Chapter 1

Sixty Years of Hydride Reductions

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A survey of hydride reductions in organic chemistry from its beginnings has been made. Persuaded by Alfred Stock's book entitled "The Hydrides of Boron and Silicon" that he received as a graduation gift in 1936 from his classmate (now his wife) Sarah Baylen, the senior author undertook research with Professor H. I. Schlesinger and Dr. A. B. Burg, exploring the chemistry of diborane. His Ph.D. research, begun in 1936 involved a study of the reaction of diborane with aldehydes and ketones, and other compounds with a carbonyl group. This development initiated the hydride era of organic reductions. Necessities of WWII research led to the discovery of sodium borohydride and the discovery of the alkali metal hydride route to diborane. The systematic study to modify sodium borohydride and lithium aluminum hydride led to a broad spectrum of reagents for selective reductions. It is now possible to selectively reduce one functional group in the presence of another. The study of the reduction characteristics of sodium borohydride led to the discovery of hydroboration and the versatile chemistry of organoboranes. An examination of the hydroboration of α-pinene led to the discovery of an efficient asymmetric hydroboration agent, diisopinocampheylborane, Ipc_2BH. This led to the devlopment of a general asymmetric synthesis and to the discovery of efficient reagents for asymmetric reduction. Research progressed, one discovery leading to another, opening up a whole new continent of chemistry.

We are nearing the close of a century that witnessed unprecedented scientific and technological progress that was probably unimaginable even half a century ago. While the overall advancement of science and technology is phenomenal, in reality it has taken place over several generations, made possible by the untiring dedication of the scientists involved to their research. In fact, every decade achieved significant advances, permitting the next generation to move forward in their own pursuit of knowledge. Later developments might cause some of the work of the earlier workers to appear trivial. However, one can only admire the tenacity of the pioneers whose steadfastness has led us to where we are today.

In chemistry, the invention and perfection of new sophisticated instruments and methodologies have facilitated the analysis of reaction intermediates and products. Newer industries catering to the needs of chemists have decreased the necessity of having to prepare many of the starting materials and reagents.

0097–6156/96/0641–0001$17.50/0

The senior author has had the rare good fortune to carry out research on one topic for sixty years, developing it from its very beginnings. As in any scientific research his sixty-year career has been a combination of serendipities and the systematic research that followed the initial observations. It is the capability of the scientist to observe and infer when one stumbles upon the unexpected that makes research so fascinating.

Hydride reductions have come a long way since the observation that diborane rapidly reduces aldehydes and ketones, the development of the alkali metal hydride route to diborane, and the discoveries of sodium borohydride (SBH) and lithium aluminum hydride (LAH). The area is so vast that it is impossible to condense all of the literature on reductions involving these and other modified hydride reagents in a short review such as this. Several monographs and books and tens of reviews have appeared in this area (*1-13*). We have given references to several of the reviews that have appeared pertaining to each area in the corresponding sections of this chapter. Any of the earlier reviews that has not been mentioned or the original work not included is due solely to the limitations of space. Discussion of the applications of most of the reagents described herein are made in two recent multi-volume series (*14, 15*). We would call the reader's attention to these reviews for a comprehensive knowledge of hydride reagents for reduction.

We shall attempt to take the readers through a chronological tour of the development of the hydride reduction area so that they can appreciate how research can progress, where one observation can open new major areas of study.

Beginnings

Pre-Borohydride Era. At the beginning of this century, the reduction of an aldehyde, ketone or carboxylic acid ester was carried out by the generation of hydrogen from zinc dust, sodium amalgum, or iron and acetic acid (*16*). Later, sodium in ethanol (*17*) or zinc and sodium hydroxide in ethanol (*18*) were used for this purpose. In the second quarter of this century, independent research by Verley (*19*), Meerwein (*20*) and Ponndorf (*21*) led to the M-P-V reduction (*22*) whereby the reduction of an aldehyde or ketone was achieved with the aluminum alkoxides of *sec*-alcohols.

All of these procedures were made obsolete by a reaction carried out in search of a solvent to purify sodium borohydride!

Diborane for Carbonyl Reductions

The interest of chemists in structural theory and their curiosity in unravelling the mysterious electron-deficient structure of a simple compound, such as diborane (*23*) led Schlesinger to the synthesis of borane-carbonyl (*24*) and to the examination of reactions of diborane with aldehydes and ketones. This study initiated the hydride era of organic reductions. It was soon discovered that aldehydes and ketones react rapidly with diborane even at low temperatures in the absence of solvents to produce dialkoxy derivatives, which can be rapidly hydrolyzed to the corresponding alcohols (eq 1-2) (*25*).

$$4\ R_2CO + B_2H_6 \rightarrow 2\ (R_2CHO)_2BH \xrightarrow{6\ H_2O} 4\ R_2CHOH + 2\ H_2 + 2\ B(OH)_3 \quad (1)$$

$$4\ RCHO + B_2H_6 \rightarrow 2\ (RCH_2O)_2BH \xrightarrow{6\ H_2O} 4\ RCH_2OH + 2\ H_2 + 2\ B(OH)_3 \quad (2)$$

However, the lack of availability of diborane hindered progress in the application of this "easy" procedure for reductions. The situation was changed by the necessities of war research.

World War II Research and Preparation of Sodium Borohydride - A Historical Perspective.

A request from the National Defense Research Committee (NDRC) to investigate the synthesis of volatile compounds of uranium having low molecular weight, but without the corrosive properties of UF_6, led Schlesinger's group to extend the method of preparation of other metal borohydrides, such as aluminum and beryllium borohydride (*26-28*) (which happened to be the most volatile compounds of these metals), to uranium borohydride (eq 3-6) (*29*).

$$3\ LiEt + 2\ B_2H_6 \longrightarrow 3\ LiBH_4 + BEt_3 \quad (3)$$

$$3\ BeMe_2 + 4\ B_2H_6 \longrightarrow 3\ Be(BH_4)_2 + 2\ BMe_3 \quad \text{sp } 91^\circ C \quad (4)$$

$$AlMe_3 + 2\ B_2H_6 \longrightarrow Al(BH_4)_3 + BMe_3 \quad \text{bp } 45\ ^\circ C \quad (5)$$

$$UF_4 + 2\ Al(BH_4)_3 \longrightarrow U(BH_4)_4 + 2\ AlF_2(BH_4) \quad (6)$$

But the need for the then rare species diborane hampered progress. This problem was circumvented by a series of reactions to achieve a practical procedure for the preparation of uranium borohydride. We discovered that lithium hydride readily reacts with boron trifluoride-etherate in ethyl ether (EE) to produce diborane, which was subsequently transformed into $U(BH_4)_4$ (eq 7-10) (*30-32*).

$$6\ LiH + 8\ BF_3 \xrightarrow{EE} B_2H_6\uparrow + 6\ LiBF_4\downarrow \quad (7)$$

$$2\ LiH + B_2H_6 \xrightarrow{EE} 2\ LiBH_4 \quad (8)$$

$$AlCl_3 + 3\ LiBH_4 \longrightarrow Al(BH_4)_3\uparrow + 3\ LiCl \quad (9)$$

$$UF_4 + 2\ Al(BH_4)_3 \longrightarrow U(BH_4)_4 + 2\ AlF_2(BH_4) \quad (10)$$

The lack of an available supply of LiH during the war became an impediment. The corresponding reaction with sodium hydride failed in EE, though it was discovered several years later that other solvents, such as THF and diglyme, not available in 1940, facilitate the reaction. The necessity to synthesize sodium borohydride led to the following sequence (eq 11-15) (*33*).

$$NaH + B(OMe)_3 \xrightarrow{\text{reflux}} NaBH(OMe)_3 \quad (11)$$

$$6\ NaBH(OMe)_3 + 8\ BF_3 \longrightarrow B_2H_6\uparrow + 6\ NaBF_4 + 6\ B(OMe)_3 \quad (12)$$

$$2\ NaBH(OMe)_3 + B_2H_6 \longrightarrow 2\ NaBH_4 + 2\ B(OMe)_3 \quad (13)$$

$$AlCl_3 + 3\ NaBH_4 \longrightarrow Al(BH_4)_3\uparrow + 3\ NaCl \quad (14)$$

$$UF_4 + 2\ Al(BH_4)_3 \longrightarrow U(BH_4)_4 + 2\ AlF_2(BH_4) \quad (15)$$

The problem of handling UF_6 had been mastered, so that the NDRC was no longer interested in $U(BH_4)_4$. Fortunately, the Signal Corps was interested in exploiting the feasibility of sodium borohydride for the field generation of hydrogen. The demand led to a more practical preparation of sodium borohydride (*34*), by the treatment of sodium hydride with methyl borate at 250 °C (eq 16).

$$4\ NaH + B(OCH_3)_3 \xrightarrow{250\ ^\circ C} NaBH_4 + 3\ NaOCH_3 \quad (16)$$

During the search for a proper solvent to separate the two solid products, we observed that sodium borohydride dissolved in acetone with a vigorous reaction. However, it could not be recovered by the removal of the solvent (eq 17-18). *The discovery of sodium borohydride as a hydrogenating agent was thus made!*

$$NaBH_4 + 4\ (CH_3)_2CO \longrightarrow NaB[OCH(CH_3)_2]_4 \quad (17)$$

$$NaB[OCH(CH_3)_2]_4 + 2\ H_2O \longrightarrow 4\ (CH_3)_2CHOH + NaB(OH)_4 \quad (18)$$

The difference in solubility of sodium borohydride and sodium methoxide in ammonia is exploited to purify the former. It proved more convenient to use isopropylamine. This is the basis of the current industrial process for preparing millions of pounds of sodium borohydride per year.

Lithium Aluminum Hydride.

The procedure developed for the preparation of borohydrides was extended for the synthesis of the corresponding aluminum derivatives. Thus lithium aluminum hydride was synthesized from lithium hydride and aluminum chloride in EE, using a small quantity of LAH to facilitate the reduction (eq 19-21) (*35*).

$$4\ LiH + AlCl_3 \longrightarrow LiAlH_4 + 3\ LiCl \quad (19)$$

$$3\ LiAlH_4 + AlCl_3 \longrightarrow 4\ AlH_3 + 3\ LiCl \quad (20)$$

$$4\ AlH_3 + 4\ LiH \longrightarrow 4\ LiAlH_4 \quad (21)$$

Selective Reductions

Two Extremes of a Broad Spectrum.

The discovery of SBH and LAH revolutionized the reduction of functional groups in organic chemistry. These reagents are not speciality chemicals any more. Lithium aluminum hydride is capable of reducing practically all organic functional groups, such as aldehydes, ketones, acid chlorides, carboxylic esters, acids and anhydrides, lactones, nitriles, amides, oximes, azo and hydrazo compounds, sulfoxides, etc. (*36*). It reduces alkyl and aryl halides to the corresponding hydrocarbon (*37*). Although LAH reduces a *tert*-amide to the corresponding amine, 1-acylaziridines are reduced to the corresponding aldehydes (*38*). On the other hand, sodium borohydride is a remarkably gentle reducing agent. It readily reduces only aldehydes, ketones and acid chlorides (*39*). There was a need to find a family of reducing agents with capabilities between these two extremes and our systematic research led to the development of a series of reagents that lie between and even beyond these extremes (Table 1).

We modified these reagents, either by decreasing the reducing power of LAH or by increasing that of SBH to make a complete spectrum of reagents for selective reductions. We studied (1) the influence of solvents, (2) the effect of cations, (3) the effect of introducing substituents of varying steric and electronic requirements in the complex, (4) the development of acidic reducing agents, such as alane and borane, and (5) the effect of introducing substituents into these acidic reagents.

A standard set of 56 functional groups were chosen for testing the capability of the modified reagents in tetrahydrofuran (THF) at 0 °C (*39*).

This study marked the beginning of the Selective Reductions Era.

Others have also made important contributions to this area, as discussed below.

Table 1. Two extremes in selective reductions

	$NaBH_4$	$LiAlH_4$
RCHO	+	+
R_2CO	+	+
RCOCl	+	+
RCO_2R'	–	+
RCO_2H	–	+
$RCONR'_2$	–	+
RCN	–	+
RNO_2	–	+
$RCH{=}CH_2$	–	–

Effect of Solvents. The very high reactivity of LAH restricted the choice of solvents to hydrocarbons, ethers and *tert*-amines. It is generally used in EE, THF and diglyme, in all of which it is a powerful reducing agent. Sodium borohydride is a better reducing agent in water and alcohols. This reagent is not soluble in EE and is sparingly soluble in THF. Although it is soluble in diglyme, the reducing power is curtailed to the extent that even acetone is not rapidly reduced in this solvent.

Effect of Cations. Changing the cations from lithium to sodium in the metal aluminum hydride did not alter the reactivity very much (*40*). While sodium borohydride is soluble in diglyme (DG) and triglyme, lithium borohydride is soluble in simple ether solvents, such as EE and THF. Also there is a marked difference in the reactivity of these two borohydrides (*41*). Thus, sodium borohydride reduces esters only very sluggishly, whereas lithium borohydride reduces them rapidly (eq 22).

$$RCH_2OH \xleftarrow{LiBH_4} RCOOR' \xrightarrow{NaBH_4} \text{No or slow reaction} \quad (22)$$

A convenient procedure to convert SBH to LBH using lithium halide in simple ether solvents was developed (*42*). The addition of one equiv of lithium chloride or lithium bromide to a one molar solution of sodium borohydride generates lithium borohydride with precipitation of sodium halide. The reagent can be used without the removal of the salt (eq 23) (*43*).

$$RCOOEt \xrightarrow{NaBH_4\text{-}LiBr} RCH_2OH \quad (23)$$

Kollonitsch and coworkers achieved rapid reduction of esters by sodium borohydride in the presence of Li, Mg, Ca, Ba, and Sr salts (*44,45*). Preparation of zinc borohydride from sodium borohydride (eq 24) and the reactions have been reported (*46,47*). Nöth (*48*) and Yoon (*49*) carried out a systematic study of the preparative method and concluded that the reagent is not the simple $Zn(BH_4)_2$, but a complex mixture of borohydrides.

$$2\ NaBH_4 + ZnCl_2 \longrightarrow \text{"}Zn(BH_4)_2\text{"} + 2\ NaCl \quad (24)$$

Addition of 0.33 molar equiv of aluminum chloride to sodium borohydride in diglyme results in a clear solution that has much enhanced reducing power, approaching that of lithium aluminum hydride (eq 25) (*50*). The reduction of an

unsaturated ester, ethyl oleate, using this reagent mixture (*51,52*) led to the discovery of hydroboration!

$$3\ NaBH_4 + AlCl_3 \rightleftharpoons Al(BH_4)_3 + 3\ NaCl \qquad (25)$$

Nöth reported that the ^{11}B NMR of such solutions in diglyme indicate the presence of several species, such as $NaBH_4$, NaB_2H_7, $NaAlCl_3BH_4$ and $NaAlCl_3H$ (*53*).

Effect Of Substituents

Alkoxyaluminohydrides. A systematic study of the reaction of lithium aluminum hydride in ethereal solvents with *pri-*, *sec-* and *tert*-alcohols using hydride analysis (*54*) and ^{27}Al NMR spectroscopy (Ramachandran, P. V.; Gong, B., unpublished data) reveals that an equilibrium exists between various alkoxy derivatives. Both the *pri-* and *sec*-alcohols provide the tetraalkoxy derivative with four equiv of the alcohol (eq 26-28). However, the *tert*-alcohol does not react past the trialkoxyaluminohydride stage (eq 29). While methanol and ethanol provide the corresponding trialkoxyaluminohydride derivative cleanly, 2-propanol provides only the tetraalkoxy derivative irrespective of the molar equiv of the alcohol used.

$$LiAlH_4 + 4\ MeOH \longrightarrow LiAl(MeO)_4 + 4\ H_2\uparrow \qquad (26)$$

$$LiAlH_4 + 4\ EtOH \longrightarrow LiAl(EtO)_4 + 4\ H_2\uparrow \qquad (27)$$

$$LiAlH_4 + 4\ i\text{-}PrOH \longrightarrow LiAl(i\text{-}PrO)_4 + 4\ H_2\uparrow \qquad (28)$$

$$LiAlH_4 + 3\ t\text{-}BuOH \longrightarrow LiAl(t\text{-}BuO)_3H + 3\ H_2\uparrow \qquad (29)$$

Lithium tri-*tert*-butoxyaluminohydride proved to be exceptionally stable in the solid form or in ether solvents (*54, 55*). Substitution of the hydride with alkoxy groups decreases the reducing power of the substituted LAH considerably. The reagent reduces aldehydes, ketones and acid chlorides (*56*). Lactones and epoxides react slowly, whereas carboxylic acids and esters do not react with the exception of aryl esters. This reagent is capable of reducing nitriles (eq 30), *tert*-amides (eq 31) and aromatic acid chlorides (eq 32) to aldehydes in excellent yield (*57*) .

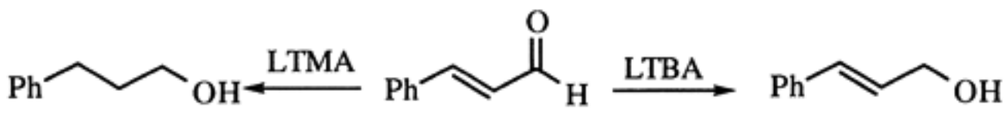
$$RCOCl + LiAl(t\text{-}BuO)_3H \longrightarrow RCHO + LiCl + Al(t\text{-}BuO)_3 \qquad (30)$$

$$RCN + LiAl(t\text{-}BuO)_3H \longrightarrow \longrightarrow RCHO \qquad (31)$$

$$RCONR'_2 + LiAl(t\text{-}BuO)_3H \longrightarrow \longrightarrow RCHO \qquad (32)$$

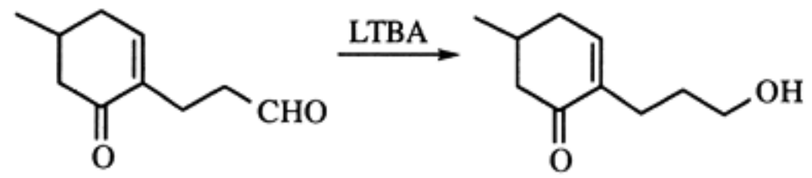
The corresponding sodium tri-*tert*-butoxyaluminohydride is capable of reducing aliphatic acid chlorides as well (*58*).

Lithium trimethoxyaluminohydride (LTMA) (*59*) and lithium triethoxyaluminohydride (LTEA) (*60*) are powerful reducing agents, closely resembling LAH, but more selective. LTEA reduces aromatic and aliphatic nitriles, and *tert*-amides to the corresponding aldehdydes. The difference in the reducing characteristics of LTBA and LTMA is shown in eq 33.



(33)

LTBA can be very selective, distinguishing between the carbonyl groups of aldehydes and ketones (eq 34) (*61*).



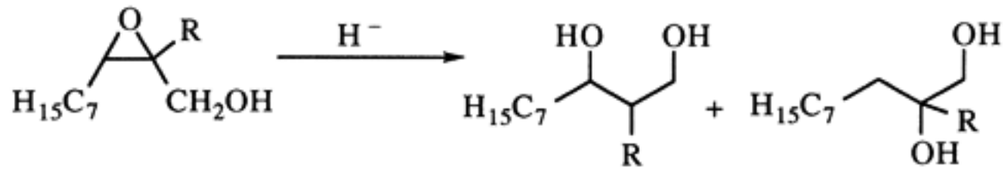
(34)

The increased steric requirements of the alkoxy groups of the reagent aids in a more stereoselective reduction of certain bicyclic ketones.

Sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) (Red-Al, Vitride, Alkadride) is a stable dialkoxyaluminum hydride that resembles LAH in its reducing capabilities, but possesses unique properties, such as higher solubility in ether solvents and aromatic hydrocarbons, and thermal stability (*62*) (eq 35).

$$NaAlH_4 + 2\ MeOCH_2CH_2OH \longrightarrow NaAlH_2(OCH_2CH_2OMe)_2 \qquad (35)$$

It shows selective behavior in the reactions of epoxides. Unsymmetrical epoxides are opened with preferential attack at the least substituted carbon (eq 36) (*63*).



(36)

R = H, LAH	4	:	1
R = H, Red-Al	100	:	1
R = Me, Red-Al	1	:	100

Recently Harashima prepared a series of substituted Red-Al with even higher selectivity than Red-Al itself (eq 37) (*64*).

$$NaAlH_2(OCH_2CH_2OMe)_2 + ROH \longrightarrow NaAlHOR(OCH_2CH_2OMe)_2 + H_2 \qquad (37)$$

Monoalkoxyaluminumtrihydride. Our systematic study of the reaction of LAH and SAH with a series of alcohols, phenols, diols, triols, pri- and sec-amines using simultaneous hydride and ^{27}Al NMR analysis has identified several new trialkoxy and dialkoxy species derived from both hydride reagents. Most importantly, we observed that the reaction of SAH with tricyclohexylcarbinol provides a stable trihydrido species (eq 38). The ^{27}Al NMR spectra of this product in THF reveals a quartet at δ 107 ppm. With a second equiv of the carbinol, it forms a solid dihydroaluminum compound and adds no more of the carbinol (Ramachandran, P. V.; Gong, B., unpublished data).

$$NaAlH_4 + Chx_3COH \longrightarrow NaAlH_3OCChx_3 + H_2 \qquad (38)$$

Reductions by alkoxyaluminum hydrides have been thoroughly reviewed by Malek (*12, 13*).

Alkoxyborohydrides. Unlike the aluminohydrides, the alkoxyborohydrides cannot be synthesized by the treatment of sodium borohydride with the corresponding alcohols. They are prepared by the treatment of the borate esters with the corresponding metal hydrides in the absence of solvents (eq 39). However, they undergo rapid disproportionation in solvents (*65*).

$$4\ (MeO)_3B + 4\ NaH \xrightarrow{\text{neat}} 4\ Na(MeO)_3BH \xrightarrow{\text{THF}} NaBH_4 + 3\ NaB(OMe)_4 \quad (39)$$

Although trimethoxy- and triethoxyborohydrides disproportionate, the corresponding triisopropoxyborohydrides are stable (eq 40-42) (*66, 67*). They are mild reducing agents, similar to SBH or LTBA.

$$NaH + (i\text{-}PrO)_3B \xrightarrow[170\ h]{\text{THF, reflux}} Na(i\text{-}PrO)_3BH \quad (40)$$

$$NaH + (i\text{-}PrO)_3B \xrightarrow[130\ ^\circ C,\ 1h]{\text{Triglyme}} Na(i\text{-}PrO)_3BH \quad (41)$$

$$KH + (i\text{-}PrO)_3B \xrightarrow[1\ h]{\text{THF, RT}} K(i\text{-}PrO)_3BH \quad (KIPBH) \quad (42)$$

Aminoborohydrides. Although sodium aminoborohydrides have been known for quite some time (*68, 69*), recently Singaram and coworkers described an efficient synthesis of lithium aminoborohydrides (eq. 43) (*70*). Unlike the alkoxyborohydrides, the aminoborohydrides are very powerful reducing agents that are capable of performing virtually all of the transformations for which LAH is currently used. Yet, the reagents are stable to air, similar to SBH.

$$BH_3{\bullet}SMe_2 + R_2NH \longrightarrow R_2NH{\bullet}BH_3 \xrightarrow{n\text{-BuLi}} LiR_2NBH_3 + n\text{-BuH} \quad (43)$$
$$\downarrow$$
$$SMe_2$$

A series of lithium aminoborohydrides of varying steric and electronic requirements have been synthesized. The chemistry of these reagents are reviewed by Singaram and coworkers in this book.

Acyloxyborohydrides. The treatment of SBH with carboxylic acids provides the corresponding acyloxyborohydrides (*71*). Gribble and coworkers showed the applicability of acyloxyborohydrides, especially sodium triacetoxyborohydride for reductions (eq. 44) (*72*). These reagents have extended the scope of SBH. They are selective in reducing aldehydes in the presence of ketones. Morover, α- and β-hydroxy ketones are reduced cleanly to *anti*-diols.

$$NaBH_4 + 3\ RCOOH \longrightarrow NaBH(OCOR)_3 + 3\ H_2 \quad (44)$$

Tetra-*n*-butylammonium- (*73*) and tetramethylammonium triacetoxyborohydride (eq 45-46) are more selective than the sodium counterpart for reductions. Evans described the synthesis of tetramethylammonium triacetoxyborohydride for the stereoselective reduction of β–hydroxy ketones to the corresponding *anti*-diols (*74*).

$$NaBH_4 + Me_4NOH \longrightarrow Me_4NBH_4 \quad (45)$$

$$Me_4NBH_4 + 3\ AcOH \longrightarrow Me_4N(AcO)_3BH \quad (46)$$

These derivatives are discussed in detail elsewhere in this book by Gribble and also by Abdel-Magid.

Sulfurated Borohydride. Lalancette and coworkers reported the synthesis of a sulfurated borohydride by the treatment of SBH with sulfur at room temperature in

appropriate organic solvents (eq 47) (*75*). This reagent is capable of reducing oximes to the corresponding amines with yields depending on the steric requirement of the oxime (*76*).

$$NaBH_4 + 3\ S \longrightarrow NaBH_2S_3 + H_2 \quad (47)$$

Alkylaluminohydrides. The syntheses and reactions of lithium *n*-butyl- (*77*) and lithium *tert*-butyl(diisobutyl)aluminum hydrides (*78*) have been reported (eq 48).

$$i\text{-}Bu_2AlH + RLi \longrightarrow Li[i\text{-}Bu_2RAlH] \quad (R = n\text{-Bu},\ t\text{-Bu}) \quad (48)$$

Alkylborohydrides.

Trialkylborohydrides. The addition of metal hydrides to trialkylboranes provide the corresponding borohydrides (eq 49). Although these compounds were prepared during WW-II research (*33*), the exceptional reducing power of these borohydrides were discovered during a study of the carbonylation of organoboranes catalyzed by LTBA (*79*).

$$LiH + Et_3B \xrightarrow[25\ ^\circ C]{\text{THF}} LiEt_3BH\ (\text{Super-Hydride}) \quad (49)$$

Our initial aim in the selective reductions project was to increase the reducing power of SBH to bring it closer to LAH in the spectrum of reagents. However, we encountered a borohydride, lithium triethylborohydride, that is far more powerful than LAH. Due to the superior hydridic qualities, the trialkylborohydrides have been termed "Super Hydrides". Increase in the steric bulk of the alkyl groups of these trialkylborohydrides make these reagents more selective than LAH without compromising their reductive capability.

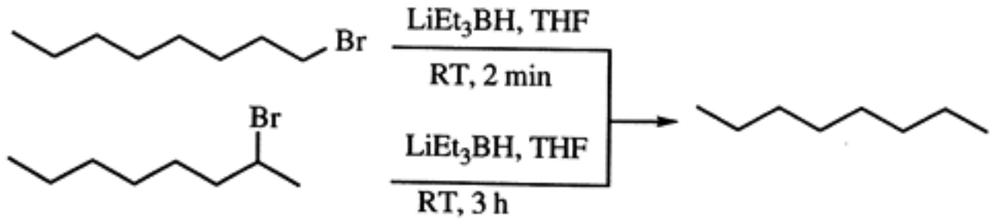
Alternate methods for their synthesis were also discovered (*80-82*), especially for hindered trialkylborohydrides, such as tri-*sec*-butylborohydrides (eq 50).

$$LiAlH(OMe)_3 + sec\text{-}Bu_3B \xrightarrow[25\ ^\circ C]{\text{THF}} \underset{(\text{L-Selectride})}{Li\text{-}sec\text{-}Bu_3BH} + Al(OMe)_3 \quad (50)$$

Corey had shown that treatment of trialkylboranes with *t*-butyllithium provides the corresponding trialkylborohydrides (*82*). This was applied in the synthesis of Selectrides (eq 51) (*80*).

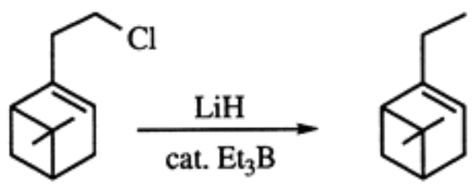
$$t\text{-BuLi} + Sia_3B \xrightarrow[-78\ ^\circ C]{\text{THF}} LiSia_3BH\ (\text{LS-Selectride}) \quad (51)$$

Super Hydride. Lithium triethylborohydride (Super Hydride) is used for reductive dehalogenation. It exhibits enormous nucleophilic power in S_N2 displacement reactions with alkyl halides, 10^4 fold more powerful than $LiBH_4$ (eq 52) (*83*).



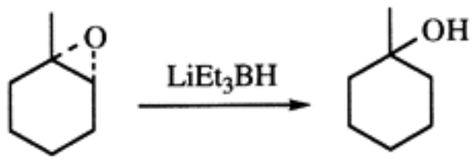
(52)

It has been observed that the dehalogenation can be achieved by *in situ* generated Super Hydride, using lithium hydride and catalytic amounts of Et_3B (eq 53) (*84*).



(53)

It is stereospecific in the reductive opening of epoxides (eq. 54) (*85*).



99% yield
≥99% *tert*- (54)

The exceptional nature of Super Hydride and its applications in organic reductions has been reviewed in detail (*86*).

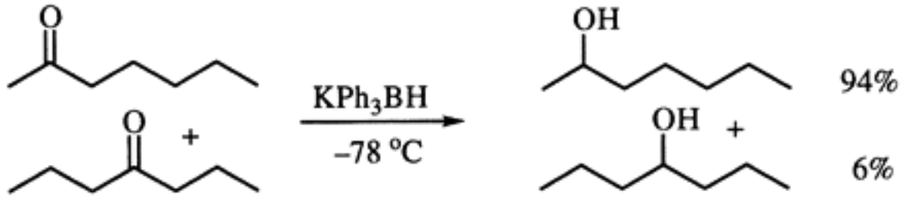
Yoon and coworkers reported the preparation of potassium triethylborohydride (eq 55). This reagent is milder than the corresponding lithium analog (*87*).

$$KH + Et_3B \xrightarrow[25\ ^\circ C,\ 24\ h]{THF} KEt_3BH \qquad (55)$$

They also reported the synthesis of a bulky Super Hydride from triphenylborane (eq 56) (*88*).

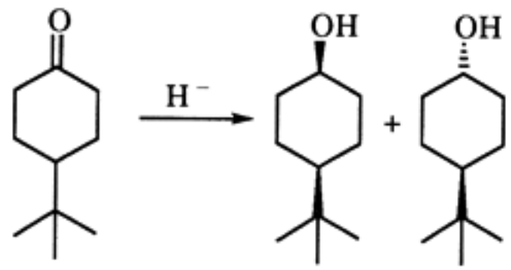
$$KH + Ph_3B \xrightarrow[25\ ^\circ C,\ 6h]{THF} KPh_3BH \qquad (56)$$

This reagent is capable of discriminating in the selective reduction of a mixture of 2- and 4-heptanones (eq 57) (*88*).



94%
6% (57)

Selectrides. Hindered trialkylborohydrides, such as K- (*66, 89*) and L-Selectrides (*90*) reduce cyclic and bicyclic ketones to the corresponding alcohols with remarkable stereoselectivity. LS-Selectride (*91*) achieves the best selectivity of them all (eq 58).



	cis : *trans*
$NaBH_4$	= 13 : 87
L-Selectride	= 96.5 : 3.5
LS-Selectride	= 99.5 : 0.5

(58)

Mono- and Dialkylborohydrides. We established convenient procedures for the preparation of mono- and dialkylborohydrides from the corresponding borinates and boronates, respectively, by treatment with LAH (eq 59-60) (*92, 93*).

$$RB(OR')_2 + LiAlH_4 \xrightarrow[0\ ^\circ C,\ 15\ min.]{n\text{-pentane-EE}} LiRBH_3 + AlH(OR')_2\downarrow \qquad (59)$$

R = Me, *n*-Bu, *t*-Bu, Ph, etc.

$$R_2BOR' + LiAlH_4 \xrightarrow[0\ ^\circ C,\ 15\ min.]{n\text{-pentane-EE}} LiR_2BH_2 + AlH_2OR' \qquad (60)$$

R = Me, *n*-Bu, *t*-Bu, Ph, etc.

The monohydrodialkoxyalane produced from the reaction of the boronate (eq 59) precipitates out, whereas the dihydromonoalkoxyalane produced from the borinate (eq 60) is soluble in pentane-EE. Hence we used lithium monoethoxyaluminum hydride for the syntheses of dialkylborohydrides (eq 61) (*93*).

$$R_2BOR'_2 + LiAl(OEt)H_3 \xrightarrow[0\ ^\circ C,\ 15\ min.]{n\text{-pentane-EE}} LiR_2BH_2 + AlH(OEt)OR'\downarrow \qquad (61)$$

R = Me, *n*-Bu, *t*-Bu, Ph, etc.

The boronates necessary for these reactions can be obtained via hydroboration reactions or from the alkylmetals or alkyl Grignard reagents as shown in eq 62 and 63 (*95*). These procedures provide an efficient general route to synthesize different types of alkylborohydrides, including lithium methylborohydride, that are not available via the routes discussed thus far.

$$RMgX + B(OMe)_3 \longrightarrow RB(OMe)_2 + MgX(OMe)\downarrow \qquad (62)$$

$$RLi + B(OMe)_3 \longrightarrow RB(OMe)_2 + LiOMe \qquad (63)$$

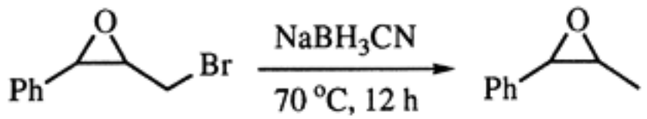
These procedures are applicable for the syntheses of optically active borohydrides (R = chiral) as well. The capability of these borohydrides in asymmetric reduction has not been explored. However, efficient procedures to convert these alkylborohydrides into the corresponding chiral alkylboranes have been established (*vide infra*).

Cyanoborohydride. Wittig synthesized the first cyanoborohydride by treating $LiBH_4$ with HCN (*96*). The corresponding reaction of sodium borohydride with hydrogen cyanide provides a white crystalline solid, sodium cyanoborohydride, which is a much milder and more selective reagent than the parent reagent (eq 64) (*97*). An improved process for the preparation of sodium cyanoborohydride involves the reaction of sodium cyanide with borane-THF (eq 64) (*98*). The stability of this reagent

in acid solutions down to pH 3, and its solubility in THF, water, methanol, HMPA, DMF, sulfolane, etc. make it a unique reagent.

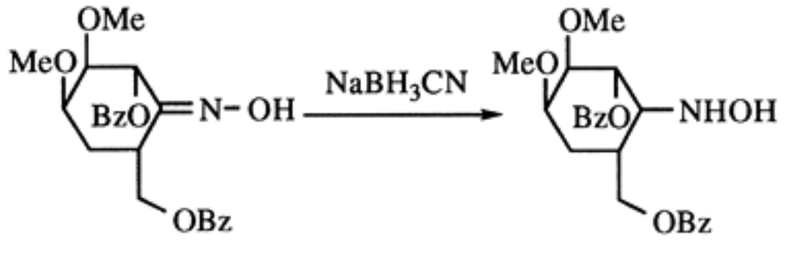
$$NaBH_4 + HCN \xrightarrow[H_2]{THF} NaBH_3CN \longleftarrow BH_3{\bullet}THF + NaCN \qquad (64)$$

$NaBH_3CN$ reduces alkyl halides and tosylates to the corresponding alkanes in the presence of a variety of reactive functional groups, such as aldehyde, ketone, epoxide, cyano, ester, carboxylic acid, amide, etc. (eq 65) (*99*).

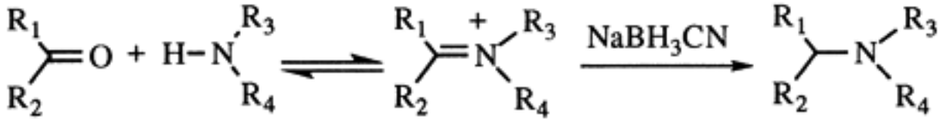


(65)

This reagent is widely used for the reduction of ketoximes to hydroxylamines (eq 66) (*100, 101*) and for the reductive amination of aldehydes and ketones (eq 67) (*100*).

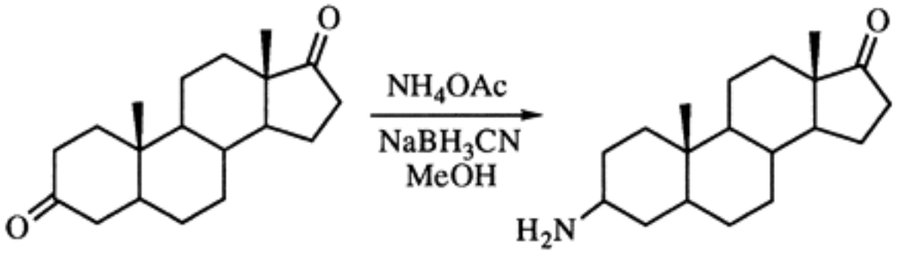


(66)



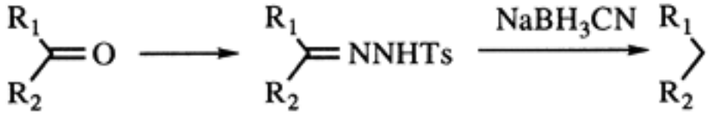
(67)

An unhindered ketone is selectively aminated in the presence of a relatively hindered ketone (eq 68) (*102*).



(68)

Another important application of sodium cyanoborohydride is the reduction of tosylhydrazones to the corresponding alkanes (eq 69) (*103*).

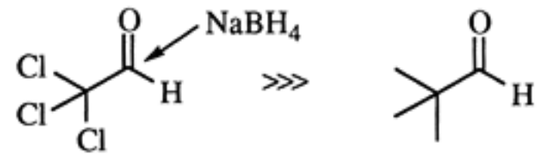


(69)

The applications of sodium cyanoborohydride in organic syntheses have been reviewed earlier (*98*, *104-105*).

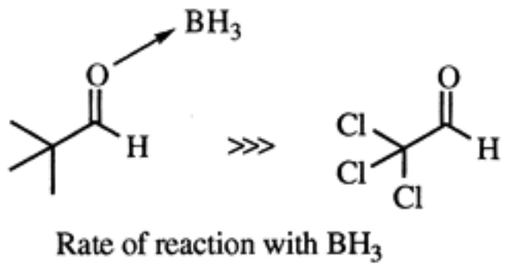
Acidic Reducing Agents

So far discussions were made of complex borohydrides and aluminohydrides whose application in reduction involve transfer of the hydride moiety to an electron deficient center of the substrate (*106,107*). In other words, the reagents are nucleophilic. Accordingly, substituents that enhance the electron deficiency at the reaction site increased the rate of reduction. For example, SBH in diglyme reduces chloral and acetyl chloride much more rapidly than aldehydes and ketones, for example, pivalaldehyde.



Rate of reaction with $NaBH_4$

On the other hand, diborane and alane are electron deficient molecules and hence behave as Lewis acids. Consequently, reduction involving these molecules are expected to involve an electrophilic attack on the center of highest electron density. Thus, pivalaldehyde is reduced much faster than chloral.



Rate of reaction with BH_3

Alane. Aluminum hydride, AlH_3, can be prepared by the treatment of LAH with $AlCl_3$ in EE. However, AlH_3 in EE is unstable and polymerizes relatively rapidly (*108*). This reagent is conveniently prepared by the addition of the calculated amount of 100% sulfuric acid to a standardized solution of LAH or SAH in THF (eq 70) (*109*).

$$2\ LiAlH_4 + H_2SO_4 \xrightarrow{THF} Li_2SO_4\downarrow + 2\ AlH_3 + 2\ H_2\uparrow \qquad (70)$$

Apparently, coordination of the AlH_3 with the THF prevents the rapid association of the AlH_3 that is observed in EE.

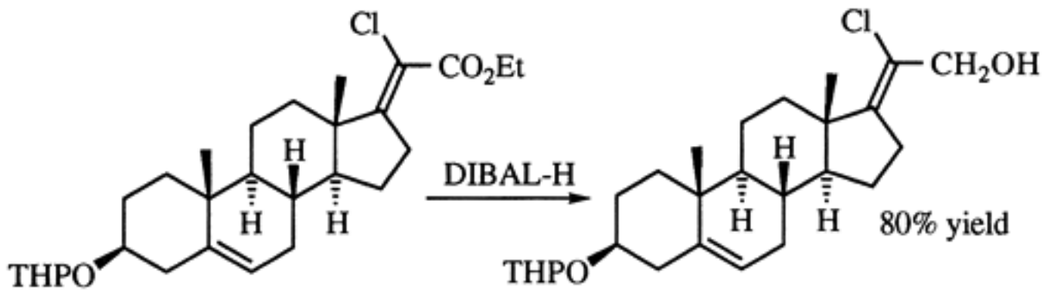
AlH_3 is used for the selective reduction of carboxylic acid esters to the corresponding alcohols in the presence of halogen and nitro substituents (*110*). Another application of this reagent is for the reduction of *tert*-amides to the corresponding amines in excellent yields. This becomes especially important since this reduction is compatible for amides with unsaturation present. Utilization of borane-THF for this purpose results in concurrent hydroboration.

Alane-Amine Complex. Wiberg and coworkers reported a 1:1 and 1:2 complex of alane with trimethylamine in 1952 (*108*). Recently, Marlett and Park described the reducing power of AlH_3-amine complexes (*111*). The utility of alane-triethylamine complex was systematically studied by us (*112*). This complex permits the convenient use of alane in organic synthesis with high efficiency. SAH is preferred for the preparation of alane since the salt formed, NaCl, has very little solubility in THF and can be easily removed by filtration (eq 71-72).

$$NaAlH_4 + HCl \longrightarrow AlH_3 + NaCl\downarrow + H_2\uparrow \quad (71)$$

$$AlH_3 + Et_3N \longrightarrow H_3Al{\bullet}NEt_3 \quad (72)$$

Dialkylalanes. The preparation and reactions of dialkylalanes have been reviewed before (*113*). One of the most widely used dialkylalane is diisobutylaluminum hydride, DIBAL-H (*114*). A representative application of DIBAL-H is the reduction of α,β-unsaturated esters to the corresponding allylic alcohols (eq 73) (*115*).

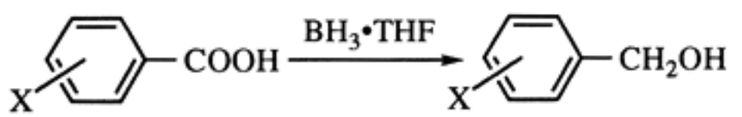


(73)

Borane. Originally we carried out all of the reactions involving diborane in the gas phase in vacuum lines (*25*). Then we discovered that diborane can be conveniently generated by the treatment of SBH in diglyme with boron-trifluoride-etherate (eq 74) (*116*) and reactions were carried out by bubbling the gaseous diborane into solutions of the compound in EE, THF, or DG. Other methods of preparation are discussed in two early reviews (*117, 118*). We soon discovered that borane can be conveniently used as a monomer by complexing with a suitable ligand. Borane is now commonly used as a complex in THF, $H_3B{\bullet}THF$, or a dimethyl sulfide complex, $H_3B{\bullet}SMe_2$, used in THF or other solvents.

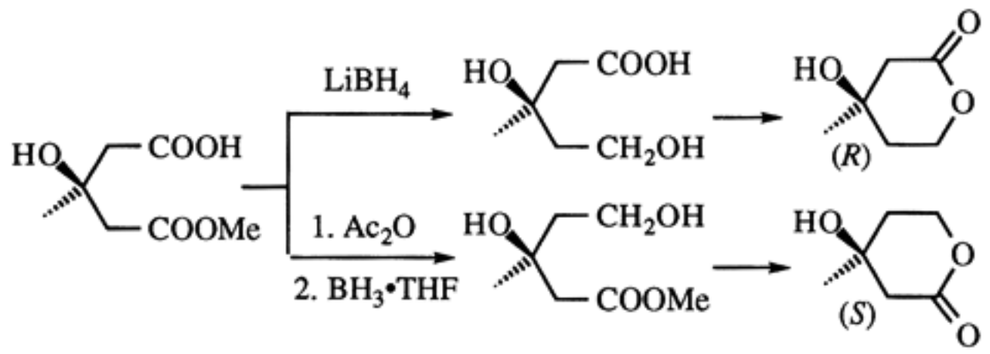
$$3\ NaBH_4 + 4\ BF_3 \xrightarrow{DG} 2\ B_2H_6\uparrow + 3\ NaBF_4 \quad (74)$$

Borane-Tetrahydrofuran. The reactivity of borane depends on the complexing agent also, since the mechanism of reaction involves prior dissociation and formation of free borane (*119*). Borane-THF is prepared by passing gaseous diborane through THF (*120, 121*). Although a 4 *M* solution can be prepared, it loses some of the borane upon storage and THF is slowly cleaved to give *n*-BuO–B< moieties. Hence it is currently marketed as a 1*M* solution. This reagent is capable of reducing aldehydes, ketones, lactones, carboxylic acids, *tert*-amides, and nitriles (*121*). Acid chlorides, epoxides, and esters are reduced slowly. Borane-THF can tolerate a variety of functional groups. One of the important application of borane-THF has been in the rapid and quantitative reduction of carboxylic acids to the corresponding alcohols under remarkably mild conditions in the presence of various functional groups (eq 75) (*122*).



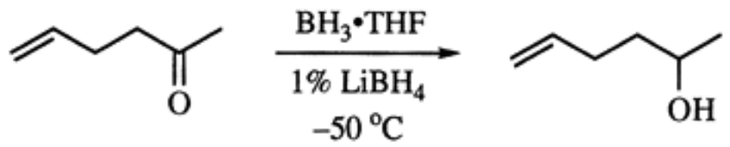
X = Cl, Br, I, NO_2, CN, COOEt, etc. (75)

The remarkable difference in the behavior of the borohydride and borane reagents toward the nature of the substrate has been exploited in the synthesis of both (*R*)- and (*S*)-mevalonolactone from a common precursor (eq 76) (*123*).



(76)

Recently, Arase and coworkers reported a lithium borohydride catalyzed selective reduction of the carbonyl group of conjugated and unconjugated alkenones with borane-THF (eq 77) (*124*). This methodology provides an efficient synthesis of allylic alcohols and other enols.



(77)

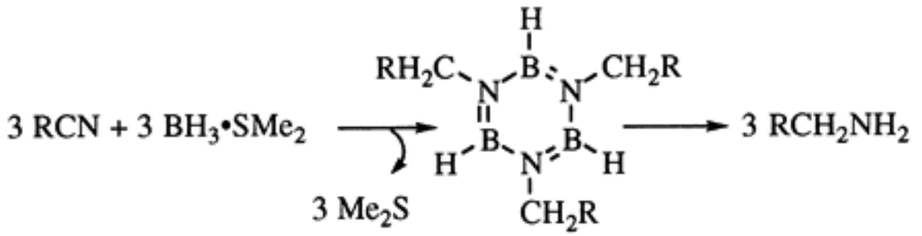
Borane-Dimethyl Sulfide Complex. Although borane can be used conveniently as borane-THF, the low concentration and the necessity to add trace amounts of SBH to stabilize the reagent (diminishing the cleavage of THF) made the introduction of alternate complexes of borane desirable. Adams and co-workers introduced the dimethyl sulfide complex (*125*) for hydroboration (*126*) and subsequent research proved this to be as efficient as borane-THF. The reagent can be stored as a neat material (10 *M*) and reactions can be carried out at much higher concentrations in a variety of aprotic solvents. Alternately, one can utilize commercial solutions of 2*M* BMS in THF. Such solutions exhibit long-term stability. The reagent is capable of reducing acids, esters, amides, nitriles etc. The hydroborations and reductions are made possible by free borane produced by dissociation. Our systematic study has shown that distillation of the free dimethyl sulfide from THF solutions aids in achieving fast reaction rates. This phenomenon was taken advantage in the facile reduction of carboxylic esters, and amides (eq 78) (*127*).

$$RCOOEt \xrightarrow{BH_3{\bullet}SMe_2} RCH_2OH \quad (78)$$

pri-Amides are reduced by one equiv of hydride from BMS whereas sec- and tert-amides need one equiv of the borane to complex with the amine product formed. This requirement for excess diborane is avoided by using one equiv of boron trifluoride-etherate. Thus, we have achieved efficient reduction of both aliphatic and aromatic *pri*-, *sec*-, and *tert*-amides (eq 79) (*127*).

$$RCONR'_2 \xrightarrow[BF_3{\bullet}EE]{2/3\ BH_3{\bullet}SMe_2} RCH_2NR'_2 \quad (79)$$

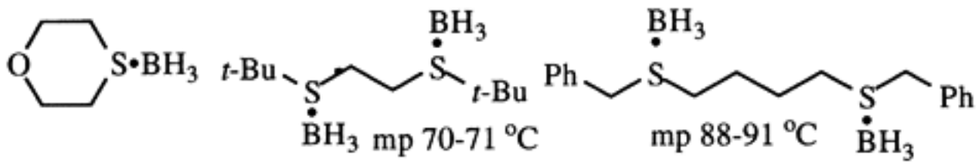
BMS reduces nitriles via the formation of borazines (eq 80). This mechanism alters the stoichiometry of the reaction so that three equiv of hydride are required to give a quantitative yield of the amine product (*127*).



(80)

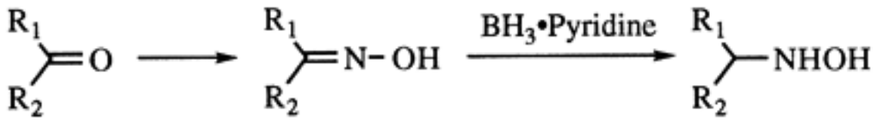
The applications of BMS in hydroborations, reductions and in organic syntheses have been reviewed on several occasions (*128-133*).

Several other sulfide complexes of borane have been reported. Adams observed that tetrahydrothiophene is a weaker base toward BH_3 than dimethyl sulfide. However, contrary to expectations, the complex is less reactive than BMS (*126*). We have shown that borane-1,4-thioxane complex (*134*) avoids the stench of the volatile dimethylsulfide component and more readily provides borane than BMS. We have since developed several new sulfide complexes for hydroboration (Brown, H. C.; Zaidlewicz, M., unpublished results). Several solid borane-sulfide complexes have also been reported in the literature (*135*).



Borane-amines. Although amine-boranes have been known for several decades (*136, 137*), they have not yet found significant use in organic reductions and syntheses as one might expect. This may be due to the strong coordination of the nitrogen lone pair and the boron, since dissociation appears to be a key step for reaction. We have now synthesized several new amine-boranes that are strong enough to form a stable complex, but weak enough to liberate free borane for hydroborations and reductions (Brown, H. C.; Zaidlewicz, M.; Dalvi, P. V., unpublished results).

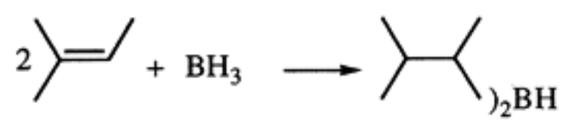
One of the borane-amines currently available that deserve special attention is pyridine-borane (*136*). This reagent is capable of reducing aldehyde oximes to the corresponding hydroxylamines (eq 81) (*138*) and is also used for reductive aminations (*139*).



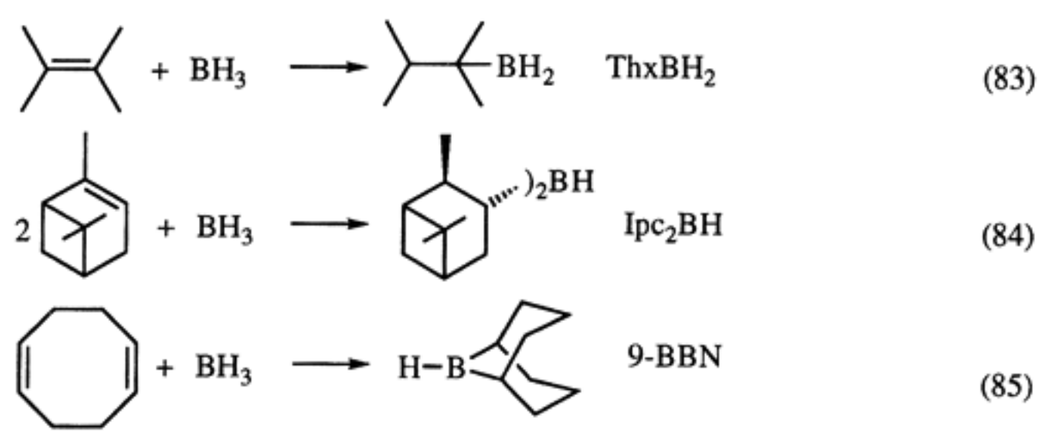
(81)

Alkylboranes. The synthesis of alkylboranes can be achieved from olefins, acetylenes, and dienes directly by hydroboration or from lithium alkylborohydrides by treatment with a proper acidic reagent.

From Olefins via Hydroboration. The hydroboration of simple alkenes with borane generally proceeds directly to the formation of the trialkylborane, R_3B. However, in a number of instances, it has proved possible to control the hydroboration reaction to achieve the synthesis of monoalkylboranes, RBH_2, dialkylboranes, R_2BH, and cyclic boranes (eq 82-85) (*140-142*).



Sia_2BH (82)



(83)

(84)

(85)

These boranes have found unique applications in organic syntheses which have been discussed in several reviews and books (*128-133*). Of particular interest is diisopinocampheylborane, derived by the hydroboration of α-pinene. This reagent achieved the first non-enzymatic asymmetric reaction achieving very high ee by the hydroboration of a prochiral *cis*-olefin. *This reaction marked the beginning of non-enzymatic asymmetric synthesis in high ee.*

The α-pinene-boron moiety exhibits remarkable efficacy as a chiral auxiliary (Figure 1) (*143-146*).

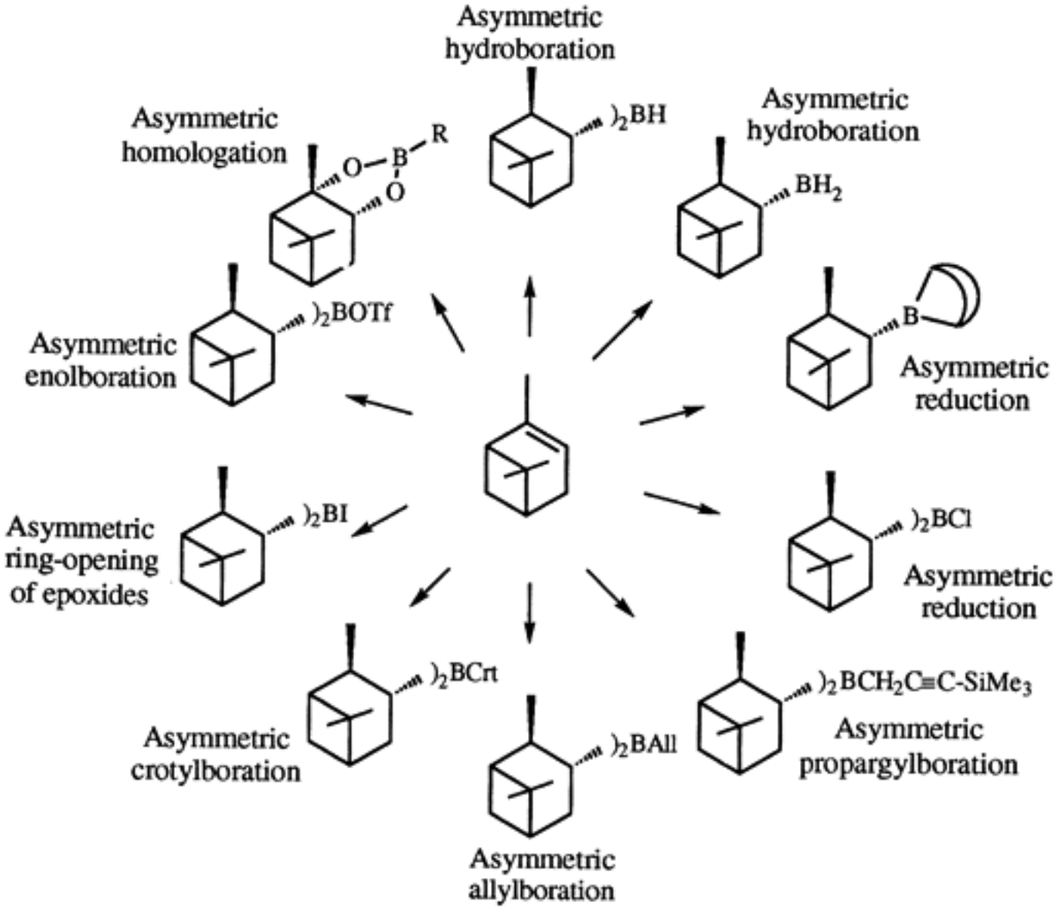


Figure 1. α-Pinene: A Super Chiral Auxiliary

From Borohydrides. While the boranes discussed above are prepared via direct hydroboration, there are several alkylboranes, methylborane for example, that can not be obtained via this route. We discovered an efficient general synthesis of mono- and dialkylboranes from the corresponding borohydrides (eq 86-87), which in turn can be obtained from the corresponding borinates and boronates, respectively (eq 59-60). This procedure allows the syntheses of boranes, such as methylborane and *t*-butylborane, etc. that are inaccessible via hydroboration.

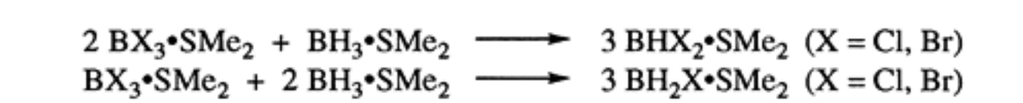
$$LiR_2BH_2 + HCl \longrightarrow R_2BH + LiCl + H_2 \quad (86)$$

$$LiRBH_3 + HCl \longrightarrow RBH_2 + LiCl + H_2 \quad (87)$$

We examined convenient procedures for the generation of the boranes from the borohydrides (*147*). A major advantage of this procedure is the synthesis of optically pure boranes from optically pure borinates and boronates for a general synthesis of optically pure organic molecules (eq 88) (*148*).

$$LiR^*BH_3 + HCl \longrightarrow R^*BH_2 + LiCl + H_2 \quad (88)$$

Masamune applied this procedure for the synthesis of an optically active borolane (eq 89) (*149*).

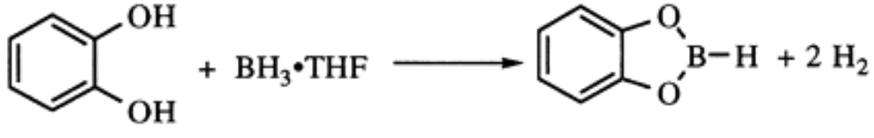


(89)

The simple synthesis of the R*B< moiety through hydroboration with R^*BH_2 and the ability to substitute the boron atom by other atoms and groups with complete retention makes possible a general asymmetric synthesis, as indicated in Figure 2. (Reactions that have been demonstrated experimentally are shown by arrows with solid lines.)

We have reviewed our general asymmetric synthetic procedures earlier (Figure 2) (*143-146*) and they will not be discussed here.

Alkoxyboranes. Due to their decreased Lewis acidity, dialkoxyboranes, such as 4,4,6-trimethyl-1,3,2-dioxaborinane (*150*) are very poor reducing agents. However, the acidity can be increased by using appropriate diols, such as catechol. Thus, the treatment of borane-THF and catechol readily provides catecholborane, a very mild reducing and hydroborating agent (eq 90) (*151*). The reducing characteristics of catecholborane have been explored in detail (*152*). This reagent has been a favorite for transition metal catalyzed hydroborations (*153*) and oxazaborolidine catalyzed asymmetric reductions (*154*).



(90)

Haloboranes. Reagents that are stronger Lewis acids than borane were synthesized by substituting hydrogen with halogen, such as bromine and chlorine. The synthesis was conveniently achieved by redistribution (eq 91-92) (*155*).

$$2\,BX_3{\bullet}SMe_2 + BH_3{\bullet}SMe_2 \longrightarrow 3\,BHX_2{\bullet}SMe_2 \;(X = Cl, Br) \quad (91)$$

$$BX_3{\bullet}SMe_2 + 2\,BH_3{\bullet}SMe_2 \longrightarrow 3\,BH_2X{\bullet}SMe_2 \;(X = Cl, Br) \quad (92)$$

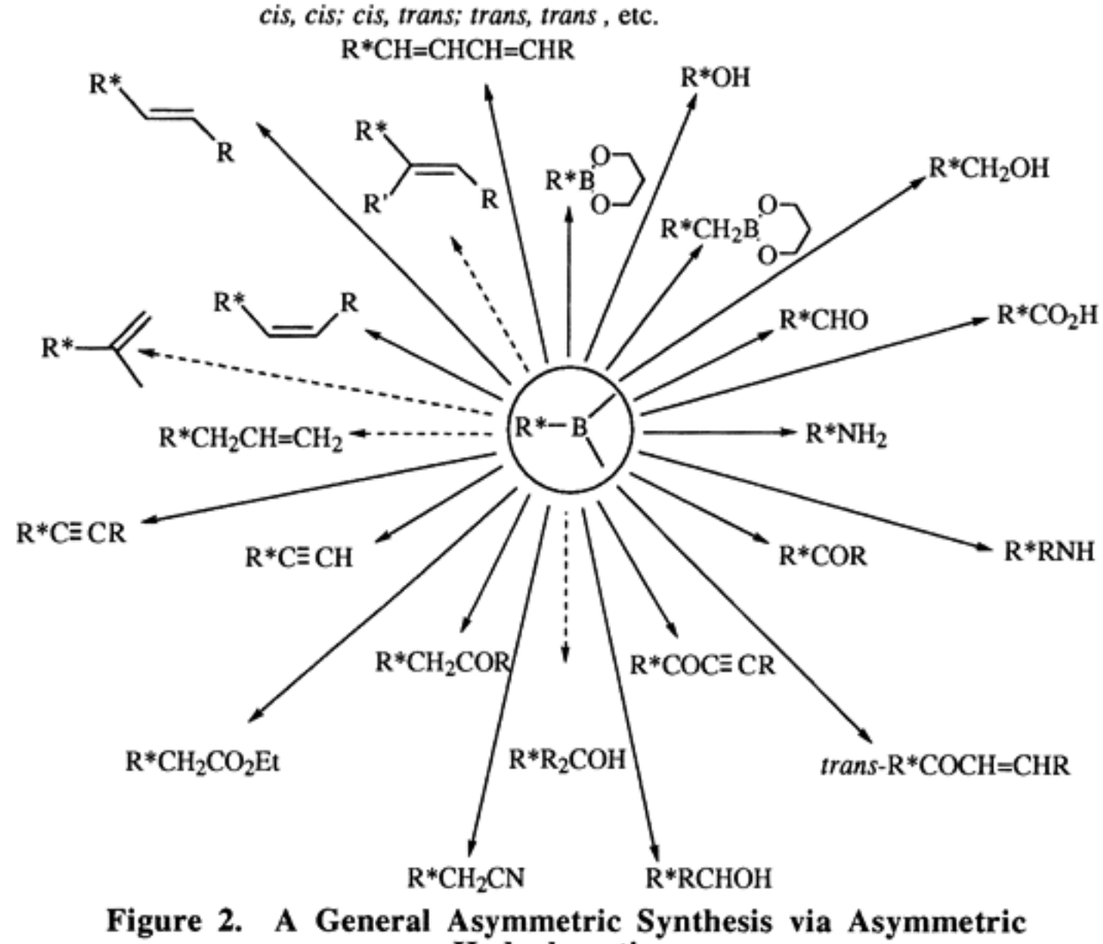


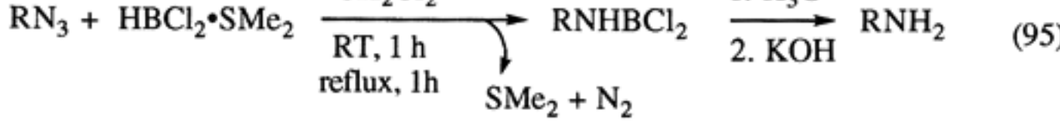
Figure 2. A General Asymmetric Synthesis via Asymmetric Hydroboration

Dichloroborane and monochloroborane are conveniently synthesized as the etherates by treating lithium borohydride with a stoichiometric quantity of boron trichloride in EE as the solvent (eq 93-94) (*156*).

$$LiBH_4 + BCl_3 \xrightarrow{EE} 2\,BH_2Cl{\bullet}EE + LiCl \quad (93)$$

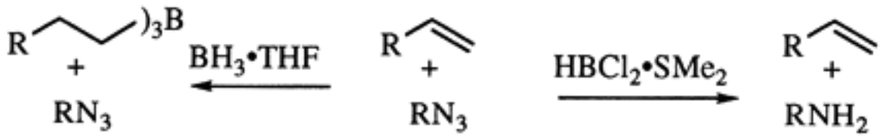
$$LiBH_4 + 3\,BCl_3 \xrightarrow{EE} 4\,BHCl_2{\bullet}EE + LiCl \quad (94)$$

These chloroborane reagents have found unique applications for selective reductions. For example, dichloroborane-methylsulfide reduces many types of azides to the corresponding amines in high yield (eq 95) (*157*).



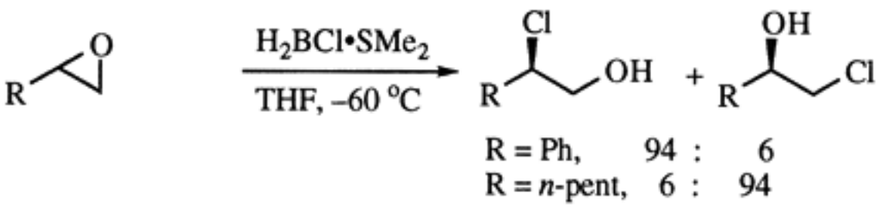
(95)

This reaction allows the selective reduction of an azide in the presence of an olefin by dichloroborane, or the hydroboration of an olefin in the presence of an azide by borane-THF (eq 96) (Salunkhe, A. M., unpublished results).



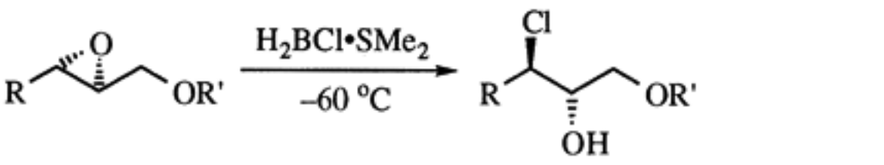
(96)

Monochloroborane-dimethyl sulfide is an efficient reagent for the chemo- and regioselective opening of epoxides (eq 97, *158*).



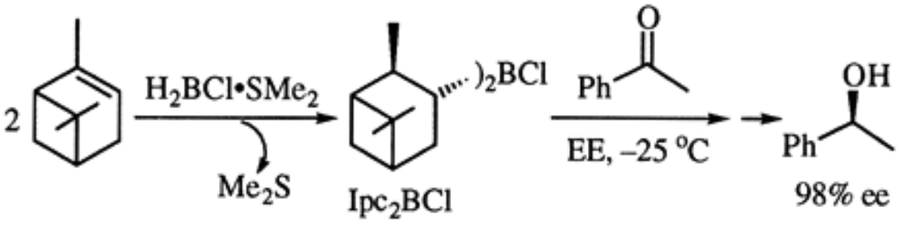
(97)

α-Oxysubstituted epoxides are cleaved to provide the corresponding regio- and stereodefined *anti*-chlorohydrin (eq 98) (*159*). The reaction is believed to proceed with anchimeric assistance from the side-chain oxygen.



(98)

Alkylchloroboranes. Chloroborane-dimethylsulfide hydroborates two equiv of unhindered olefins to provide the corresponding dialkylchloroborane. One such compound, *B*-chlorodiisopinocampheylborane (Aldrich: DIP-Chloride) has been shown to be an excellent asymmetric reducing agent (eq 99) (*160*). This reagent is discussed by us in another chapter in this book.



(99)

When the olefin is hindered, such as 2,3-dimethyl-2-butene (thexylene), the hydroboration stops at the monoalkylchloroborane stage providing thexylchloroborane-dimethylsulfide (eq 100) (*161*). This reagent reveals certain unique properties. For example, it reduces carboxylic acids partially, efficiently and quantitatively, to the corresponding aldehydes (eq 101) (*162*).

(100)

(101)

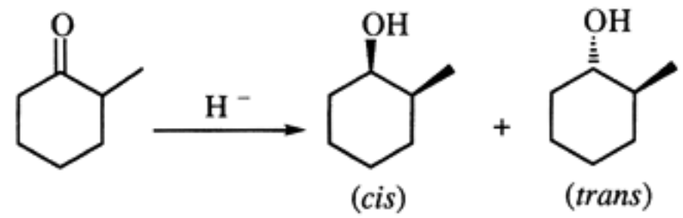
Chemoselectivity and Stereoselectivity in Reductions

Chemoselectivity is important in organic reductions. Many of the modified reagents discussed in this review are capable of achieving chemoselective reduction.

Stereoselectivity in acyclic and cyclic reductions is achieved by controlling the steric requirements of the reagents. These subjects including the mechanistic aspects of acyclic and cyclic stereoselection (Cram, Cornforth, anti-Cram, Karabatsos, and Felkin models) have been reviewed in detail by Greeves (*163*).

Table 2 summarizes the steric control achieved by several reagents discussed in this review for the reduction of 2-methylcyclohexanone.

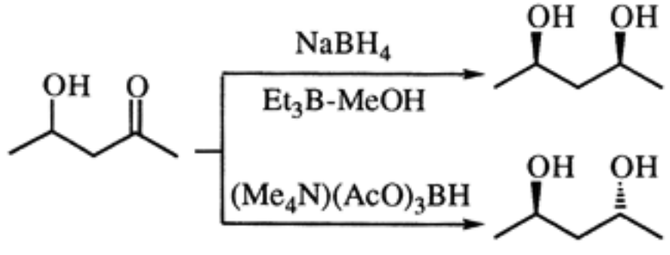
Table 2. Diastereoselective Reduction of 2-Methylcyclohexanone



Reagent	% *cis*	% *trans*
LAH	25	65
SBH	31	69
LBH	30	70
LTMA	31-72[a]	69-28[a]
LTBA	27	73
L-Selectride	99.3	0.7
K-Selectride	>99	<1
$LiSia_3BH$	99.7	0.3
KIPBH	92	8
Diborane	74	26
Sia_2BH	79	21
Chx_2BH	94	6
9-BBN	40	60
$ThxBHCl•SMe_2$	95	5

[a]Depends on the solvent.

One of the interesting applications of borohydride reductions in organic syntheses has been the stereoselctive reduction of β-diketones or β-hydroxy ketones to diols, an especially valuable transformation due to the importance of such polyols in antibiotics and other natural products. Hence methodologies for the selective synthesis of either the *syn*- or *anti*-diol from the corresponding hydroxy ketone have been developed. Narasaka (*164*) and Prasad (*165*) developed methods for the synthesis of essentially pure *syn* diols and Evans (*166*) developed procedures for the preparation of essentially pure *anti*-diols (eq 102).



(102)

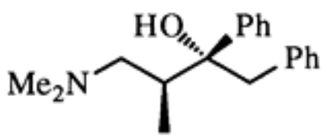
Asymmetric Reduction

We have discussed the beginnings of diborane, sodium borohydride, lithium aluminum hydride, and many modifications thereof. Ever since chemists became familiar with

these reagents, they have modified them with different chiral auxiliaries to achieve asymmetric reduction. Although the initial attempts by Bothner-By (*167*) and Landor and coworkers (*168*) to modify LAH did not achieve much asymmetry in the reduction of ketones, subsequent research has led to several quite successful asymmetric reducing agents.

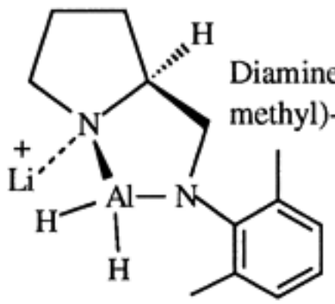
LAH Modified Reagents. Several alcohols, amines, amino alcohols, diols and triols have been used to modifiy LAH to prepare asymmetric reducing agents. This subject has been reviewed several times (*169-173*). The following are some of the most successful reagents developed by Mosher (*174*), Mukaiyama (*175*), Terashima (*176*), Fujisawa (*177*), Vigneron (*178*) and Noyori (*179*).

$LiAlH_4$ + Darvon Alcohol (*174*)



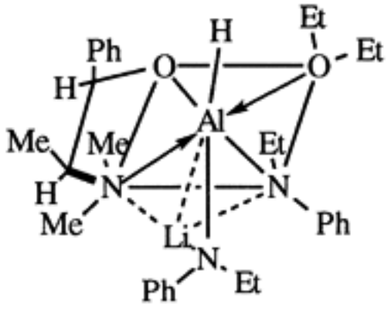
Darvon alcohol

$LiAlH_4$ + Diamine (*175*)

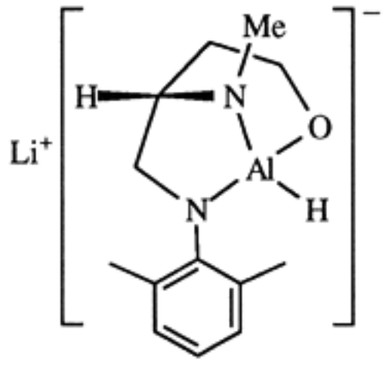


Diamine = (S)- -(2,6-Xylidino-methyl)-pyrrolidine

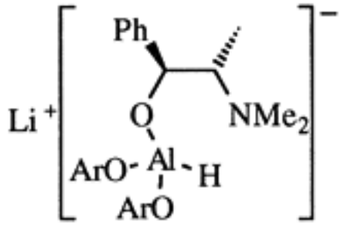
$LiAlH_4$ + MEP + NEA (*176*)



$LiAlH_4$ + Aminobutanol (*177*)

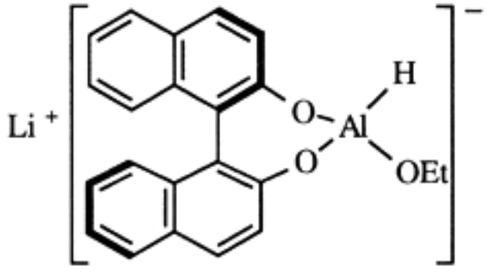


$LiAlH_4$ + MEP + ArOH (*178*)



ArOH = 3,5-dimethyl phenol

$LiAlH_4$ + Binaphthol + EtOH (*179*)

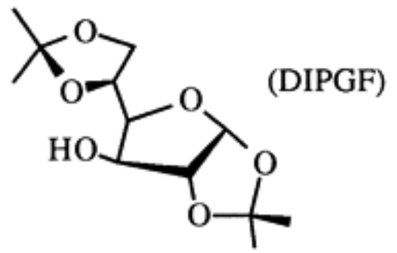


Binal-H

SAH modified Reagents. We synthesized the corresponding reagents by treating sodium aluminum hydride with Darvon alcohol, N-methylephedrine, menthol, and binaphthol and carried out the asymmetric reduction of prochiral ketones. In all of the cases studied, we obtained results similar to or slightly better than those obtained with the lithium analog (Ramachandran, P. V.; Gong, B., unpublished data).

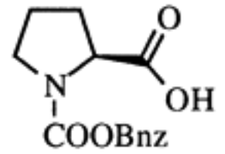
Borohydride Reagents. Attempts to modify SBH with several optically active acids, including amino acids, have not led to any highly successful reducing agent thus far. This subject has been reviewed previously (*173, 180*). Morrison (*181*) and Hirao (*182*) and their coworkers modified SBH with two equiv of carboxylic acid and 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose. Yamada and coworkers prepared a reagent from SBH and *N*-benzyloxycarbonylproline that achieves high ee for the reduction of imines (*183*) Modifications of SBH with mandelic (*184*), lactic (*185*), tartaric (*186, 187*), camphanic or malic acids (*187*) have also been reported.

$NaBH_4$ + *i*-Pr-COOH + DIPGF



(DIPGF)

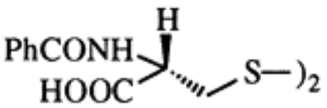
$NaBH_4$ + 3



However, Soai and coworkers transformed lithium borohydride using *N, N*-dibenzoylcysteine (DBC) and *tert*-butanol into a reagent capable of reducing aromatic β-keto esters to the corresponding hydroxy esters in very high ee (*188*).

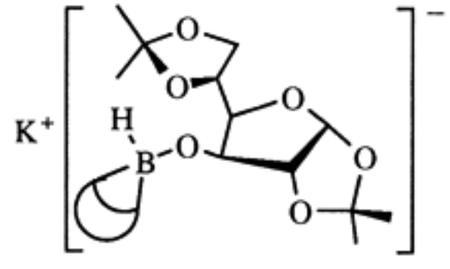
$LiBH_4$ + DBC + *t*-BuOH

DBC =



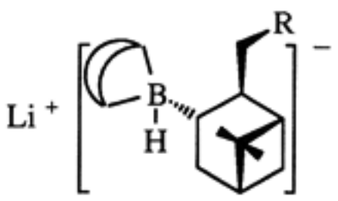
We have shown that the same results can be achieved by preparing the reagent from sodium borohydride and catalytic amounts of lithium borohydride or lithium chloride (Ramachandran, P. V.; Teodorovic´, A. V., unpublished data).

We synthesized several chiral dialkylmonoalkoxy- and alkyldialkoxyborohydrides from the corresponding borinates or boronates by treatment with KH and tested them for the reduction of ketones (*189*). We identified potassium 9-*O*-(1,2;5,6-di-*O*-isopropylidene-α-*D*-glucofuranosyl)-9-boratabicyclo-[3.3.1]nonane (K-Glucoride) as an unusually efficient reagent for the reduction of hindered aromatic ketones, and α-keto esters (*190*). Hutchins and coworkers applied this reagent for the reduction of phosphinamides (*191*) and Cho and coworkers used it for the reduction of imines (*192*).



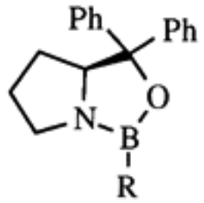
K-Glucoride

Chiral Super Hydrides. Lithium (*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonyl) hydride (Alpine-Hydride) prepared from α-pinene is a poor reagent for the reduction of ketones (*193*). Midland synthesized the corresponding borohydride from nopol benzyl ether (NB-Enantride) and it proved to be an excellent reagent for the reduction of straight chain aliphatic ketones (*194*). Several analogs of this reagent have been prepared that are moderately successful (*195*) (Weissman, S. A.; Ramachandran, P. V. *Tetrahedron Lett.*, in press).

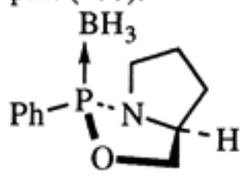


R = H (Alpine-Hydride)
R = OMe
R = NEt_2
R = $N(i\text{-}Bu)_2$
R = CH_3 (Eapine-Hydride)
R = CH_2OMe
R = CH_2OBnz (NB-Enantride)
R = CH_2NEt_2
R = $CH_2N(i\text{-}Bu)_2$

Oxazaborolidines. Although several chemists attempted the modifications of borane with different chiral auxiliaries (*180*), it was the systematic study of Hirao, Itsuno and coworkers using amino alcohols, derived from amino acids, that led to superior borane-modified reagents for asymmetric reduction (*196*). Itsuno and coworkers revealed the catalytic nature of the aminoalcohol-borane system (*197*). Corey and coworkers identified the catalyst as oxazaborolidines (*198*). A flood of oxazaborolidines that achieve moderate to good enantiomeric excess have been reported in the literature since then and continues to be reported. This subject has been reviewed before (*199*) and is also the subject of a chapter by Quallich in this book.



Buono and coworkers have shown that oxazaphospholidines also act as asymmetric catalytsts for reductions with borane. However the ee achieved is much poorer than those of the boron counterpart (*200*).



Conclusions

Persuaded by Alfred Stock's book entitiled "The Hydrides of Boron and Silicon" which he received as a graduation gift in 1936 from his classmate Sarah Baylen (now his wife), the senior author undertook research with Professor H. I. Schlesinger and Dr. A. B. Burg, exploring the chemistry of diborane.

The Ph.D. study of the reaction of diborane with aldehydes and ketones opened up the hydride era of organic reductions. The study of this reaction led to the discovery of alkali metal borohydrides. Study of the reducing characteristics of the aluminohydrides and borohydrides led to the addition of a wide variety of reducing agents for selective reductions to the organic chemist's arsenal. The capabilities of several of the reagents that fill in the spectrum between and beyond sodium borohydride and lithium aluminumhydride are summarized in Table 3.

Study of the reducing characteristics of sodium borohydride led to the discovery of hydroboration. Hydroboration provided both simple synthetic routes to organoboranes and a wide variety of organoborane reagents. Investigations established that these compounds have a most versatile chemistry. This study provided in 1961 the first non-enzymatic asymmetric synthesis in high ee and opened another significant area of research to chemists. Clearly, a Major New Continent of Chemistry was discovered

sixty years ago. The landmarks of the sixty-year hydride reduction projects are the following.

1. Beginnings
2. Volatile Compounds of Uranium
3. Alkali Metal Route to Diborane
4. Alkali Metal Borohydrides
5. Selective Reductions
6. Hydroborations
7. Versatile Organoboranes
8. Asymmetric Hydroboration
9. Asymmetric Synthesis Made Easy
10. α-Pinene: Superior Chiral Auxiliary
11. Asymmetric Reductions
12. Asymmetric Allyl- and Crotylboration
13. Asymmetric Enolborations
14. Asymmetric Opening of Meso Epoxides

Table 3. Broad spectrum of selective reducing agents

	KIPBH	$NaBH_4$	LTBA	$LiBH_4$	$Al(BH_4)_3$	BH_3•THF	Sia_2BH	9-BBN	AlH_3	LTMA	$LiAlH_4$	$LiEt_3BH$
RCHO	+	+	+	+	+	+	+	+	+	+	+	+
R_2CO	+	+	+	+	+	+	+	+	+	+	+	+
RCOCl	+	+	+	+	+	–	–	+	+	+	+	+
RCO_2R'	–	–	±	+	+	±	–	±	+	+	+	+
RCO_2H	–	–	–	–	+	+	+	±	+	+	+	+
$RCONR'_2$	–	–	–	–	–	+	+	+	+	+	+	–
RCN	–	–	–	–	–	+	–	±	+	+	+	+
RNO_2	–	–	–	–	–	–	–	–	+	+	+	+
$RCH{=}CH_2$	–	–	–	–	–	+	+	+	–	–	–	–

It will require a new generation of chemists to continue this exploration and apply the riches of the New Continent for the good of Mankind.

Acknowledgment

The financial assistance from the United States Army Research Office for this program for the past 40+ years which made most of the study reported in this chapter possible is gratefully acknowledged.

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