exert an influence on the reactivity of diborane in ether solvents is the possible ionic dissociation of diborane in these solvents. Evidence for ionic dissociation is indicated by the measurable conductances of diborane solutions in diglyme and in THF.[75] Other workers also found that BH_3–THF conducts an electric current rather well and suggested the formation of the ionic complex **14**,[76,77] which was attributed to a small amount of ionization of **13** (eq 15).[24]



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3. *Borane–Alkyl Sulfide Complexes*

The first reported preparation of a borane–alkyl sulfide complex was by Burg and Wagner.[57] Condensation of dimethyl sulfide and diborane on a vacuum line produced a stable, liquid adduct of borane–methyl sulfide (BMS) (eq 16). BMS was found to melt in the range −40 to −38 °C. Based on vapor tension measurements, the normal boiling point for BMS was calculated to be 97 °C.[57]

$$2(CH_3)_2S + B_2H_6 \longrightarrow (CH_3)_2{:}BH_3 \qquad (16)$$

The stability of BMS at room temperature was surprising and prompted a more detailed study of borane–alkyl sulfide complexes by Stone and coworkers.[78,79] BMS is obviously much more stable than the corresponding dimethyl ether adduct **12**, but the reverse is true for the boron trifluoride adducts. Thus, the stability decreases in the order: $Me_2O{:}BF_3 > Me_2S{:}BF_3$.[78] Moreover, BMS is more stable than $Me_2S{:}BF_3$.[78] A series of borane–alkyl sulfide complexes was prepared and found to be clearly more stable than the corresponding complexes with ethers.[79] The stability of BH_3–thioether complexes decreases in the order BMS $\simeq Et_2S{:}BH_3 > (CH_2)_4S{:}BH_3$. This is in contrast to the BH_3–ether complexes which decrease in stability in the order BH_3–THF $> Me_2O{:}BH_3 > Et_2O{:}BH_3$. Interestingly, all of these results can be rationalized in terms of the hard and soft acids and bases (HSAB) concept of chemical interaction.[80]

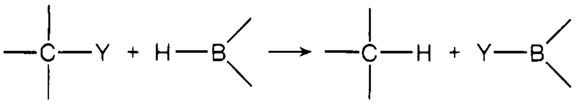
The physical and chemical properties of BMS make this reagent an attractive source for BH_3, and its numerous advantages over BH_3–THF as a storable reagent were first discussed by Adams and co-workers.[81] The BH_3–THF reagent possesses certain characteristics which limit its preparation, storage, and use as a commercial source of BH_3, namely: (1) BH_3–THF can only be sold as a dilute solution (1 M) in THF (1.5 wt % BH_3), (2) THF is slowly cleaved by BH_3 at room temperature, (3) sodium borohydride (<5 mol %) is added to BH_3–THF to inhibit the cleavage of THF, and (4) THF is a relatively expensive solvent and at times has been in short supply.

Fortunately, BMS has been found to overcome all of these disadvantages. BMS has a molar concentration of BH_3 *ten times* that of the BH_3–THF reagent. It can be stored for months at room temperature without loss of hydride activity and is apparently stable indefinitely when refrigerated. Also, BMS is soluble in and unreactive toward a wide variety of aprotic solvents including ethyl ether, THF, hexane, heptane, toluene, xylene, methylene chloride, glyme, and diglyme. BMS dissolves readily in alcohols with the quantitative evolution of hydrogen. However, it is insoluble in water and only very slow hydrolysis occurs. The addition of water to ether solutions of BMS results in rapid hydrolysis.

We recently reported that quantitative hydroborations with BMS are possible under mild conditions in a variety of aprotic solvents such as ethyl ether, THF, hexane, toluene, and methylene chloride.[82] The vastly improved air stability and ease of handling of this reagent have resulted in its use as a hydroboration reagent in an undergraduate laboratory.[83] The successful hydroboration of alkenes with BMS prompted similar studies with BMS as a reducing agent.[84] The results of these investigations make it apparent that BMS is a very useful reagent for the reduction of organic functional groups.

III. Reductive Cleavage

In general, this section deals with those reactions which involve the reductive cleavage of a C–Y single bond (eq 17). The

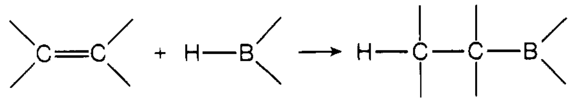


(17)

following sections then discuss the reduction of multiple bonds in organic functional groups containing sulfur, nitrogen, or oxygen. Naturally some overlap is inevitable, but, by subdividing the sections into discussions of specific functional groups, the retrieval of information about the reducing characteristics of diborane should be simplified. Also included in this section are a few reductions which do not proceed in a single, simple step as shown in eq 17. However, as in the case of hydroboration–protonolysis of alkenes, an overall reduction does occur.

A. Alkenes and Alkynes

Unsaturated derivatives are readily converted into organoboranes via hydroboration (eq 18 and 19). A systematic study



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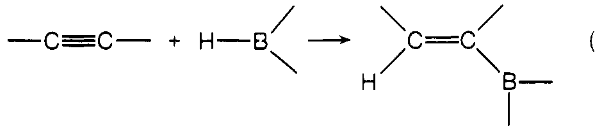


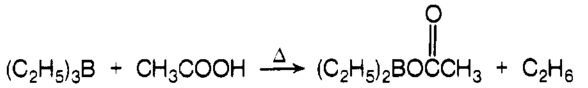
(19)

of the hydroboration reaction by Brown and coworkers revealed that the reaction is essentially quantitative with remarkably wide applicability, involves a cis regioselective addition, and can tolerate almost all functional groups.[7,11]

Trialkylboranes are remarkably stable toward water, hydrogen sulfide, alcohols, and phenols. Temperatures >200 °C for extended periods are necessary to achieve even partial hydrolysis using the above proton sources.[85] Interestingly, the addition of alkali to water even further stabilizes the trialkylborane toward hydrolysis in most cases.[86,87]

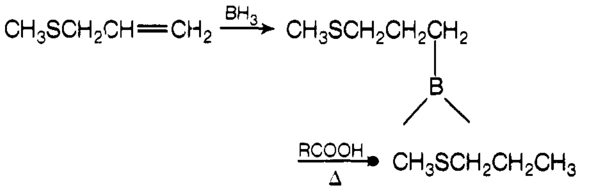
Treatment of trialkylboranes with concentrated mineral acids facilitates the hydrolysis. However, even heating at reflux with mineral acids brings about the protonolysis of only one of the three alkyl groups.[89]

Somewhat unexpectedly, organoboranes are susceptible to attack by carboxylic acids. Thus, triethylborane is converted into diethylboron acetate and ethane under relatively mild conditions (eq 20).[90]



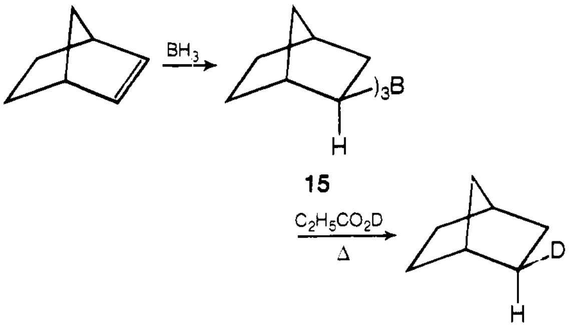
$$(C_2H_5)_3B + CH_3COOH \xrightarrow{\Delta} (C_2H_5)_2BOC(=O)CH_3 + C_2H_6 \quad (20)$$

A detailed investigation of the action of carboxylic acids on organoboranes revealed that two of the three groups can be removed by excess glacial acetic acid at room temperature. All three groups can generally be removed by refluxing the organoborane in diglyme solution with a moderate excess of propionic acid for 2-3 h.[91,92] Consequently, this hydroboration–protonolysis procedure provides a convenient noncatalytic means of hydrogenating carbon–carbon double bonds in compounds where usual catalytic hydrogenation is difficult (eq 21).[91]



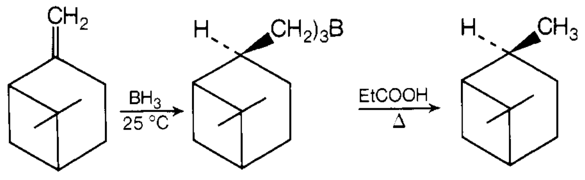
(21)

The protonolysis reaction proceeds with complete retention of configuration as shown by the deuterolysis of tri-*exo*-norbornylborane (**15**) (eq 22).[93] The preparation of *cis*-pinane (**16**) also illustrates the stereoselectivity of this process (eq 23).[94]



15

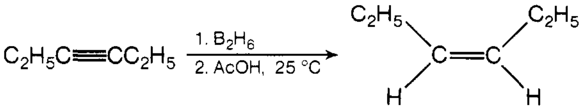
(22)



(23)

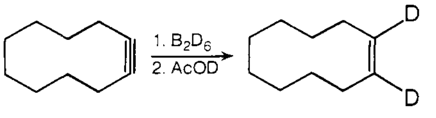
16

Vinylboranes, formed by the hydroboration of alkynes, undergo complete protonolysis with acetic acid at 0 °C.[95] This reaction provides a convenient procedure for the conversion of internal alkynes into *cis*-alkenes with excellent stereochemical purity (eq 24).[95] The synthesis of *cis*-cyclodecene-*1,2-d*$_2$ illustrates an interesting application of this process (eq 25).[96]



(24)

68% isolated
>99% cis

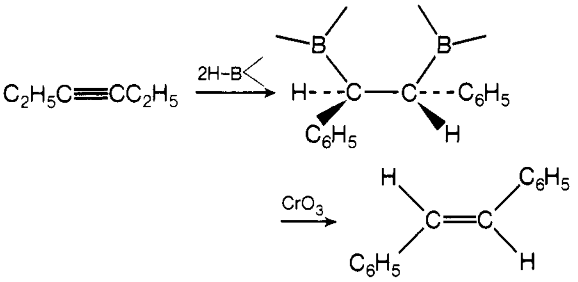


(25)

Under forcing conditions, organoboranes undergo partial hydrogenation to alkanes plus alkyldiboranes.[97] No catalyst is required, but high temperatures (160–200 °C) and high pressures of hydrogen (200–300 atm) are required.[97] The ease of hydrogenation increases with increasing molecular weight.

The hydrogenolysis of trialkylboranes indicates that boranes should be effective homogeneous catalysts for the hydrogenation of alkenes. Such an application has been reported, and the results show that the reaction is particularly valuable when applied to the reduction of high polymers in solution.[98]

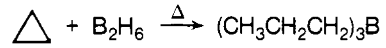
Recently, dihydroboration with BH_3–THF followed by treatment with chromium trioxide in pyridine was used for the conversion of 1,2-cyclotridecadiene to cyclotridecene[99] and for the conversion of diphenylacetylene to *trans*-stilbene.[100] These reactions are proposed to involve a chromium trioxide induced cis elimination of an intermediate vicinal diorganoborane. With diphenylacetylene, the process gives *trans*-stilbene as the only isolated product in 70% yield (eq 26).[100]



(26)

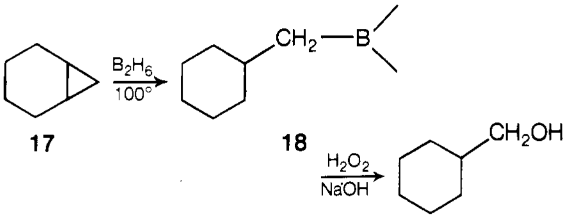
B. Cyclopropanes

Carbon-carbon σ bonds are normally very resistant to attack by boron hydrides. Only with the strained cyclopropane ring does a reductive cleavage occur. Even in this case, a period of hours at 80–100 °C in the gas phase is required to give a complex mixture from which tri-*n*-propylborane can be separated (eq 27).[101]



$$\triangle + B_2H_6 \xrightarrow{\Delta} (CH_3CH_2CH_2)_3B \quad (27)$$

This reductive cleavage of cyclopropanes was examined in detail by Rickborn and Wood.[102,103] They found that norcarane (**17**) and diborane react smoothly at 100 °C in the absence of solvent (liquid phase) to give almost exclusively the primary alkylborane (**18**). Alkaline peroxide oxidation then gave cyclohexylmethanol in good yield (eq 28).[102] Only a 2–3% yield of cycloheptanol is formed concurrently. In general, the cleavage reaction is quite regioselective. The major product is always derived from addition of hydrogen to the most substituted and boron to the least substituted carbon.[103] Interestingly, the cyclopropane cleavage reaction is inhibited by ethereal solvents. A detailed study of the cleavage of 1-methylnorcarane indicated that the reaction is highly regioselective but inherently nonstereospecific; i.e., a 60:40 mixture of *cis*- and *trans*-2-methylcyclohexylmethanol was the maximum selectivity observed.[103]



17 **18**

(28)

C. Organic Halides

Primary, secondary, and tertiary alkyl fluorides, chlorides, bromides, and iodides are all inert toward diborane and the various borane–Lewis base complexes. Also, no reaction occurs between borane and aryl fluorides, chlorides, bromides, or iodides. Even under forcing conditions (1 h at reflux), primary alkyl bromides and iodides are stable to BH_3–THF.[104] Under similar conditions, $LiAlH_4$ is extremely reactive.[105] Under solvolytic conditions, sodium borohydride reacts with readily ionizable secondary and tertiary organic halides to give good yields of the corresponding hydrocarbons (eq 29).[106] Only in the very special

$$RX \longrightarrow R^+ + X^-$$

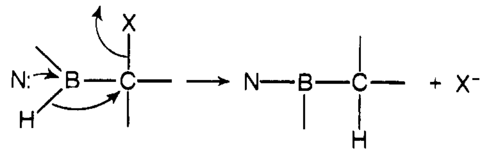
$$R^+ + NaBH_4 \longrightarrow Na^+ + RH + BH_3 \qquad (29)$$

case of an aralkyl halide in nitromethane solvent is reduction with diborane possible (eq 30).[107] However, the presence of sodium

$$(C_6H_5)_3CCl \xrightarrow[MeNO_2]{B_2H_6} (C_6H_5)_3CH \qquad (30)$$

borohydride as a stabilizer in commercial BH_3-THF must be considered when using this reagent for the reduction of an organic compound containing a readily ionizable halide; i.e., a small amount of side reaction can occur as shown in eq 29.

In contrast to the inertness of saturated alkyl halides, unsaturated alkyl halides react rapidly with diborane. The first step in the reaction undoubtedly involves hydroboration to give a haloalkylborane. The proximity of the halogen to the boron then determines the product that will be formed. A nucleophilic (N:) attack on boron is required to give either α-transfer (eq 31), β-elimination (eq 32), or cyclization (eq 33). When more than three carbon atoms separate the halogen and boron, the intermediate is stable toward nucleophilic reagents, and alkaline peroxide oxidation gives the halo alcohol.[108]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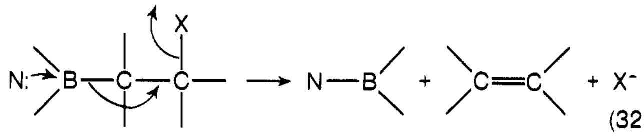
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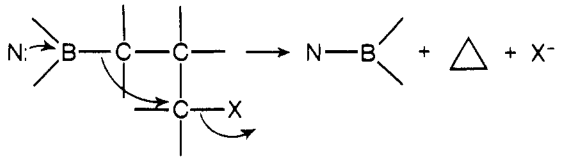
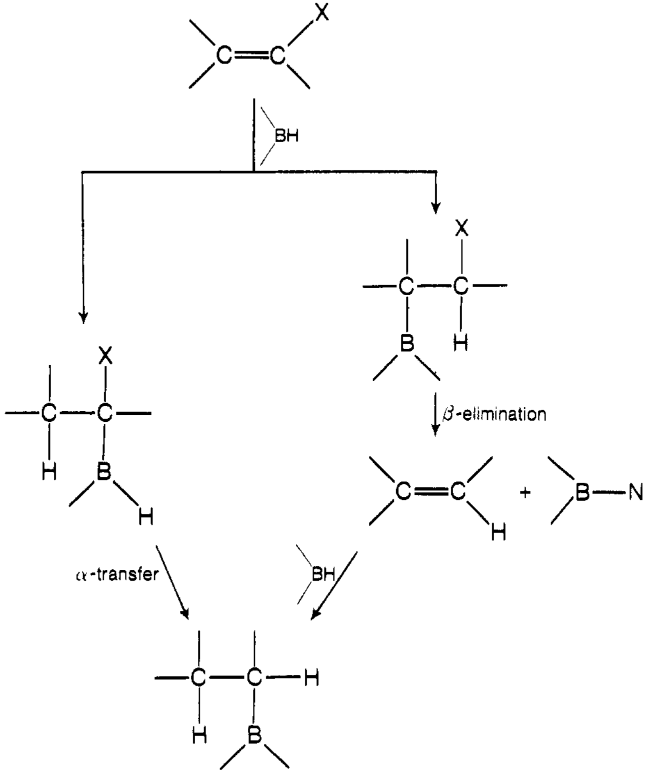

(33)

The mechanistic aspects of the hydroboration of vinyl halides have been discussed thoroughly by Pasto and Snyder[109] and by Brown and Sharp.[34] For α-transfer and β-elimination, the ether used as a solvent for the hydroboration reaction is sufficiently reactive to induce the rearrangements. The alkene formed upon β-elimination would, of course, undergo subsequent hydroboration to give an alkylborane. Thus, the final product resulting from the reaction of a vinylic halide with BH_3-THF is an alkylborane regardless of the initial position of attack by boron. This is illustrated in Scheme I.

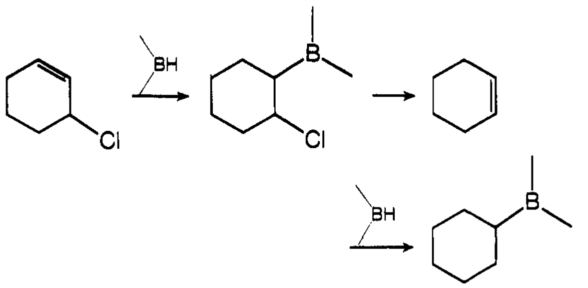
An early investigation by Stone and coworkers on the reaction of diborane with perfluoroethylene showed that completely hydrogenated ethylborane derivatives were the only alkylboron products formed.[110,111] Although not recognized at the time, these results can be explained by the mechanism shown in Scheme I.

The reaction shown in eq 33 was originally observed by Hawthorne and Dupont during a study of the hydroboration of vinyl chloride and allyl chloride.[112] The cyclization requires a strong base, such as hydroxide ion, as a nucleophile. This reaction was later reinvestigated by Köster and coworkers[113] and was developed into a convenient procedure for the synthesis of cyclopropanes by Brown and Rhodes.[114]

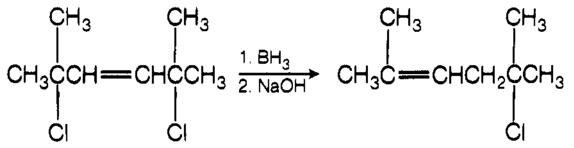
SCHEME I



In systems where either β-elimination or cyclization can occur, β-elimination is usually favored. For example, hydroboration of 3-chlorocyclohexene gives a cyclohexylborane (eq 34)[115] and hydroboration of 2,5-dichloro-2,5-dimethyl-3-hexene gives 5-chloro-2,5-dimethyl-2-hexene (eq 35).[116]



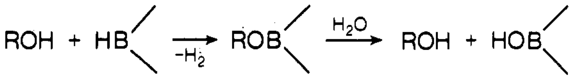
(34)



$$CH_3C(CH_3)(Cl)CH{=}CHC(CH_3)(Cl)CH_3 \xrightarrow[2.\ NaOH]{1.\ BH_3} CH_3C(CH_3){=}CHCH_2C(CH_3)(Cl)CH_3 \qquad (35)$$

D. Alcohols

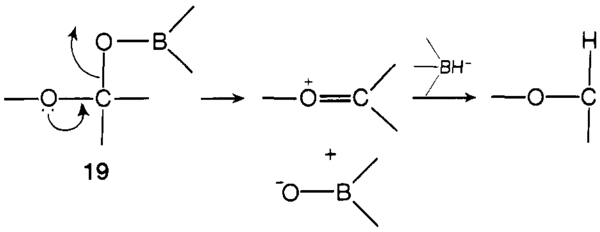
As previously discussed, alcohols normally react rapidly with diborane to give alkoxyboranes. Hydrogenolysis of the carbon–oxygen bond usually does not occur. Thus, the alcohol is regenerated upon hydrolytic workup (eq 36).



$$ROH + HB< \xrightarrow[-H_2]{} ROB< \xrightarrow{H_2O} ROH + HOB< \qquad (36)$$

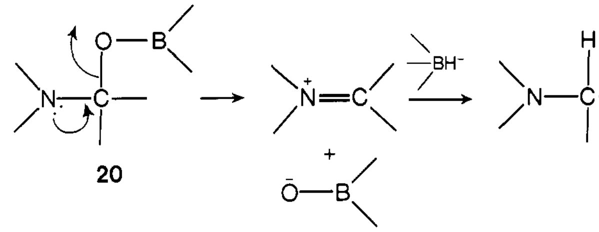
However, this does not mean that reductive cleavage of the carbon–oxygen σ bond is unimportant in borane reductions. When the intermediate alkoxyboron compound is of the correct structural type, cleavage of the carbon–oxygen bond becomes the major reaction pathway. Equations 37–40 illustrate a variety of known carbon–oxygen bond cleavages.

Although the mechanism may be more complex, the presence of an *electron-donating* atom is required before cleavage of the C–O bond is observed in a C–O–B type of intermediate. Other examples are known and will appear later, but intermediates



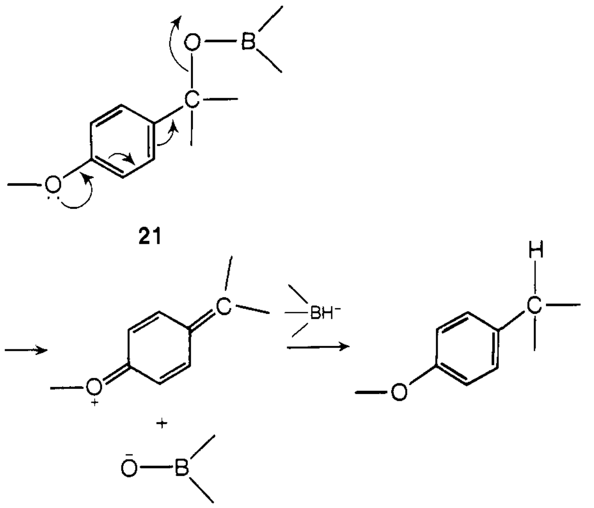
19

(37)



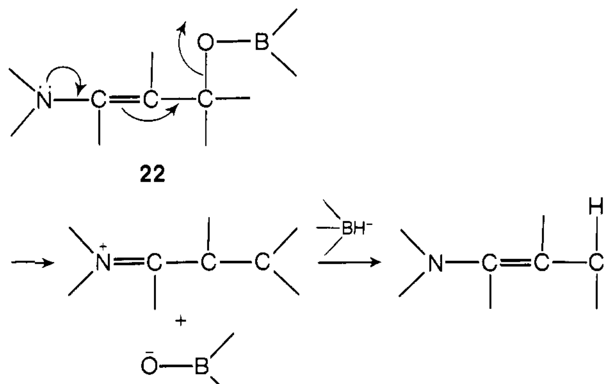
20

(38)



21

(39)

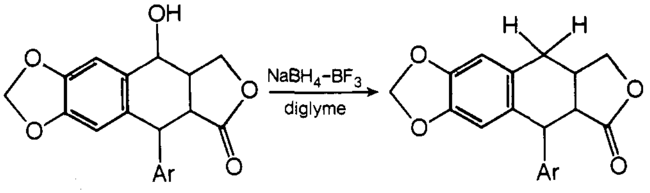


22

(40)

19–**22** illustrate the generality of this *electron-donation induced cleavage.*

Obviously, intermediate **19** is formed during the reaction of esters and lactones with borane, and the importance of eq 37 will become apparent later in the section dealing with the reduction of this functional group (vide infra, section VI.E). Also, both intermediate **20** and eq 38 constitute the reaction pathway observed in the facile reduction of amides with borane reagents (vide infra, section VI.F). Intermediates of the type illustrated by **22** can be formed by reduction of the corresponding aldehyde or ketone, and examples will be discussed in section VI.A. Finally, intermediates corresponding to **21** are not only formed during the reduction of certain aldehydes and ketones but can also arise directly from an appropriate alcohol. Reductive cleavage (eq 39) of the alcohol then results. Specific examples are illustrated by eq 41–43.



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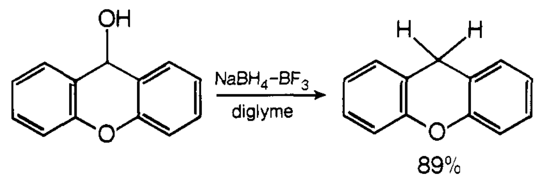
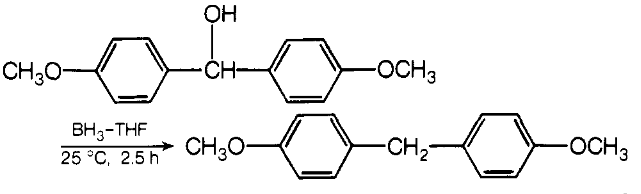


89%

(42)[118]

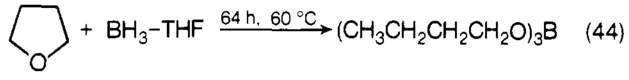


82%

(43)[119]

E. Ethers

The obvious importance of ether solvents in diborane chemistry would seem to indicate that such solvents must be chemically inert toward diborane. However, this is not the case. The formation of borane–ether complexes is known to occur, but more crucially, reductive cleavage of ether linkages by diborane is also known. Fortunately, reductive cleavage is a relatively slow reaction under normal conditions.[120,121] With BH_3-THF, heating for an extended period of time in a sealed tube is necessary to obtain a reasonable yield of tri-*n*-butyl borate (eq 44).[120]



$$+ BH_3\text{-THF} \xrightarrow{64\text{ h},\ 60\ ^\circ\text{C}} (CH_3CH_2CH_2CH_2O)_3B \quad (44)$$

The reductive cleavage of THF by BH_3-THF is of negligible importance for the laboratory use of this reagent. The BH_3-THF reagent is stable for several months when prepared and stored at 0 °C under nitrogen.[35] The reagent does lose 1–3% of the available BH_3 per day when stored at ordinary temperatures (25–30 °C).[121] This becomes a major problem during the manufacture, storage, and shipment of the commercial material. Fortunately, Brown discovered that small amounts of dissolved sodium borohydride stabilize the BH_3-THF reagent and effectively eliminate the loss of hydride due to reductive cleavage.[121] This observation resulted in the reagent becoming commercially available. The stabilized BH_3-THF reagent shows no loss in active hydride after 2 weeks at 25 °C and only a 3% loss after 8 weeks at 25 °C.[121] Even so, whenever possible, the reagent should be stored at 0 °C to maintain maximum hydride activity.

Recently, Kollonitsch suggested that sodium borohydride, instead of stabilizing the BH_3-THF reagent, might actually cause a generation of pressure to occur due to a reaction as shown in eq 45.[122]

$$B_2H_6 + NaBH_4 \xrightarrow{\Delta} \underset{\mathbf{23}}{NaB_3H_8} + H_2 \quad (45)$$

This formation of sodium triborohydride (**23**) is known to occur through a reaction of diborane with sodium borohydride, but the conditions required call for heating a diglyme solution in a sealed tube for 2 h at 100 °C.[123] Under such drastic conditions, diborane alone undergoes decomposition with formation of higher boron hydrides plus hydrogen.[2] Such a pressure buildup could conceivably occur with BH_3-THF, if the reagent was stored improperly, e.g., if stored for an extended period of time at or above room temperature. However, if the stabilized BH_3-THF reagent is stored and handled properly, the generation of excessive amounts of pressure does not become a problem.

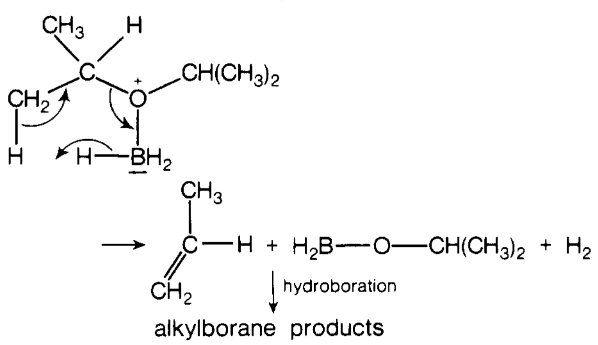
The stabilization of the BH_3–THF reagent by the addition of $NaBH_4$ not only offers a practical solution to a serious problem but also adds support to a suggestion originally advanced by Breuer[124] and later collaborated by Jackson.[125] These investigators adequately demonstrated that when the BH_3–THF reagent is prepared by the Brown procedure[35] (eq 4), the reagent is invariably contaminated with trace amounts of boron trifluoride. Apparently, even the washing of the diborane stream by passing it through a solution of $NaBH_4$ in diglyme fails to completely remove the boron trifluoride.[125] Therefore, the instability of BH_3–THF is probably due to the presence of trace amounts of boron trifluoride which catalyzes the reductive cleavage by forming a complex with THF. The $NaBH_4$ apparently stabilizes the solution by reacting with the trace amounts of boron trifluoride (eq 4).

In addition to enhancing the reductive cleavage of ether, the presence of BF_3 or $NaBH_4$ can have a pronounced effect on the reactivity of diborane toward other functional groups. Numerous examples will be presented in later sections to illustrate this point.

Obviously, the method used to prepare the borane reagent determines what impurities may be present to effect the results obtained for a given reduction. There are, in reality, four different "borane" reducing agents, and each can show a different reactivity. The most reactive is the in situ generated reagent (actually a number of reagents are possible depending upon the solvent and the order of addition and whether $NaBH_4$ or BF_3 is used in excess). The least reactive would be high-purity B_2H_6 that has been prepared and purified using one of the vacuum-line procedures.[30,31] Finally, two forms of the BH_3–THF reagent are possible and both are widely used. There is the reagent prepared by the Brown procedure[35] which sometimes contains traces of BF_3, and there is the commercial reagent which *always* contains a trace amount of $NaBH_4$.

The presence of these trace impurities is not always detrimental to the reaction under study. Occasionally, vastly improved results are achieved because of the presence of catalytic amounts of either BF_3 or $NaBH_4$. However, it is very important to understand what effect the presence of either BF_3 or $NaBH_4$ will have on the reaction under investigation. The catalytic effect of either BF_3 or $NaBH_4$ will occasionally be used and discussed in this section and in later sections to explain some otherwise unusual results.

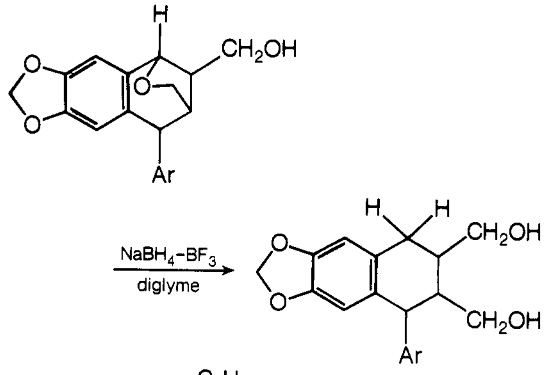
Reductive cleavage reactions have been observed for ethers other than THF. The in situ generation of diborane in diglyme results in detectable amounts of the monomethyl ether of diethylene glycol, the product formed upon ether cleavage of diglyme.[126] Also, diborane was observed to react with diglyme at temperatures above 30 °C with formation of methane,[72] and 1-methyltetrahydrofuran gave 2-pentanol after hydrolysis.[120] Finally, diborane reacts with diisopropyl ether at 80 °C to give a mixture of products that can be rationalized by assuming a novel type of ether cleavage (eq 46).[127]



(46)

Reagents other than BF_3 can enhance the cleavage of ether by diborane. For example, cleavage of diglyme by diborane occurs rapidly at low temperatures in the presence of either mercaptans[128] or elemental halogens.[129] These reactions undoubtedly involve a B–X type of cleavage reagent and do not involve a reductive cleavage by a boron hydride.

As was observed for the hydrogenolysis of alcohols, the presence of electron-donating groups greatly enhances the ease of reductive cleavage. Two specific examples are illustrated (eq 47 and 48). The reactions shown in eq 47 and 48 presumably involve intermediates analogous to **21** and **22**, respectively. However, in the above cases (eq 47 and 48), the leaving group is probably RO-B<⁻ instead of ⁻O-B<.



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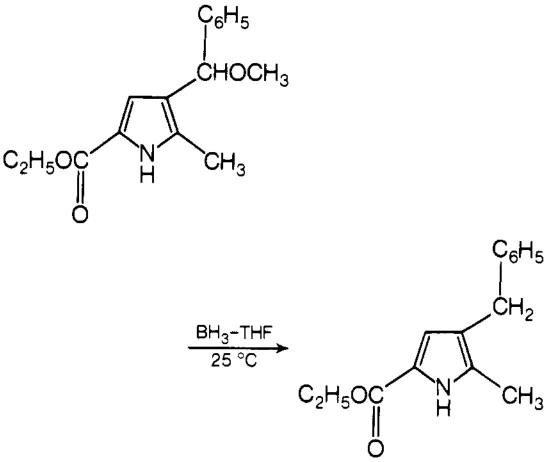
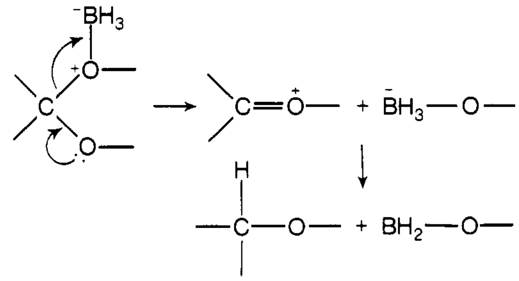


(48)[130]

Acetals and ketals are reductively cleaved with borane reagents under milder conditions (2–3 h at 25–30 °C) than are required for simple ethers.[131,132] A probable reaction pathway is illustrated in eq 49. This mechanism has obvious similarities to the reaction shown in eq 37 and is a straightforward extension of the idea of electron-donation induced cleavage that must be operating in eq 47 and 48. Interestingly, the $NaBH_4$–BF_3 reagent (internal generation of B_2H_6) gives somewhat higher yields than externally generated diborane.[133] A few specific examples are illustrated in eq 50–52. Although it has not been included in these equations and will generally be omitted in later equations, a



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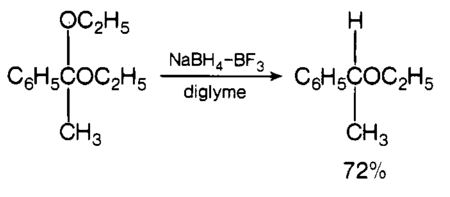
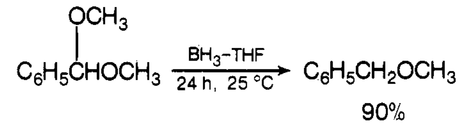


$$C_6H_5\overset{OC_2H_5}{\underset{CH_3}{C}}OC_2H_5 \xrightarrow[\text{diglyme}]{NaBH_4\text{-}BF_3} C_6H_5\overset{H}{\underset{CH_3}{C}}OC_2H_5$$

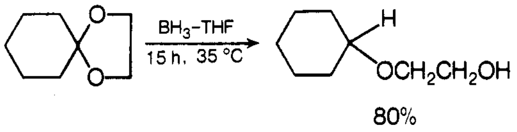
72%

(50)[131]



$$C_6H_5\overset{OCH_3}{CH}OCH_3 \xrightarrow[24\ h,\ 25\ ^\circ C]{BH_3\text{-}THF} C_6H_5CH_2OCH_3 \quad 90\%$$

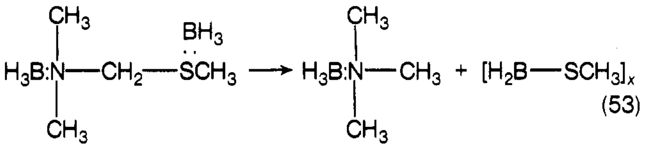
(51)[132]



(52)[132]

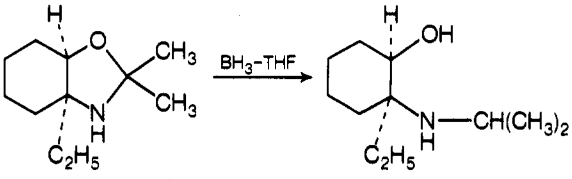
hydrolysis step is usually necessary in the examples of borane reductions presented herein.

Thioketals are inert toward diborane,[134] but an aminomethyl sulfide–bisborane adduct was very unstable even at room temperature and decomposed to an amine–borane with cleavage of a carbon–sulfur bond (eq 53).[135]

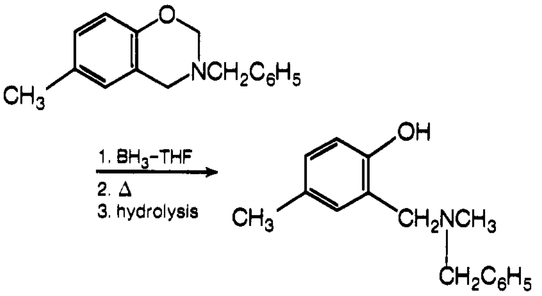


$$H_3B{:}\overset{CH_3}{\underset{CH_3}{N}}—CH_2—\overset{BH_3}{\overset{..}{S}}CH_3 \longrightarrow H_3B{:}\overset{CH_3}{\underset{CH_3}{N}}—CH_3 + [H_2B—SCH_3]_x \quad (53)$$

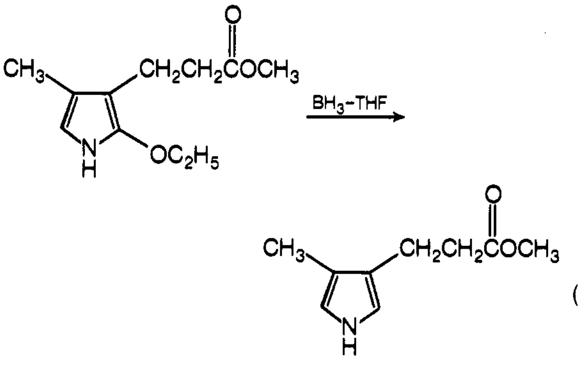
Various 1,3-amino ethers are also known to react readily with borane reagents giving carbon–oxygen bond cleavage (eq 54–56).



(54)[136]



(55)[137]



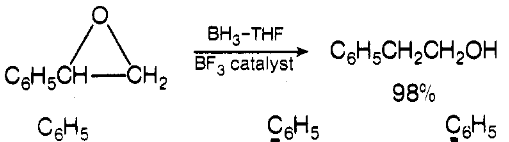
(56)[138]

F. Epoxides

In the first reported reaction of an epoxide with diborane, a dialkoxyborane plus a solid polymer were formed as products.[139] The reductive ring opening occurred rapidly even at −80 °C. As part of a study of the reaction of representative organic compounds with the NaBH$_4$–BF$_3$ reagent in diglyme, Brown and Subba Rao found that the reduction of epoxides was fast (complete after 0.5 h at 25 °C).[10] A later detailed investigation by Pasto and co-workers indicated the reduction of epoxides with BH$_3$–THF occurs slowly at room temperature.[140] More critically, a complex mixture of products results from the use of BH$_3$–THF.[140] The reason for this apparent discrepancy between the earlier work of Brown[10] and the later work of Pasto[140] must be that either NaBH$_4$ or BF$_3$ is acting to catalyze the reaction of diborane with epoxides.

Consequently, the BH$_3$–THF reagent, which contains neither a strong base (NaBH$_4$) nor a strong acid (BF$_3$) is a much milder reducing agent toward epoxides than the reagent prepared in situ from NaBH$_4$ and BF$_3$. Brown recently duplicated the complex results obtained for the BH$_3$–THF reduction of epoxides.[24]

Brown and Yoon have demonstrated the pronounced catalytic action of both NaBH$_4$ and BF$_3$ on the reduction of epoxides with BH$_3$-THF.[141,142] For example, in the presence of catalytic quantities of boron trifluoride, styrene oxide and related epoxides undergo quantitative regioselective reductive opening reactions (eq 57 and 58).[141] Also, in the presence of catalytic quantities of sodium borohydride, aliphatic epoxides undergo rapid, quantitative reductive ring opening (eq 59 and 60).[142]



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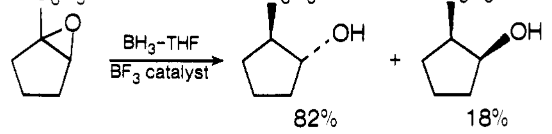

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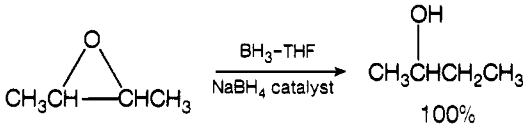

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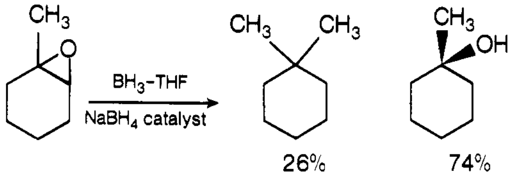
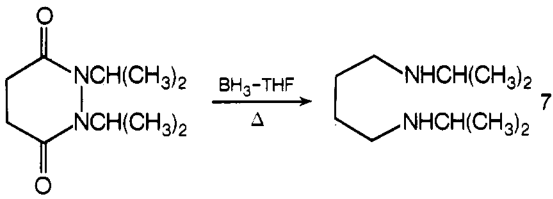


(60)

G. Miscellaneous

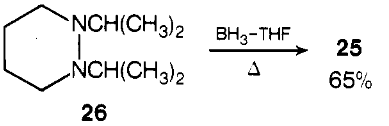
The sulfur–sulfur bond in an organic disulfide is normally quite unreactive toward diborane and BH$_3$-THF.[24] However, carbon–sulfur bond cleavage occurs with triphenylmethyl sulfide derivatives giving triphenylmethane as the only organic product.[143]

The nitrogen–nitrogen single bond is also very unreactive toward BH$_3$-THF. The only reported cleavage of this bond occurred when a perhydropyridazine-3,6-dione (**24**) was treated with a large excess of BH$_3$-THF at reflux (eq 61).[144] It is very likely that the formation of **25** occurred via the perhydropyridazine (**26**) because **26** is converted into **25** under similar reaction conditions (eq 62).[144]



(61)

24 **25**



(62)

26

IV. Reduction of Organic Sulfur Compounds

Dimethyl sulfoxide is reduced to dimethyl sulfide with BH_3-THF at a moderate rate at 0 °C.[24] However, all other sulfur derivatives examined, including aromatic and aliphatic sulfones and cyclohexyl tosylate, were inert to BH_3-THF under the standard conditions.[24] An aromatic sulfone also failed to react with the $NaBH_4$-BF_3 reagent at 25 °C.[10] In contrast to this observed inertness of organic sulfones, sulfur dioxide reacts smoothly with diborane to give hydrogen sulfide, sulfur, and boric acid.[107,145]

V. Reduction of Organic Nitrogen Compounds

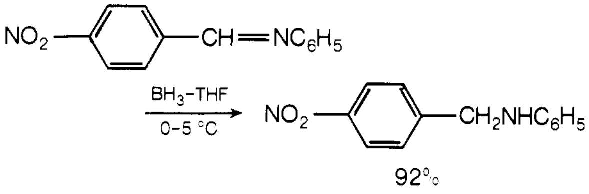
A variety of organic functional groups containing a multiple bonded nitrogen are reduced with borane reagents. Most of the effort has been directed toward the reduction of imines, oximes, nitro derivatives, and nitriles. The reaction of borane reagents with these functional groups will be discussed in detail in individual sections. However, a number of other nitrogen-containing groups undergo reaction with diborane.

Diazomethane reacts readily with BH_3-THF giving an almost quantitative yield of a highly crystalline, boron-containing polymethylene.[146] Diborane reacts with organic isocyanates and isothiocyanates to give thermally unstable diadducts at low temperatures.[147] At higher temperatures decomposition leads to complex mixtures which include aminoboranes and boron-nitrogen cyclic trimers. Also, the pyridine-borane adduct is stable at room temperature[148] but decomposes upon heating, sometimes violently, and should never be distilled.[149] Finally, pyridine *N*-oxide is reduced at a moderate rate, but hydride uptake and examination of the ir spectra of the product revealed evidence for attack on the aromatic ring.[24]

A. Imines

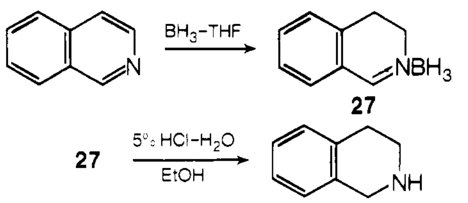
1. Simple Alkyl-Substituted Imines

The reduction of Schiff bases with BH_3-THF proceeds under very mild conditions giving excellent yields of the corresponding amines.[150] A specific example is shown in eq 63, but this reduction and similar reductions of Schiff bases can also be carried out with the milder reducing agent, sodium borohydride. Consequently, the borane reagents would appear to be of limited utility for imine reductions.



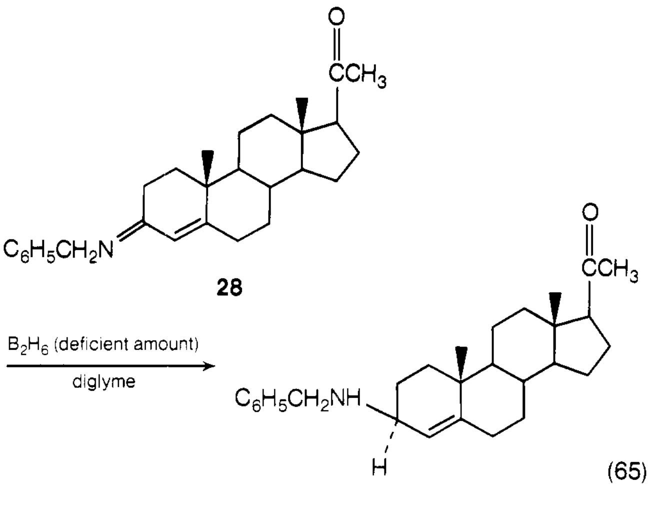
(63)

With a number of specific systems, diborane either exhibits a superior selectivity or gives a product that is not possible using sodium borohydride as the reducing agent. For example, isoquinoline reacts with BH_3-THF giving an intermediate dihydroisoquinoline-borane adduct (**27**), which is reduced further to tetrahydroisoquinoline upon treatment with dilute aqueous hydrochloric acid in ethanol (eq 64).[151]



(64)

The selectivity of diborane is illustrated by the reported reduction of an imine group in the presence of a ketone (eq 65).[152] When sodium borohydride in methanol was used as the reducing agent, both the imine and ketone were readily reduced (eq 66).[152]



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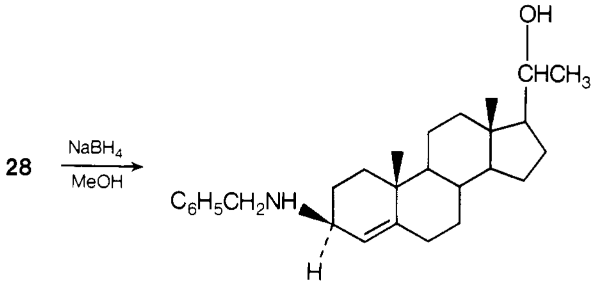
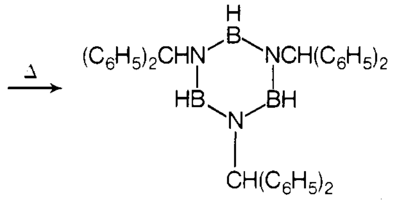


(66)

Some interesting boron-containing heterocyclic products are possible via reduction of imines. For example, diborane and diphenylketimine react in hexane at 20 °C to precipitate an adduct identified as **29**, which eliminates hydrogen slowly at 20 °C and, upon heating, trimerizes to the borazine **30** (eq 67).[153]

$$(C_6H_5)_2C{=}NH \xrightarrow[20°]{B_2H_6} (C_6H_5)_2C{=}NH{:}BH_3$$

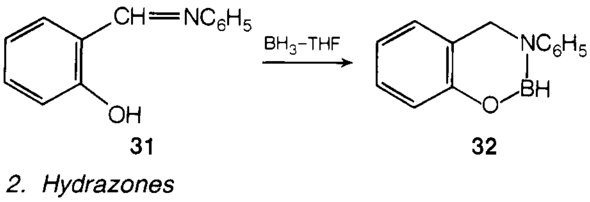
29



(67)

30

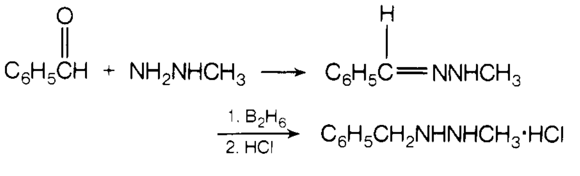
Also, the Schiff base **31** reacts with BH_3-THF to give compound **32** (eq 68).[154] This organic boron compound (**32**) is thermally stable and can be vacuum distilled without decomposition.



(68)

2. Hydrazones

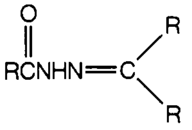
Addition of diborane to a hydrazone in diglyme gives no reduction. However, subsequent saturation with anhydrous hydrogen chloride gives 1,2-dialkylhydrazines as mono- or dihydrochlorides in excellent yields.[155] A one-flask condensation-reduction sequence is possible. A specific example is shown in eq 69. This reaction was found to be particularly useful in



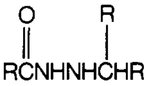
$$C_6H_5\overset{O}{\overset{\|}{C}}H + NH_2NHCH_3 \longrightarrow C_6H_5\overset{H}{\overset{|}{C}}{=}NNHCH_3 \xrightarrow[2.\ HCl]{1.\ B_2H_6} C_6H_5CH_2NHNHCH_3{\cdot}HCl \quad (69)$$

cases where $LiAlH_4$ reduction gave only partial reduction or extensive nitrogen–nitrogen bond cleavage.[155]

2,4-Dinitrophenylhydrazones are stable toward BH_3–THF and in certain special cases are useful as carbonyl-protecting groups during hydroboration.[156] Also, carboxyhydrazones (**33**) are completely inert toward BH_3–THF.[157] Reduction with aqueous sodium borohydride gives carboxyhydrazines (**34**) in good yields.[157]



33

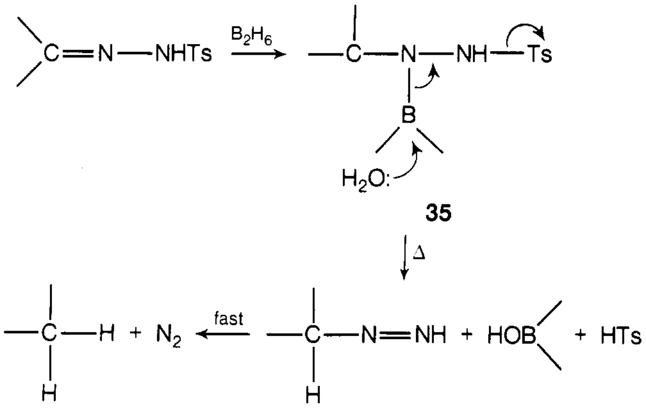


34

Caglioti and coworkers have found that sodium borohydride is also a very suitable and convenient reagent for the reduction of tosylhydrazones of aldehydes and ketones.[158] Hydrolytic workup gives the hydrocarbon. Thus, this reaction provides a mild and useful procedure for the deoxygenation of aldehydes and ketones.[159]

An investigation of the action of various reducing hydrides on tosylhydrazones indicated that diborane can be used if, following the reduction, the reaction mixture is heated at reflux with water.[160] A possible reaction pathway is shown in Scheme II.[161] Interestingly, if the intermediate **35** is treated in the cold with water, then the tosylhydrazine can be isolated.[162]

SCHEME II



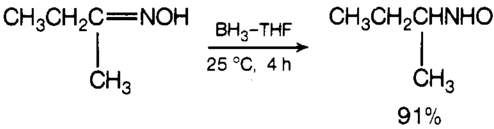
B. Oximes

The reduction of the readily available aldoximes and ketoximes with BH_3–THF provides a facile and convenient synthesis of N-monosubstituted hydroxylamines.[163] When the oxime is added to BH_3–THF, a slow reduction occurs and only a part of the expected hydrogen is liberated.[24] However, if the order of addition is reversed, the reaction proceeds readily with the utilization of two hydrides, one for hydrogen evolution and one for reduction. Hydrolysis then gives the *N*-alkyl hydroxylamine in good yield.[24,163] It is not clear whether this reduction involves an initial attack on the acidic hydrogen followed by addition of the boron hydride to the carbon–nitrogen double bond,[163] or if the addition of B–H occurs prior to hydrogen evolution.[164]

Irrespective of the precise mechanism, this reduction of oximes with BH_3–THF provides an attractive synthetic route to the corresponding hydroxylamines (eq 70 and 71).[163]

BMS can also be used as the reducing agent and offers, as an advantage, a much simpler isolation procedure.[84] Equation 72 gives a specific example.

The reduction of aliphatic oximes with BH_3–THF leads to an intermediate which can be hydrolyzed with either aqueous acid or base. However, α-aryl oxime reduction intermediates must be hydrolyzed with aqueous acid; on basic hydrolysis they disproportionate to amines and oximes.[163] Also, diaryl oximes are unreactive toward BH_3–THF even after 12 h at reflux.[163]



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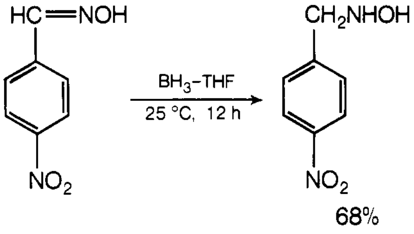

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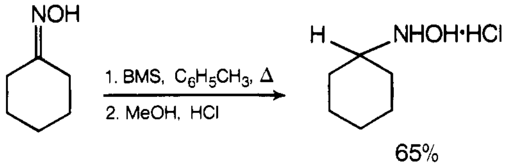
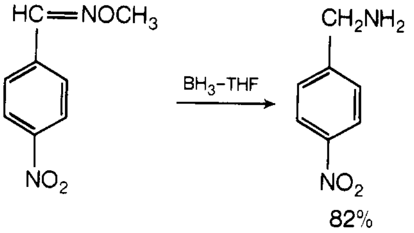


(72)

Heating the intermediate from the BH_3–THF reduction of an aliphatic oxime to 105–110 °C in a diglyme–THF solvent system gives complete reduction to the corresponding amine.[165] On the other hand, oxime ethers and oxime acetates are reduced readily at 25 °C.[165,166] Hydrolysis then gives excellent yields of the corresponding amines (eq 73–75).



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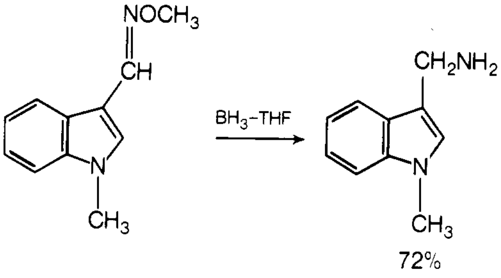
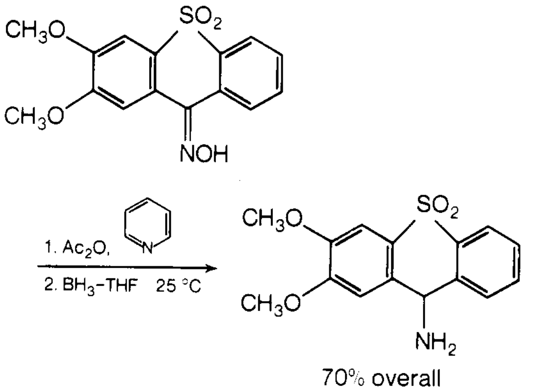


(74)[165]

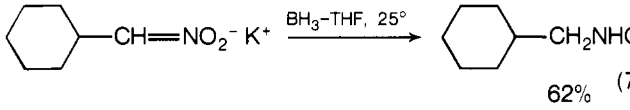


(75)[167]

C. Nitro Compounds and Related Derivatives

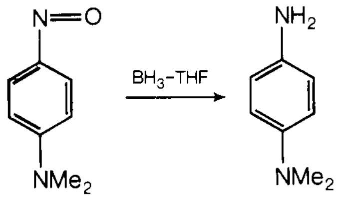
Nitrobenzene and 1-nitropropane fail to react with either the $NaBH_4$–BF_3 reagent[10] or with BH_3–THF[24] in any reasonable time under normal conditions. Also, the aryl nitro group fails to react with BMS even under somewhat more vigorous conditions.[84] Azoxybenzene is unreactive, but azobenzene is reduced at a moderate rate, utilizing two hydrides with hydrogen evolution and giving aniline upon hydrolysis.[24]

Even though the nitro group is very inert, salts of nitroalkanes are readily reduced to hydroxylamines with BH_3–THF (eq 76).[168] Presumably, the anion provides a point of attack for the electrophilic borane species.

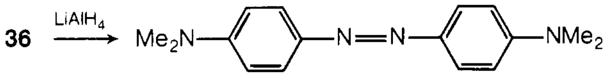


(76)

The reduction of aromatic nitroso compounds with BH_3–THF at 25 °C affords the corresponding amines in good yields.[169] Interestingly, reduction of *p*-nitroso-*N,N*-dimethylaniline (**36**) with BH_3–THF gives the amino compound **37** in 64% yield (eq 77), while $LiAlH_4$ reduction of **36** gives the azo compound **38** in 80% yield (eq 78).[169]



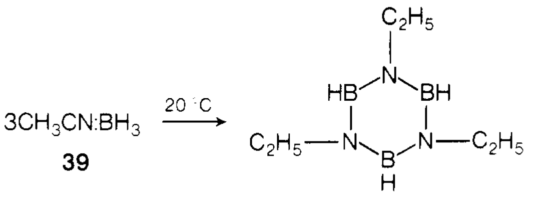
36 **37**, 64% (77)



38, 80% (78)

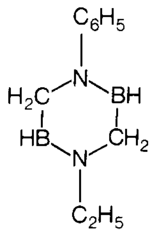
D. Nitriles

Acetonitrile reacts with diborane at low temperatures to form a borane adduct (**39**).[170] Upon warming to ~20 °C this adduct decomposes to give about a 50% yield of *N,N,N*-triethylborazine (**40**) (eq 79).[170] On a larger scale this adduct **39** can decompose explosively into hydrogen and **40** plus higher molecular weight byproducts.[171] Therefore, a safer procedure was developed whereby gaseous diborane (diluted with nitrogen) is slowly added to refluxing acetonitrile to give **40** as the major volatile product in 35–40% yield.[171]

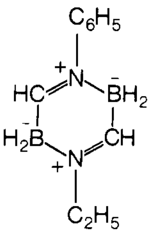


39 **40** (79)

Phenyl isocyanide also reacts readily with diborane to give a 1:1 adduct dimer as a white, crystalline solid.[172,173] The solvent has a pronounced effect upon the product formed. When the reaction is run in dimethyl ether at −111 °C, the dimer product has structure **41**.[172] However, if the reaction is run in petroleum ether at −65 °C, the dimer product has structure **42**.[173]

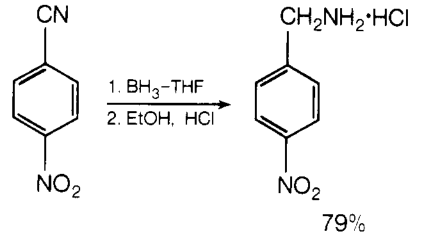


41



42

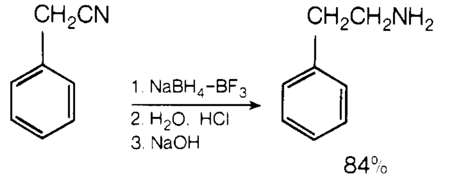
The BH_3–THF reagent reacts slowly at 0 °C with both aliphatic and aromatic nitriles.[24] However, by using an excess of borane reagent and a higher temperature, excellent isolated yields of amines are possible upon acid hydrolysis of the intermediate borazines (eq 80 and 81).[10] The $NaBH_4$–BF_3 reagent gives similar results (eq 82).[10]



(80)

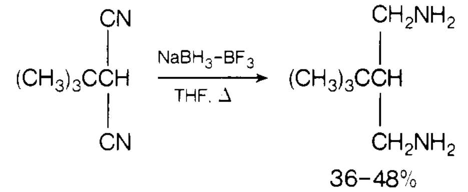
$$N\equiv C(CH_2)_4C\equiv N \xrightarrow[\text{2. EtOH, HCl}]{\text{1. BH}_3\text{-THF}} H_2NCH_2(CH_2)_4CH_2NH_2\cdot HCl$$

74% (81)



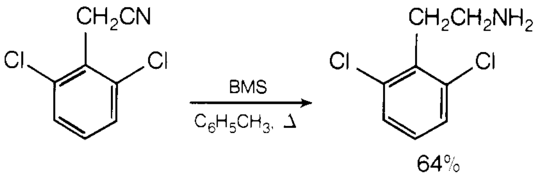
(82)

A detailed procedure is available for the reduction of a dinitrile (eq 83).[174] Also, BMS is a useful reagent for the preparation of amines via reduction of nitriles (eq 84).[84]



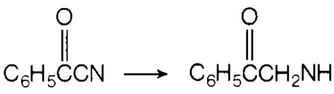
$$(CH_3)_3CCH(CN)_2 \xrightarrow[\text{THF, }\Delta]{NaBH_3\text{-}BF_3} (CH_3)_3CCH(CH_2NH_2)_2$$

36–48% (83)



(84)

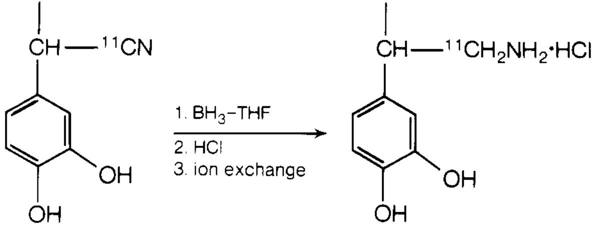
Equations 80 and 84 give some indication of the selectivity that is possible for the borane reduction of nitriles. The investigations by Brown and co-workers seem to indicate that nitriles are reduced faster than esters or acid chlorides.[10,24] Naturally, alkyl halide substituted nitriles can be reduced with diborane without difficulty. Even in the case of trichloroacetonitrile and trifluoroacetonitrile, reaction with diborane proceeds without loss of halogens.[175] The selective reduction shown in eq 85 is also possible using BH_3–THF.[176]



$$C_6H_5C(=O)CN \longrightarrow C_6H_5C(=O)CH_2NH_2$$

60% (85)

Recently, an interesting nitrile reduction step was used in the preparation of ^{11}C-labeled norepinephrine hydrochloride (**43**) (eq 86).[177] This reaction was not studied in detail or in general, but it should be possible to apply this procedure to other cyanohydrins. Thus, this procedure should provide a general syn-



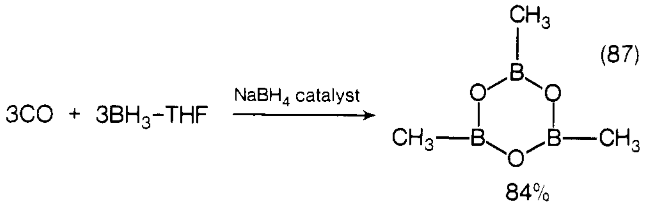
43 (86)

thetic route to β-amino alcohols and, more importantly, a convenient new procedure for the preparation of physiologically active 2-amino-1-phenylethanol derivatives.

VI. Reduction of Organic Oxygen Compounds

Without a doubt, the borane reduction that has received the most attention is the reaction with the carbon-oxygen double bond. A wide variety of organic functional types contain a carbonyl group. These reductions will be discussed in detail in the following sections dealing with the specific functional groups.

As was discussed previously in this review, the different borane reagents possess different reactivities, and this important fact will become even more evident in the discussions dealing with the reduction of the carbon-oxygen double bonds. But first the reaction of BH_3-THF with carbon monoxide should be mentioned as a particularly informative example. At atmospheric pressure and room temperature only a small quantity of carbon monoxide is absorbed by BH_3-THF. However, in the presence of a small catalytic quantity of sodium borohydride, the absorption of carbon monoxide is rapid (complete in 2 h) and provides a convenient synthesis of trimethylboroxine (eq 87).[178]



(87)

The reactivity of acid chlorides toward borane reagents has become an area of minor controversy. Different results have been obtained depending upon the borane reagent used. Since this functional group is readily reduced with sodium borohydride, there is little interest in studying the synthetic possibility of using BH_3-THF. However, the complete understanding of the reactivity of BH_3-THF is important when applying this reagent to selective reduction problems.[24] Consequently, a short discussion on the reactivity of acid chlorides is appropriate.

In the original investigation,[5] which involved the use of diborane in the absence of a solvent, the reaction with acetyl chloride was very slow. On the other hand, aldehydes and ketones reacted rapidly. Yet the introduction of chlorine substituents α to the carbonyl group completely altered the high reactivity. Thus, chloral failed to exhibit any reactivity toward diborane. The donor properties of these carbonyl groups toward boron trifluoride was correlated with their reactivity toward diborane.[5] Consequently, the diborane reaction was proposed to involve an initial formation of a borane addition compound (**11**) which subsequently converted to products (eq 14).[5]

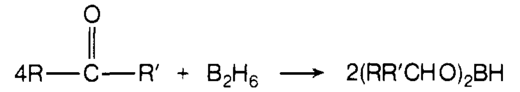
Support for this mechanism is available for the reaction of diborane with acetone in the absence of a solvent.[53,179] Interestingly, the reaction in the gas phase is catalyzed by Lewis bases, such as diethyl ether and THF, and THF is a more active catalyst than diethyl ether.[180] Consequently, it is not surprising that BH_3-THF is a stronger reducing agent than diborane when diborane is used in the absence of a solvent.

Even though diborane fails to react with acid chlorides, BH_3-THF reacts with both aliphatic and aromatic acid chlorides. The reaction is very slow at 0 °C being only about 50% complete after 48 h.[24] Also, acid chlorides containing electronegative substituents are reduced more readily by BH_3-THF than the parent acid chlorides.[181] Thus, the observed rates are reported to decrease in the order: $CCl_3COCl > CH_2ClCOCl \gg CH_3COCl > C_6H_5COCl$.

Evidently there is a marked difference in the effect that electronegative substituents exert on the reactivity of carbonyl derivatives toward BH_3-THF when compared with their reactivity toward diborane. Brown has explained this apparent discrepancy by proposing that the effect of electronegative substituents on the rates of reduction of carbonyl derivatives may be merely a reflection of a change in mechanism brought about by the use of THF as a solvent.[24] In this solvent the more highly substituted acid chlorides may be undergoing nucleophilic attack by the small concentration of borohydride anion produced by the unsymmetrical ionization of BH_3-THF (eq 15), rather than the more usual electrophilic attack by the Lewis acid, BH_3. Thus, chloral is inert toward diborane but is reduced with BH_3-THF.[181]

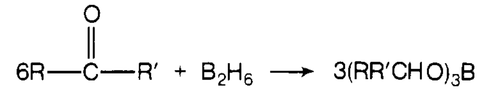
A. Aldehydes and Ketones

Excess diborane reacts readily at room temperature with aldehydes and ketones to yield the corresponding dialkoxy derivatives of borane (eq 88).[5] All attempts to isolate the mono-



$$4R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}R' + B_2H_6 \longrightarrow 2(RR'CHO)_2BH \qquad (88)$$

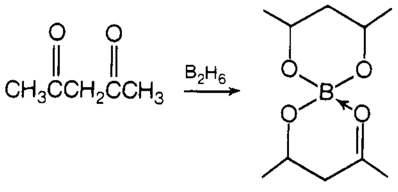
alkoxy derivative have been unsuccessful.[5,180] When an excess of aldehyde or ketone is used, the trialkyl borate is formed (eq 89).[5]



$$6R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}R' + B_2H_6 \longrightarrow 3(RR'CHO)_3B \qquad (89)$$

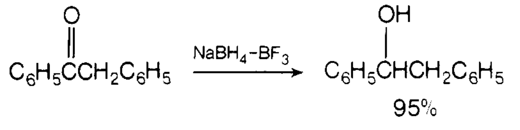
The BH_3-THF reagent reacts similarly. For example, the reaction of 2 equiv of acetone with 1 equiv of BH_3-THF gave a 95% yield of diisopropoxyborane.[182] Aliphatic and aromatic aldehydes and dialiphatic, monoaromatic, and alicyclic ketones all react rapidly with BH_3-THF at 0 °C.[24] Only with benzophenone is the rate considerably slower, probably a consequence of the combined steric and electronic effects of the phenyl groups.[24]

The reduction of acetylacetone is interesting and is reported to give the chelated compound **44** (eq 90).[183] Also, Subba Rao reported the reduction of a large variety of ketones using both externally generated diborane and the $NaBH_4$-BF_3 reagent.[118] Equations 91–93 give a few representative examples.

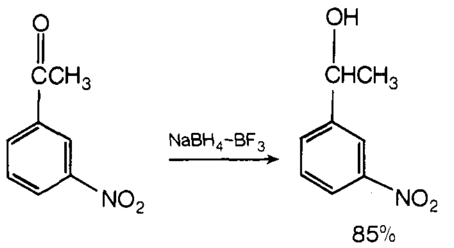


(90)

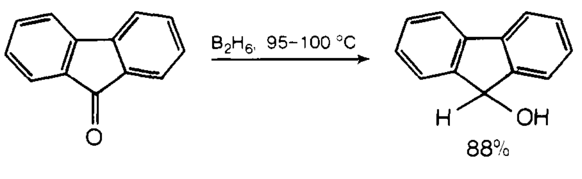
44



$$C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}CH_2C_6H_5 \xrightarrow{NaBH_4\text{-}BF_3} \underset{95\%}{C_6H_5\overset{\overset{\displaystyle OH}{|}}{C}HCH_2C_6H_5} \qquad (91)$$



(92)

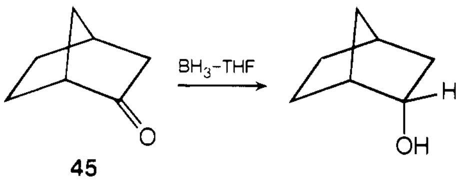


(93)

Sodium borohydride is a much milder reducing agent than either BH_3-THF or the $NaBH_4$-BF_3 reagent and is normally the reagent of choice for the preparation of alcohols via reduction of aldehydes and ketones. However, with a number of systems, reduction with a borane reagent gives a selectivity or a product that is not possible using sodium borohydride.

1. Cyclic Ketones: Stereochemistry

The reduction of norcamphor (**45**) with BH_3-THF is unusually stereoselective (eq 94).[24] Numerous other cyclic ketones have been reduced with borane reagents, and in most cases the yield of alcohol is nearly quantitative. The complete stereochemical results are summarized in Table I.



45

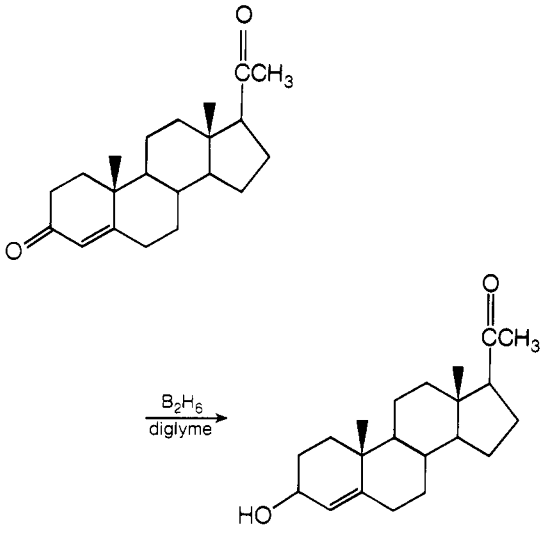
$$\frac{\text{endo}}{\text{exo}} = \frac{98}{2}$$

(94)

The stereoselectivity observed for the reduction of ketones by the borane reagents is interesting, but superior reagents[191] and procedures[192] are now available for the stereospecific synthesis of cyclic alcohols.

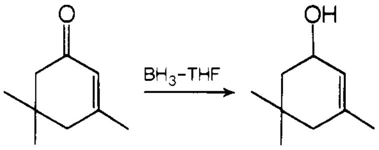
2. α,β-Unsaturated Aldehydes and Ketones

The borane reduction of α,β-unsaturated carbonyl systems does not provide a general synthetic procedure for the preparation of allylic alcohols.[193] Only two examples are known, and both involve the reduction of a β-disubstituted system (eq 95 and 96). Even in these cases, hydroboration of the carbon-carbon double bond competes as a side reaction and proceeds to completion when sufficient borane reagent is used.



70%

(95)[194]

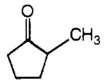
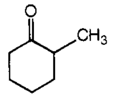
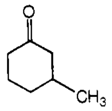
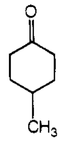
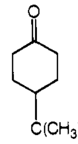
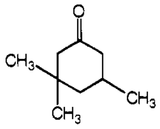
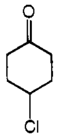
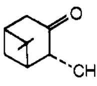
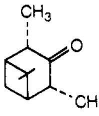
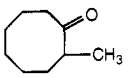


46

(96)[195]

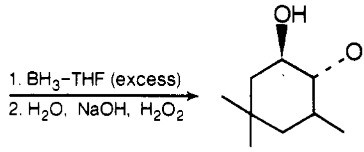
The double bond may undergo hydroboration directly, or a 1,4-addition of boron hydride may occur. Reduction of **46** with excess BH_3-THF probably involves a direct hydroboration of the carbon-carbon double bond.[195] The 1,2-diol **47** is obtained upon alkaline-peroxide oxidation (eq 97). Reduction of **48** with BH_3-THF probably involves a 1,4-addition of boron hydride to the α,β-unsaturated system because the enol **49** is obtained in quantitative yield upon hydrolysis (eq 98).[196]

TABLE I. Reduction of Cyclic Ketones

Ketone	Reducing agent and conditions[a]	Alcohol product Major epimer, %		Ref
	A B	trans trans	75 69	184 185
	A B	trans trans	74 65	184 185
	C A	cis cis	92 88	186 187
	C A	trans trans	89 85	186 188
	A B	trans trans	90 92	188 189
	A	trans	66[b]	187
	C	cis	69	186
	A	cis	90	190
	A	trans	75	190
	A	cis	82	184

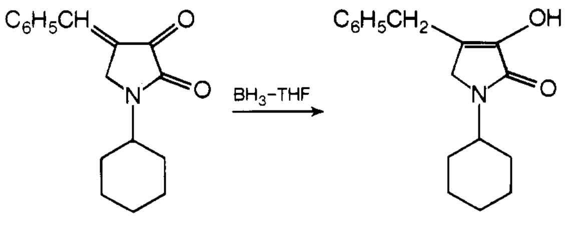
[a] A, BH_3—THF at 0 °C; B, B_2H_6 in diglyme at 0 °C; C, BH_3—THF at an unspecified temperature. [b] Only a 61% isolated yield of alcohol.

46



65% (97)

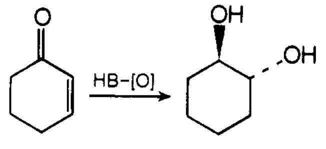
47



(98)

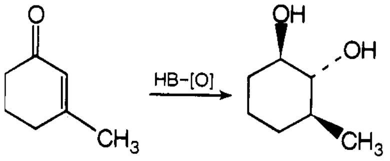
48 **49**

In addition to the hydroboration-oxidation (HB-[O]) of **46**, other α,β-unsaturated ketones can be converted into trans 1,2-diols using this procedure. Equations 99–104 give some additional examples.

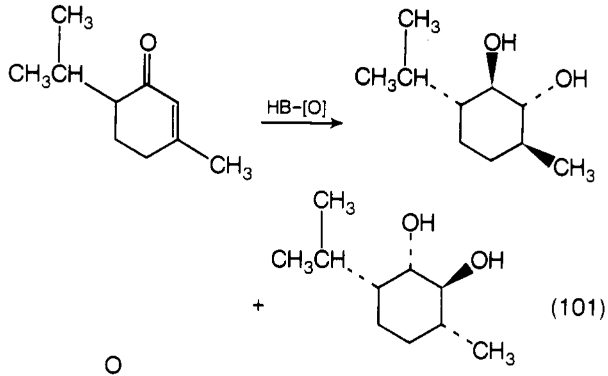


50 **51**

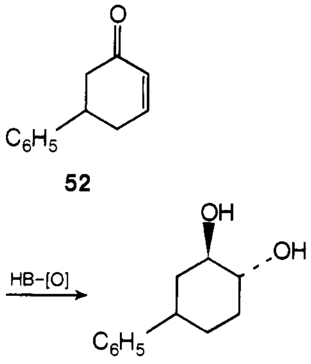
60% total yield of diol
86% isomer **51** (99)[197]



70% (100)[195]



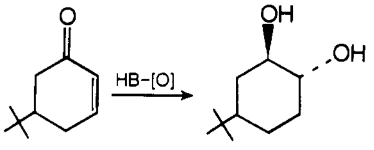
(101)[198]



52

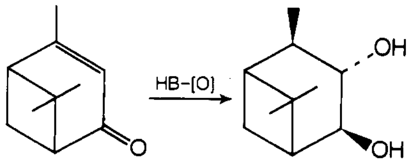
53

59% total yield of diol
76% isomer **53** (102)[197]



54 **55**

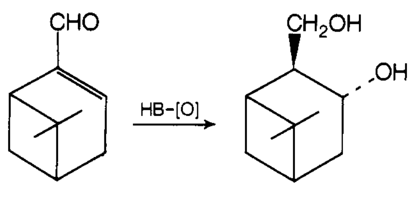
56% total yield of diol
81% isomer **55** (103)[197]



50% (104)[199]

The HB-[O] of **50, 52,** and **54** also gives substantial amounts of the 1,3-diol; i.e., the diol product collected for these three cases contained, in addition to the trans 1,2-diol, the 1,3-diol in the amount of 8, 24, and 19%, respectively.[197]

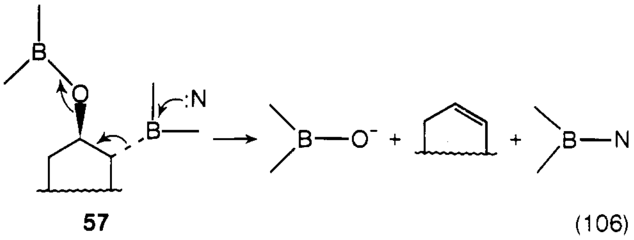
The only reported HB-[O] of an α,β-unsaturated aldehyde resulted in the isolation of the 1,3-diol **56** as the major product (eq 105).[199]



56

55% (105)

The major organoborane product formed upon hydroboration of cyclic α,β-unsaturated ketones must have the structure **57**, which would be expected to undergo a trans elimination when treated with an appropriate nucleophile (eq 106).

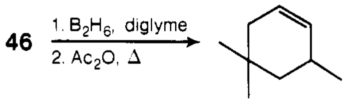


57

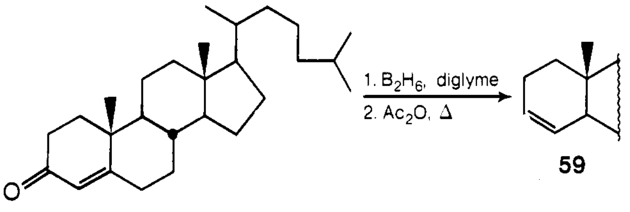
(106)

The ionic pathway depicted in eq 106 is not the only possible mechanism for alkene formation. Alternatively, with an appropriate reagent, the reaction pathway could involve a six-membered cyclic transition state.[200] Irrespective of the precise mechanism, this reaction has been developed by Caglioti and coworkers into a useful alkene synthesis.[201-203]

The Caglioti alkene synthesis involves the hydroboration of a β-disubstituted α,β-unsaturated ketone followed by heating the organoborane in the presence of acetic anhydride. Isophorone (**46**) is converted to a single alkene using this procedure (eq 107).[204] However, the process is most useful in the steroid field for the efficient and stereospecific conversion of Δ^4-3-keto chromophores to Δ^3-5α-alkenes. The conversion of cholest-4-en-3-one (**58**) to the corresponding Δ^3-5α derivative **59** is representative (eq 108).[202]



(107)



58 **59**

(108)

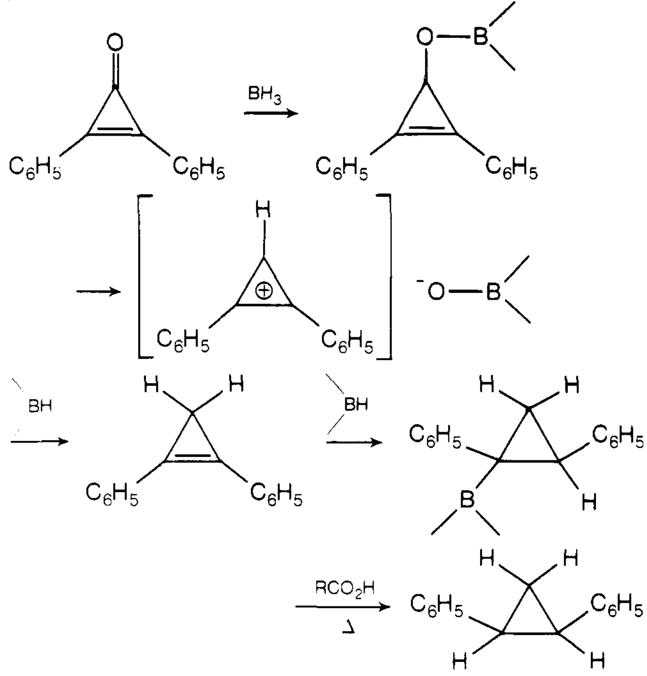
3. *Aldehydes and Ketones Containing Electron-Donating Substituents*

The electron-donation induced reductive cleavage of carbon–oxygen bonds illustrated in eq 39 and 40 is of fundamental importance in the reduction of aldehydes and ketones with borane reagents. Intermediates corresponding to **21** and **22** are formed during the reduction of many functionally substituted carbonyl compounds. The reductive cleavage is known to be catalyzed by trace amounts of both BF_3[124] and $NaBH_4$.[119] Thus, the $NaBH_4$–BF_3 reagent shows a greater tendency to undergo the reactions shown in eq 39 and 40 than does externally generated diborane.[119] The exact mechanism is unknown, but in all cases an intermediate closely related to **21** or **22** is probably involved. For the reduction of certain systems, this process is an unfortunate and undesirable side reaction. However, if the product of choice is the alcohol, then sodium borohydride should be used for the reduction.

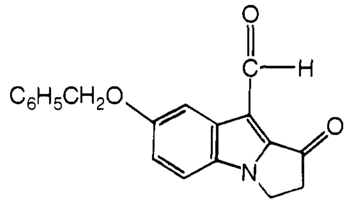
In many cases the methylene derivative is the product of choice. Consequently, the reduction of these appropriately substituted carbonyl compounds with a borane reagent provides a mild, synthetically useful deoxygenation procedure. A large variety of aldehydes and ketones are known to undergo this deoxygenation reaction, and Table II contains at least one representative example from each type of system. The borane deoxygenation of xanthone and pyrrole derivatives is particularly important and has been widely utilized.

An interesting further example of electron-donation-induced cleavage is provided by the reaction of excess diborane with diphenylcyclopropenone.[212] The product is an organoborane that yields *cis*-1,2-diphenylcyclopropane upon protonolysis. This product can be rationalized by the reaction pathway shown in Scheme III.

SCHEME III



With an appropriately substituted dicarbonyl system, exactly opposite selectivities are possible for BH_3-THF vs. sodium borohydride. For example, with sodium borohydride the 1-keto group in compound **60** is reduced faster than the 9-formyl group, which was the exact opposite of the selectivity desired.[213]



60

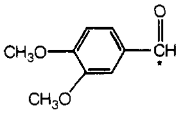
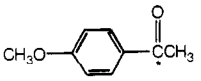
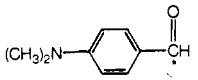
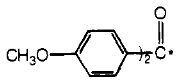
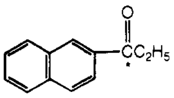
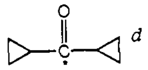
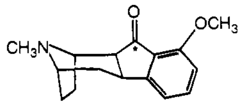
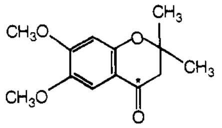
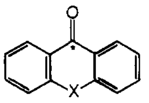
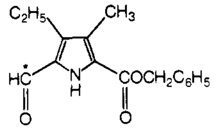
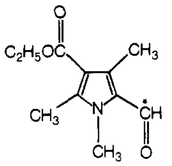
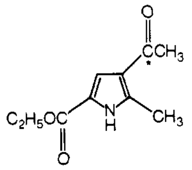
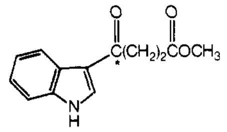
Fortunately, preferential reduction of the 9-formyl group is possible using BH_3-THF giving the desired 9-hydroxymethyl-1-one in a 67% yield of recrystallized material.[213] The 1-keto group apparently stabilizes the potentially labile 9-hydroxymethyl group.

B. Quinones

p-Benzoquinone reacts slowly with BH_3-THF utilizing two hydrides, one for reduction and one for hydrogen evolution.[24] This stoichiometry corresponds to reduction to hydroquinone. In fact, Brown and coworkers isolated a quantitative yield of hydroquinone following methanolysis.[24] A probable mechanism is indicated in Scheme IV.

An interesting application of this reduction involves the conversion of the 5,8-quinolinedione **61** to the 5,8-dihydroxyquinoline **62** in an 86% isolated yield (eq 109).[214]

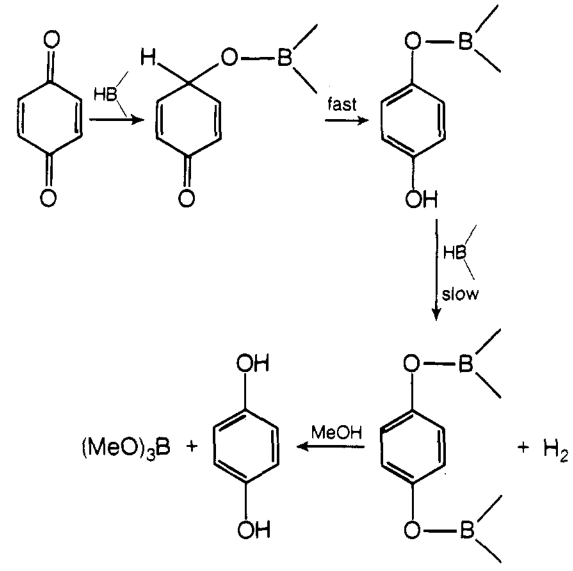
TABLE II. Borane Deoxygenation of Aldehydes and Ketones Containing Electron-Donating Substituents

Carbonyl derivative	Reducing agent[a]	Methylene product[b] % yield	Ref
	A	95	119
	A	88	118
	A B[c]	72 95	119 119
	A C	65 90	119 119
	D	"Good"	205
 [d]	E	80	124
	F	86	206
	C	85	207
 X = O X = S	G G	100 100	208 208
	G	16	209
	A	93	210
	G	89	130
	H	51	211

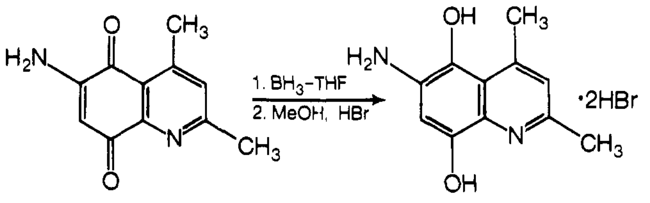
[a] A, $NaBH_4$—BF_3 in diglyme; B, B_2H_6 in diglyme with added $NaBH_4$; C, B_2H_6 in diglyme; D, A plus a large excess of BF_3; E, BH_3—THF plus excess BF_3; F, BH_3—THF then heating at reflux; G, BH_3—THF at 0—25 °C; H, G plus added ethyl acetate to inhibit reduction of ester. [b] The carbonyl marked with an asterisk is converted to —CH_2— to give the product. [c] In the absence of added $NaBH_4$, a 95% yield of alcohol is obtained, see ref 119. [d] Under similar conditions methyl cyclopropyl ketone gives a quantitative yield of alcohol; see ref 124.

Anthraquinone reacts extremely slowly with BH_3-THF showing only one hydride uptake after 7 days without hydrogen evolution.[24] However, the $NaBH_4$-BF_3 reagent in the presence of excess boron trifluoride achieves the complete reduction of

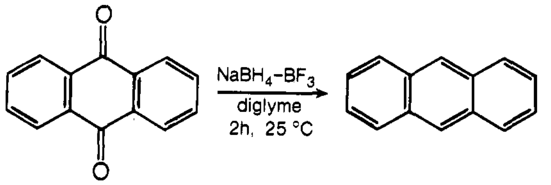
SCHEME IV



anthraquinone and its derivatives to the corresponding anthracenes in yields of 60–70% (eq 110).[215]



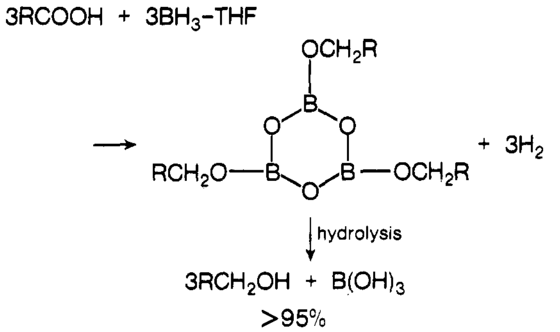
61 **62** (109)



(110)

C. Carboxylic Acids

Both aliphatic and aromatic carboxylic acids are reduced by BH$_3$-THF to the corresponding primary alcohols rapidly and quantitatively under remarkably mild conditions (eq 111).[24] For hexanoic acid the reduction goes to completion in <0.5 h at 0 °C. For benzoic acid the reduction proceeds somewhat slowly at 0 °C but is complete in <0.5 h at 25 °C.[216]

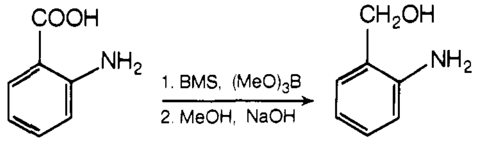


(111)

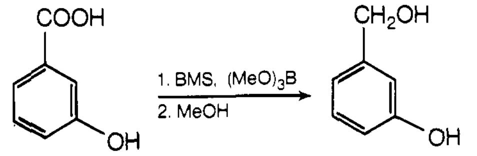
The obvious potential of this reaction for selective reductions in multifunctional molecules resulted in a detailed study of the scope of this reduction.[216] This recently reported investigation by Brown and coworkers[216] adequately summarizes the reactivity and selectivity that is observed for the reaction of BH$_3$-THF with carboxylic acids. Also, some mechanistic possibilities are given.[216] Consequently, only a minimum amount of additional discussion is necessary to fully appreciate the synthetic utility of this borane reduction.

The recent selective reduction investigations by Brown and coworkers have centered around the BH$_3$-THF reagent. However, the more reactive NaBH$_4$-BF$_3$ reagent also reacts cleanly and quantitatively with carboxylic acids.[10] BMS is another borane reagent that is showing particular promise as a reducing agent for organic functional groups.[84] For example, aliphatic carboxylic acids react readily at 25 °C with BMS in a variety of solvents, and this reaction has been developed into a useful synthetic procedure (eq 112).[84] Aromatic carboxylic acids react very slowly with BMS, but reduction occurs rapidly in the presence of trimethyl borate.[217] Equations 113–115 give specific examples of the synthetic utility along with the isolated yield of pure product.[217]

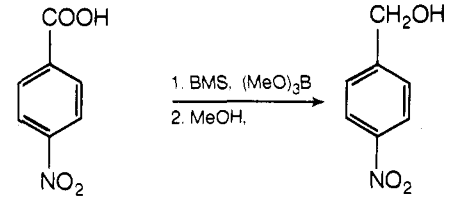
$$\mathrm{Br(CH_2)_{10}COOH} \xrightarrow[\text{2. MeOH}]{\text{1. BMS, Et}_2\text{O}} \underset{95\%}{\mathrm{Br(CH_2)_{10}CH_2OH}} \qquad (112)$$



94% (113)

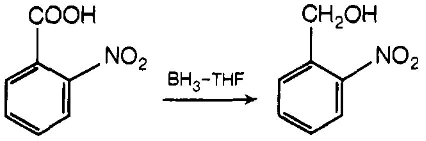


99% (114)

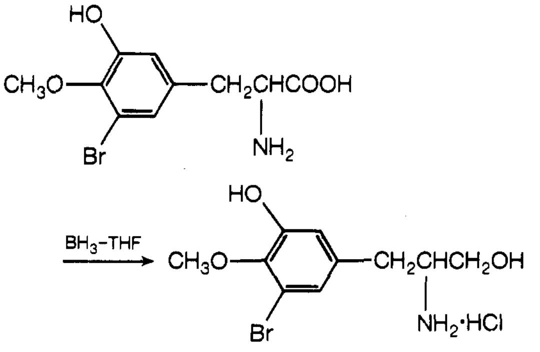


98% (115)

The use of borane reagents provides a highly convenient synthetic procedure for the selective reduction of the carboxylic acid group in the presence of other potentially reactive functional groups. Numerous examples could be cited, but the following equations, 116–134, should be sufficient to indicate the selectivity that is possible. For simplicity the hydrolysis step has been omitted in these examples, and the yield given is for the isolated purified product.

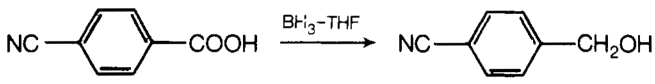


100% (116)[218]

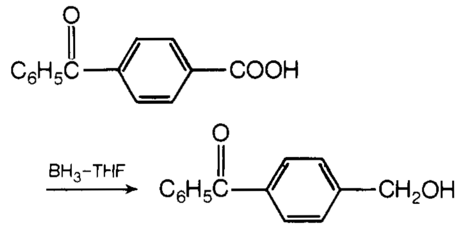


(117)[219]

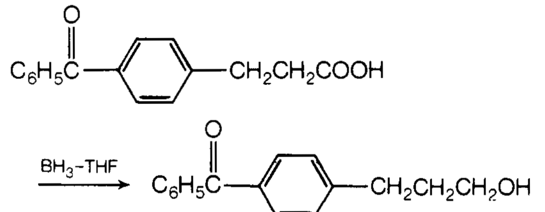
80%



82% (118)[216]

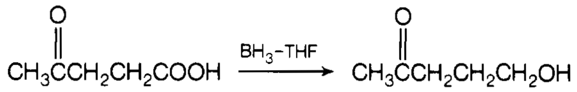


59% (119)[176]



(120)[176]

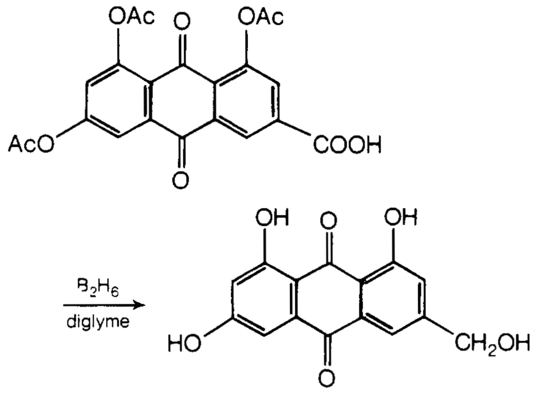
60%



$$CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2COOH \xrightarrow{BH_3\text{-}THF} CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2OH$$

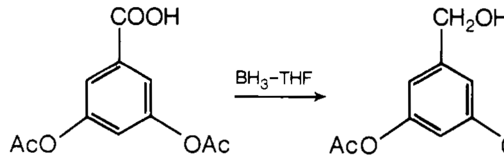
60%

(121)[176]

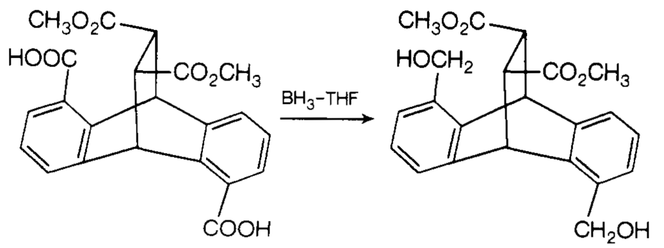


(122)[215]

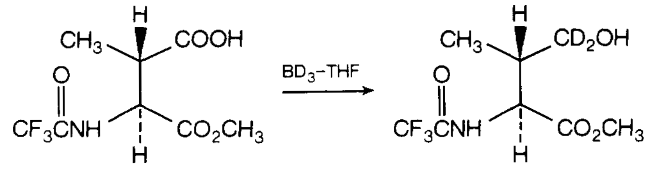
60%



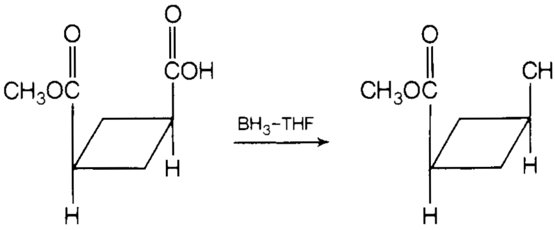
66% (123)[220]



72% (124)[221]

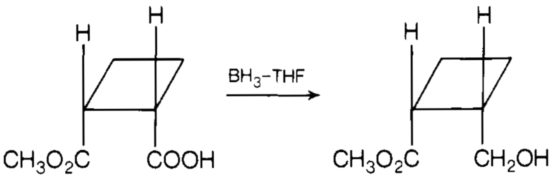


(125)[222]



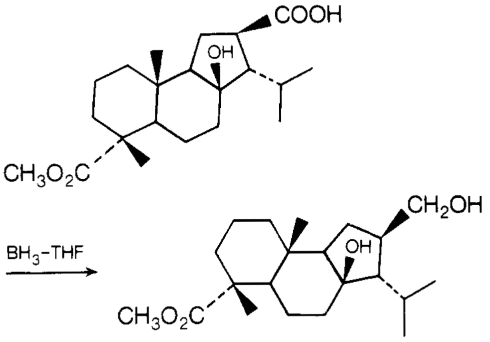
60%

(126)[223]

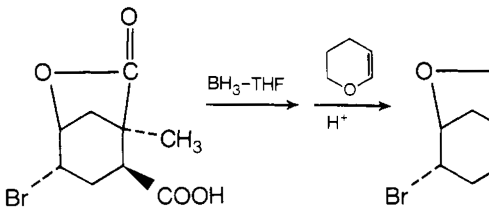


70%

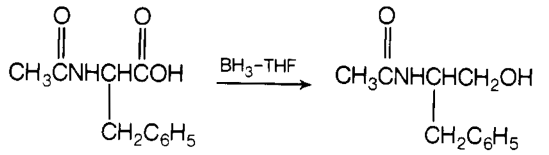
(127)[224]



70% (128)[225]



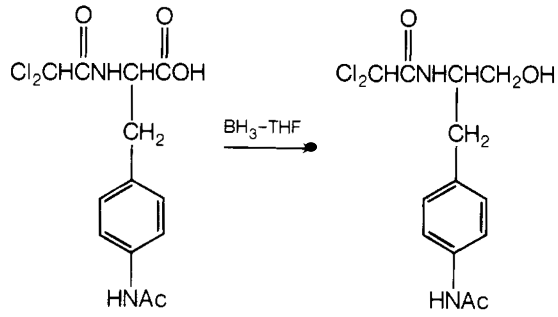
86% (129)[226]



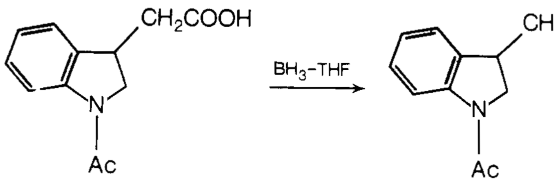
$$CH_3\overset{\overset{O}{\|}}{C}NH\underset{\underset{CH_2C_6H_5}{|}}{C}H\overset{\overset{O}{\|}}{C}OH \xrightarrow{BH_3\text{-}THF} CH_3\overset{\overset{O}{\|}}{C}NH\underset{\underset{CH_2C_6H_5}{|}}{C}HCH_2OH$$

49%

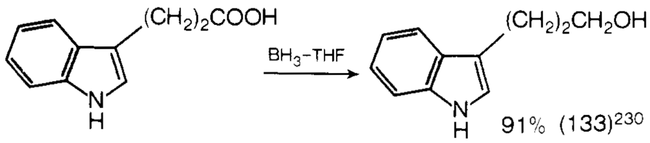
(130)[227]



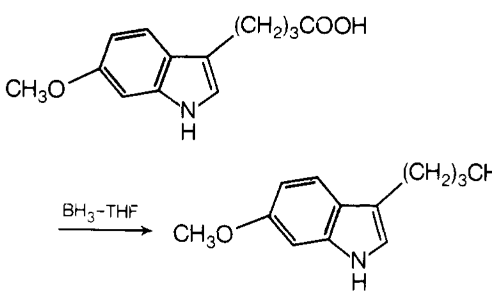
(131)[228]



(132)[229]



91% (133)[230]



55% (134)[231]

Equations 115 and 116 illustrate the reduction of carboxylic acid groups in the presence of nitro groups. The preparation of amino alcohols is shown by eq 113 and 117. The nitrile group (eq 118) and the keto group (eq 119–121) are both less reactive toward BH_3-THF than the carboxylic acid group. The quinone group (eq 122), ester group (eq 123–128), and amide group (eq 125, 130–132) are all much less reactive.

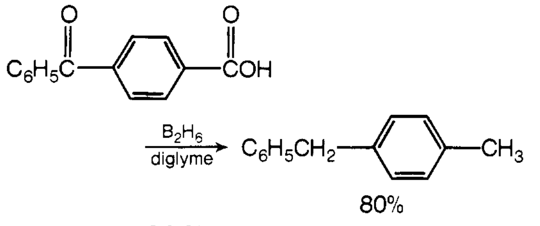
The mild conditions and selectivity indicate the potential for carrying out carboxylic acid reductions on complex biological systems. A few such applications have been reported. For example, the $NaBH_4$–BF_3 reagent transforms carboxylic acid groups to neutral hydroxymethyl groups in both monosaccharide acids and acidic polysaccharides.[232] This procedure was later used as part of a structural determination of the polysaccharide alginic acid.[233] A comparison was made between the results obtained with internally generated diborane vs. the results obtained with externally generated diborane.[234] The best selectivity was observed with externally generated diborane.[234]

Another biochemical application relies on the relative ease with which carboxyl groups are reduced when compared with the less reactive amide linkage. Thus, a series of dipeptides (as *N*-trifluoroacyls) was treated with BH_3-THF to give 62–100% reduction of the C-terminal amino acid.[235] This procedure was later applied to a series of polypeptides and naturally occurring proteins.[236] Specific reduction of the free carboxyl groups was achieved even in these complex systems.[236] Interestingly, if *N*-acyl amino acids are used instead of *N*-trifluoroacyl, then a substantial amount of amide reduction is also observed.[237]

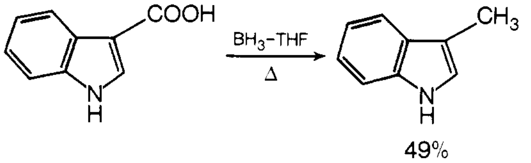
Obviously, in most, if not all of these examples, the BH_3–THF reagent is superior to $LiAlH_4$. In a specific case the $LiAlH_4$ reduction of polysiloxanes containing terminal carboxyl groups results in extensive reductive cleavage of silicon-oxygen bonds.[238] However, the terminal carboxyl groups are reduced cleanly with BH_3·THF.[238]

Selective reductions are not always possible. Reaction of the ozonide of 10-undecenoic acid with BH_3–THF gives 1,10-decanediol.[239] Within sufficient BH_3–THF a minor amount of 10-hydroxydecanoic acid is obtained.[239]

When appropriate electron-donating groups are present, complete reduction to a methyl group is possible (eq 135 and 136).



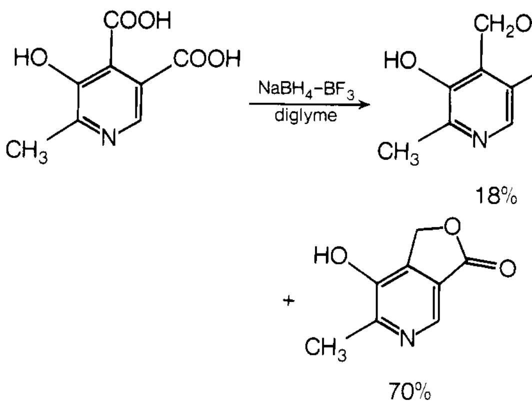
(135)[118]



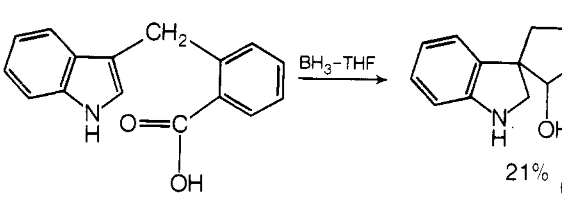
(136)[240]

Dicarboxylic and hydroxycarboxylic acids occasionally react with borane reagents to give insoluble, polymeric intermediates. Once these insoluble polymers form, the inevitable result is an incomplete reduction. Two procedures are available which prevent the formation of these insoluble intermediates. The reduction can be carried out in the presence of trimethyl borate,[217,241] or the starting material can first be acylated.[242] Acylation also increases the solubility of these acids in ether solvents.

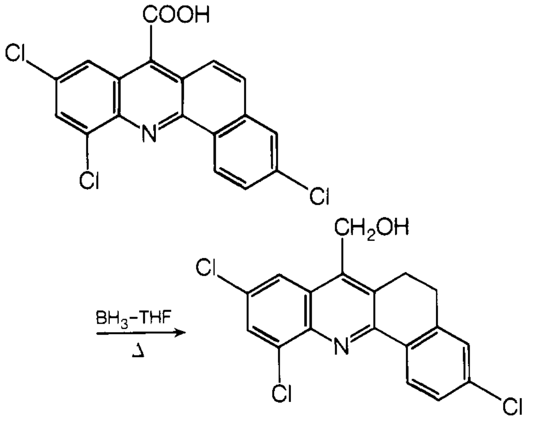
As is often the case when complex systems are treated with reactive reagents, some unusual and unexpected results have been obtained for the borane reduction of a few carboxylic acids (eq 137–139). Interestingly, reduction of the nonchlorinated derivative of the species shown in eq 139 did not result in reduction of the double bond.[245]



(137)[243]

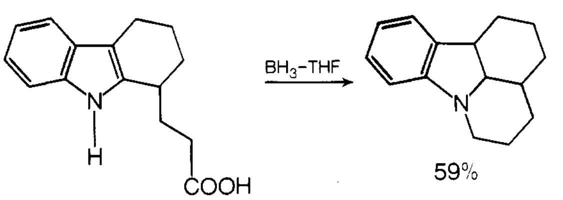


21% (138)[244]



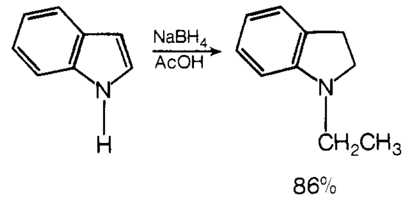
(139)[245]

Reduction of the acid **63** with BH_3-THF results in both cyclization and reduction of the indole double bond (eq 140).[246] This



63

(140)

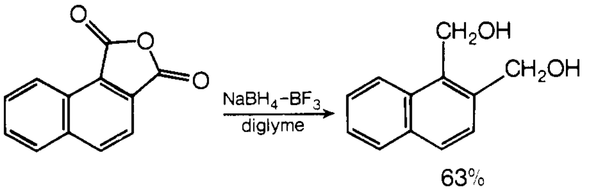


(141)

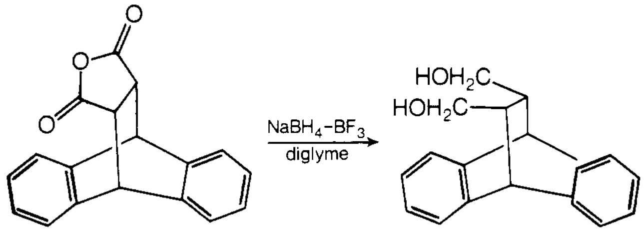
reductive alkylation of indole to give *N*-alkylindolines is also possible using just sodium borohydride (eq 141).[39]

D. Carboxylic Acid Anhydrides

n-Hexanoic acid anhydride and benzoic acid anhydride are satisfactorily reduced with BH_3-THF giving a 94% isolated yield of 1-hexanol and an 82% isolated yield of benzyl alcohol, respectively.[247] Both aliphatic and aromatic cyclic anhydrides have been reduced using the $NaBH_4$-BF_3 reagent in diglyme.[248] The only isolated product in either case is the diol (eq 142 and 143).

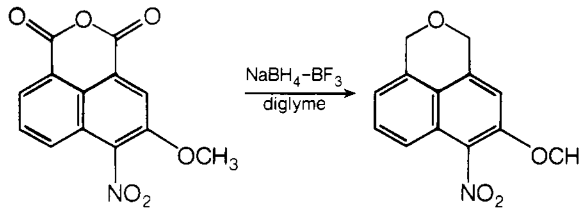


(142)



(143)

On the other hand, reduction of 1,8-naphthalic anhydrides yields the corresponding cyclic ether, a 2,1,3-*peri*-naphthopyran, as the sole isolated product.[248,249] Equation 144 illustrates a specific example.[249]

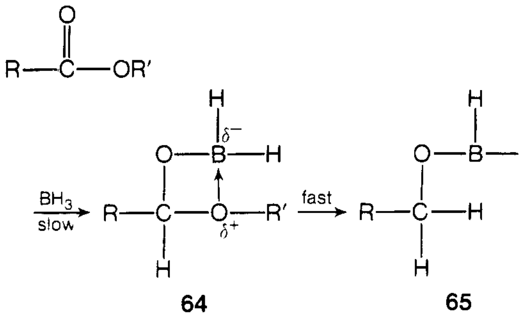


(144)

E. Esters and Lactones

Aliphatic acid esters and lactones are reduced relatively slowly with BH_3-THF at 0 °C.[24] A 12–24-h period is required for complete conversion to the corresponding alcohol. Phenyl acetate is reduced somewhat more slowly, but the aromatic acid esters and lactones are almost completely unreactive at 0 °C exhibiting only 4–6% uptake of hydride after 24 h.[24] Apparently, resonance of the aromatic ring with the carbonyl group renders the group less susceptible to electrophilic attack by the borane species.

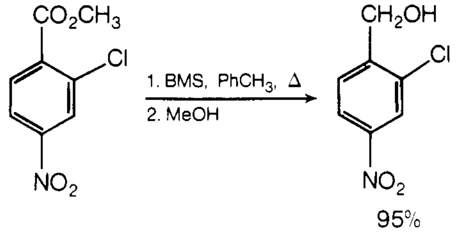
In general, the lower reactivity of the ester group is probably a result of the electron-withdrawing inductive effect of oxygen on the carbonyl group. When the carbonyl group is bonded to two oxygens, the group is even less reactive. For example, carbonate esters[104] and polycarbonates[250] are stable toward BH_3-THF at room temperature.[251] Steric hindrance can also lower the reactivity of esters. Thus, trimethylacetate esters are stable toward BH_3-THF at room temperature.[104] During the reduction of esters to alcohols, there is no detectable aldehyde formation, indicating that a stable intermediate is not formed.[24] A probable mechanism, which explains all of the above results is shown in eq 145.



(145)

Intermediate **64** is probably very unstable, and a rapid intra- or intermolecular hydride transfer occurs to give the stable intermediate **65.** This hydride transfer could be promoted by an intramolecular coordination of boron and oxygen in structure **64.**

The BMS reagent can be used to reduce a variety of functional groups and is particularly useful for the high-temperature reduction of normally unreactive esters. Equation 146 illustrates

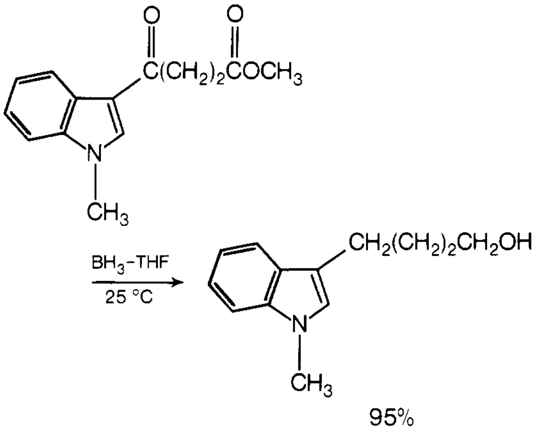


(146)

a specific example where a relatively high reaction temperature was found to be necessary but still did not result in reduction of a nitro group.[84]

During the selective reduction of a more reactive group with BH_3-THF, the slow reduction of an ester group can sometimes present a problem. However, Jackson and coworkers found that the reduction of an aliphatic ester group is inhibited if the BH_3-THF reduction is carried out in the presence of ethyl acetate.[252] This procedure was then used to achieve an otherwise very difficult selective reduction; see reducing agent H in Table II.

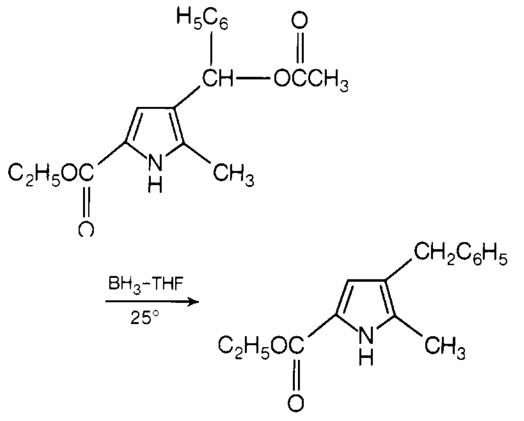
The reduction of simple esters to alcohols using a borane reagent has found only limited applications in organic syntheses. The reaction could be used more often because 24 h at 0 °C is usually sufficient to convert most aliphatic acid esters to the corresponding alcohols. The borane reagents fail to react with many other functional groups under such mild conditions. A few ester reductions have been reported, and eq 147 gives a specific example.[253]



(147)

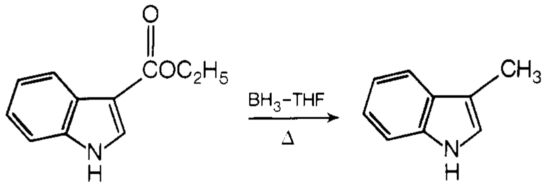
Electron-donation-induced reductive cleavage via an intermediate analogous to **22** can also occur during borane reduction of esters. This results in the complete reduction of a carboxylic acid ester group to a methyl group. Again the examples are found in derivatives of pyrrole and indole (eq 148–150).

Reduction of an appropriately substituted lactone with a borane reagent can result in complete deoxygenation of the carbonyl group to give an ether. Again an electron-donation-induced reductive cleavage can be used to rationalize the results with a mechanism similar to that shown in eq 37 being a likely pos-



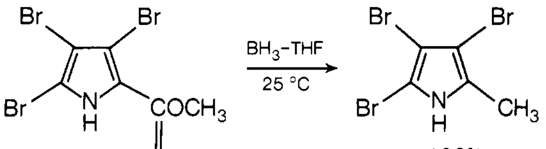
(148)[130]

100%



(149)[240]

only product by TLC



(150)[254]

100%

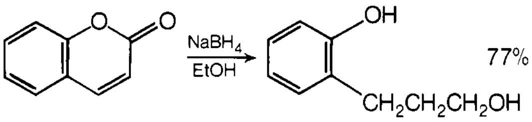
sibility. Coumarin derivatives seem particularly prone to undergo deoxygenation upon reaction with diborane. However, a mixture of products is usually obtained, and an oxidation step is required to remove boron from the product. Various mechanistic schemes have been advanced to explain the variety of products.[255,256] Equations 151–155 give some representative examples of the products that are possible. These results indicate how extremely sensitive this system is to both reaction conditions and substituents.

The reaction of δ-lactones with various borane reagents has been studied extensively by Pettit and coworkers.[259] Steroidal δ-lactones were examined in the most detail and experimental conditions were developed for the conversion of these lactones to cyclic ethers. This is another example of an electron-donation-induced reductive cleavage which probably involves a pathway similar to that shown in eq 37. The original procedure used by Pettit consisted of treating the lactone with diborane in the presence of a large excess of boron trifluoride.[260] He later found that the ester → ether reaction was favored if the ester or lactone was derived from a tertiary, hindered alcohol,[261] but branching next to the carbonyl had little influence on the yield of ether and only decreased the rate of reduction.[262] Also, boron trichloride could be used in place of boron trifluoride, but BCl_3 offered no improvement in the yield of ether.[263]

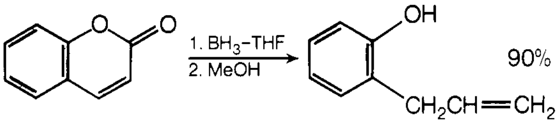
Recently, Pettit found that the large excess of BF_3 is not necessary in many cases; i.e., the $NaBH_4$–BF_3 reagent or a large excess of BH_3–THF gives essentially analogous results.[259] A large number of cyclic ethers have been prepared using these procedures. Equations 156–158 give a few specific examples.

A mechanism which is consistent with all of the above observations is depicted in Scheme V. Intramolecular coordination of boron and oxygen in intermediate **66** is apparently hindered by the bulky R′ group. The presence of boron trifluoride presumably enhances the reductive cleavage leading to the onium ion **68**.

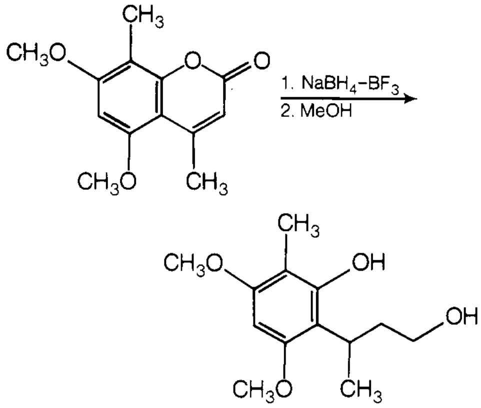
Under carefully controlled conditions, these steroidal δ-lac-



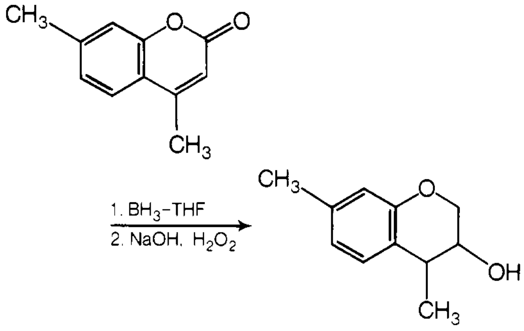
77% (151)[257]



90% (152)[125]

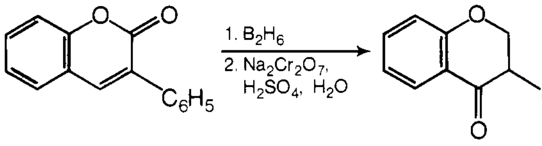


89% (153)[125]

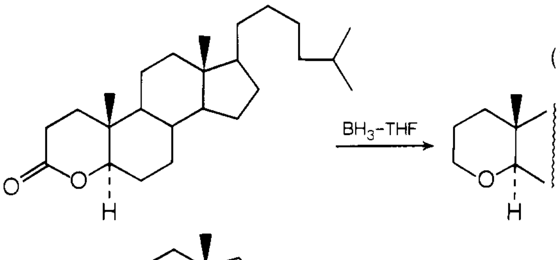


(154)[255]

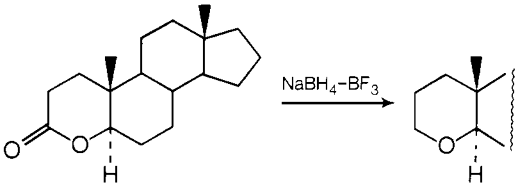
49%



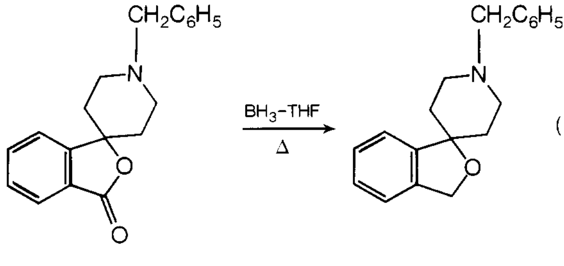
~25% (155)[258]



(156)[264]

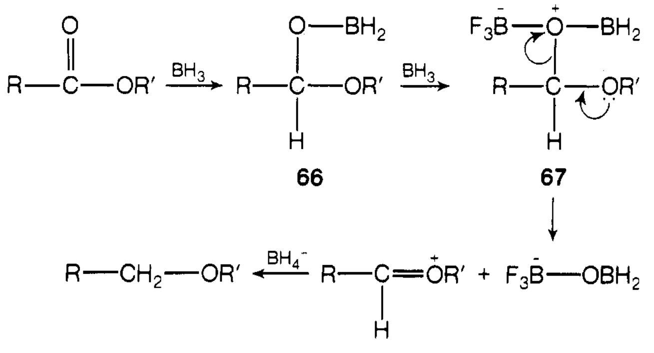


(157)[265]



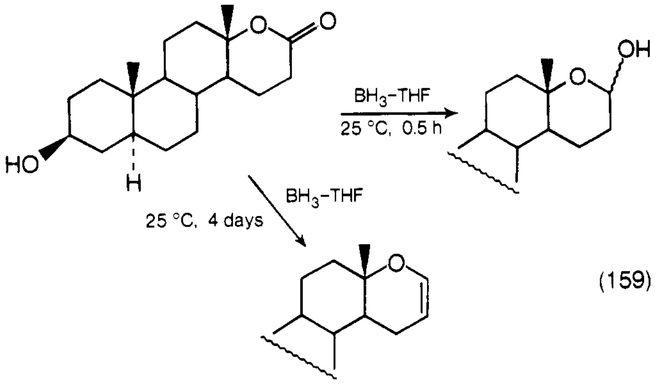
(158)[266]

SCHEME V



66 67 68

tones are converted to either cyclic hemiacetals[267,268] or dihydropyran derivatives (eq 159).[268]



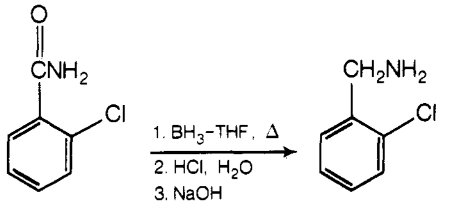
(159)

52%

F. Amides

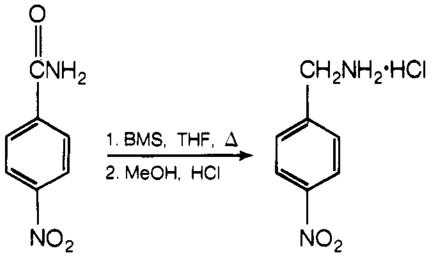
Primary, secondary, and tertiary amides derived from both aliphatic and aromatic carboxylic acids are reduced rapidly with the BH_3-THF reagent in refluxing THF. Acidic or basic hydrolysis then provides the corresponding amine in excellent yield. The reduction of amides with diborane was originally investigated by Brown and Heim,[269] and recently a full report of their detailed study became available.[270] Consequently, only a minimum amount of additional discussion is necessary to fully appreciate the synthetic utility of this important reaction.

Commercial BH_3-THF (eq 160),[218] BMS (eq 161),[84] and the



(160)

86%

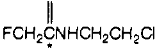
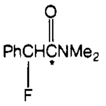
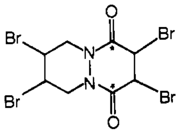
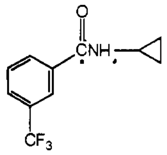
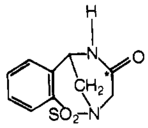
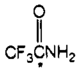
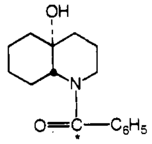
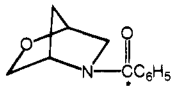
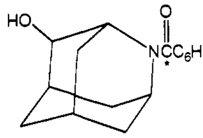
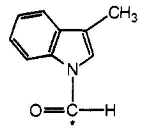
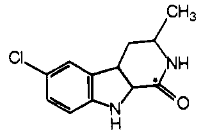
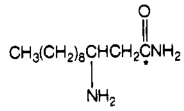
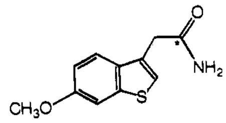
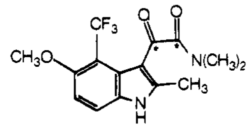


(161)

72%

$NaBH_4$-BF_3 reagent[10] have all been used for amide reductions. In general, this reaction provides a convenient synthetic procedure for the selective reduction of amides and has been used extensively over the past 10 years, since the appearance of Brown's original communication.[269]

TABLE III. Borane Reduction of Amides: Examples Where $LiAlH_4$ Reduction Failed

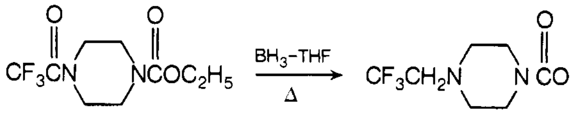
Amide	Reducing agent[a] and conditions	Amine product[b] % yield	Ref
 $FCH_2\overset{O}{\overset{\|}{\underset{*}{C}}}NHCH_2CH_2Cl$	A	83	279
 $PhCH\underset{F}{\vert}\overset{O}{\overset{\|}{\underset{*}{C}}}NMe_2$	A	53	289
	B	60	290
	B	93	291
	B	80	294
 $CF_3\overset{O}{\overset{\|}{\underset{*}{C}}}NH_2$	C	44	296
	B	91	298
	B	90	286
	B	90	300
	A	49	301
	B	33	275
 $CH_3(CH_2)_8\underset{NH_2}{\underset{\vert}{C}}HCH_2\overset{O}{\overset{\|}{\underset{*}{C}}}NH_2$	B	78	276
	B	61	281
	B	34	240

[a] A, BH_3THF at room temperature; B BH_3—THF at room temperature followed by reflux; C, $NaBH_4$—BF_3 in diglyme. [b] The carbonyl marked with an asterisk is converted to —CH_2—to give the amine product.

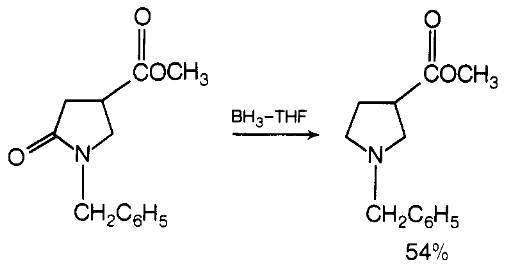
The synthesis of natural products and new pharmaceuticals are two important areas where many applications and advances have been made using this reduction of amides. For example, the reduction of an amide functional group with BH_3–THF provided one of the key steps in the synthesis of the naturally occurring polyamine, *sym*-homospermidine.[271] An amide reduction was involved in an interesting synthesis of the eburnamine alkaloid ring system.[272] Also, amide reductions with borane reagents have been used for the preparation of indolines,[229] catecholamines,[273] dehydrobufotenine,[274] tetrahydrocarbolines,[275] desoxypithecolobines,[276] lysergic acid,[277] and derivatives of ephedrine.[278]

Numerous chemicals of interest and importance in medicinal chemistry have been prepared through an amide reduction with a borane reagent. A few specific examples include derivatives of 2-fluoroethylamine[279] (potential carcinolytic agents), derivatives of *N*-(2-haloethyl)benzylamine[280] (antineoplastic agents), 1-deaza-1-thiareserpine[281] (antihypertensive), 6-(*N*-alkyl-*N*-arylamino)pyrimidines[282] (potential antimetabolites), various derivatives of 1,4-benzodiazepine[283-285] (antianxiety drugs), derivatives of 2-oxa-5-azabicyclo[2.2.1]heptane[286] (anticholinergic agents), 1,2-dihydro-3*H*-imidazo[1,5-*a*]indol-3-ones[287] (CNS activity), and bis(4-aminophenyl) sulfone derivatives[288] (antileprotic agents).

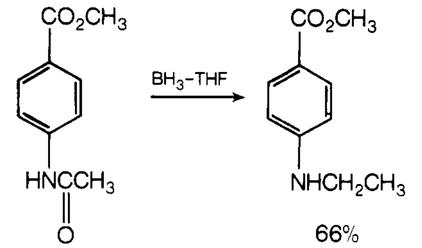
Various other metal hydride reagents are known to reduce amides to amines, but lithium aluminum hydride is probably the most widely used alternative to the borane reagents. However, $LiAlH_4$ is an extremely powerful reducing agent which will attack a large variety of sensitive functional groups. Thus, the utility of $LiAlH_4$ as a selective reducing agent is rather limited. Specific examples of groups that have been reported to be attacked by $LiAlH_4$ during attempted amide reductions include α-fluoro,[279,289] α-bromo,[290] *N*-cyclopropyl,[291] trifluoromethylaryl,[240,291-293] and sulfonyl.[294] Also, $LiAlH_4$ reductions of trifluoroacetamides are reported to be extremely violent,[295,296] and other trifluoromethyl groups are known to undergo complete hydrogenolysis with $LiAlH_4$.[297] Finally, reductive cleavage of the *N*-benzyl group is usually a serious problem during $LiAlH_4$ reduction of benzamide derivatives.[286,298,299] Fortunately, amides which contain the above substituents or structural features are readily and cleanly reduced to amines using one of the borane reagents. Table III lists a variety of specific examples where reduction with $LiAlH_4$ failed, but reduction with a borane reagent was successful. Only the results of the borane reduction are reported in Table III. The original reference should be consulted for the product or products obtained through attempted $LiAlH_4$ reduction.



(162)



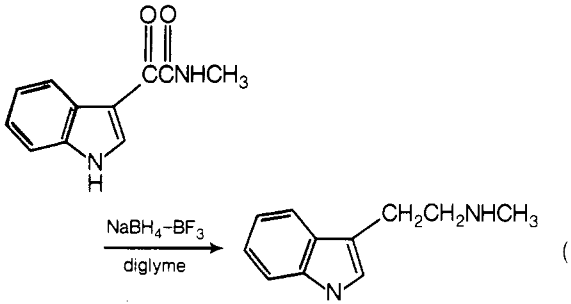
(163)



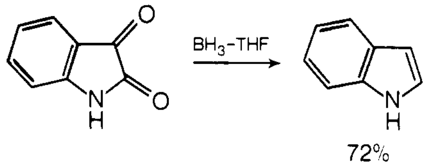
(164)

In addition to the selective reductions shown in Table III, the BH_3–THF reagent will also reduce an amide substituents in the presence of either a carbamate (eq 162)[302] or an ester (eq 163 and 164).[303]

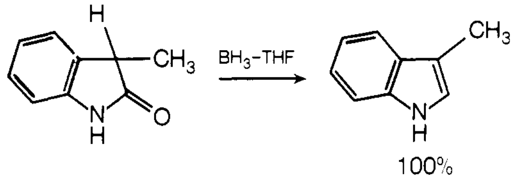
Some unusual borane reductions have been reported for indole carbonyl derivatives. Three examples are given in eq 165–167.



(165)[210]



(166)[304]



(167)[304]

Recently, two interesting applications of this amide reduction procedure have appeared. The borane reduction of a diamide was used as one of the key steps in the synthesis of a new class of compounds, the diaza-polyoxa-macrobicyclic systems, so-called "cryptates".[305] Finally, borane reduction of an *N*-acyl,*N'*-tosylhydrazine enabled the development of a convenient procedure for the conversion of a carboxylic acid group to a methyl group.[306]

The preceding discussion and examples should indicate that the BH_3–THF reagent is usually the reducing agent of choice for the conversion of amides to the corresponding amines.

VII. Conclusions

Brown and Korytnyk established the relative rates of reduction by BH_3–THF for a number of representative classes of organic compounds.[307] The results of these competitive experiments indicate that the rate of reaction decreases in the order: carboxylic acids > alkenes > ketones > nitriles > epoxides > esters > acid chlorides. However, the reactivity of a given functional group can be greatly modified by the organic structure to which it is attached. It is important to recognize that these relative reactivities must be considered approximate values for simple, representative groups, and may be altered or even inverted by modifications in the molecular structure. Hopefully, the present review will help to further define the reactivity of the borane reducing agents and will assist organic chemists in deciding when it would be advantageous to utilize a borane reduction to solve a synthetic problem.

It is interesting to note that the reduction of an organic compound with diborane was first disclosed at an American Chemical Society meeting in Milwaukee[5] and now, 37 years later, Milwaukee is also the site of the first major effort to commercialize this reaction. Finally it is ironic that the United States government spent millions of dollars on two separate research projects to develop the chemistry of sodium borohydride and diborane for unsuccessful military applications, while today the most important and successful applications for these chemicals are for the synthesis of new pharmaceuticals.

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