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FORTY YEARS OF HYDRIDE REDUCTIONS[1]

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Abstract—Forty years ago, it was observed that diborane, a hydride, reduces aldehydes and ketones with exceptional ease even at 0°. Since then various hydride reagents have evolved for the convenient reduction of typical organic functional groups. Electrophilic reducing agents such as borane and alane possess markedly different reducing characteristics than those of nucleophilic reducing agents such as sodium borohydride and lithium aluminum hydride. Explorations have revealed means of both enhancing and diminishing the electrophilic character of borane and alane on the one hand and both enhancing and diminishing the nucleophilic character of borohydrides and aluminohydrides on the other. Such derivatives reveal unique characteristics making possible valuable selective reductions, not practical previously. These developments have completely altered the procedures normally used in organic chemistry for the reduction of functional groups.

I. INTRODUCTION

Forty years ago there appeared in the March 1939 issue of the *Journal of the American Chemical Society* a publication, "Hydrides of Boron—XI. The Reaction of Diborane with Organic Compounds Containing a Carbonyl Group," which reports the first application of hydrides for the reduction of organic functional groups.[2] It appears of interest to trace the research developments which led from this original observation to the present situation where hydrides are usually the reagents of choice for such reductions.[3,4]

II. REDUCTION TECHNIQUES PRIOR TO THE HYDRIDE ERA

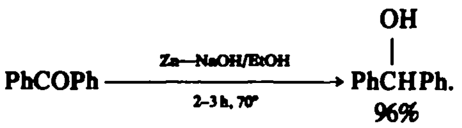
Before discussing the origins and the evolution of various hydride reagents, it is of interest to review briefly the various non-hydridic procedures that were developed for the reduction of organic functional groups prior to the discovery of hydride reagents. For example, let us consider the reduction of carbonyl groups in aldehydes, ketones, and carboxylic acid esters to give the corresponding carbinols—a most frequently encountered transformation in organic chemistry.

Reduction of aldehydes to the corresponding alcohols was achieved by zinc dust + acetic acid, sodium amalgam + acetic acid, sodium in toluene + acetic acid or iron + acetic acid[5] (Eqn 1).

$$CH_3(CH_2)_5CHO \xrightarrow[6\text{–}7\,h,\ 100^\circ]{Fe,\ HOAc} \underset{80\%}{CH_3(CH_2)_5CH_2OH}. \tag{1}$$

Simple ketones, such as 2-heptanone, were reduced to the corresponding alcohols by sodium in ethanol.[6] Diaryl ketones were reduced by zinc and sodium hydroxide mixture in ethanol[7] (Eqns 2 and 3).

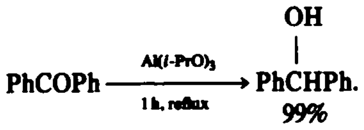
$$CH_3CO(CH_2)_4CH_3 \xrightarrow{Na,\ EtOH} \underset{65\%}{CH_3\overset{\displaystyle OH}{\overset{|}{C}}H(CH_2)_4CH_3} \tag{2}$$



$$PhCOPh \xrightarrow[2\text{–}3\,h,\ 70^\circ]{Zn\text{—}NaOH/EtOH} \underset{96\%}{Ph\overset{\displaystyle OH}{\overset{|}{C}}HPh}. \tag{3}$$

In the year 1925 it was independently discovered by Verley[8] as well as Meerwein and Schmidt[9] that an aldehyde can be reduced to the corresponding carbinol with aluminum ethoxide in ethanol. In 1926 Ponndorf found that by utilizing aluminum alkoxides of secondary alcohols, such as isopropyl alcohol, aldehydes as well as ketones could be reduced satisfactorily.[10] In 1937 Lund applied this method to a variety of aldehydes and ketones, and explored the scope and applicability of the Meerwein–Ponndorf–Verley reaction[11,12] (Eqns 4 and 5).

$$CH_3CH{=}CHCHO \xrightarrow[\text{8–9 h, 110°}]{\text{Al-}i\text{-PrOH}} \underset{60\%}{CH_3CH{=}CHCH_2OH} \tag{4}$$



$$PhCOPh \xrightarrow[\text{1 h, reflux}]{Al(i\text{-PrO})_3} \underset{99\%}{PhCH(OH)Ph}. \tag{5}$$

Carboxylic acid esters were reduced to the corresponding alcohols by sodium-ethanol mixtures (Boureault and Blanc method)[13] (Eqn 6).

$$n\text{-}C_{11}H_{23}COOEt \xrightarrow[\text{steam bath}]{\text{Na—EtOH}} \underset{65–75\%}{n\text{-}C_{11}H_{23}CH_2OH}. \tag{6}$$

The non-hydridic reduction procedures for the reduction of carbonyl groups often require elevated temperatures, long reaction times and result in low yields of the desired products. However, the discovery of metal hydrides and complex metal hydrides has dramatically changed the situation, not only for the reduction of carbonyl groups, but for reduction of a wide variety of other organic functional groups.

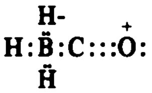
III. ORIGINS OF THE HYDRIDE REDUCING AGENTS

1. *Discovery of diborane as a reducing agent*

In the 1930s, the structure of diborane was a subject of considerable study and speculation.[14] Professor H. I. Schlesinger at the University of Chicago was studying the reactions of diborane in the hope of obtaining information that would throw light on the problem of the unusual structure, then formulated as an electron-deficient ethane-like assembly. In September 1936 the synthesis of borane–carbonyl was completed[15] (Eqn 7).

$$1/2(BH_3)_2 + CO \rightleftharpoons H_3B:CO. \tag{7}$$

There was considerable discussion as to whether the product was a simple addition compound (1), or whether the reaction had involved a migration of a hydride unit from boron to carbon (2).



1

2

It was thought that 2 might exhibit some of the characteristics of an aldehyde. Consequently, it was decided to examine the behavior of dibroane with typical organic compounds containing carbonyl, such as aldehydes, ketones, esters, and acid chlorides, in the hope that this study would contribute to an understanding of the structure of borane–carbonyl. This study led to the discovery that simple aldehydes and ketones (in the absence of solvents) react rapidly with diborane at 0° (even at −78°).[2] The dialkoxy derivatives produced are readily hydrolyzed by water to give the corresponding alcohols (Eqns 8 and 9).

$$2R_2CO + 1/2(BH_3)_2 \rightarrow (R_2CHO)_2BH \tag{8}$$

$$(R_2CHO)_2BH + 3H_2O \rightarrow 2R_2CHOH + H_2 + B(OH)_3. \tag{9}$$

The reactions with methyl formate and ethyl acetate were slower, but quantitative reductions were achieved. No appreciable reaction was observed with chloral, acetyl chloride and carbonyl chloride.

In 1939 when this study was published,[2] the organic chemist had available no really satisfactory method for reducing the carbonyl group of aldehydes and ketones under mild conditions. Considerable interest in this development might have been anticipated. However, there were negligible reprint requests for the publication. Interest in this development among organic chemists was minimal. Why was there no interest?

At that time, diborane was a chemical rarity, available only in milligram quantities through complex preparative procedures. The first synthetic route to diborane developed in 1912 by Stock involved the preparation and hydrolysis of magnesium boride followed by thermal decomposition of higher boron hydrides formed in 0.5% yield.[14,16]

The best method then available for its preparation was the reaction of boron chloride with hydrogen in the silent electric discharge[17] (Eqns 10 and 11).

$$2BCl_3 + 5H_2 \xrightarrow[\text{discharge}]{\text{silent}} B_2H_5Cl + 5HCl \qquad (10)$$

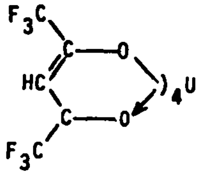
$$6B_2H_5Cl \xrightarrow{\Delta} 5B_2H_6 + 2BCl_3. \qquad (11)$$

The only apparatus available in the United States was located in Professor Schlesinger's personal laboratory. The production rate was 0.5 g/24 hr. It was common for an investigator in other parts of the country to come to the University of Chicago, prepare a small quantity of diborane, and then carry it with him back to his laboratory. How could an organic chemist think of utilizing such a rare chemical for synthetic transformations?

It would be nice to report that one of the original investigators, Prof. H. I. Schlesinger, Dr. Anton B. Burg, or the senior author of this review, had the foresight to recognize that the development of a practical synthesis of diborane would make this procedure of major interest to organic chemists throughout the world. But that was not the case. However, such a procedure was later developed by two of these investigators, H. I. Schlesinger and H. C. Brown, as a result of the requirements of research supporting the war effort.

2. *Volatile compounds of uranium*

This situation was altered in late 1940 as a result of pressure engendered by World War II. Professor Schlesinger was asked by the National Defense Agency to investigate the synthesis of new volatile compounds of uranium and the senior author, as his research assistant, participated in the research. The requirement was that the compound possess a volatility of at least 0.1 mm at a temperature where it would be stable for relatively long periods of time. The initial effort explored uranium acetylacetonates and related derivatives. Indeed, uranium (IV) hexafluoroacetonyl acetone apparently possessed satisfactory characteristics (3).



MW 1066

3

However, when the results were reported to headquarters, the investigators were informed of an important requirement previously not made known to them—it was desirable that the compound have as low a molecular weight as possible, preferably not greater than 238!

Just prior to this time, aluminum borohydride and beryllium borohydride had been synthesized in Schlesinger's laboratory[18–20] (Eqns 12–14).

$$CaB_6 + 10Cl_2 \rightarrow CaCl_2 + 6BCl_3 \qquad (12)$$

$$2BCl_3 + 6H_2 \rightarrow B_2H_6 + 6HCl \qquad (13)$$

$$(CH_3)_3Al + 2B_2H_6 \rightarrow (CH_3)_3B + Al(BH_4)_3. \tag{14}$$

These compounds are the most volatile derivatives known for these metals. Accordingly, it was decided to undertake the preparation of uranium borohydride by treatment of uranium(IV) fluoride with aluminum borohydride. Indeed, the very first experiment gave uranium borohydride as green volatile crystals[21] (Eqn 15).

$$UF_4 + 2Al(BH_4)_3 \rightarrow U(BH_4)_4 + 2AlF_2(BF_4). \tag{15}$$

Accordingly, the research efforts in this direction were increased and the group was requested to synthesize uranium(IV) borohydride in pound quantities for large-scale testing.

3. *The alkali metal hydride route to diborane—the practical procedure*

As pointed out earlier, the methods available for the production of diborane were not satisfactory for large-scale preparations. These procedures made available diborane in relatively small quantities, inadequate for the synthesis of aluminum borohydride and finally to the conversion to uranium(IV) borohydride in the desired quantities. Accordingly, alternative methods for the synthesis of diborane were explored.

Soon it was discovered that lithium hydride would reduce boron trifluoride in ethyl ether solution to give diborane[22] which readily reacted with lithium hydride to form lithium borohydride.[23] Lithium borohydride reacted with aluminum chloride to produce aluminum borohydride which could be utilized in the synthesis of uranium borohydride[24] (Eqns 16–19).

$$6LiH + 8BF_3{:}OEt_2 \xrightarrow{Et_2O} (BH_3)_2 + 6LiBF_4 \tag{16}$$

$$LiH + 1/2(BH_3)_2 \xrightarrow{Et_2O} LiBH_4 \tag{17}$$

$$AlCl_3 + 3LiBH_4 \xrightarrow{\Delta} Al(BH_4)_3\uparrow + 3LiCl \tag{18}$$

$$UF_4 + 2Al(BH_4)_3 \rightarrow U(BH_4)_4\uparrow + 2AlF_2(BH_4). \tag{19}$$

This was a major improvement over the previous procedure, which involved many more difficult steps. However, the group was informed by headquarters that lithium hydride could not be used. At that time lithium hydride was in very short supply and could not be spared for the synthesis of uranium borohydride on a commercial scale; on the other hand, the supply of sodium was ample. Could not sodium hydride be utilized in place of the lithium hydride? Unfortunately, the corresponding reaction with sodium hydride failed to proceed in ethyl ether. (However, many years later it was found that these reactions proceed nicely in other solvents not then available, solvents such as tetrahydrofuran and diglyme.)[25]

A new compound, sodium trimethoxyborohydride[26] solved the problem. This compound was very active and achieved the desired transformations without any solvent[22,23] (Eqns 20–24).

$$NaH + B(OCH_3) \rightarrow NaBH(OCH_3)_3 \tag{20}$$

$$6NaBH(OCH_3)_3 + 8BF_3{:}OEt_2 \rightarrow (BH_3)_2 + 6B(OCH_3)_3 + 6NaBF_4 + 8Et_2O \tag{21}$$

$$NaBH(OCH_3)_3 + 1/2(BH_3)_2 \rightarrow NaBH_4 + B(OCH_3)_3 \tag{22}$$

$$AlCl_3 + 3NaBH_4 \rightarrow Al(BH_4)_3\uparrow + 3NaCl \tag{23}$$

$$UF_4 + 2Al(BH_4)_3 \rightarrow U(BH_4)_4\uparrow + 2AlF_2(BH_4). \tag{24}$$

However, by this time the problems encountered in the use of uranium hexafluoride had been overcome and there was no longer any need for other volatile compounds of uranium. Nevertheless, this research was responsible for the development of practical procedures for diborane synthesis.

4. *Alkali metal borohydrides*

At this point (1943), the Signal Corps learned about the new chemical, sodium borohydride, and wanted to explore the feasibility of utilizing this for the field generation of hydrogen. Consequently, under their sponsorship improved methods for preparing sodium borohydride and catalysts to facilitate its hydrolysis were explored. It was soon discovered that sodium borohydride could readily be prepared by treating sodium hydride with methyl borate at 250° (Eqn 25).[27]

$$4NaH + B(OCH_3)_3 \xrightarrow{250^\circ} NaBH_4 + 3NaOCH_3. \tag{25}$$

This is the basis of the present industrial process for sodium borohydride.

The reaction provides a mixture of two solids, sodium borohydride and sodium methoxide. It was necessary to find a solvent that would separate these two components. A number of solvents were explored. One such solvent tested was acetone. A vigorous reaction was observed. Hydrolysis with dilute acid produced no active hydrogen. Analysis showed the presence of four moles of isopropyl alcohol per mole of sodium borohydride introduced. Obviously, sodium borohydride was a facile hydrogenating agent capable of reducing the carbonyl groups of aldehydes and ketones in the manner previously demonstrated for diborane. In this way it was discovered that sodium borohydride is a valuable reagent for the hydrogenation of organic molecules (Eqn 26).

$$\begin{array}{c} NaBH_4 + 4(CH_3)_2C{=}O \rightarrow NaB[OCH(CH_3)_2]_4 \\ \downarrow {\scriptstyle H_2O} \\ 4(CH_3)_2CHOH \\ + \\ NaB(OH)_4. \end{array} \tag{26}$$

5. *Synthesis of lithium aluminum hydride*

The alkali metal hydride route was successfully extended for the synthesis of the corresponding aluminum derivatives. Thus, lithium aluminum hydride was synthesized in 1945 by the reaction of lithium hydride and aluminum chloride in ether solution[28] (Eqns 27–29).

$$4LiH + AlCl_3 \xrightarrow{Et_2O} LiAlH_4 + 3LiCl \tag{27}$$

$$3LiAlH_4 + AlCl_3 \rightarrow 4AlH_3 + 3LiCl \tag{28}$$

$$4AlH_3 + 4LiH \rightarrow 4LiAlH_4. \tag{29}$$

Aluminum hydride is probably an intermediate in this reaction.

IV. HYDRIDES AS REDUCING AGENTS FOR ORGANIC FUNCTIONAL GROUPS

1. *Early explorations*

The discovery of sodium borohydride[23] in 1942 and of lithium aluminum hydride[28] in 1945 brought about a revolutionary change in procedures for the reduction of functional groups in organic molecules.[4,29] Today, faced with the problem of reducing an organic functional group, such as CO, COOR or CN, the synthetic organic chemist will rarely undertake to use the conventional techniques such as the Meerwein–Ponndorf–Verley reaction (aldehydes and ketones), the Bouveault–Blanc procedure (esters), or catalytic hydrogenation (nitriles). The two complex hydrides (lithium aluminum hydride and sodium borohydride) provide a simple and convenient route for the reduction of such functional groups and they are invariably used in laboratory synthesis involving such transformations. Indeed, numerous major applications in various phases of chemical research have appeared for both the reagents and are still continuing to appear.

However, it should be pointed out that in spite of their great convenience these two reagents suffer from certain limitations. As first described by W. G. Brown *et al.*,[4,29] lithium aluminum hydride is an exceedingly powerful reducing agent, capable of reducing practically all organic functional groups. Consequently, it is quite difficult to apply this reagent for the selective reduction of a multifunctional molecule. On the other hand, sodium borohydride is a remarkably mild reducing agent.[29] It readily reduces only aldehydes, ketones and acid chlorides. Consequently, it is useful primarily for selective reductions involving these relatively reactive groups.

$NaBH_4$	$LiAlH_4$
very mild	very powerful

Both these reagents represent two extremes of a possible broad spectrum. This situation made it desirable to develop means of controlling the reducing power of such reagents. If such control could be achieved, either by decreasing the reducing power of lithium aluminum hydride or by increasing that of sodium borohydride, or both, the organic chemist would have available a complete spectrum of reagents for selective reductions. With organic research undertaking the synthesis of structures of increasing complexity, there was an evident and growing need for reagents possessing a high degree of selectivity. Accordingly, we undertook a program of research on "Selective Reductions", to explore these possibilities.

2. *Modification of reducing characteristics of the parent hydrides*

Five means of controlling the reducing power of the complex hydrides suggested themselves: (1) influence of solvents on the reducing power of the complex hydride; (2) variations of cation in the complex hydride that might alter the reducing power; (3) introduction of substituents in the complex ion that might exert marked steric and electronic influences upon the reactivity of the substituted complex ion; (4) the development of acidic reducing agents such as borane and alane which might exhibit entirely different relative reactivities towards functional groups; (5) effect of introducing substituent groups into such acidic reducing agents.

3. *Methodology for the exploration of general characteristics of the new reagents*

Objectives. For defining the reducing characteristics of each new reagent, its reactivity was determined towards a group of 56 representative organic compounds (in the recent years the group has expanded to over 70 compounds) containing the more common functional groups of interest in reductions. The reactions were carried out under standard conditions (usually tetrahydrofuran solvent, 0°). Normally, four equivalents of hydride per mole of the functional group was employed. The solutions were permitted to stand for varying intervals of time, and then aliquots were analyzed for residual hydride. In this way we are able to define the approximate rate and stoichiometry of the reaction. In this review we shall attempt to define the characteristics of each reagent in terms of its behavior toward twelve representative organic functional groups: aldehyde, ketone, acid chloride, lactone, epoxide, ester, carboxylic acid, carboxylic acid salt, *tert*-amide, nitrile, aromatic nitro compound and olefin. Such an exploratory study conducted under standard reaction conditions gave us an insight into the possible areas of application for the new reagent. This was usually followed by detailed exploration of the new reagent for the specific transformation(s).

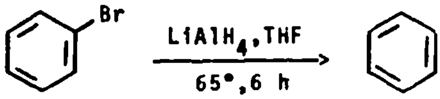
V. EVOLUTION OF VARIOUS HYDRIDE REAGENTS AND THEIR APPLICATION IN ORGANIC SYNTHESIS

1. *Lithium aluminum hydride*

Lithium aluminum hydride is an exceptionally powerful reducing agent capable of reducing almost all of the organic functional groups rapidly to the lower or the lowest reduced state.[29] It is soluble in a variety of ethereal solvents—ethyl ether, tetrahydrofuran, monoglyme, diglyme and triglyme. Our exploratory study of the reactivity of this reagent (0°, THF) towards representative organic functional groups is summarized below.[30]

aldehyde → alcohol
ketone → alcohol
acid chloride → alcohol
lactone → glycol
epoxide → alcohol
ester → alcohol
carboxylic acid → alcohol
carboxylic acid salt → alcohol
tert-amide → amine
nitrile → amine
nitro → azo, etc.
olefin → no reaction.

The great power of lithium aluminum hydride as a reducing agent is indicated by the relatively rapid reduction of aromatic halides[31] (Eqns 30–32).



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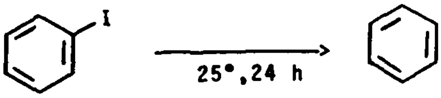

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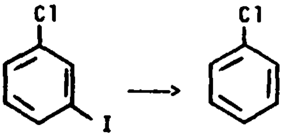
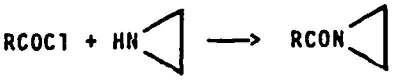


95% (32)

Unexpectedly, the reduction of 1-acylaziridines with lithium aluminum hydride stops at the first stage, providing a simple and convenient synthetic route to the corresponding aldehydes[32] (Eqns 33 and 34).



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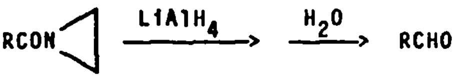
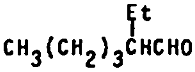


(34)

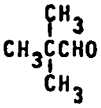
$CH_3(CH_2)_4CHO$

81%



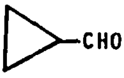
$CH_3(CH_2)_3\overset{Et}{C}HCHO$

77%



$CH_3\underset{CH_3}{\overset{CH_3}{C}}CHO$

79%



67%

2. *Sodium borohydride*

Sodium borohydride represents the other extreme of the spectrum, being a very mild reducing agent. In hydroxylic solvents it reduces aldehydes and ketones rapidly at 25°, but is essentially inert to other functional groups. The reactivity of sodium borohydride towards the representative organic functional groups may be summarized as follows:[33]

aldehyde → alcohol
ketone → alcohol
acid chloride → reaction with solvent
lactone → slow reaction
epoxide → slow reaction
ester → slow reaction
carboxylic acid → reacts, no reduction
carboxylic acid salt → no reaction
tert-amide → no reaction
nitrile → no reaction
nitro → no reaction
olefin → no reaction.

The two extremes provided by these two reagents are shown in Table 1.

In aqueous solvents sodium borohydride reacts with ionizable alkyl halides and related derivatives to give the corresponding hydrocarbon. The reaction appears to involve the capture of the carbonium ion

Table 1. Comparison of sodium borohydride vs lithium aluminum hydride

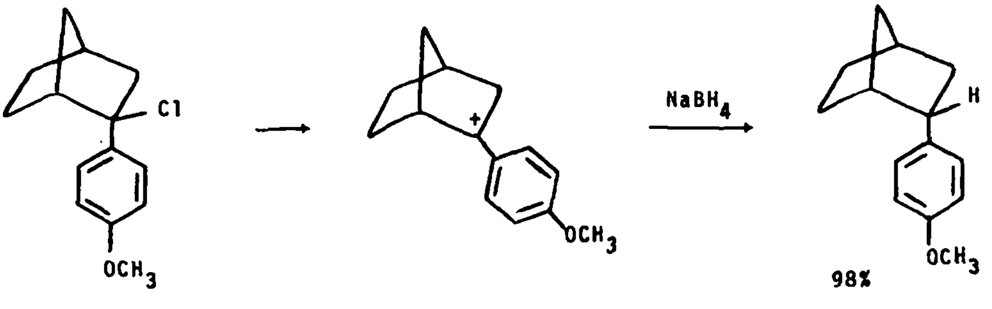
	NaBH$_4$ in EtOH										LiAlH$_4$ in THF
Aldehyde	+										+
Ketone	+										+
Acid chloride	R										+
Lactone	-										+
Epoxide	-										+
Ester	-										+
Acid	-										+
Acid salt	-										+
tert-Amide	-										+
Nitrile	-										+
Nitro	-										+
Olefin	-										-

(+) = Rapid reaction. (-) = Insignificant reaction

R = Reaction with solvent

formed in the solvolysis by the borohydride anion. The reaction has proven very useful for exploring the structure of carbonium ions produced in such solvolysis[34] (Eqns 35–37).

$$RX \rightarrow R^+ + X^- \xrightarrow{NaBH_4} RH \qquad (35)$$



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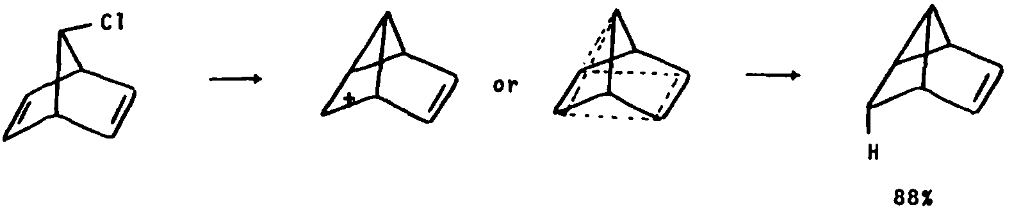
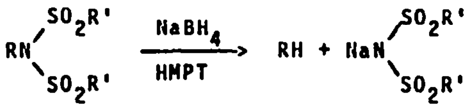


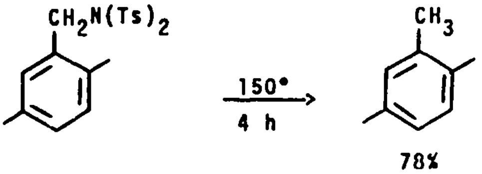
(37)

Recently, sodium borohydride has been successfully employed for the reductive deamination of primary amines through their sulfonimide derivatives[35] (Eqns 38–41).



$$RN\begin{matrix} SO_2R' \\ SO_2R' \end{matrix} \xrightarrow[HMPT]{NaBH_4} RH + NaN\begin{matrix} SO_2R' \\ SO_2R' \end{matrix} \qquad (38)$$

$$CH_3(CH_2)_9N(Ts)_2 \xrightarrow[8\ h]{175^\circ} \underset{91\%}{CH_3(CH_2)_8CH_3} \qquad (39)$$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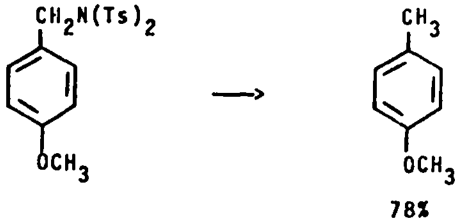

(41)

3. *Effect of solvents*

Could the reducing power of these complex hydrides be modified by changing the solvent? To provide an answer for this question, sodium borohydride was more advantageous than lithium aluminum hydride since it may be used in a much wider range of solvents. Thus, it is highly soluble in water and its solutions in aqueous alkali are quite stable. Such aqueous solutions readily reduce aldehydes and ketones even in cases where the solubility of the compounds in the aqueous system are quite limited (Eqn 42).

$$\begin{array}{l} 4R_2CO + NaBH_4 \rightarrow Na[B(OCHR_2)_4] \\ \qquad\qquad\qquad\qquad \downarrow H_2O \\ \qquad\qquad\qquad NaB(OH)_4 + 4R_2CHOH. \end{array} \qquad (42)$$

Sodium borohydride is also readily soluble in various alcohol solvents. Although it reacts rapidly with methanol liberating hydrogen, the corresponding reaction in ethanol is much slower.[36] Consequently, ethanol possesses the obvious advantage of permitting reductions in homogeneous solution with relatively little loss of reducing agent through this side reaction with the solvent. In isopropyl alcohol sodium borohydride has a modest solubility (0.1 M at 25°). The solution appears to be indefinitely stable. Kinetic examination of the rate of reaction of aldehydes and ketones with sodium borohydride in isopropyl alcohol indicated a vast difference in reactivity between benzaldehyde and acetophenone with a factor of 400 in rate constant.[37,38] It is evident that aldehyde groups should readily be reduced selectively in the presence of related ketone groupings. Indeed this has been confirmed recently.[39]

Sodium borohydride is insoluble in ethyl ether, only slightly soluble in tetrahydrofuran, but readily soluble in diglyme (dimethyl ether of diethylene glycol) and triglyme (dimethyl ether of triethylene glycol). These solutions in diglyme and triglyme have proven useful for the generation of diborane[25] and for the hydroboration of olefins.[40,41] However, instead of enhancing the reducing power of sodium borohydride these solvents appear to decrease it. Thus, no significant reduction of acetone was observed in diglyme solution under conditions where the ketone is quantitatively reduced in aqueous or alcohol solution in a matter of minutes.

Recently, dipolar aprotic solvents such as dimethyl sulfoxide, sulfolane, and hexamethylphosphotriamide have been utilized in certain sodium borohydride reductions.[35,42] It is reported that the reducing power of sodium borohydride is enhanced in these solvents. However, no detailed systematic study with a variety of functional groups is available.

The influence of solvents on the reducing power of lithium aluminum hydride has not been explored. The very high reactivity of the reagent severely restricts the choice of solvents to hydrocarbons, ethers and tertiary amines. It is generally utilized in ethyl ether, tetrahydrofuran, and diglyme, in which it is a powerful reducing agent, with no significant difference apparent in its reducing power. No systematic study of this reagent in either tertiary amines or hydrocarbon solvents is available.

4. *Effects of different cations*

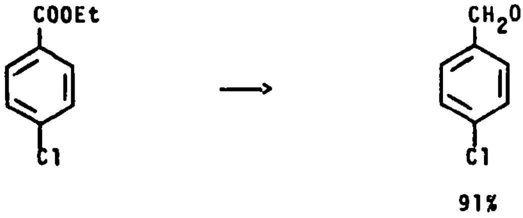
Preliminary exploratory experiments on the reduction characteristics of lithium and sodium borohydrides revealed marked differences in their reactivities. Thus, sodium borohydride reduces esters only sluggishly, whereas lithium borohydride reduces such esters quite rapidly.[43]

The addition of an equivalent quantity of lithium chloride or lithium bromide to a one molar solution of sodium borohydride in diglyme results in the formation of a precipitate of sodium halide and the formation *in situ* of lithium borohydride. The reduction characteristics of lithium chloride-sodium borohydride in diglyme are summarized as follows:[39,44]

aldehyde → alcohol
ketone → alcohol
acid chloride → alcohol
lactone → glycol
epoxide → alcohol
ester → alcohol
carboxylic acid → no reaction
carboxylic acid salt → no reaction
tert-amide → no reaction
nitrile → no reaction
nitro → reaction
olefin → no reaction.

The reagent can be utilized directly, without removing the precipitated salt. At 100°, a number of representative esters are reduced to the corresponding carbinols quantitatively in a 1–3 hr reaction period with $NaBH_4$–LiBr reagent. Under identical conditions sodium borohydride alone brings about only slight reduction of such esters[39] (Eqns 43–45).

$$CH_3(CH_2)_{16}COOEt \xrightarrow{NaBH_4\text{—}LiBr} CH_3(CH_2)_{16}CH_2OH \tag{43}$$



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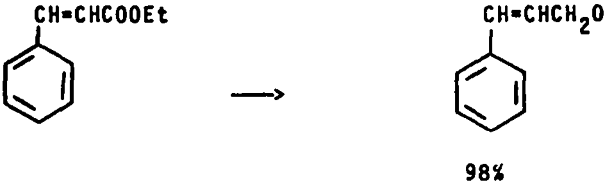
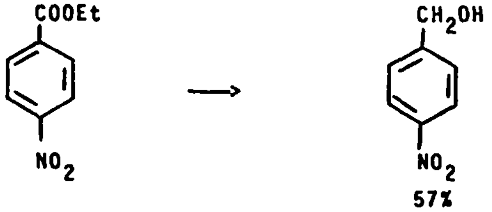


(45)

Recent studies in our laboratories indicate that sodium borohydride–lithium chloride mixtures in refluxing monoglyme are quite efficient for quantitative reduction of esters to the corresponding alcohols.[45]

Ions of higher ionic potential would be expected to be even more effective. Thus the addition of equivalent amount of solid magnesium halide to diglyme solutions of sodium borohydride brings about the reduction of esters[39] (Eqns 46 and 47).

$$CH_3(CH_2)_{16}COOEt \xrightarrow[\text{DG } 100^\circ]{NaBH_4\text{—}MgCl_2} \underset{74\%}{CH_3(CH_2)_{16}CH_2OH} \tag{46}$$



(47)

Kollonitsch and coworkers have achieved rapid reduction of esters by sodium borohydride in the presence of Li, Mg, Ca, Ba and Sr salts.[46,47]

Indeed, recent research in our laboratories confirms that calcium borohydride in refluxing tetrahydrofuran is an effective reducing agent for the reduction of esters.[45]

Addition of one equivalent of aluminum chloride to three equivalents of sodium borohydride solution in diglyme provides a clear solution.[48] No precipitate of sodium chloride is observed. Nevertheless, the resulting solutions exhibit markedly enhanced reducing power, approaching that of lithium aluminum hydride itself. The reactivity of this new reagent towards representative organic functional groups at 25° is as follows:

aldehyde → alcohol
ketone → alcohol
acid chloride → alcohol
lactone → alcohol
epoxide → alcohol
ester → alcohol
carboxylic acid → alcohol
carboxylic acid salt → no reaction
tert-amide → amine
nitrile → amine
nitro → no reaction
olefin → organoborane.

It should be mentioned that during the exploration of this reagent an anomaly was encountered in the quantitative studies of ethyl oleate.[40,41] The exploration of this anomaly led to the discovery of hydroboration.

The failure to obtain a precipitate of sodium chloride suggests that the reaction proceeds to produce an equilibrium amount of aluminum borohydride, with the equilibrium being shifted to completion as the aluminum borohydride reacts with the organic compound[48b] (Eqn 48).

$$AlCl_3 + 3NaBH_4 \rightleftharpoons Al(BH_4)_3 + 3NaCl. \tag{48}$$

A number of aluminohydrides containing cations other than lithium have been synthesized.[4a,49] These all appear to be very powerful reducing agents and the available data do not allow us to draw any conclusion as to the effect of the cation on the reducing power of the aluminohydride anion.

5. *Effect of substituents—substituted aluminohydrides and borohydrides*

(A) *Alkoxyaluminohydrides.* Aluminum alkoxides are known to exist as dimers, oligomers or even as polymers. For example, aluminum methoxide is a polymer and aluminum *tert*-butoxide is a dimer. The reaction of alkali metal hydride with aluminum alkoxides as a possible route to alkoxyaluminohydride proved to be sluggish. However, this reaction has been applied as a synthetic route to sodium triethoxy-aluminohydride by treating the "monomeric α-form" of aluminum ethoxide with sodium hydride in tetrahydrofuran in an autoclave at 70–90°.[50,51]

In our exploratory studies we found that standard solutions of lithium aluminum hydride in ethereal solvents readily react with primary, secondary and tertiary alcohols.[30] Consequently, this reaction appeared to offer a more convenient route to the alkoxyaluminohydrides. Thus, the addition of 4 moles of methyl, ethyl or isopropyl alcohol at 25° to the ether solution of lithium aluminum hydride results in the evolution of 4 moles of hydrogen and the precipitation of the corresponding lithium tetraalkoxyaluminohydrides. However, the addition of 4 moles of tert-butyl alcohol results in the formation of only 3 moles of hydrogen[52,53] (Eqns 49–52).

$$LiAlH_4 + 4MeOH \xrightarrow[25°]{Et_2O} LiAl(OMe)_4\downarrow + 4H_2\uparrow \tag{49}$$

$$LiAlH_4 + 4EtOH \longrightarrow LiAl(OEt)_4\downarrow + 4H_2\uparrow \tag{50}$$

$$LiAlH_4 + 4i\text{-}PrOH \longrightarrow LiAl(O\text{-}i\text{-}Pr)_4\downarrow + 4H_2\uparrow \tag{51}$$

$$LiAlH_4 + 3t\text{-}BuOH \longrightarrow Li(t\text{-}BuO)_3AlH\downarrow + 3H_2\uparrow \tag{52}$$

The product of the reaction, lithium tri-*tert*-butoxyaluminohydride, is only slightly soluble in ethyl ether but readily soluble in tetrahydrofuran and diglyme. The reaction of a fourth mole of *tert*-butyl alcohol requires prolonged reaction time at elevated temperatures (Eqn 53).

$$\mathrm{Li}(t\text{-BuO})_3\mathrm{AlH} + t\text{-BuOH} \xrightarrow[\text{slow}]{\text{THF, reflux}} \mathrm{LiAl(O}\text{-}t\text{-Bu)}_4\downarrow + \mathrm{H}_2\uparrow . \tag{53}$$

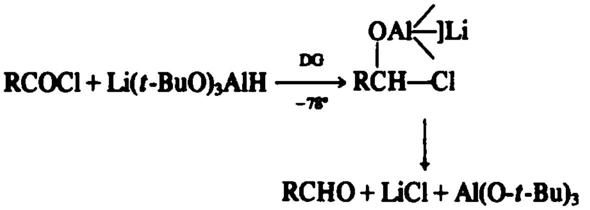
Lithium tri-*tert*-butoxyaluminohydride proved to be exceptionally stable both as solid as well as in ethereal solutions. It could be sublimed at 280° at 2 mm pressure.

The failure of lithium tri-*tert*-butoxyaluminohydride to react with excess *tert*-butyl alcohol at 25° suggested that this reagent should have reducing properties quite different from that of the parent compound. Indeed this proved to be true. The general reduction characteristics of this reagent in tetrahydrofuran at 0° are given below:[54]

aldehyde → alcohol
ketone → alcohol
acid chloride → alcohol
lactone → glycol (slow)
epoxide → alcohol (slow)
ester → slow reaction
carboxylic acid → no reaction
carboxylic acid salt → no reaction
tert-amide → no reaction
nitrile → no reaction
nitro → no reaction
olefin → no reaction.

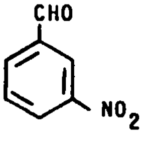
Thus, the three *tert*-butoxy groups have greatly diminished the reducing power of the parent reagent. Indeed the reducing characteristics of the reagent are so mild that the reagent resembles sodium borohydride much more than it does lithium aluminum hydride.

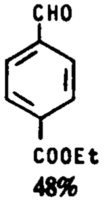
Lithium tri-*tert*-butoxyaluminohydride can selectively reduce acid chlorides to the corresponding aldehydes in diglyme solution at −80°.[55] In the case of aromatic acid chlorides, the yields of the aldehydes are excellent (60–90%). The reaction can tolerate a variety of substituents such as nitro, cyano, carbethoxy, etc. (Eqn 54).



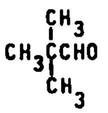
$$\mathrm{RCOCl} + \mathrm{Li}(t\text{-BuO})_3\mathrm{AlH} \xrightarrow[-78^\circ]{\mathrm{DG}} \mathrm{RCH(OAl\overline{<}]Li)\text{—}Cl} \longrightarrow \mathrm{RCHO} + \mathrm{LiCl} + \mathrm{Al(O}\text{-}t\text{-Bu)}_3 \tag{54}$$

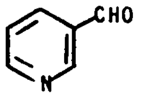

87%

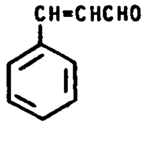

88%

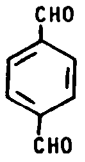

48%

The reaction is applicable to aliphatic, heterocyclic and unsaturated acid chlorides, as well as those derived from di- and polycarbosylic acids.

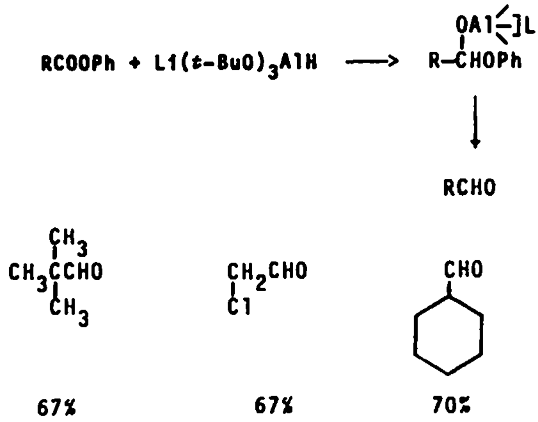

58%


69%


71%


82%

Although lithium tri-*tert*-butoxyaluminohydride reacts very sluggishly with alkyl esters, such as ethyl caproate, it is quite reactive towards aryl esters; it can selectively reduce such esters to the corresponding aldehydes in good yields[56] (Eqn 55).



(55)

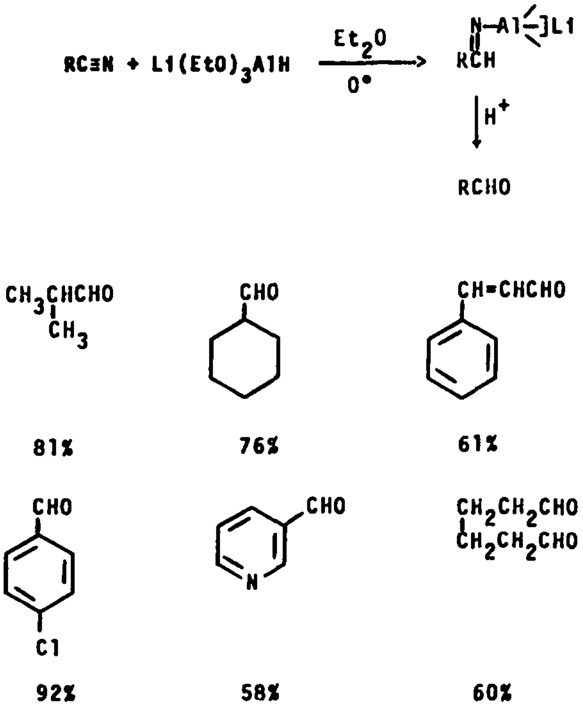
In synthetic work it is frequently desirable to proceed from carboxylic acid derivatives other than the acid chlorides to the corresponding aldehydes. The possibility of converting the dimethylamides and nitriles to aldehydes was explored. In both the cases, poor results were realized with lithium aluminum hydride and no reaction was observed with lithium tri-*tert*-butoxyaluminohydride. Consequently, other alkoxy derivatives of lithium aluminum hydride were explored.

Treatment of 1 mole of lithium aluminum hydride solution in ethyl ether with 3 moles of ethyl alcohol or 1.5 moles of ethyl acetate yields crude lithium triethoxyaluminohydride[57] (Eqns 56 and 57).

$$\mathrm{LiAlH_4 + 3EtOH \xrightarrow[0^\circ]{Et_2O} Li(EtO)_3AlH + 3H_2\uparrow} \tag{56}$$

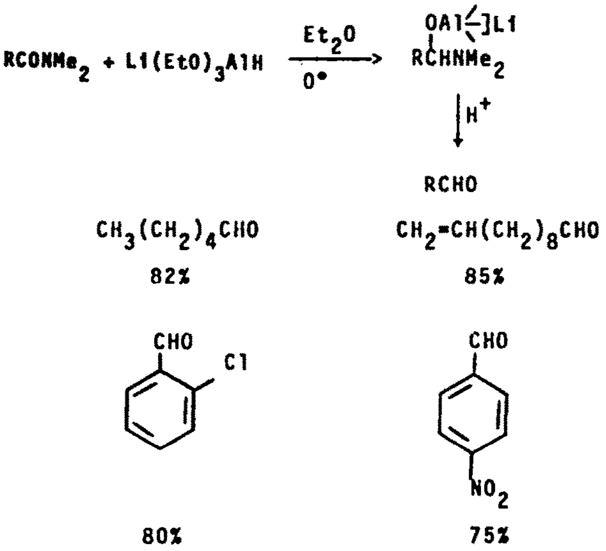
$$\mathrm{LiAlH_4 + 1.5CH_3COOEt \xrightarrow[0^\circ]{Et_2O} Li(EtO)_3AlH.} \tag{57}$$

This reagent selectively reduces aromatic as well as aliphatic nitriles to the corresponding aldehydes in yields of 70–90%. The reaction is simple and general[57] (Eqn 58).



(58)

Likewise, lithium triethoxyaluminohydride is highly efficient for the selective reduction of tertiary amides to the corresponding aldehydes[58] (Eqn 59).



(59)

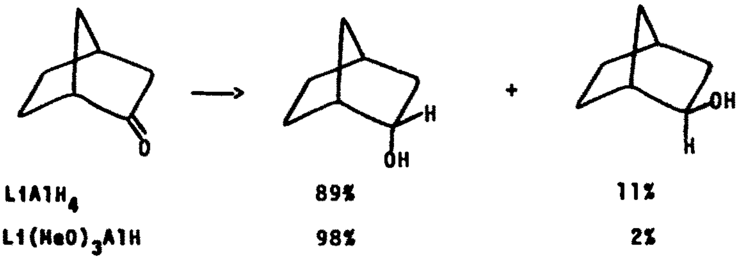
Addition of three moles of methyl alcohol to one mole of lithium aluminum hydride produces lithium trimethoxyaluminohydride[53] (Eqn 60).

$$LiAlH_4 + 3MeOH \xrightarrow[0^\circ]{THF} Li(MeO)_3AlH + 3H_2\uparrow . \qquad (60)$$

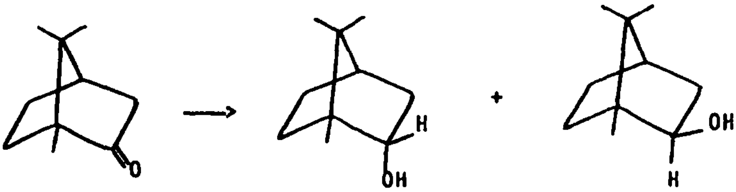
In contrast to the behavior of lithium tri-*tert*-butoxyaluminohydride, lithium trimethoxyaluminohydride is a powerful reducing agent, resembling closely its parent hydride[59] (lithium aluminum hydride):

aldehyde → alcohol
ketone → alcohol
acid chloride → alcohol
lactone → glycol
epoxide → alcohol (slow)
ester → alcohol
carboxylic acid → alcohol
carboxylic acid salt → alcohol
tert-amide → amine
nitrile → amine
nitro → reaction
olefin → no reaction.

Lithium trimethoxyaluminohydride revealed major advantages over lithium aluminum hydride for the stereoselective reduction of certain bicyclic ketones[60] (Eqns 61 and 62).



(61)



(62)

$LiAlH_4$	8%	92%
$Li(MeO)_3AlH$	1%	99%

In the recent years a number of trialkylborohydrides have evolved as attractive reducing agents for such steric control reductions. These derivatives will be discussed later.

B. *Alkoxyborohydrides*. Simple trialkoxyborohydrides such as sodium trimethoxyborohydride and sodium triethoxyborohydride are readily synthesized from sodium hydride and the borate esters in the absence of solvent. Unfortunately, these compounds undergo rapid disproportionation in solvents to sodium borohydride and sodium tetraalkoxyborohydride[61] (Eqns 63 and 64).

$$(MeO)_3B + NaH \rightarrow Na(MeO)_3BH \quad (63)$$

$$Na(MeO)_3BH \xrightarrow{THF} NaBH_4\downarrow + 3NaB(OMe)_4. \quad (64)$$

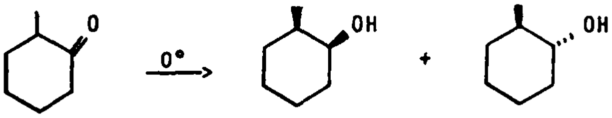
However, the more hindered derivatives synthesized in ethereal solvents appear to be stable. For the synthesis of such hindered derivatives the more recently developed potassium hydride route brings the reaction to completion under very mild conditions[62] (Eqns 65–67).

$$NaH + (i\text{-}PrO)_3B \xrightarrow[170\,h]{THF,\ reflux} Na(i\text{-}PrO)_3BH \quad (65)$$

$$NaH + (i\text{-}PrO)_3B \xrightarrow[130°,\ 1\,h]{Triglyme} Na(i\text{-}PrO)_3BH \quad (66)$$

$$KH + (i\text{-}PrO)_3B \xrightarrow[1\,h]{THF,\ 25°} K(i\text{-}PrO)_3BH \quad (67)$$

The reduction characteristics of potassium triisopropoxyborohydride in tetrahydrofuran have been explored briefly.[63] The reagent behaves as an exceptionally mild reducing agent, similar to sodium borohydride and lithium tri-*tert*-butoxyaluminohydride. It reduces aldehydes and ketones rapidly and quantitatively. Under these conditions, it is essentially inert to almost all other organic functional groups. In contrast to sodium borohydride and lithium tri-*tert*-butoxyaluminohydride, this reagent has the ability to introduce remarkable steric control into the reduction of cyclic ketones (Eqn 68).



(68)

$NaBH_4$	31%	69%
$Li(t\text{-}BuO)_3AlH$	27%	73%
$K(i\text{-}PrO)_3BH$	92%	8%

C. *Alkylborohydrides*. Addition compounds of alkali metal hydrides with trialkylboranes were first discovered during war research (1942–1945)[26,64] (Eqns 69 and 70).

$$LiH + Me_3B \rightarrow LiMe_3BH \quad (69)$$

$$NaH + Et_3B \rightarrow NaEt_3BH. \quad (70)$$

However, relatively little attention was devoted to these derivatives following their discovery. A brief study of lithium triethylborohydride indicated it to be a more powerful reducing agent than the parent hydride, lithium borohydride.[65]

The exceptional characteristics of trialkylborohydrides were discovered during our research involving the hydride induced carbonylation of organoboranes.[66] It was observed that the addition of equimolar quantity of triethylborane to a tetrahydrofuran solution of lithium tri-*tert*-butoxyaluminohydride resulted in a vigorous exothermic reaction and the rapid disappearance of the active hydride. Hydrolysis of the reaction mixture indicated the concurrent formation of 1-butanol (from reductive cleavage of tetrahydrofuran). Even a catalytic quantity of triethylborane was effective[67] (Fig. 1). How could even trace quantities of triethylborane convert such a mild reducing agent to the one capable of reductively cleaving THF?

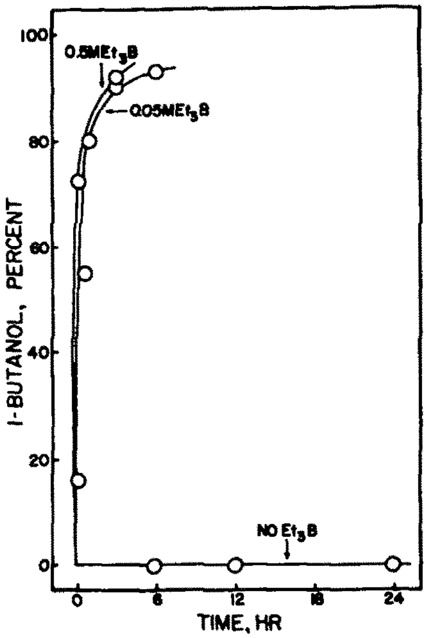
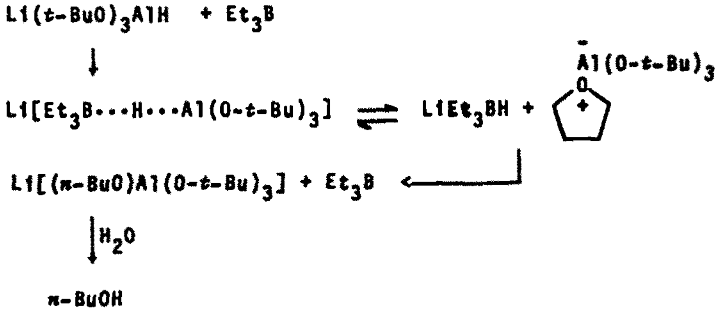


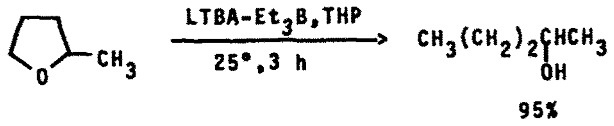
Fig. 1. Reductive cleavage of tetrahydrofuran at 25° by lithium tri-*t*-butoxyaluminohydride (0.5 M) in the absence and presence of triethylborane.

Further research in this direction revealed that the reaction involves lithium triethylborohydride and aluminum *tert*-butoxide as intermediates[68] (Eqn 71).



(71)

The reductive cleavage of tetrahydropyran (THP) is quite sluggish. Consequently, the lithium tri-*tert*-butoxyaluminohydride-triethylborane system was explored in tetrahydropyran solvent for the reductive cleavage of the more reactive cyclic ethers. This has led to some very interesting synthetic transformations[67] (Eqns 72–74).



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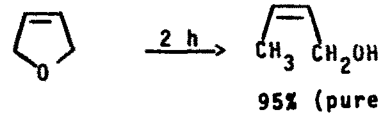

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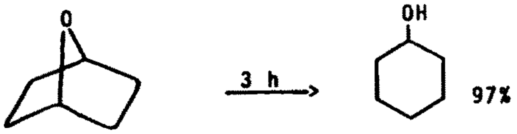


(74)

These investigations led us to believe that lithium triethylborohydride should possess exceptional hydride transfer ability. Accordingly, we undertook a major new program to synthesize a variety of alkali metal trialkylborohydrides and to explore their chemistry. Because of their superior hydridic qualities, these reagents have been called, "Super Hydrides", a term truly representative of their extraordinary hydridic activity.

A simple approach for the synthesis of these derivatives would be the reaction between alkali metal hydrides and the trialkylboranes. Hydroboration of olefins has made available trialkylboranes of varying structural features.[3c,40,41] Lithium hydride as well as lithium deuteride react with a variety of unhindered trialkylboranes to give lithium trialkylborohydrides and deuterides. The yields are essentially quantitative. However, with hindered trialkylboranes such as tri-*sec*-butylborane we encountered a major synthetic difficulty[69] (Eqns 75–77).

$$\mathrm{LiH} + \mathrm{R_3B} \xrightarrow[0.25\text{–}6.0\,\mathrm{h}]{\mathrm{THF},\,65^\circ} \underset{>95\%}{\mathrm{LiR_3BH}} \tag{75}$$

$$\mathrm{R} = \mathrm{Me, Et}, n\text{-}\mathrm{Bu}, i\text{-}\mathrm{Bu}$$

$$\mathrm{LiD} + \mathrm{Et_3B} \xrightarrow[1\,\mathrm{h}]{\mathrm{THF},\,65^\circ} \underset{100\%}{\mathrm{LiEt_3BD}} \tag{76}$$

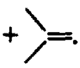
$$\mathrm{LiH} + s\text{-}\mathrm{Bu_3B} \xrightarrow[24\,\mathrm{h}]{\mathrm{THF},\,65^\circ} \underset{10\%.}{\mathrm{Li}s\text{-}\mathrm{Bu_3BH}} \tag{77}$$

A number of methods have been developed for the synthesis of alkali metal trialkylborohydrides carrying hindered alkyl substituents in quantitative yield[62,70–73] (Eqns 78–81).

$$s\text{-}\mathrm{Bu_3B} + \mathrm{NaH} \xrightarrow[3\,\mathrm{h}]{\mathrm{THF},\,65^\circ} \mathrm{Na}s\text{-}\mathrm{Bu_3BH} \tag{78}$$

$$s\text{-}\mathrm{Bu_3B} + \mathrm{KH} \xrightarrow[0.25\,\mathrm{h}]{\mathrm{THF},\,25^\circ} \mathrm{K}s\text{-}\mathrm{Bu_3BH} \tag{79}$$

$$s\text{-}\mathrm{Bu_3B} + \mathrm{Li(MeO)_3AlH} \xrightarrow[25^\circ,\,0.25\,\mathrm{h}]{\mathrm{THF}} \mathrm{Li}s\text{-}\mathrm{Bu_3BH} + [\mathrm{Al(OMe)_3}]\downarrow \tag{80}$$

$$s\text{-}\mathrm{Bu_3B} + t\text{-}\mathrm{BuLi} \xrightarrow[-78^\circ]{\mathrm{THF}} \mathrm{Li}s\text{-}\mathrm{Bu_3BH} +$$  . (81)

Lithium triethylborohydride (Super Hydride) is an extraordinarily powerful reducing agent, far more powerful than lithium aluminum hydride and lithium borohydride, as revealed by the rates of reduction of *n*-octyl chloride represented graphically[74] (Fig. 2).

The reagent is exceptionally useful for the reductive dehalogenation of alkyl halides. The reaction exhibits typical characteristics of a nucleophilic displacement of the S_N2 type. Even neopentyl halides and cycloalkyl halides are reduced cleanly to the desired products without any rearrangement. Unlike lithium aluminum hydride[31] the reagent is inert to aryl halides and should be valuable for the reduction of alkyl halides without simultaneous attack on aromatic halogen (Eqns 82–87).

$$\mathrm{CH_3(CH_2)_6CH_2Br} \xrightarrow[25^\circ,\,2\,\mathrm{min}]{\mathrm{LiEt_3BH,\,THF}} \underset{100\%}{\mathrm{CH_3(CH_2)_6CH_3}} \tag{82}$$

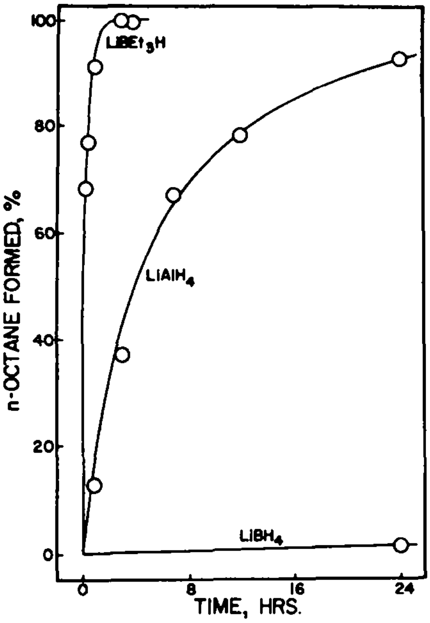
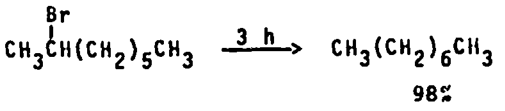
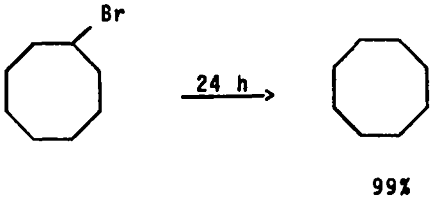


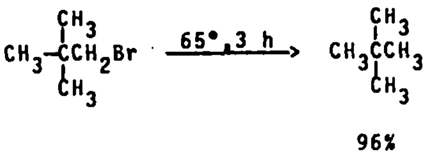
Fig. 2. Rates of reduction of *n*-octyl chloride (0.25 M) with representative complex metal hydrides (0.5 M) in tetrahydrofuran at 25°.



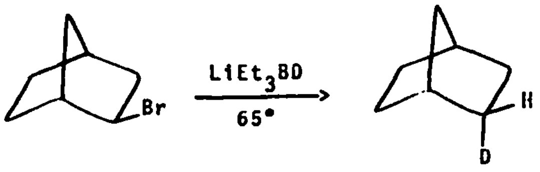
$$CH_3\overset{Br}{\overset{|}{C}}H(CH_2)_5CH_3 \xrightarrow{3\ h} \underset{98\%}{CH_3(CH_2)_6CH_3} \qquad (83)$$



(84)



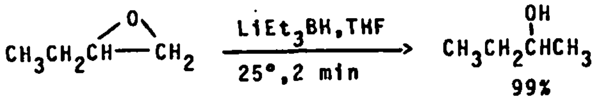
$$CH_3\!-\!\underset{CH_3}{\overset{CH_3}{C}}CH_2Br \xrightarrow{65°,3\ h} \underset{96\%}{CH_3\underset{CH_3}{\overset{CH_3}{C}}CH_3} \qquad (85)$$



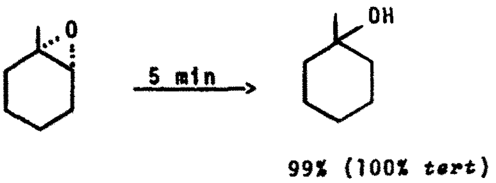
(86)

$$ArX \longrightarrow \text{no reaction} \qquad (87)$$

Lithium triethylborohydride in THF possesses remarkable ability for the facile, regio- and stereospecific reductive opening of epoxides to give the Markovnikov alcohol in excellent isomeric purity[75] (Eqns 88 and 89).

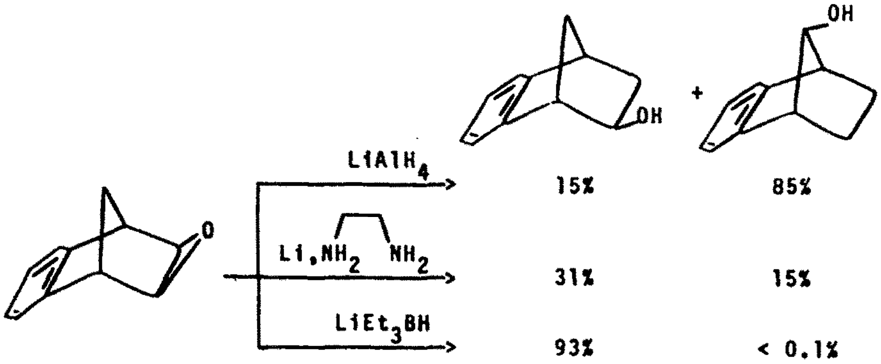


$$CH_3CH_2\overset{O}{CH\!-\!CH_2} \xrightarrow[25°,2\ min]{LiEt_3BH,THF} \underset{99\%}{CH_3CH_2\overset{OH}{\overset{|}{C}}HCH_3} \qquad (88)$$



(89)

The advantage of Super Hydride is especially evident for the reduction of labile bicyclic epoxides prone to electrophilic rearrangement (Eqn 90).



(90)

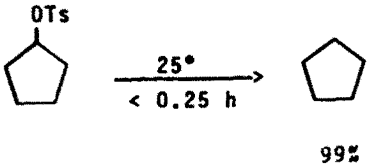
Super Hydride reduces quaternary ammonium salts rapidly and cleanly to the corresponding amines in quantitative yield. The reagent is capable of discriminating between Me and Et groups[76] (Eqns 91 and 92).

$$CH_3(CH_2)_5\overset{+}{N}(CH_3)_3\overset{-}{I} \xrightarrow[65°, 4\,h]{LiEt_3BH, THF} \underset{100\%}{CH_3(CH_2)_5N(CH_3)_2} \quad (91)$$

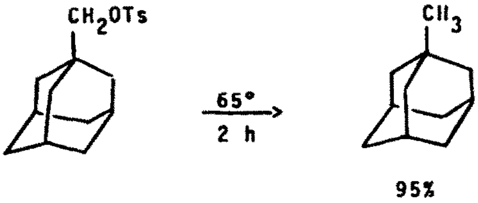
$$Ph\overset{+}{N}(C_2H_5)(CH_3)_2\overset{-}{I} \xrightarrow[0.75\,h]{25°} \underset{96\%}{PhN(C_2H_5)CH_3} + \underset{4\%}{PhN(CH_3)_2}. \quad (92)$$

Super Hydride provides an advantageous and convenient procedure for the deoxygenation of alcohols through the reduction of their *p*-toluenesulfonate esters. The reaction is applicable to tosylates derived from acyclic, cyclic and hindered alcohols[77,78] (Eqns 93–96).

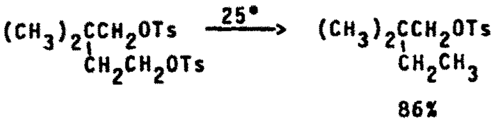
$$CH_3(CH_2)_6CH_2OTs \xrightarrow[25°, 0.25\,h]{LiEt_3BH, THF} \underset{99\%}{CH_3(CH_2)_6CH_3} \quad (93)$$



(94)

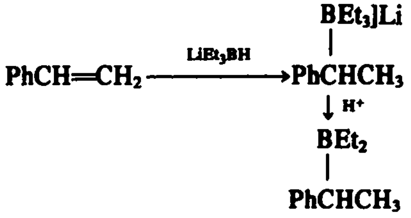


(95)



$$(CH_3)_2\underset{CH_2CH_2OTs}{C}CH_2OTs \xrightarrow{25°} \underset{86\%}{(CH_3)_2\underset{CH_2CH_3}{C}CH_2OTs} \quad (96)$$

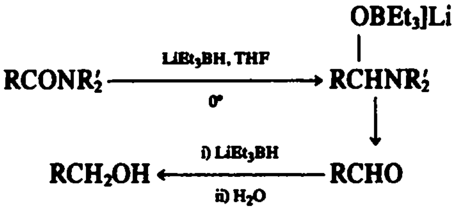
Lithium triethylborohydride adds to substituted styrenes under relatively mild conditions to give the corresponding tetraalkylborates, readily hydrolyzed to the corresponding saturated hydrocarbons or protonolyzed with strong acids to the mixed trialkylboranes containing a benzylic group. This reaction provides a convenient entry into Markovnikov trialkylboranes[79] (Eqns 97 and 98).



$$\mathrm{PhCH{=}CH_2} \xrightarrow{\mathrm{LiEt_3BH}} \mathrm{Ph\overset{\overset{BEt_3]Li}{|}}{C}HCH_3} \xrightarrow{\mathrm{H^+}} \mathrm{Ph\overset{\overset{BEt_2}{|}}{C}HCH_3} \qquad (97)$$

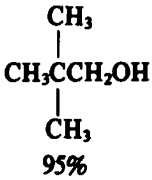
$$\mathrm{PhCH{=}CH_2} \xrightarrow{\mathrm{Et_2BH}} \mathrm{PhCH_2CH_2BEt_2}. \qquad (98)$$

Reduction of tertiary amides with lithium triethylborohydride proceeds with C–N fission providing the corresponding alcohol and not the amine as the reaction product[80] (Eqn 99).



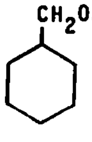
$$\mathrm{RCONR'_2} \xrightarrow[0^\circ]{\mathrm{LiEt_3BH,\,THF}} \mathrm{R\overset{\overset{OBEt_3]Li}{|}}{C}HNR'_2} \longrightarrow \mathrm{RCHO} \xrightarrow[\mathrm{ii)\,H_2O}]{\mathrm{i)\,LiEt_3BH}} \mathrm{RCH_2OH} \qquad (99)$$

$\mathrm{CH_3(CH_2)_5CH_2OH}$
80%

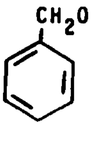


$$\mathrm{CH_3\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}CH_2OH}$$

95%

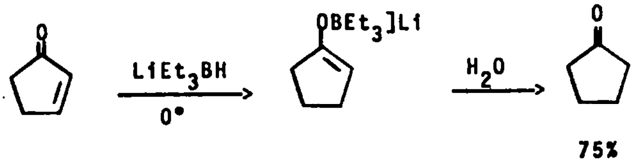


71%

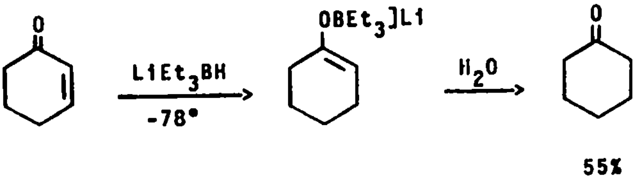


100%

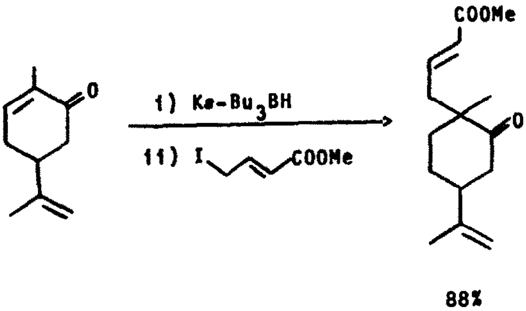
Alkali metal trialkylborohydrides reduce α,β-enones and α,β-enoates in a conjugate fashion (1,4-reduction). This provides a convenient method for the generation of enolates which are trapped with a variety of electrophiles[81,82] (Eqns 100–103).



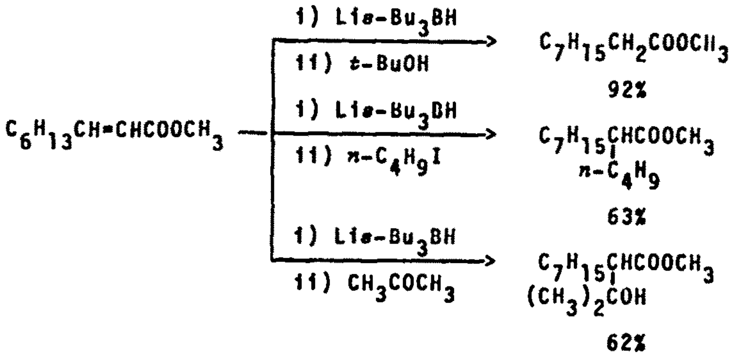
(100)



(101)

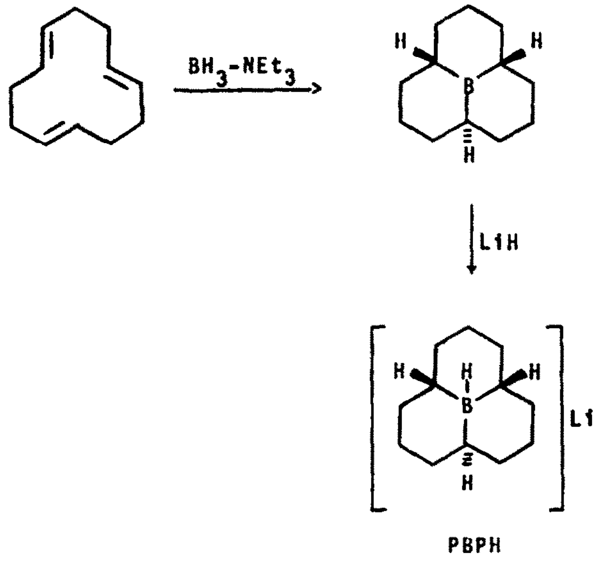


(102)

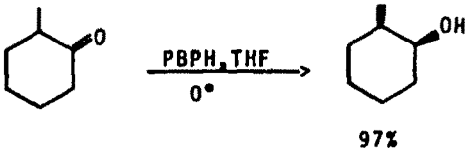


(103)

Aldehydes and ketones (both alkyl and aryl) are reduced by alkali metal trialkylborohydrides rapidly and quantitatively to the corresponding alcohols even at −78°. One of the remarkable features of trialkylborohydrides is their unusual ability to introduce steric control into the reduction of cyclic ketones, first recognized in our laboratory with lithium perhydro-9b-boraphenalyl hydride[83] (PBPH) (Eqns 104 and 105).

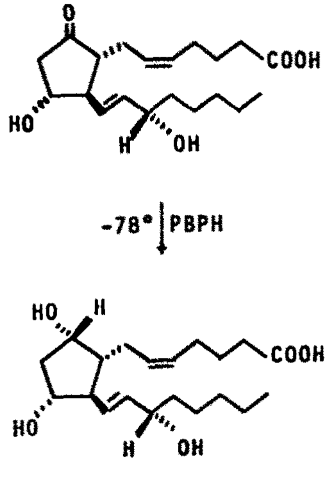


(104)



(105)

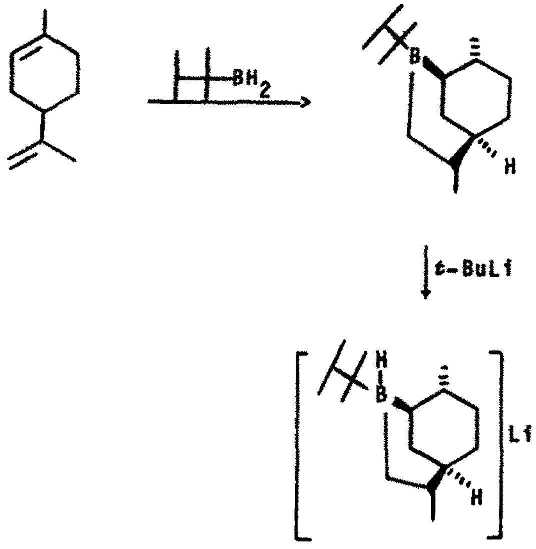
This resulted in its immediate application in the synthesis of prostaglandins[84] (Eqn 104).



99% (pure $F_{2\alpha}$)

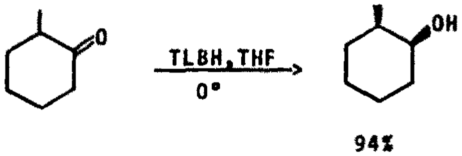
(106)

Thexyllimonylborane, obtained by the cyclic hydroboration of limonene with thexylborane, has been converted to the corresponding trialkylborohydride.[72,85] This is also useful in prostaglandin transformations[86] (Eqns 107 and 108).



TLBH

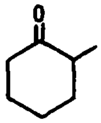
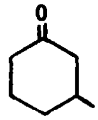
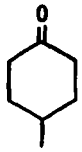
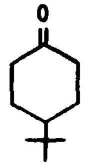
(107)



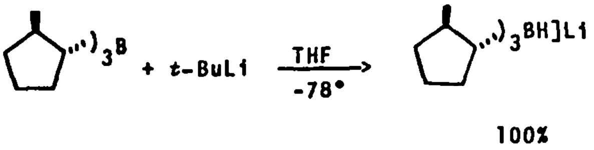
94%

(108)

Hindered trialkylborohydrides, lithium and potassium tri-*sec*-butylborohydrides, reduce cyclic and bicyclic ketones to the corresponding alcohols with remarkable stereoselectivity.[62,87] Tri-*sec*-butylborohydride exhibits considerable superiority over PBPH and TLBH as indicated by the following comparative study at 0° in THF.

Ketone	Less stable isomer	Less stable isomer		
		PBPH	TLBH	Li*s*-Bu$_3$BH
	*cis*	97	94	>99
	*trans*	59	67	89
	*cis*	52	64	85
	*cis*	54	71	93

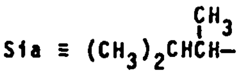
It was desirable to have a reagent that would reduce even 3- and 4-alkylcyclohexanones to the corresponding alcohols in 99% or better stereoselectively. Recently, we have synthesized two even more hindered trialkylborohydrides—lithium tris(*trans*-2-methylcyclopentyl)-borohydride and lithium trisiamylborohydride—both of them containing three β-methyl substituted secondary alkyl groups[88] (Eqns 109 and 110).



(109)

$$\mathrm{Sia_3B} + t\text{-}\mathrm{BuLi} \xrightarrow[-78°]{\mathrm{THF}} \mathrm{LiSia_3BH} \quad (110)$$

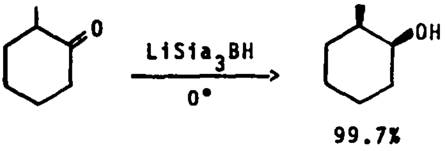
100%



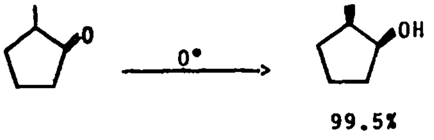
$$\mathrm{Sia} \equiv (\mathrm{CH_3})_2\mathrm{CH}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}\mathrm{H}-$$

These reagents can also be prepared from lithium trimethoxyaluminohydride[73] in place of *tert*-butyllithium.

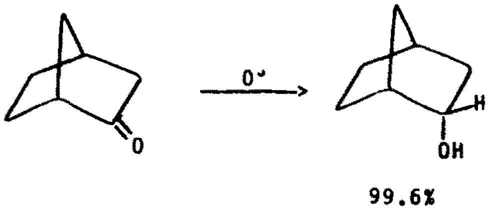
Lithium trisiamylborohydride reduces cyclic ketones with super stereoselectivity (Eqns 111–113).



(111)

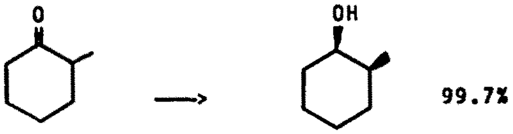


(112)

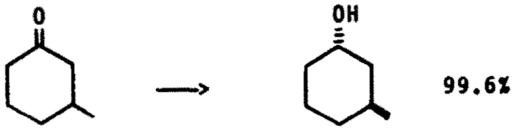


(113)

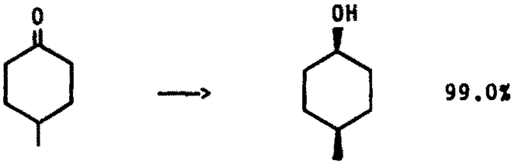
Thus, 2-, 3- and 4-alkylcyclohexanones—all are reduced with lithium trisiamylborohydride at −78° in ≥99% stereoselectivity (Eqns 114–116).



(114)



(115)

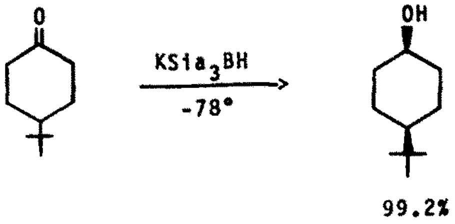


(116)

The corresponding potassium derivative synthesized recently by a catalytic process is equally effective[89] (Eqns 117–119).

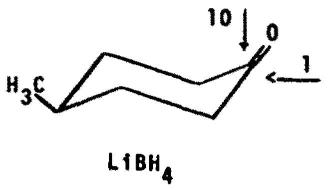
$$\mathrm{KH} + \underset{\text{catalytic}}{(i\text{-PrO})_3\mathrm{B}} \longrightarrow \mathrm{K}(i\text{-PrO})_3\mathrm{BH} \qquad (117)$$

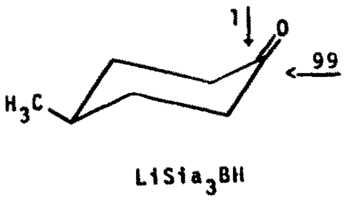
$$\mathrm{K}(i\text{-PrO})_3\mathrm{BH} + \mathrm{Sia_3B} \longrightarrow \mathrm{KSia_3BH} + (i\text{-PrO})_3\mathrm{B} \qquad (118)$$



(119)

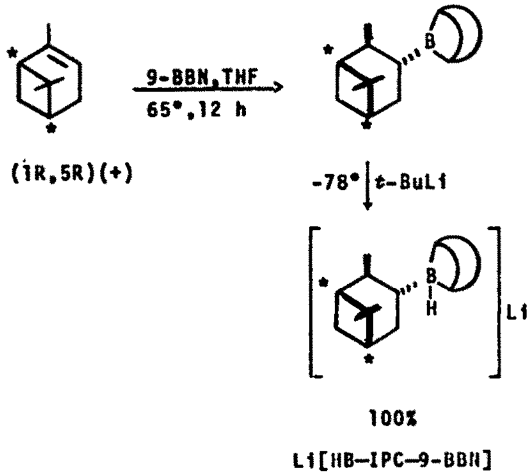
By introducing highly hindered alkyl substituents in the borohydride anion, we are drastically altering the direction of attack on a cyclic ketone.





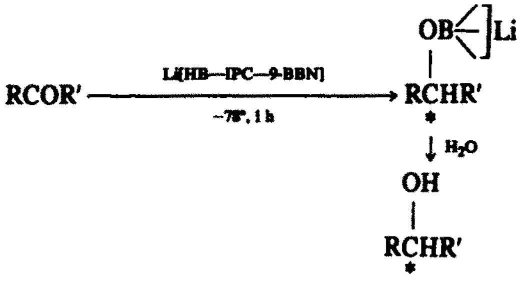
We have synthesized a trialkylborohydride containing an asymmetric alkyl group, lithium *B*-

isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride[90] (Eqn 120).



(120)

The reagent reduces rapidly and quantitatively a wide variety of ketones to the corresponding alcohols. The alcohols produced are optically active. The alcohols obtained with this new reagent [from (+)-α-pinene] are consistently enriched in the *R* enantiomer (Eqn 121).



$$\mathrm{RCOR'} \xrightarrow[-78^\circ,\,1\,\mathrm{h}]{\mathrm{Li[HB-IPC-9\text{-}BBN]}} \mathrm{R\underset{*}{C}HR'}\;(\mathrm{OB}\langle\,]\mathrm{Li}) \xrightarrow{H_2O} \mathrm{R\underset{*}{C}HR'}\;(\mathrm{OH}) \qquad (121)$$

R	R′	% e.e.	Config.
Et	Me	29	R
i-Bu	Me	16	R
i-Pr	Me	36	R
t-Bu	Me	3	R
Ph	Me	17	R

We have recently examined the reactivity of lithium triethylborohydride towards seventy organic compounds containing the representative functional groups in defining the hydride transfer property of the chemical (0°, THF). Preliminary results clearly indicate that trialkylborohydrides are the most powerful hydride doners currently available:[91]

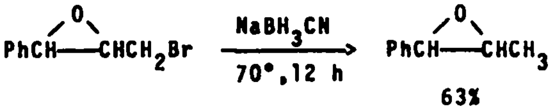
aldehyde → alcohol
ketone → alcohol
acid chloride → alcohol
lactone → glycol
epoxide → alcohol
ester → alcohol
carboxylic acid → reaction, no reduction
carboxylic acid salt → no reaction
tert-amide → alcohol
nitrile → amine
nitro → reaction
olefin → no reaction.

D. *Cyanoborohydride.* Sodium cyanoborohydride synthesized from sodium borohydride and hydrogen cyanide is a white crystalline solid, m.p. 240°[92] (Eqn 122).

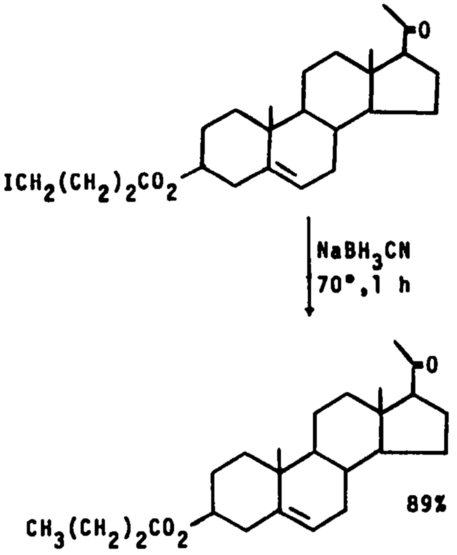
$$NaBH_4 + HCN \xrightarrow{THF} NaBH_3CN + H_2. \qquad (122)$$

It possesses certain unique characteristics which renders it a very valuable selective reducing agent. Unlike other hydride reagents, it is stable in acid solutions down to pH 3. It is soluble in tetrahydrofuran methanol, water, and in some dipolar aprotic solvents (HMPA, DMF, sulfolane).

Sodium cyanoborohydride in HMPA efficiently and selectively reduces alkyl halides and tosylates to the corresponding alkanes in the presence of a variety of other reactive functional groups, such as aldehyde, ketone, epoxide, cyano, ester, carboxylic acid, amide, etc.[93] (Eqns 123 and 124).

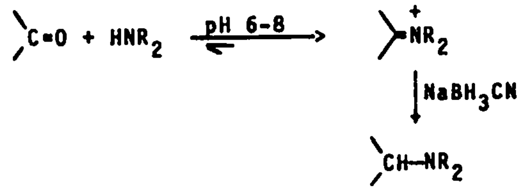


(123)

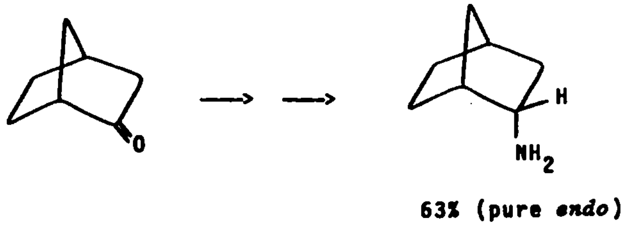


(124)

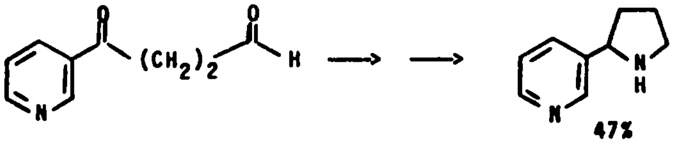
Aldehydes and ketones are reductively aminated to the corresponding amines by the reduction of the imines generated *in situ*[94] (Eqns 125–128).



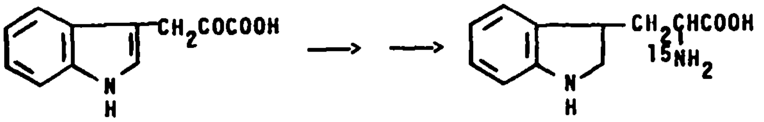
(125)



(126)

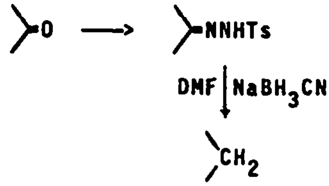


(127)

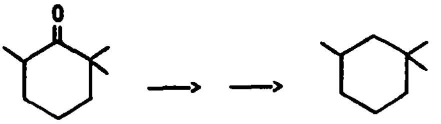


(128)

Sodium cyanoborohydride is quite effective for the facile reduction of tosylhydrazones derived from aldehydes and ketones to the corresponding alkanes in excellent yields[95] (Eqns 129–131).



(129)



(130)

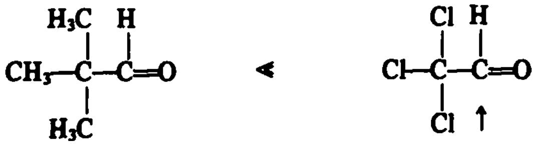
92%

$CH_3CO(CH_2)_3COO(CH_2)_6CN \longrightarrow \longrightarrow CH_3(CH_2)_4COO(CH_2)_6CN$ (131)

96%

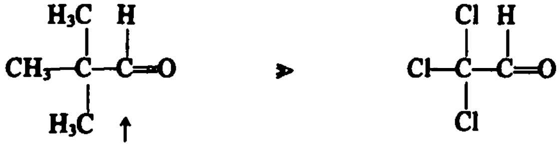
6. *Acidic reducing agents*

Reductions involving complex borohydrides and aluminohydrides as well as their modified reagents appear to involve transfer of the hydride moiety from the complex anion to an electron deficient center of the functional group.[37,96] Consequently, these are called nucleophilic reducing agents. Substituents which enhance the electron deficiency at the reaction site increase the rate of hydride transfer. For example, sodium borohydride in diglyme reduces chloral and acetyl chloride much more rapidly than simple aldehydes and ketones.



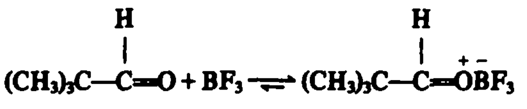
preferential attack by NaBH$_4$

On the other hand, diborane is a strong Lewis acid (electron deficient molecule). It forms stable addition compounds with tertiary amines. Consequently, the reactions involving diborane are expected to involve a preferable electrophilic attack on the centers of highest electron density.

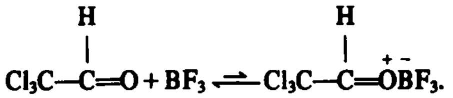


preferential attack by B$_2$H$_6$

It was pointed out earlier that the carbonyl groups of simple aldehydes and ketones react rapidly with diborane whereas the carbonyl groups of chloral and acid chloride are inert to this reagent. Further, those aldehydes and ketones which react with diborane also form stable addition compounds with boron trifluoride whereas chloral and acetyl chloride form only weak complexes (Eqns 132 and 133).



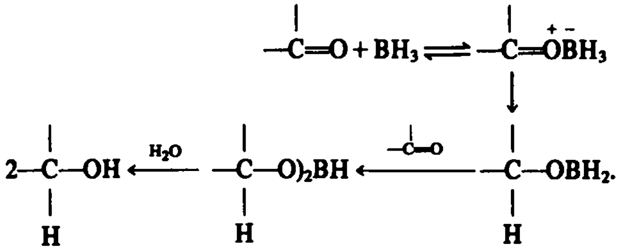
$$(CH_3)_3C\text{—}\overset{\overset{\displaystyle H}{|}}{C}{=}O + BF_3 \rightleftharpoons (CH_3)_3C\text{—}\overset{\overset{\displaystyle H}{|}}{C}{=}\overset{+}{O}\overset{-}{B}F_3 \qquad (132)$$



$$Cl_3C-\overset{\overset{\displaystyle H}{|}}{C}=O+BF_3 \rightleftharpoons Cl_3C-\overset{\overset{\displaystyle H}{|}}{C}=\overset{+}{O}\overset{-}{B}F_3. \qquad (133)$$

The reaction of diborane with the carbonyl group should also involve a similar complexation followed by hydride transfer[2] (Eqns 134 and 135).

$$B_2H_6 \rightleftharpoons 2BH_3 \qquad (134)$$



$$\begin{aligned} &-\overset{|}{C}=O+BH_3 \rightleftharpoons -\overset{|}{C}=\overset{+}{O}\overset{-}{B}H_3 \\ &\qquad\qquad\qquad\qquad \downarrow \\ 2-\underset{\underset{\displaystyle H}{|}}{\overset{|}{C}}-OH \xleftarrow{H_2O} (-\underset{\underset{\displaystyle H}{|}}{\overset{|}{C}}-O)_2BH &\xleftarrow{-\overset{|}{C}=O} -\underset{\underset{\displaystyle H}{|}}{\overset{|}{C}}-OBH_2. \end{aligned} \qquad (135)$$

Similarly, alane (aluminum hydride) is also a Lewis acid forming stable addition compounds with tertiary amines.[97] In contrast to the nucleophilic character of sodium borohydride and lithium aluminum hydride, borane and alane should function as electrophilic (acidic) reducing agents. Consequently, it was of interest to explore the reducing characteristics of such reagents which markedly differ in their characteristics. It was also of interest to examine the influence of various substituents such as alkoxy, halogen, and alkyl on the reducing characteristics of such acidic reducing agents.

A. *Diborane.* Diborane is a gas (b.p. −92.5°), highly reactive to air and moisture. It is sparingly soluble in ethyl ether, diglyme and hydrocarbon solvents: It readily dissolves in tetrahydrofuran in which it exists as the borane-tetrahydrofuran addition compound. A standard solution of borane·THF in tetrahydrofuran can be conveniently prepared by treating sodium borohydride in diglyme with boron trifluoride etherate and passing the gas as generated into tetrahydrofuran[98] (Eqn 136).

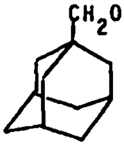
$$3NaBH_4+4BF_3:OEt_2 \rightarrow 4BH_3+3NaBF_4. \qquad (136)$$

The original experiments on the reducing characteristics of diborane were carried out in vacuum lines without any solvent. In our early explorations on the reducing characteristics of diborane, diborane was externally generated in a separate flask and passed into the compound dissolved in a suitable solvent.[99,100] Later we found it convenient to utilize a standard solution of borane in tetrahydrofuran for exploring the reducing characteristics of the reagent as well as the applicability of the reagent for synthetic transformations. The general reducing characteristics of borane–THF at 0° toward representative organic functional group is summarized as follows:[101]

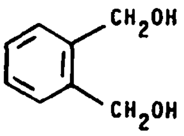
aldehyde → alcohol
ketone → alcohol
acid chloride → very slow reaction
lactone → glycol
epoxide → alcohol (very slow)
ester → alcohol (slow)
carboxylic acid → alcohol (very fast)
carboxylic acid salt → no reduction
tert-amide → amine
nitrile → amine
nitro → no reduction
olefin → organoborane.

Aliphatic and aromatic carboxylic acids are reduced rapidly and quantitatively to the corresponding alcohols by borane in tetrahydrofuran, either at 0° or 25° (or even at −78°). (In view of the usual inertness of carboxylic acids toward many reducing agents, this high reactivity toward borane must be considered exceptional.) The reaction is applicable to a variety of structures such as sterically hindered acids, di- and polycarboxylic acids, phenolic acids, amino acids, etc.[102] (Eqn 137).

$$\begin{tikzcd} RCOOH \arrow[r, "BH_3\text{-}THF"] & RCH_2OBO \arrow[d, "H_2O"] \\ & RCH_2OH \end{tikzcd} \qquad (137)$$



95%



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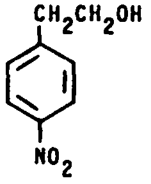

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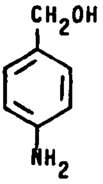
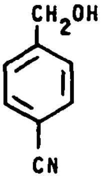


80%

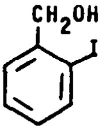
Unlike the conventional reagents, borane–THF can tolerate a variety of functional groups and a number of functionalized alcohols have been prepared from the corresponding carboxylic acids in excellent isolated yields.

$BrCH_2(CH_2)_9CH_2OH$ 91%

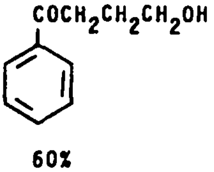
$HOCH_2(CH_2)_4COOC_2H_5$ 88%



82%



92%

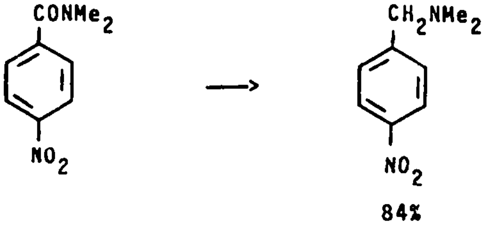


60%

Another major application of borane–THF is the facile reduction of primary, secondary, and tertiary amides to the corresponding amines. Here again the reaction can withstand a number of less reactive functional groups[103] (Eqns 138–140).

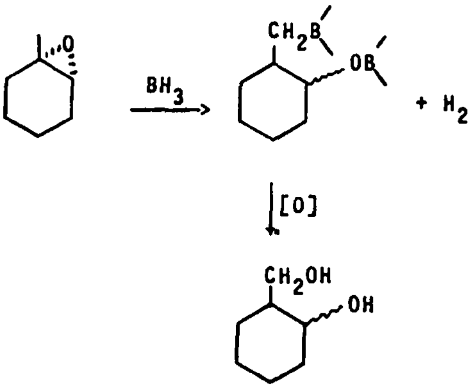
$$CH_3(CH_2)_4CONH_2 \xrightarrow{BH_3\text{-}THF} \underset{87\%}{CH_3(CH_2)_4CH_2NH_2} \qquad (138)$$

$$CH_3(CH_2)_4CONHMe \longrightarrow \underset{98\%}{CH_3(CH_2)_4CH_2NHMe} \qquad (139)$$



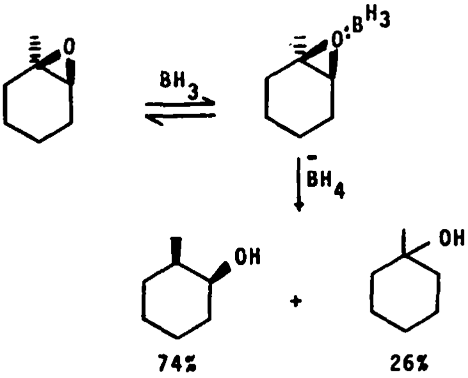
(140)

The reductive properties of diborane can be enhanced and the course of the reaction entirely modified by the introduction of catalytic quantities of sodium borohydride or boron trifluoride. The reaction of borane with 1-methylcyclohexene oxide and styrene oxide is very sluggish and complex.[101] For example, the reaction of 1-methylcyclohexene oxide with borane–THF utilizes 2 moles of "hydride" per mole of epoxide, with 1 mole of hydrogen being evolved (Eqn 141).



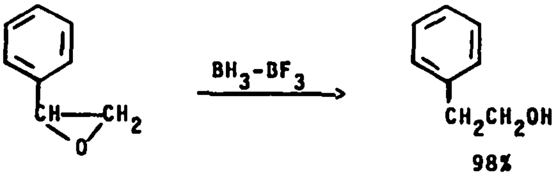
(141)

Addition of catalytic quantities of sodium borohydride dramatically increased the rate of the reaction; moreover, the course of the reaction is changed drastically resulting in anti-Markovnikov opening of the epoxide ring[104] (Eqn 142).

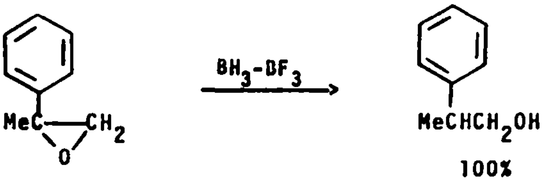


(142)

Similarly, the introduction of a small quantity of boron trifluoride greatly facilitates the reduction of styrene oxide and related epoxides in an anti-Markovnikov direction[105] (Eqns 143 and 144).

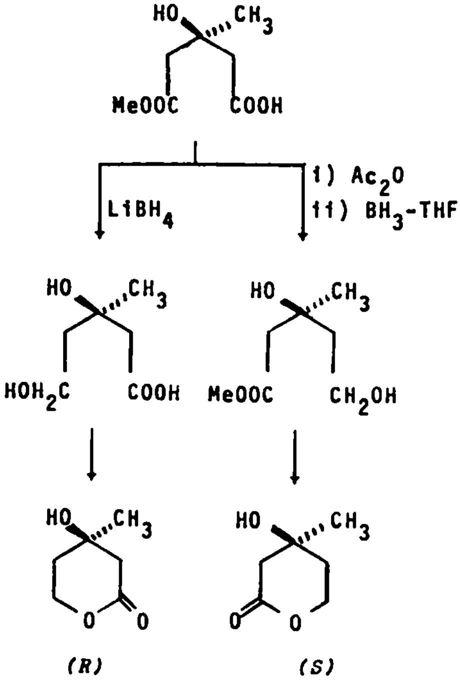


(143)



(144)

Estimation of the relative reactivity of various organic functional groups toward diborane by extensive competition experiments revealed the following order of reactivity:[100] carboxylic acids > olefins > ketones > nitriles > epoxides > esters > acid chlorides. On the other hand, toward alkali metal borohydride the order observed is: acid chlorides > ketones > epoxides > esters > nitriles > carboxylic acids. With such markedly different reactivities, the judicious use of either diborane or alkali metal borohydride permits the selective reduction of one group in the presence of a second or the reverse, as exemplified by the synthesis of both (*R*)- and (*S*)-mevalonolactone[106] (Eqn 145).

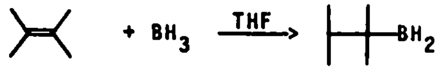


(145)

Until recently, the majority of borane reductions were carried out in tetrahydrofuran as the solvent. The recently introduced borane–methyl sulfide complex has several advantages[107] over borane–THF. It is exceptionally stable, soluble in a variety of aprotic solvents, such as ethyl ether, tetrahydrofuran, hexane, toluene, methylene chloride, diglyme, etc. Further, the reactivity of borane–methyl sulfide towards organic functional groups parallels that of borane–THF. It is equally effective for the reduction of organic functional groups.[108]

B. *Alkylboranes*. The discovery of the hydroboration reaction[40,41] has made available a number of partially alkylated boranes containing either one or two alkyl groups on boron depending on the steric nature of the olefin.

Thexylborane, a monoalkylborane, can be prepared by the hydroboration of 2,3-dimethyl-2-butene with borane in 1:1 stoichiometry[109] (Eqn 146).



(146)

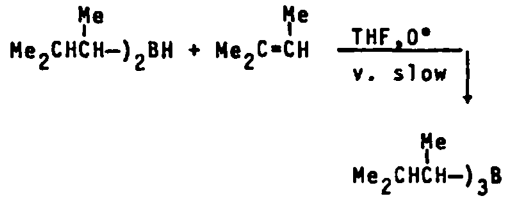
It is a mild reducing agent:[110]

aldehyde → alcohol
ketone → alcohol
acid chloride → very slow reduction

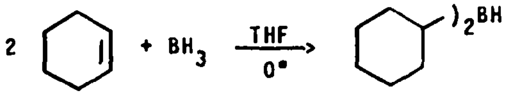
lactone → slow reduction
epoxide → slow reduction
ester → very slow reduction
carboxylic acid → slow reduction
tert-amide → slow reduction
nitrile → slow reduction
nitro → no reaction
olefin → organoborane.

Hydroboration of certain hindered olefins or structurally suited dienes yield preferentially dialkylboranes. Thus, hydroboration of 2-methyl-2-butene rapidly forms the dialkylborane, disiamylborane (Sia_2BH).[111] The addition of the third mole of olefin is very sluggish. Similarly, dicyclohexylborane ($CHex_2BH$) and diisopinocampheylborane (IPC_2BH) (an asymmetric dialkylborane) can be prepared by the hydroboration of the corresponding olefins.[112] More recently, diisopinocampheylborane has been synthesized in very high purity (chemical as well as optical)[113] (Eqns 147–150).

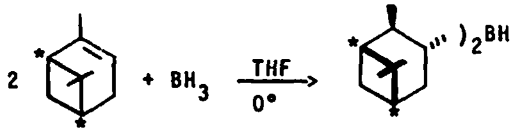
$$2\ Me_2C{=}\overset{Me}{C}H + BH_3 \xrightarrow[\text{fast}]{THF,\,0°} Me_2CH\overset{Me}{C}H\text{—})_2BH \qquad (147)$$



$$Me_2CH\overset{Me}{C}H\text{—})_2BH + Me_2C{=}\overset{Me}{C}H \xrightarrow[\text{v. slow}]{THF,\,0°} Me_2CH\overset{Me}{C}H\text{—})_3B \qquad (148)$$



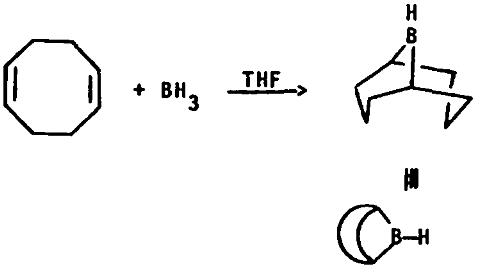
(149)



(150)

(+)-(1R,5R) (−)-(1R,2S,3R,5R)

Cyclic hydroboration of 1,5-cyclooctadiene yields a bicyclic dialkylborane, 9-borabicyclo[3.3.1]-nonane (9-BBN).[114] It exhibits certain unique physical and chemical characteristics. It is a white crystalline solid (m.p. 154–155°), thermally stable, relatively insensitive to air and soluble in a variety of organic solvents (Eqn 151).



(151)

A detailed study of the reduction characteristics of disiamylborane in tetrahydrofuran at 0° has been carried out. The results of this investigation indicate the following characteristics:[115]

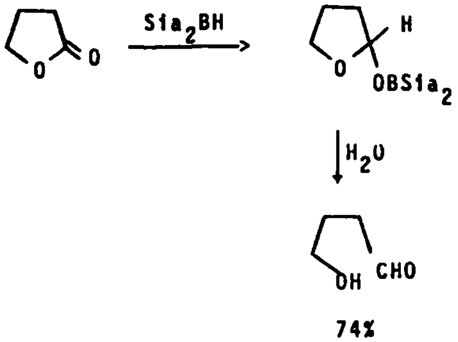
aldehyde → alcohol
ketone → alcohol

acid chloride → very slow reaction
lactone → hydroxyaldehyde
epoxide → very slow reaction
ester → very slow reaction
carboxylic acid → no reduction
carboxylic acid salt → no reduction
tert-amide → aldehyde
nitrile → very slow reaction
nitro → very slow reaction
olefin → organoborane.

Recently, 9-borabicyclo[3.3.1]nonane has been explored as a reducing agent in tetrahydrofuran at 25°. The general characteristics of this reagent are summarized below:[116]

aldehyde → alcohol
ketone → alcohol
acid chloride → alcohol
lactone → diol
epoxide → very slow reaction
ester → alcohol (moderate)
carboxylic acid → alcohol (very slow)
tert-amide → alcohol
nitrile → very slow reaction
nitro → very slow reaction
olefin → organoborane.

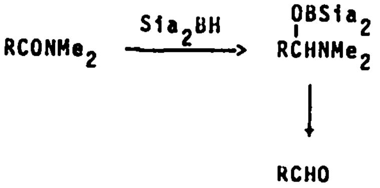
One of the major applications of disiamylborane is the selective reduction of lactones to hydroxyaldehyde[117] (Eqn 152).



(152)

The reaction appears to be general. A number of interesting applications of this reagent for this type of transformation have been reported.[115]

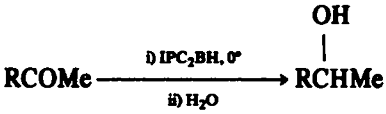
Preliminary investigations indicate that disiamylborane exhibits promise for the selective reduction of tertiary amides to the corresponding aldehyde (Eqn 153).



$$\mathrm{RCONMe_2} \xrightarrow{\mathrm{Sia_2BH}} \underset{\displaystyle\downarrow \atop \displaystyle\mathrm{RCHO}}{\overset{\mathrm{OBSia_2}\atop |}{\mathrm{RCHNMe_2}}}$$

(153)

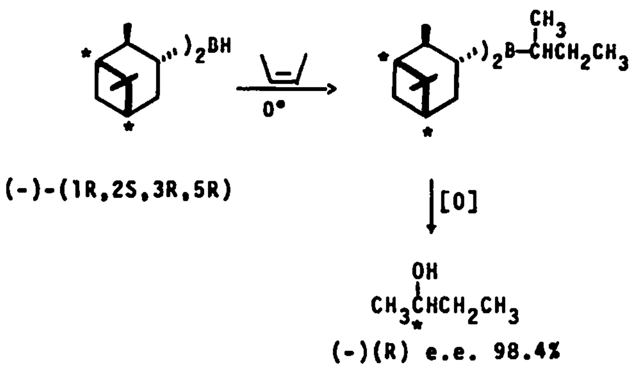
Recently, diisopinocampheylborane of high optical purity has been examined for the asymmetric reduction of a representative series of alkyl methyl ketones. Asymmetric induction in the alcohol products in the range of 9–37% was observed[118] (Eqn 154).



$$\mathrm{RCOMe}\xrightarrow[\text{ii) } H_2O]{\text{i) IPC}_2\text{BH, 0°}}\overset{\displaystyle OH}{\mathrm{RCHMe}}\qquad(154)$$

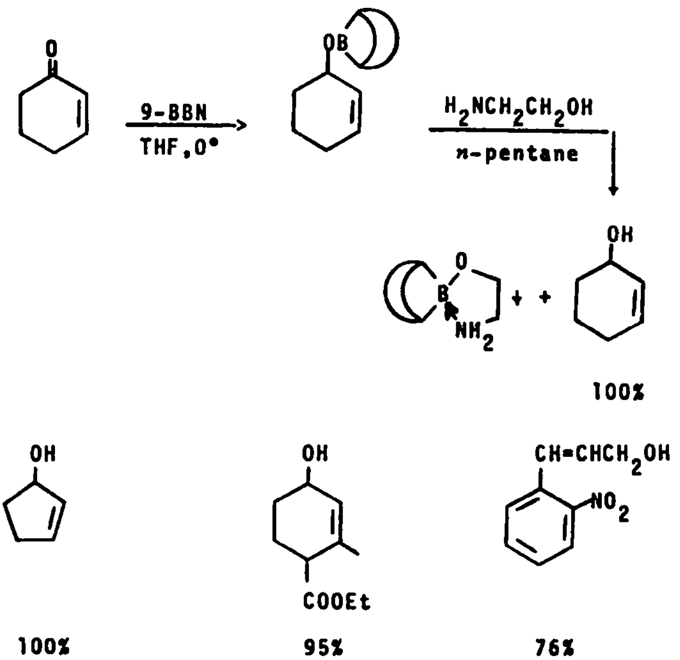
R	e.e. %	Config.
Et	13.5	S
i-Pr	37.0	S
t-Bu	20.0	S
Ph	9.0	R

Even more important, this new reagent achieves the asymmetric hydroboration of *cis*-2-butene to give after oxidation 2-butanol in an optical purity as high as 98.5%[113] (Eqn 155).



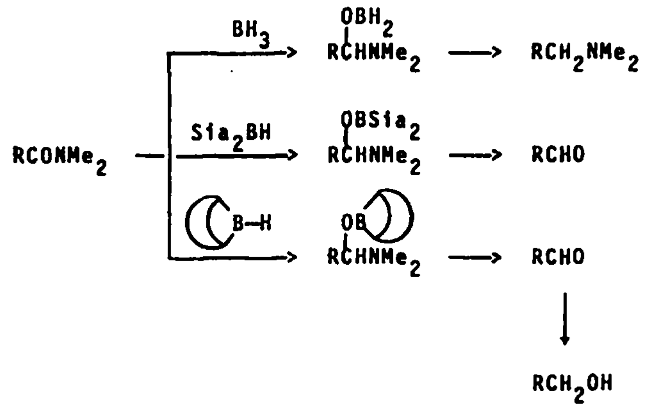
(155)

9-Borabicyclo[3.3.1]nonane reduces α,β-unsaturated aldehydes and ketones rapidly and quantitatively to the corresponding allylic alcohols. The development of a unique non-aqueous work-up procedure renders possible the isolation of the alcohols in excellent yields. Unlike the conventional reagents, the mildness of 9-BBN permits the presence of almost any other functional group such as ester, amide, carboxylic acid, nitro, halogen, nitrile, etc.[119] (Eqn 156).



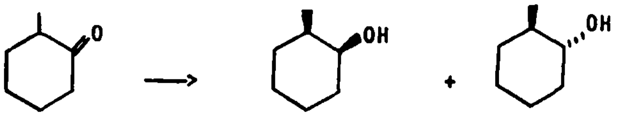
(156)

Reduction of tertiary amides to alcohols represents another promising area of application for 9-BBN, yet to be explored in detail. It should be pointed out that we are now in a position to control the course of this reaction using various reagents to get three different products (Eqn 157).



(157)

Dialkylboranes are consistent reagents for introducing steric control in the reduction of cyclic ketones. Increasing the size of the alkyl substituent(s) on boron enhances the stereoselectivity dramatically[120] (Eqn 158).



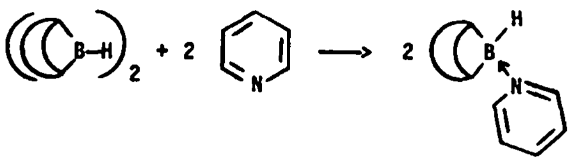
(158)

BH_3	74%	26%
9-BBN	40%	60%
Sia_2BH	79%	21%
$CHex_2BH$	94%	6%
IPC_2BH	94%	6%

The reagents are remarkably consistent in directing the reduction of both 2-alkylcycloalkanones and bicyclic ketones from the less hindered side to yield predominantly the less stable of the two possible isomers.

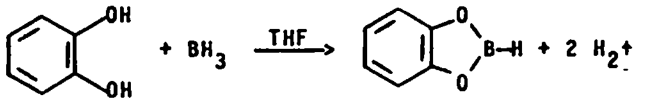
	Less stable isomer, %		
Ketone	$LiAlH_4$	BH_3	IPC_2BH
2-Methylcyclobutanone	25	41	83
2-Methylcyclopentanone	21	25	94
2-Methylcyclohexanone	25	26	94
2-Methylcycloheptanone	73	74	98
2-Methylcyclooctanone	73	82	98
Norcamphor	90	98	94
Camphor	90	52	100

Recently, 9-borabicyclo[3.3.1]nonane-pyridine complex has been found to reduce selectively aldehydes in the presence of keto and many other functional groups[121] (Eqn 159).



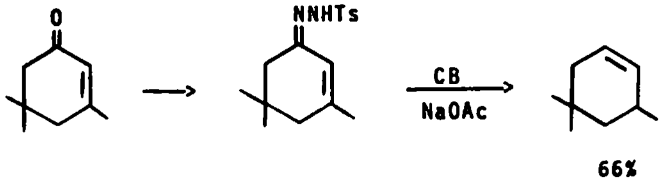
(159)

C. *Alkoxyborane.* Catechol reacts with borane to produce a new useful reducing agent, catecholborane (CB)[122,123] (Eqn 160).

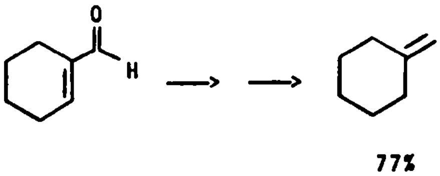


(160)

The reducing characteristics of this new reagent has been explored in detail.[124] The reagent is quite useful for the deoxygenation of α,β-unsaturated aldehydes and ketones through the reduction of their tosylhydrazones[125] (Eqn 161 and 162).



(161)



(162)

D. *Haloboranes*. Procedures have been developed for the convenient synthesis of mono- and dichloroboranes[126] (Eqns 163–166).

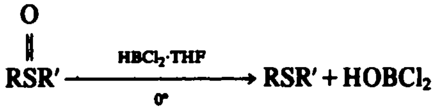
$$2BH_3+BCl_3 \xrightarrow[0°]{\text{THF, THP}} 3BH_2Cl \tag{163}$$

$$BH_3+2BCl_3 \xrightarrow[0°]{\text{THF-THP}} 3BHCl_2 \tag{164}$$

$$2BH_3\cdot SMe_2+Cl_3B\cdot SMe_2 \xrightarrow{25°} 3H_2BCl\cdot SMe_2 \tag{165}$$

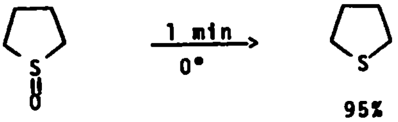
$$BH_3\cdot SMe_2+2Cl_3B\cdot SMe_2 \xrightarrow{25°} 3HBCl_2\cdot SMe_2. \tag{166}$$

Aliphatic sulfoxides are rapidly deoxygenated to the corresponding sulfides in excellent yields by dichloroborane in tetrahydrofuran at 0° in a matter of minutes. The reaction can tolerate a variety of other reactive functional groups such as ketone, ester, amide, etc.[127] (Eqns 167–170).



$$R\overset{\overset{O}{\|}}{S}R' \xrightarrow[0°]{HBCl_2\cdot THF} RSR'+HOBCl_2 \tag{167}$$

$$(CH_3)_2S{=}O \xrightarrow[0°]{1\ \text{min}} \underset{99\%}{(CH_3)_2S} \tag{168}$$



(169)

$$(Ph)_2S{=}O \xrightarrow[25°]{24\ \text{h}} \underset{90\%}{(Ph)_2S}. \tag{170}$$

E. *Alane*. Aluminum hydride prepared by the reaction of lithium aluminum hydride and aluminum chloride in ethyl ether is unstable and tends to polymerize.[28,128] A convenient method for preparing aluminum hydride solution is the addition of the calculated quantity of 100% sulfuric acid to a standardized solution of lithium aluminum hydride in tetrahydrofuran[129] (Eqns 171–173).

$$3LiAlH_4 + AlCl_3 \xrightarrow{Et_2O} 3LiCl\downarrow + 4AlH_3\downarrow \quad (171)$$

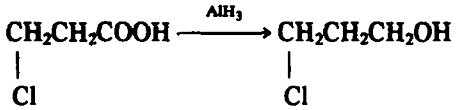
$$3LiAlH_4 + AlCl_3 \xrightarrow{THF} 3LiCl + 4AlH_3 \quad (172)$$

$$2LiAlH_4 + H_2SO_4 \xrightarrow{THF} Li_2SO_4 + 2AlH_3 + 2H_2\uparrow . \quad (173)$$

Application of the reagent at 0° in THF to the standard group of compounds led to the following reactivity:[129]

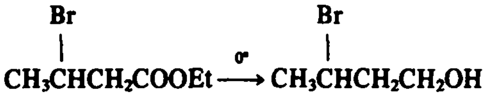
aldehyde → alcohol
ketone → alcohol
acid chloride → alcohol
lactone → glycol
epoxide → alcohol
ester → alcohol
carboxylic acid → alcohol
carboxylic acid salt → alcohol
tert-amide → amine
nitrile → amine
nitro → very slow reaction
olefin → no reaction.

Aluminum hydride offers promise for the selective reduction of carboxylic acid esters to the corresponding alcohols in the presence of halogen and nitro substituents[130] (Eqns 174–176).



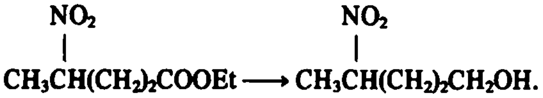
$$\underset{\displaystyle |\atop Cl}{CH_2}CH_2COOH \xrightarrow{AlH_3} \underset{\displaystyle |\atop Cl}{CH_2}CH_2CH_2OH \quad (174)$$

89%



$$CH_3\overset{Br\atop |}{C}HCH_2COOEt \xrightarrow{0^\circ} CH_3\overset{Br\atop |}{C}HCH_2CH_2OH \quad (175)$$

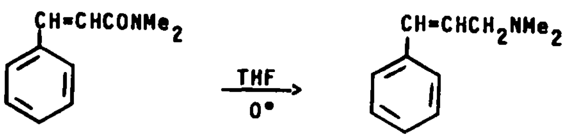
93%



$$CH_3\overset{NO_2\atop |}{C}H(CH_2)_2COOEt \longrightarrow CH_3\overset{NO_2\atop |}{C}H(CH_2)_2CH_2OH. \quad (176)$$

80%

The reagent is quite useful for the reduction of tertiary amides to the corresponding amines in excellent yields; the utility is especially evident for the reduction of amides containing unsaturation where borane–THF cannot be applied (Eqn 177).



(177)

$LiAlH_4$	0%
AlH_3	94%

Another important application of aluminum hydride is the clean reduction of nitriles such as allyl cyanide and benzyl cyanide where the α-position is doubly activated. The corresponding amines are obtained in excellent yields. Reduction with lithium aluminum hydride is often complicated by concurrent attack of lithium aluminum hydride on the activated α-hydrogen atom resulting in poor yields of the desired products (Eqns 178 and 179).

$$CH_2{=}CHCH_2CN \xrightarrow[25^\circ]{AlH_3} \underset{83\%}{CH_2{=}CHCH_2CH_2NH_2} \tag{178}$$

$$Ph_2CHCN \rightarrow \underset{98\%}{Ph_2CHCH_2NH_2}. \tag{179}$$

F. *Dialkylalanes.* Numerous interesting applications of diisobutylaluminum hydride as a selective reducing agent have been reported in the literature such as the selective reduction of α,β-unsaturated enones to the corresponding allylic alcohols,[131] reduction of carboxylic acid esters to the corresponding aldehydes,[132] etc.[133] Unfortunately, no systematic examination of the reducing characteristics of this reagent under standardized conditions is available at the present time.

VI. SUMMARY ON REDUCTIONS

The systematic exploration of the reducing characteristics of various hydride reagents that have evolved during the course of forty years (1939–1979) has led to the better understanding and appreciation of the scope and applicability of each reagent. The reactivities of hydride reagents toward various organic functional groups at 0–25° under standard conditions are summarized in Table 2. Symbol (+) indicates rapid reaction; symbol (−) indicates very slow or insignificant reaction; symbol (±) indicates a borderline case, the reactivity being sensitive to the structure of the functional group (both steric and electronic effects). A quick inspection of Table 2 reveals that by judicious choice of reducing agent it should be possible to reduce one group selectively in the presence of a second or to carry out the reverse operation.

For example, it should be possible to selectively reduce an acid chloride in the presence of an ester grouping with sodium borohydride or 9-BBN. On the other hand, an ester grouping should be selectively reducible in the presence of an acid chloride by borane–THF. Similarly, borane–THF will selectively

Table 2. Summary of behavior of various functional groups toward the hydride reagents

	NaBH$_4$ in ethanol	Li(O-t-Bu)$_3$AlH	NaBH$_4$ + LiCl in Diglyme	NaBH$_4$ + AlCl$_3$ in Diglyme	BH$_3$ in THF	Sia$_2$BH in THF	9-BBN in THF	AlH$_3$ in THF	Li(OMe)$_3$AlH in THF	LiAlH$_4$ in THF	LiEt$_3$BH in THF
Aldehyde	+	+	+	+	+	+	+	+	+	+	+
Ketone	+	+	+	+	+	+	+	+	+	+	+
Acid chloride	R	+	+	+	−	−	+	+	+	+	+
Lactone	−	±	+	+	+	+	+	+	+	+	+
Epoxide	−	±	+	+	+	±	±	+	+	+	+
Ester	−	±	+	+	±	−	±	+	+	+	+
Acid	−	−	−	+	+	−	±	+	+	+	−
Acid salt	−	−	−	−	−	−	−	+	+	+	−
tert-Amide	−	−	−	−	+	+	+	+	+	+	+
Nitrile	−	−	−	−	+	−	±	+	+	+	+
Nitro	−	−	−	−	−	−	−	−	+	+	+
Olefin	−	−	−	−	+	+	+	−	−	−	−

R = Reacts with solvent; reduced in non-hydroxylic solvent reduce the carboxylic acid group in the presence of an ester grouping; the reverse operation, selective reduction of an ester group in the presence of a carboxylic acid group can be achieved by lithium borohydride or lithium triethylborohydride. However, a word of caution is in order. The reactivities of the various functional groups can be greatly altered by the structures containing them. Consequently, these generalizations must be used with caution in predicting the behavior of greatly modified systems.

VII. CONCLUSIONS

Forty years ago it was first discovered that diborane reduces aldehydes and ketones rapidly. Unfortunately, the chemical rarity of diborane at the time prevented organic chemists from utilizing this reagent as a reducing agent. Subsequently, the development of practical synthetic routes to diborane, the discovery of sodium borohydride, and later, of lithium aluminum hydride made such hydride reducing agents readily available to the organic chemist. There then resulted rapid progress in the development of new reducing agents and in the exploration of their scope and applicability in organic synthesis. Still we are in constant search of new selective reducing agents that are capable of reacting with a specific functional group in the presence of other functional groups. Today an organic chemist has a choice of specific hydride reagents for achieving specific synthetic transformation. Even more important, the majority of these reagents are now commercially available to facilitate application of these new reagents by chemists.[134]

Finally, the primary objective of this review was to trace major developments, largely in our own research program, which led from the initial observation of the reducing action of a hydride, diborane, to the present time when we have numerous reagents, methods, and applications based on such hydrides for selective reductions in organic chemistry. It should be pointed out that many other workers have contributed to the present state of hydride reductions. It is unfortunate that the special objectives of the present review made it impossible to do full justice to their individual contributions.

VIII. EPILOGUE

It is evident from this review that the senior author provides an unambiguous example of the oft criticized research worker who continues extending his Ph.D. Thesis for many, many years—forty years in this case, with the end not yet in sight. However, it has been a most fruitful journey. And there is an intense pleasure in observing a field of knowledge and practice develop from almost nothing into a major area of which every organic chemist engaged in synthesis must be familiar. Moreover, the field of hydride reductions provides a beautiful example of how such major new areas can develop from inauspicious beginnings. Here also it is not inappropriate to quote, as was done earlier for the hydroboration area:[135]

"Tall oaks from little acorns grow."

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$$AlCl_3 + NaBH_4 \xrightleftharpoons{\text{Diglyme}} NaCl_3Al \cdot BH_4$$

$$NaCl_3Al \cdot BH_4 + NaBH_4 \rightarrow NaAlCl_3H + NaB_2H_7.$$

Further reaction will only proceed if this system is disturbed; see H. Nöth, *Proc. Hydride Symposium II*, p. 51. Metalgesellschaft AG, Frankfurt (1974).

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