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, diisopinocampheyloborane, lpc2BH. This led to the development 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 in 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.

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REDUCTIONS IN ORGANIC SYNTHESIS

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 alkaline 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 amalgam, or iron and acetic acid (16). Later, sodium in ethanol (17) or zinc in sodium hydroxide in ethanol (18) were used for this purpose. In the second quarter of this century, independent research by Verley (19), Meehl (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 dialkoxo derivatives, which can be rapidly hydrolyzed to the corresponding alcohols (eq 1-2-25).

\[ 4 \text{RCHO} + 2 \text{BH}_3 \rightarrow 2(\text{RCHO})_2\text{BH} \rightarrow 4 \text{RCHOH} + 2 \text{H}_2 + 2 \text{B(OH)}_3 \]  
(1)

\[ 4 \text{CHO} + 2 \text{BH}_3 \rightarrow 2(\text{CH}_2\text{O})_2\text{BH} \rightarrow 4 \text{CH}_2\text{OH} + 2 \text{H}_2 + 2 \text{B(OH)}_3 \]  
(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.

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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 UF₆, 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).

\[ 3 \text{LiEt} + 2 \text{BH}_3 \rightarrow 3 \text{LiBH}_4 + \text{BEt}_3 \]  
(3)

\[ 3 \text{BeMe}_2 + 4 \text{BH}_3 \rightarrow 3 \text{Be(BH)}_2 + 2 \text{BMe}_3 \]  
(4)

\[ \text{AlMe}_3 + 2 \text{BH}_3 \rightarrow \text{Al(BH)}_3 + \text{BMe}_3 \]  
(5)

\[ \text{UF}_4 + 2 \text{Al(BH)}_3 \rightarrow \text{U(BH)}_4 + 2 \text{AlF}_2 \]  
(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 (eq 7-10) (30-32).

\[ 6 \text{LiH} + 8 \text{BF}_3 \rightarrow \text{EE} \rightarrow \text{B}_2\text{H}_6 \uparrow + 6 \text{LiBF}_4 \]  
(7)

\[ 2 \text{LiH} + \text{BH}_3 \rightarrow \text{EE} \rightarrow 2 \text{LiBH}_4 \]  
(8)

\[ \text{AlCl}_3 + 3 \text{LiBH}_4 \rightarrow \text{Al(BH)}_4 + 3 \text{LiCl} \]  
(9)

\[ \text{UF}_4 + 2 \text{Al(BH)}_3 \rightarrow \text{U(BH)}_4 + 2 \text{AlF}_2 \]  
(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).

\[ \text{NaH} + \text{B(OEt)}_3 \rightarrow \text{reflux} \rightarrow \text{NaBH(OEt)}_3 \]  
(11)

\[ 6 \text{NaBH(OEt)}_3 + 8 \text{BF}_3 \rightarrow \text{B}_2\text{H}_6 \uparrow + 6 \text{NaBF}_4 + 6 \text{B(OEt)}_3 \]  
(12)

\[ 2 \text{NaBH(OEt)}_3 + \text{BH}_3 \rightarrow 2 \text{NaBH}_4 + 2 \text{B(OEt)}_3 \]  
(13)

\[ \text{AlCl}_3 + 3 \text{NaBH}_4 \rightarrow \text{Al(BH)}_4 \uparrow + 3 \text{NaCl} \]  
(14)

\[ \text{UF}_4 + 2 \text{Al(BH)}_3 \rightarrow \text{U(BH)}_4 + 2 \text{AlF}_2 \]  
(15)

The problem of handling UF₆ had been mastered, so that the NDRC was no longer interested in U(BH₄)₂. 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).
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!

\[
\text{NaBH}_4 + 4 \text{(CH}_3\text{)}_2\text{CO} \rightarrow \text{NaB(OCH(CH}_3\text{)}_3\text{)}_4
\]  

(17)

\[
\text{NaB(OCH(CH}_3\text{)}_3\text{)}_4 + 2 \text{H}_2\text{O} \rightarrow 4 \text{(CH}_3\text{)}_2\text{CHOH} + \text{NaB(OH)}_4
\]  

(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).

\[
4 \text{LiH} + \text{AlCl}_3 \rightarrow \text{LiAlH}_4 + 3 \text{LiCl}
\]  

(19)

\[
3 \text{LiAlH}_4 + \text{AlCl}_3 \rightarrow 4 \text{AlH}_3 + 3 \text{LiCl}
\]  

(20)

\[
4 \text{AlH}_3 + 4 \text{LiH} \rightarrow 4 \text{LiAlH}_4
\]  

(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 specialty 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, nitrides, amides, oximes, 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 beyond these extremes (Table 1).

| 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). |

\[
\text{RCH}_2\text{OH} \rightarrow \text{LiBH}_4 \rightarrow \text{R}_{2}\text{COOR'} \rightarrow \text{NaBH}_4 \rightarrow \text{No or slow reaction}
\]  

(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).

\[
\text{RCOOEt} \rightarrow \text{NaBH}_4\cdot\text{LiBr} \rightarrow \text{RCH}_2\text{OH}
\]  

(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.

\[
2 \text{NaBH}_4 + \text{ZnCl}_2 \rightarrow \text{"Zn(BH}_4\text{)}_2 + 2 \text{NaCl}
\]  

(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 (57, 52) led to the discovery of hydroboration.

\[ 3 \text{NaBH}_4 + \text{AlCl}_3 \rightleftharpoons \text{Al(BH}_4)_3 + 3 \text{NaCl} \]  
(25)

Nöth reported that the $^{11}$B NMR of such solutions in diglyme indicate the presence of several species, such as NaBH$_4$, NaB$_2$H$_7$, NaAlCl$_3$BH$_4$ and NaAlCl$_3$H (53).

**Effect Of Substituents**

**Alkoxyaluminumhydrides.** 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.

\[
\begin{align*}
\text{LiAlH}_4 + 4 \text{MeOH} & \rightarrow \text{LiAl(MeO)}_4 + 4 \text{H}_2 \uparrow \\
\text{LiAlH}_4 + 4 \text{EtOH} & \rightarrow \text{LiAl(EtO)}_4 + 4 \text{H}_2 \uparrow \\
\text{LiAlH}_4 + 4 \text{i-PrOH} & \rightarrow \text{LiAl(i-PrO)}_4 + 4 \text{H}_2 \uparrow \\
\text{LiAlH}_4 + 3 \text{BuOH} & \rightarrow \text{LiAl(} \text{BuO} \text{)}_3 \text{H} + 3 \text{H}_2 \uparrow
\end{align*}
\]  
(26-29)

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 amyl 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).

\[
\begin{align*}
\text{RCOCI} + \text{LiAl(} \text{BuO} \text{)}_3 \text{H} & \rightarrow \text{RCHO} + \text{LiCl} + \text{Al(} \text{BuO} \text{)}_2 \\
\text{RCN} + \text{LiAl(} \text{BuO} \text{)}_3 \text{H} & \rightarrow \text{RCHO} \\
\text{RCONR}_2 + \text{LiAl(} \text{BuO} \text{)}_3 \text{H} & \rightarrow \text{RCHO}
\end{align*}
\]  
(30-32)

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 aldehydes. The difference in the reducing characteristics of LTBA and LTMA is shown in eq 33.

\[
\text{Ph} + \text{OH} \xrightarrow{\text{LTMA}} \text{Ph} + \text{OH} \xrightarrow{\text{LTBA}} \text{Ph}
\]  
(33)

LTBA can be very selective, distinguishing between the carbonyl groups of aldehydes and ketones (eq 34) (61).
Although trimethoxy- and triethoxyborohydrides disproportionate, the corresponding trisopropoxyborohydrides are stable (eq 40-42) (65, 67). They are mild reducing agents, similar to SBH or LTBA.

\[
\text{NaH} + (i-\text{PrO})_2\text{B} \quad \text{THF, reflux} \quad 170 \text{ h} \quad \text{Triglyme} \quad \text{Na}(i-\text{PrO})_2\text{BH} \quad (40)
\]

\[
\text{NaH} + (i-\text{PrO})_2\text{B} \quad 130^\circ \text{C}, 1 \text{ h} \quad \text{Na}(i-\text{PrO})_2\text{BH} \quad (41)
\]

\[
\text{KH} + (i-\text{PrO})_2\text{B} \quad \text{THF, RT} \quad 1 \text{ h} \quad \text{K}(i-\text{PrO})_2\text{BH} \quad (\text{KIPBH}) \quad (42)
\]

**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 alkylborohydrides, 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.

\[
\text{BH}_3\cdot\text{SMc}_2 + \text{R}_2\text{NH} \quad \text{R}_2\text{NH} + \text{BH}_3 \quad n\text{-BuLi} \quad \text{LiR}_2\text{NBH}_3 + n\text{-BuH} \quad (43)
\]

A series of lithium aminoborohydrides of varying steric and electronic requirements have been synthesized. The chemistry of these reagents is 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. Moreover, α- and β-hydroxy ketones are reduced cleanly to anti-diols.

\[
\text{NaBH}_4 + 3 \text{RCOOH} \quad \rightarrow \quad \text{NaBH}(_2\text{OCOR})_3 + 3 \text{H}_2 \quad (44)
\]

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).

\[
\text{NaBH}_4 + \text{Mc}_4\text{NOH} \quad \rightarrow \quad \text{Mc}_4\text{NBH}_4 \quad (45)
\]

\[
\text{Mc}_4\text{NBH}_4 + 3 \text{AcOH} \quad \rightarrow \quad \text{Mc}_4\text{N}(_2\text{AcO})_3\text{BH} \quad (46)
\]

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).

\[
\text{NaBH}_4 + 3 \text{S} \quad \rightarrow \quad \text{NaBH}_2\text{S}_3 + \text{H}_2 \quad (47)
\]

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

\[
i\text{-Bu}_2\text{AlH} + \text{RLi} \quad \rightarrow \quad \text{Li}[i\text{-Bu}_2\text{RAIH}] \quad (R = n\text{-Bu}, \text{t-Bu}) \quad (48)
\]

**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).

\[
\text{LiH} + \text{Et}_2\text{B} \quad \text{THF} \quad 25^\circ \text{C} \quad \rightarrow \quad \text{LiEt}_2\text{BH} \quad \text{(Super-Hydride)} \quad (49)
\]

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 hydride 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).

\[
\text{LiAlH}(\text{OMe})_3 + \text{sec-Bu}_2\text{B} \quad \text{THF} \quad 25^\circ \text{C} \quad \rightarrow \quad \text{Li}-\text{sec-Bu}_2\text{BH} + \text{Al}(\text{OMe})_3 \quad (\text{L-Selectride}) \quad (50)
\]

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).

\[
i\text{-BuLi} + \text{SiMe}_3\text{B} \quad \text{THF} \quad -78^\circ \text{C} \quad \rightarrow \quad \text{LiSiMe}_3\text{BH} \quad (\text{LS-Selectride}) \quad (51)
\]

**Super Hydride.** Lithium triethylborohydride (Super Hydride) is used for reductive dehalogenation. It exhibits enormous nucleophilic power in Sn2 displacement reactions with alkyl halides, 104 fold more powerful than LiBH4 (eq 52) (83).
It has been observed that the dehalogenation can be achieved by \textit{in situ} generated Super Hydride, using lithium hydride and catalytic amounts of Et\textsubscript{3}B (eq 53) \cite{84}.

\begin{equation}
\begin{array}{c}
\text{Cl} \\
\text{LiH} \\
\text{cat. Et}_3\text{B}
\end{array}
\rightarrow
\begin{array}{c}
\text{H}
\end{array}
\end{equation}

(53)

It is stereospecific in the reductive opening of epoxides (eq. 54) \cite{85}.

\begin{equation}
\begin{array}{c}
\text{O}
\end{array}
\rightarrow
\begin{array}{c}
\text{OH}
\end{array}
\end{equation}

99\% yield
\geq 99\% tert-

(54)

The exceptional nature of Super Hydride and its applications in organic reductions has been reviewed in detail \cite{86}.

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

\begin{equation}
\begin{array}{c}
\text{KH} + \text{Et}_3\text{B} \rightarrow \text{THF} \\
\text{25}^\circ\text{C}, 24\text{ h}
\end{array}
\rightarrow
\begin{array}{c}
\text{KEt}_3\text{BH}
\end{array}
\end{equation}

(55)

They also reported the synthesis of a bulky Super Hydride from triphenylborane (eq 56) \cite{88}.

\begin{equation}
\begin{array}{c}
\text{KH} + \text{Ph}_3\text{B} \rightarrow \text{THF} \\
\text{25}^\circ\text{C}, 6\text{ h}
\end{array}
\rightarrow
\begin{array}{c}
\text{KPh}_3\text{BH}
\end{array}
\end{equation}

(56)

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

\begin{equation}
\begin{array}{c}
\text{KPh}_3\text{BH} \\
\text{78}^\circ\text{C}
\end{array}
\rightarrow
\begin{array}{c}
\text{KH}
\end{array}
\end{equation}

\begin{array}{c}
\text{OE}
\end{array}
\rightarrow
\begin{array}{c}
\text{OH}
\end{array}
\end{equation}

94\%

(57)

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

\begin{equation}
\begin{array}{c}
\text{O}
\end{array}
\rightarrow
\begin{array}{c}
\text{OH}
\end{array}
\end{equation}

\begin{array}{c}
\text{cis}
\end{array}
\rightarrow
\begin{array}{c}
\text{trans}
\end{array}
\end{equation}

\begin{array}{c}
\text{NaBH}_4 = 13 : 87
\end{array}
\begin{array}{c}
\text{L-Selectride} = 96.5 : 3.5
\end{array}
\begin{array}{c}
\text{LS-Selectride} = 99.5 : 0.5
\end{array}
\end{equation}

(58)

\textbf{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) \cite{92, 93}.

\begin{equation}
\begin{array}{c}
\text{RB(OR')}_2 + \text{LiAlH}_4 \\
\text{n-pentane-EE} \\
0^\circ\text{C}, 15\text{ min}
\end{array}
\rightarrow
\begin{array}{c}
\text{LiRBH}_2 + \text{AlH(OR')}_2
\end{array}
\end{equation}

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

(59)

\begin{equation}
\begin{array}{c}
\text{R}_2\text{BOR}' + \text{LiAlH}_4 \\
\text{n-pentane-EE} \\
0^\circ\text{C}, 15\text{ min}
\end{array}
\rightarrow
\begin{array}{c}
\text{LiR}_2\text{BH}_2 + \text{AlH}_2\text{OR}'
\end{array}
\end{equation}

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

(60)

The monohydridalkoxyalane produced from the reaction of the borinate (eq 59) precipitates out, whereas the dihydromonoalkoxyalane produced from the borinate (eq 60) is soluble in pentane-EE. Hence we used lithium monooethoxyaluminum hydride for the synthesis of dialkylborohydrides (eq 61) \cite{95}.

\begin{equation}
\begin{array}{c}
\text{R}_2\text{BOR''}_2 + \text{LiAl(OEt)}_2\text{H}_3 \\
\text{n-pentane-EE} \\
0^\circ\text{C}, 15\text{ min}
\end{array}
\rightarrow
\begin{array}{c}
\text{LiR}_2\text{BH}_2 + \text{AlH(OEt)}_2\text{OR''}
\end{array}
\end{equation}

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

(61)

The boronates necessary for these reactions can be obtained via hydroboration reactions or from the alkylmetallics or alkyl Grignard reagents as shown in eq 62 and 63 \cite{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.

\begin{equation}
\begin{array}{c}
\text{RMgX} + \text{B(OMe)}_3 \\
\text{RMgX} + \text{B(OMe)}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{RF} + \text{Mg(OMe)}_3
\end{array}
\end{equation}

(62)

\begin{equation}
\begin{array}{c}
\text{RLi} + \text{B(OMe)}_3 \\
\text{RLi} + \text{B(OMe)}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{RBF} + \text{LiOMe}
\end{array}
\end{equation}

(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 \textit{vide infra}.

\textbf{Cyanoborohydride.} Wittig synthesized the first cyanoborohydride by treating LiBH\textsubscript{4} with HCN \cite{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) \cite{97}. An improved process for the preparation of sodium cyanoborohydride involves the reaction of sodium cyanide with borane-THF (eq 64) \cite{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.

\[
\text{NaBH}_4 + \text{HCN} \xrightarrow{\text{THF}} \text{NaBH}_3\text{CN} \xleftarrow{\text{H}_2} \text{BH}_3\cdot\text{THF} + \text{NaCN}
\] (64)

NaBH₃CN 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).

\[
\text{Ph} \xrightarrow{\text{NaBH}_3\text{CN}} \text{Ph} \quad 70^\circ \text{C}, 12 \text{ h}
\] (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).

\[
\begin{align*}
\text{MeO} & \xrightarrow{\text{NaBH}_3\text{CN}} \text{MeO} \\
\text{BzO} & \xrightarrow{\text{NaBH}_3\text{CN}} \text{BzO} \\
\text{OH} & \xrightarrow{\text{NaBH}_3\text{CN}} \text{OH}
\end{align*}
\] (66)

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

\[
\begin{align*}
\text{R}_1 & \xrightarrow{\text{NaBH}_3\text{CN}} \text{R}_1 \\
\text{R}_2 & \xrightarrow{\text{NaNH}_2} \text{R}_2 \\
\text{R}_3 & \xrightarrow{\text{NaNH}_2} \text{R}_3 \\
\text{R}_4 & \xrightarrow{\text{NaNH}_2} \text{R}_4
\end{align*}
\] (67)

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

\[
\begin{align*}
\text{NH}_4\text{OAc} & \xrightarrow{\text{NaBH}_3\text{CN}, \text{MeOH}} \\
\text{N}_2 & \xrightarrow{\text{NaNH}_2} \text{N}_2
\end{align*}
\] (68)

1. BROWN & RAMACHANDRAN  Sixty Years of Hydride Reductions

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 increase the rate of reduction. For example, SBI in diglyme reduces chloral and acetyl chloride much more rapidly than aldehydes and ketones, for example, pivalaldehyde.

Rate of reaction with NaBH₄

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 BH₃

Alane. Aluminum hydride, AlH₃, can be prepared by the treatment of LAH with AlCl₃ in EE. However, AlH₃ 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).

\[
2 \text{LiAlH}_4 + \text{H}_2\text{SO}_4 \xrightarrow{\text{THF}} \text{Li}_2\text{SO}_4 \downarrow + 2 \text{AlH}_3 + 2 \text{H}_2\uparrow
\] (70)

Apparently, coordination of the AlH₃ with the THF prevents the rapid association of the AlH₃ that is observed in EE.

AlH₃ 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-amines 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 Al₃H₃-ammine complexes (111). The utility of alane-trimethylamine 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).
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).

![Dialkylalane reduction](image)

**Borane.** Originally we carried out all of the reactions involving diboran in the gas phase in vacuum lines (25). Then we discovered that diboran can be conveniently generated by the treatment of 

\[ 3 \text{NaBH}_4 + 4 \text{BF}_3 \xrightarrow{\text{DG}} \text{2B}_2\text{H}_6 \uparrow + 3 \text{NaBF}_4 \]  

(74)

**Borane-Tetrahydrofuran.** The reactivity of borane depends on the complexing agent also, since its mechanism of reaction involves prior dissociation and formation of free borane (119). Borane-THF is prepared by passing gaseous diboran 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).

![Borane-Tetrahydrofuran](image)

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

![Borane-THF reduction](image)

**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 hydrosilation (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 hydrosorptions 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).

![Borane-Dimethyl Sulfide Complex](image)

**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 diboran 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).

![Borane-Dimethyl Sulfide Complex reaction](image)

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).
REDUCTIONS IN ORGANIC SYNTHESIS

3 RCN + 3 BH₃·SMe₂ → 3 RCH₂NH₂ (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 (136) observed that tetrahydrothiophene is a weaker base toward BH₃ than dimethyl sulfide. However, contrary to expectations, the complex is less reactive than BMS ([26]). 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]).

R₁ R₂
\[ \text{BH₃·Pyridine} \rightarrow \text{N₃O} \rightarrow \text{BH₃·Pyridine} \rightarrow \text{N₃O} \]

**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, R₃B. However, in a number of instances, it has proved possible to control the hydroboration reaction to achieve the synthesis of monoalkylboranes, RBH₂, dialkylboranes, R₂BH, and cyclic boranes ([eq 82-85]) ([140-142]).

2 \[ \text{BH₃} \rightarrow \text{RBH₂} \quad \text{Asymmetric hydroboration} \]

\[ \text{2BH₃} \rightarrow \text{R₂BH} \quad \text{Asymmetric hydroboration} \]

\[ \text{BH₃} \rightarrow \text{BCl₂} \quad \text{Asymmetric reduction} \]

\[ \text{BH₃} \rightarrow \text{BCls} \quad \text{Asymmetric propargylboration} \]

These boranes have found unique applications in organic syntheses which have been discussed in several reviews and books ([128-133]). Of particular interest is diisopinocampheyloborane, 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](image-url)
From Borohydrides. While the boranes discussed above are prepared via direct hydrosilation, 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 borinites and boronates, respectively (eq 59-60). This procedure allows the syntheses of boranes, such as methylborane and tert-butylborane, etc. that are inaccessible via hydrosilation.

\[
\text{LiR}_2\text{BH}_2 + \text{HCl} \rightarrow \text{R}_2\text{BH} + \text{LiCl} + \text{H}_2 \quad (86)
\]

\[
\text{LiRBH}_3 + \text{HCl} \rightarrow \text{RBH}_2 + \text{LiCl} + \text{H}_2 \quad (87)
\]

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 borinites and boronates for a general synthesis of optically pure organic molecules (eq 88) (148).

\[
\text{Li}^+\text{BH}_3 + \text{HCl} \rightarrow \text{R}^+\text{BH}_2 + \text{LiCl} + \text{H}_2 \quad (88)
\]

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

![Figure 2. A General Asymmetric Synthesis via Asymmetric Hydroboration](image)

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) (150).

\[
\text{LiBH}_4 + \text{BCl}_3 \xrightarrow{\text{EE}} 2\text{BH}_2\text{Cl} + \text{LiCl} \quad (93)
\]

\[
\text{LiBH}_4 + 3\text{BCl}_3 \xrightarrow{\text{EE}} 4\text{BHCl}_2 + \text{LiCl} \quad (94)
\]

These chlorohorborane 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) (151).

\[
\text{RN}_3 + \text{HBCl}_2\text{SMe}_2 \xrightarrow{\text{CH}_2\text{Cl}_2, \text{RT, } 1\text{h}} \text{RNHBCl}_2 \xrightarrow{2, \text{KOH}} \text{RNH}_2 \quad (95)
\]

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).

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) (152).

\[
2\text{BX}_3\text{SMe}_2 + \text{BH}_3\text{SMe}_2 \rightarrow 3\text{BH}_2\text{X}_2\text{SMe}_2 \quad (\text{X} = \text{Cl, Br}) \quad (91)
\]

\[
\text{BX}_3\text{SMe}_2 + 2\text{BH}_3\text{SMe}_2 \rightarrow 3\text{BH}_2\text{X}\text{SMe}_2 \quad (\text{X} = \text{Cl, Br}) \quad (92)
\]
REDUCTIONS IN ORGANIC SYNTHESIS

1. BROWN & RAMACHANDRAN Sixty Years of Hydride Reductions

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 Greaves (159).

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

<table>
<thead>
<tr>
<th>Reagent</th>
<th>% cis</th>
<th>% trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAH</td>
<td>25</td>
<td>65</td>
</tr>
<tr>
<td>SBH</td>
<td>31</td>
<td>69</td>
</tr>
<tr>
<td>LBH</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>LTMA</td>
<td>31.72a</td>
<td>69.28a</td>
</tr>
<tr>
<td>LTBA</td>
<td>27</td>
<td>73</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>99.3</td>
<td>0.7</td>
</tr>
<tr>
<td>K-Selectride</td>
<td>&gt;99</td>
<td>&lt;1</td>
</tr>
<tr>
<td>LiSiaB-H</td>
<td>99.7</td>
<td>0.3</td>
</tr>
<tr>
<td>KIPBH</td>
<td>92</td>
<td>8</td>
</tr>
<tr>
<td>Diborane</td>
<td>74</td>
<td>26</td>
</tr>
<tr>
<td>Si2BH</td>
<td>79</td>
<td>21</td>
</tr>
<tr>
<td>Ch2BH</td>
<td>94</td>
<td>1</td>
</tr>
<tr>
<td>9-BBN</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>ThxBHCl-SMe2</td>
<td>95</td>
<td>5</td>
</tr>
</tbody>
</table>

(a)Depends on the solvent.

One of the interesting applications of borohydride reductions in organic syntheses has been the stereoselective 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. Narayana (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).

### 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.

### 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 modify 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).

\[
\text{LiAlH}_4 + \text{Darvon Alcohol (174)}
\]

\[
\text{LiAlH}_4 + \text{Diamine (175)}
\]

\[
\text{Diamine} = (S)-(-2,6-Xylylidino-methyl)-pyrrolidine
\]

\[
\text{LiAlH}_4 + \text{MEP + NEA (176)}
\]

\[
\text{LiAlH}_4 + \text{Aminobutanol (177)}
\]

\[
\text{LiAlH}_4 + \text{MEP + ArOH (178)}
\]

\[
\text{LiAlH}_4 + \text{Binaphthol + EtOH (179)}
\]

\[
\text{ArOH} = 3,5\text{-dimethyl phenol}
\]

**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 Hirota (182) and their coworkers modified SBH with two equiv of carboxylic acid and 1,2,5,6-di-O-isopropylidene-D-glucosanose. Yamada and coworkers prepared a reagent from SBH and N-benzoxycarbonylproline that achieves high ee for the reduction of imines (183). Modifications of SBH with mandelic (184), lactic (185), tartaric (186, 187), camphoric or malic acids (187) have also been reported.

\[
\text{NaBH}_4 + i-\text{Pr-COOH + DIPGF}
\]

\[
\text{NaBH}_4 + 3 \text{ COOBnz}
\]

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

\[
\text{LiBH}_4 + \text{DBC + t-BuOH}
\]

\[
\text{DBC} = \text{PhCONHCH(OH)}_2
\]

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 dialkyl monoalkoxy- and alkyl(dialkoxyl)borohydrides 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-glucosanoyl)-9-horabicyclo-[3.3.1]nonane (K-Glucone) 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).

**Chiral Super Hydrides.** Lithium (β-isopinocamphey-9-horabicyclo[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 nopal 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).
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 aminoacohol-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 Qualllich in this book.

Buono and coworkers have shown that oxazaphospholidines also act as asymmetric catalysts 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 entitled "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 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 Chir-al Auxiliary
11. Asymmetric Reductions
12. Asymmetric Allyl- and Crotylboration
13. Asymmetric Enolborations
14. Asymmetric Opening of Meso Epoxides

<table>
<thead>
<tr>
<th>Table 3. Broad spectrum of selective reducing agents</th>
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<tr>
<td>KPBH</td>
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</tr>
<tr>
<td></td>
</tr>
<tr>
<td>RCHO</td>
</tr>
<tr>
<td>R₃CO</td>
</tr>
<tr>
<td>RCOCI</td>
</tr>
<tr>
<td>RCO₂R'</td>
</tr>
<tr>
<td>RCO₂H</td>
</tr>
<tr>
<td>RCOR'R'</td>
</tr>
<tr>
<td>RCN</td>
</tr>
<tr>
<td>RNO₂</td>
</tr>
<tr>
<td>RCH₂CH₂</td>
</tr>
</tbody>
</table>

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.

Literature Cited