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Lithium Aminoborohydrides: Powerful, Selective, Air-Stable Reducing Agents

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Abstract:

Lithium aminoborohydrides (LABs) are a new class of powerful, selective, air-stable reducing agents. LABs can be prepared as solids, as 1-2 M THF solutions, or generated in situ for immediate use. LABs can be synthesized from any primary or secondary amines, hence permitting control of the steric and electronic environment of these reagents. Solid LAB reagents can be used in dry air as easily as sodium borohydride and maintain their chemical activity for at least 6 months when stored under nitrogen or dry air at 25 °C. THF solutions of LABs retain their chemical activity for at least 9 months when stored under N_2 at 25 °C. LAB reagents are non-pyrophoric and only liberate hydrogen slowly in protic solvents above pH 4. LABs reduce aromatic and aliphatic esters at 0 °C in air. Tertiary amides are selectively reduced to the corresponding amine or alcohol, depending on the steric environment of the LAB. α,β-Unsaturated aldehydes and ketones undergo selective 1,2-reduction to the corresponding allylic alcohols. Aliphatic and aromatic azides are readily reduced to the corresponding primary amines using only 1.5 equiv of LAB. A novel tandem amination/reduction reaction has been developed in which 2-(*N,N*-dialkylamino)benzylamines are generated from 2-halobenzonitriles and lithium *N,N*-dialkylaminoborohydride (LAB) reagents. These reactions are believed to occur through a tandem S_NAr amination/reduction mechanism wherein the LAB reagent promotes halide displacement by the *N,N*-dialkylamino group and the nitrile is subsequently reduced. The (*N,N*-dialkylamino)benzylamine products of this reaction are easily isolated after a simple aqueous workup procedure in very good to excellent yields. Lithium aminoborohydride reagents initiate the amination *or* reduction of alkyl methanesulfonate esters, as dictated by reaction conditions. Alkyl methanesulfonate esters treated with unhindered LABs provide tertiary amines in excellent yield. Reduction to the corresponding alkane is achieved by using a hindered LAB reagent or by forming the highly reactive Super-Hydride reagent in situ using LAB and a catalytic amount of triethylborane.

Introduction

Since the discovery of lithium aluminum hydride ($LiAlH_4$) in 1947,[1] enormous effort has been invested in the development of safe and convenient alternatives[2] to this useful but highly reactive reagent.[3] Unfortunately, any increase in the stability of the new hydride reagents was accompanied by an even greater decrease in reactivity. Sodium bis(2-methoxy)aluminum hydride, developed in 1969 and commercially available as Vitride,[4] is a significant improvement over $LiAlH_4$. Vitride is non-pyrophoric, yet retains the reactivity of $LiAlH_4$. Unfortunately, the byproduct of Vitride, monomethoxyethanol, is a known teratogen.[4d] In 1961, the synthesis and the characterization of the reducing properties of sodium aminoborohydrides were reported.[5] Many of the functional groups reduced by $LiAlH_4$ were also reduced by sodium aminoborohydrides. These reagents were reported to reduce aldehydes and ketones to alcohols, esters to alcohols, and primary amides to amines in good to excellent yields. Several anomalous reactions were also reported with sodium dimethylaminoborohydride in which the dimethylamine portion of the reagent was transferred to give the corresponding tertiary amine. However, no further work has appeared in the literature on the use of sodium aminoborohydride reducing agents, and the goal of powerful, air-stable reducing agents seemed to be as elusive as ever. However, in 1990, the serendipitous discovery[6,7b] and subsequent characterization of the reducing properties of lithium aminoborohydrides (LAB)[6d] radically altered this picture.

The Discovery of Lithium Aminoborohydrides

During our work on the hydroboration of β,β-disubstituted enamines, we were puzzled by the unexpected formation of dihydridoaminoboranes in the reaction product (Scheme 1).[7a,b]

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§ CTG Consulting.

(1) (a) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 1197. (b) Finholt, A. E.; Bond, A. C., Jr.; Schlesinger, H. I. *J. Am. Chem. Soc.* **1947**, *69*, 1199. (c) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 2548. (d) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1948**, *70*, 3738. (e) Block, J.; Gray, H. P. *Inorg. Chem.* **1965**, *4*, 304.

(2) (a) Brown, H. C. *Hydroboration*; Benjamin-Cummings: Reading, 1980; pp 296−297. (b) Brown, H. C.; Mead, E. J. *J. Am. Chem. Soc.* **1953**, *73*, 6263. (c) Brown, H. C.; Subba-Rao, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 2582. (d) Brown, H. C.; Mead, E. J.; Schoaf, C. J. *J. Am. Chem. Soc.* **1956**, *78*, 3616. (e) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567. (f) Walker, E. R. H. *Chem. Soc. Rev.* **1976**, *5*, 23. (g) Brown, H. C.; Singaram, S.; Singaram, B. *J. Organomet. Chem.* **1982**, *239*, 43. (h) Golden, J. H.; Schreier, C.; Singaram, B.; Williamson, S. M. *Inorg. Chem.* **1992**, *31*, 1533.

(3) (a) Hudlicky, M. *Reductions in Organic Chemistry*; Ellis Horwood: Chichester, 1984; pp 20 and references cited therein. (b) Hajos, A. *Complex Hydrides*; Elsevier: New York, 1979; pp 83-86 and references cited therein.

(4) (a) Capka, M.; Chvalovsky, V; Kochloefl, K.; Kraus, M. *Collect. Czech. Chem. Commun.* **1969**, *34*, 118. (b) Cerny, V.; Malek, J.; Capka, M.; Chvalovsky, V. *Collect. Czech. Chem. Commun* **1969**, *34*, 1025. (c) Vit, J. *Eastman Org. Chem. Bull.* **1970**, *42*, 1. (d) Lerga, R. E., Ed. *The Sigma-Aldrich Library of Chemical Safety Data*, 1st ed.; Aldrich Chemical Co.: Milwaukee, 1985; p 1182.

(5) (a) The first synthesis of *sodium* aminoborohydrides was reported in 1961. Aftandilian, V. D.; Miller, H. C.; Muetterties, E. L. *J. Am. Chem. Soc.* **1961**, *83*, 2471. (b) Hutchins, R. O.; Learn, K.; El-Telbany, F.; Stercho, Y. P. *J. Org. Chem.* **1984**, *49*, 2438. (c) Keller, P. C. *J. Am. Chem. Soc.* **1969**, *91*, 1231.

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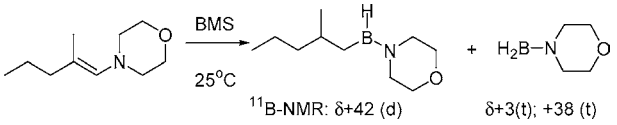
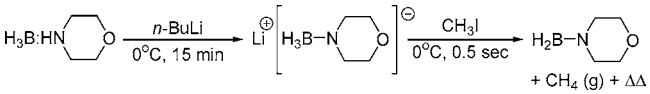
Scheme 1. **Hydroboration of *β,β*-disubstituted enamines**



Scheme 2. **Synthesis of dihydridoaminoboranes**



In order to verify this result we needed authentic samples of these aminoboranes. Consequently, we developed a new method for the synthesis of dihydridoaminoboranes (Scheme 2).[7]

Reaction of *n*-butyllithium or methyllithium with amine−borane complexes, $H_3B{:}NHR_2$, in THF, readily afforded the corresponding LABs in quantitative yields. When each of these LABs were quenched with methyl iodide at 0 °C, a violent, exothermic reaction ensued and gave the corresponding aminoboranes in high purity as determined by ^{11}B NMR (Scheme 2). Methyl iodide was known to react in such a vigorous fashion only with $LiAlH_4$ and lithium triethylborohydride ($LiEt_3BH$).[2e] This reaction suggested that the LABs were a new type of powerful reducing agent, comparable in reducing power to $LiAlH_4$ and $LiEt_3BH$.

Characterization of Spectral and Physical Properties. The method used for synthesizing LABs, shown in Scheme 2, is general, and a wide variety of amino groups are readily accommodated. Following this procedure, several representative LABs were prepared (Figure 1).

We have found two diagnostic criteria for determining the purity of LABs: ^{11}B NMR coupling constants and the reaction of LABs with methyl iodide. Although both LAB reagents and their corresponding amine−borane precursors appear as sharp quartets with virtually identical chemical shifts in their respective ^{11}B NMR spectra, the coupling constants of the LABs and the corresponding amine−boranes are quite different. The LAB reagents exhibit ^{11}B NMR *J* values of between 82 and 87 Hz. In contrast, amine−boranes have coupling constants ranging from 95−98 Hz. Additionally, LAB reagents react vigorously and exothermically with methyl iodide to liberate methane and the corresponding dihydridoaminoborane. Amine−borane complexes, however, are unreactive towards methyl iodide.

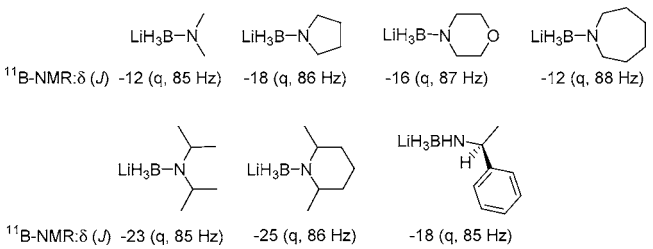


Figure 1. **LAB reagents.**

Synthesis of THF Solutions of Lithium Aminoborohydrides. THF solutions (1−2 M) of the LABs are quite stable and can be stored under nitrogen at 25 °C for at least 9 months without undergoing any decomposition or loss of hydride activity as determined by ^{11}B NMR.

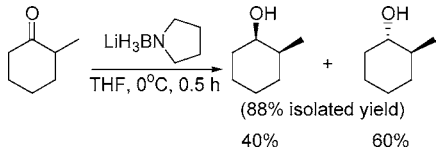
Safety Considerations.[6d−g] When synthesizing solid LABs, *it is essential that* ***no trace of n-BuLi remains*** *in the LAB*! Residual *n*-BuLi acts as a "fuse" and will cause the LAB to ignite in air. We have found that *use of a substoichiometric amount of n-BuLi (**0.95 equiv**) ensures that the resulting solid LAB is completely non-pyrophoric*. However, when generating LABs in situ, equimolar amounts of amine−borane and *n*-BuLi are routinely employed with no resulting safety problems. Acidic compounds which have a pK_a <4.0 react readily with LABs, liberating hydrogen. However, unlike the violent and potentially dangerous reaction of $LiAlH_4$ with water or methanol, hydrogen was liberated only slowly during the reaction of LABs with these solvents. Moreover, LABs were converted to the unreactive amine−borane complex on addition to either methanol or water, as indicated by ^{11}B NMR spectra. LABs that were converted to the corresponding amine−boranes by prolonged deliberate exposure to air-borne moisture were readily regenerated by deprotonation, under nitrogen, with *n*-BuLi.

Characterization of Reducing Properties. We began a systematic study of the reducing properties of LABs using lithium pyrrolidinoborohydride ($LiPyrrBH_3$) as the representative reagent.[6d] Numerous types of functional groups were readily reduced, and the products were easily isolable by a simple acidic workup to eliminate contamination by boron-containing materials. Unlike other powerful reducing agents, once the LAB has been generated, either in situ or in solid form, reductions can be performed without any precautions to exclude air. However, the exclusion of adventitious moisture was essential to maximize the yields in reductions that require refluxing or more than 1 h to complete. Thus, we recommend carrying out such reductions in tetrahydrofuran (THF) under nitrogen or an atmosphere of dry air. Additionally, recent work using solid LABs has demonstrated that these reagents can be handled in dry air with the same ease as sodium borohydride ($NaBH_4$). Whether generated in situ or used in solid form, most reductions with LABs were complete in 2−3 h at ambient temperature, although some very hindered substrates required refluxing in THF for 2−3 h to achieve a reasonable yield of the desired product.

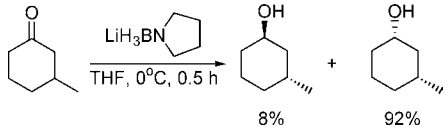
(6) (a) Fisher, G. B.; Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1992**, *33*, 4533. (b) Fuller, J. C.; Stangeland, E. L.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 257. (c) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 1091. (d) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378. (e) Singaram, B.; Fisher, G. B.; Fuller, J. C.; Harrison, J.; Goralski, C. T. U.S. Patent 5,466,798, 1995. (f) Under conditions of extremely high humidity (90−100%), lower molecular weight LABs were found to smolder and, occasionally, catch fire. However, the pyrophoricity is due to residual *n*-BuLi present in the LAB acting as a "fuse" on exposure to moist air rather than to any inherent pyrophoricity of the LAB. (g) The stability of LABs in THF solution at 25 °C was monitored by ^{11}B NMR. No accelerated rate calorimetry (ARC) studies or differential scanning calorimetry (DSC) studies have been done on THF solutions of LABs. The stability of LABs in THF solution at reflux has not been studied. It would be advisable to conduct either DSC or ARC studies, or both, on THF solutions of LABs prior to scale-up of processes employing these reagents.

(7) (a) Singaram, B.; Goralski, C. T.; Fisher, G. B. *J. Org. Chem.* **1991**, *56*, 5691. (b) Fisher, G. B.; Juarez-Brambila, J. J.; Goralski, C. T.; Wipke, W. T.; Singaram, B. *J. Am. Chem. Soc.* **1993**, *115*, 440. (c) Fisher, G. B.; Nicholson, L. W.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 7693.

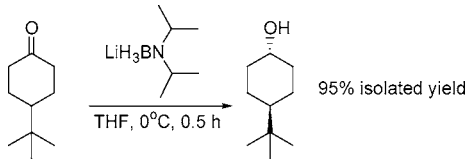
Scheme 3. **Reduction of 2-methylcyclohexanone with $LiPyrrBH_3$**



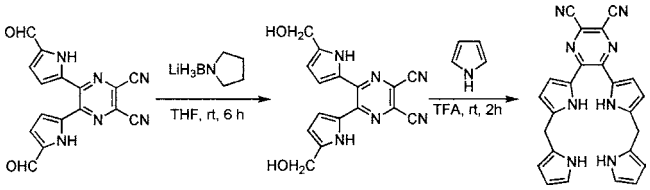
Scheme 4. **Reduction of 3-methylcyclohexanone**



Scheme 5. **Reduction of 4-*tert*-butylcyclohexanone**



Scheme 6. **Synthesis of dipyrrolylquinoxaline analogues**



Reduction of Aldehydes and Ketones. Aldehydes and ketones are easily reduced to corresponding alcohols. The reduction is generally complete in 15−30 min at 0 °C.[6d] For example, the reduction of 2-methylcyclohexanone with $LiPyrrBH_3$ gave a 40:60 ratio of *cis*- to *trans*-2-methylcyclohexanol in 88% isolated yield (Scheme 3).

Reduction of aromatic ketones was straightforward as well. Only one equivalent of LAB was required to reduce aliphatic and aromatic ketones and aldehydes. The stereoselectivity of LAB reductions of 3-substituted cyclohexanones indicates that LABs behave like unhindered hydride reagents, regardless of the size of the amine moiety. For instance, the reduction of 3-methylcyclohexanone produced *cis*-3-methylcyclohexanol as the major product (Scheme 4).[8]

Additionally, the reduction of 4-*tert*-butylcyclohexanone using lithium di-isopropylamino borohydride ($LiH_3BN(i\text{-}Pr)_2$) gave 99% *trans*-4-*tert*-butylcyclohexanol in 95% isolated yield (Scheme 5).

The simple synthesis and mild reaction conditions prompted some researchers to utilize LAB reagent in their work. In 2003, Sessler[9] et al. reported the synthesis of a new set of dipyrrolyl pyrazines utilizing lithium pyrrolidinoborohydride. The pyrazine oligopyrroles are anion receptors for various biologically important anions (Scheme 6).

Chiral LAB Reducing Agents. To date, there has been only one report in the literature describing chiral LABs and their use as reducing agents. In 1995, Kagan et al.[10] reported the preparation of two chiral lithium dialkoxyaminoborohydrides. These reagents readily reduced methyl iodide to methane (Scheme 7).

Unfortunately, reduction of acetophenone with these reagents afforded 1-phenylethanol with only 5−9% ee (Scheme 8).

Reduction of α,β-Unsaturated Aldehydes and Ketones. α,β-Unsaturated aldehydes and ketones were reduced with remarkable regioselectivity to the corresponding allylic alcohols. Although other reagents are known that give high 1,2:1,4 reduction ratios,[11] LABs are the only reducing agents that give exclusive 1,2-reduction of both α,β-unsaturated aldehydes and ketones. These results are complementary to those obtained using $LiAlH_4$ and the Luche reagent.[9] For example, the reduction of cinnamaldehyde using $LiAlH_4$ gave exclusively the corresponding unsaturated alcohol. Although the Luche reagent ($NaBH_4/CeCl_3$) gives exclusive 1,2-reduction of α,β-unsaturated ketones, it does not reduce α,β-unsaturated aldehydes. In contrast, $LiPyrrBH_3$ reduces cinnamaldehyde exclusively to the 1,2-reduction product in 95% isolated yield (Scheme 9).

(*R*)-(+)-Pulegone was reduced to the corresponding allylic alcohol, (1*R*,3*R*)-(−)-*cis*-pulegol, in 96% isolated yield (Scheme 10). Similarly, (*R*)-(−)-carvone was reduced to (1*R*,5*R*)-(−)-*cis*-carveol.

The chemoselectivity of LAB can be demonstrated on the reduction of Hagemann's ester (4-carbethoxy-3-methyl-2-cyclohexen-1-one).[6d] Only the α,β-unsaturated ketone functionality is reduced with one equivalent of $LiPyrrBH_3$, leaving the ester moiety intact (Scheme 11).

The ability of LABs to reduce α,β-unsaturated ketones to the corresponding allylic alcohol was utilized by Marshall et al. in a key step in the synthesis of rubifolide (Scheme 12).[12]

Reduction of Carboxylic Acid Esters. Although, several reducing agents are available for the reduction of esters to the corresponding alcohols,[13] all practical methodologies require the rigorous exclusion of air during the reduction. In contrast, LABs rapidly reduce both aliphatic and aromatic esters in the presence of air.[6d] For instance, ethyl octanoate was reduced, in air, to the corresponding alcohol in just 30 min at 0 °C with an isolated yield higher than 90% (Scheme 13).

Furthermore, reduction of ethyl cinnamate afforded exclusively the 1,2-reduction product, cinnamyl alcohol, in 95% isolated yield (Scheme 14). Mild reaction conditions, short reaction times, and chemoselectivity of LABs make these reagents excellent alternatives for carrying out the reduction of aliphatic or aromatic esters.[6d,10]

Recently, Braslau[14] et al. reported a new methodology for the synthesis of the *N*-alkoxyamines, which can be used as initiators in "living" free radical polymerization. Chemoselective reduction of the ester using lithium aminoborohy-

(8) For a review of the factors affecting the stereochemistry of hydride reductions of substituted cyclohexanones, see: Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449.

(9) Sessler, J. L.; Pantos, G. D.; Kataeyv, E.; Lynch, V. M. *Org. Lett.* **2003**, *5*, 4141.

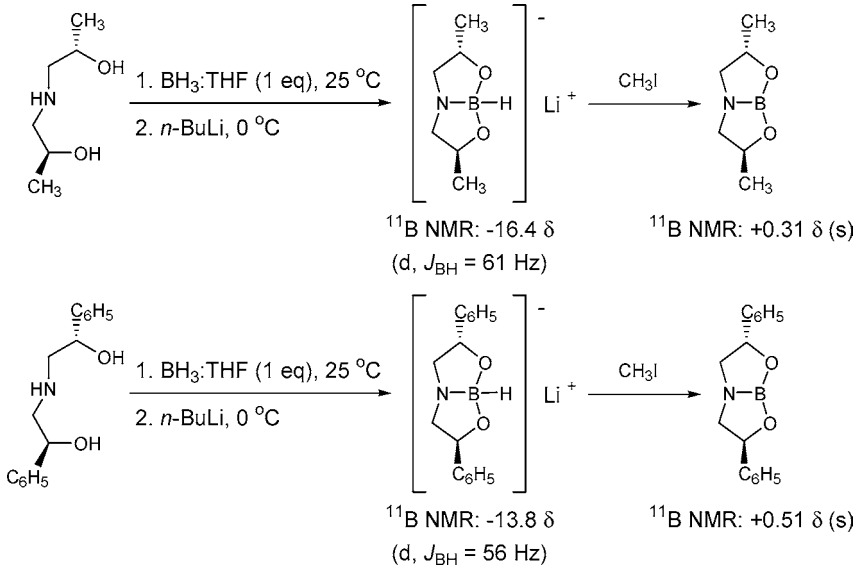
(10) Dubois, L.; Fiaud, J.-C.; Kagan, H. B. *Tetrahedron* **1995**, *51*, 3803.

(11) Please see ref 6d, footnote 8.

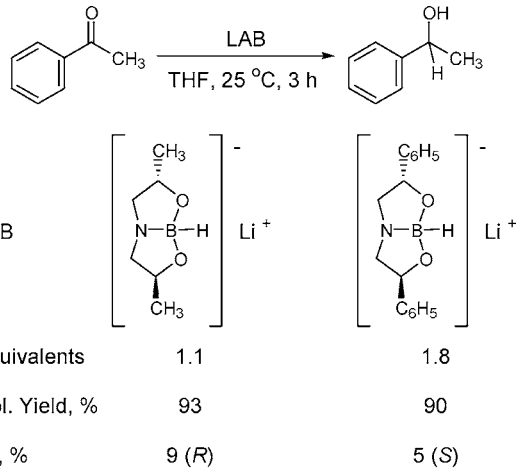
(12) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4318.

(13) (a) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153. (b) Brown, H. C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604. (c) Brown, H. C.; Mathew, C. P.; Pyun, C.; Son. J. C.; Yoon, N. M. *J. Org. Chem.* **1984**, *49*, 3091. (d) Yoon, N. M.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 2927. (e) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 1197.

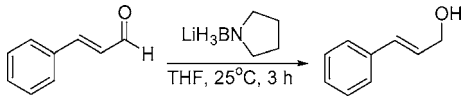
Scheme 7. **Synthesis of chiral LABS**



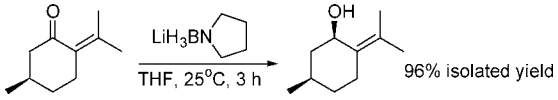
Scheme 8. **Reduction of acetophenone with chiral LAB**



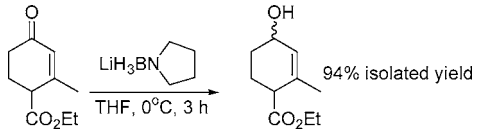
Scheme 9. **Reduction of cinnamaldehyde**



Scheme 10. **Reduction of (*R*)-(+)-pulegone**



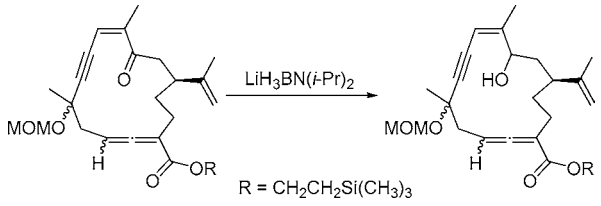
Scheme 11. **Reduction of α,*β*-unsaturated ketone in the presence of an ester**



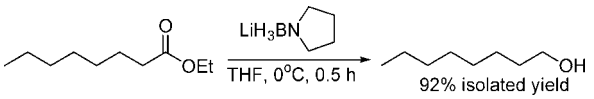
dride reagent (LAB) produced the corresponding *N*-alkoxyamine alcohol in 47% yield (Scheme 15). The free hydroxyl group can be used to append a variety of species onto the initiator or to anchor the initiator onto a solid support.

(14) Braslau, R.; Tsimelzon, A.; Gewandter, J. *Org. Lett.* **2004**, *6*, 2233.

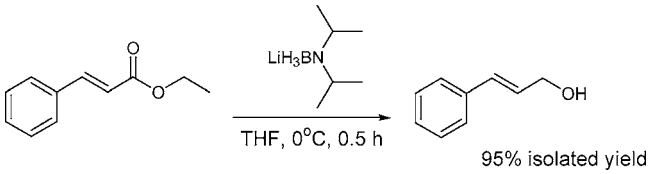
Scheme 12. **Reduction of α,*β*-unsaturated ketone in the synthesis of rubifolide**



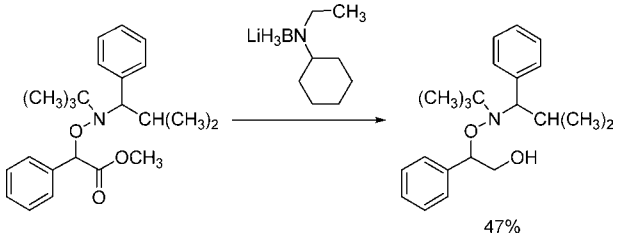
Scheme 13. **Reduction of octanoate**



Scheme 14. **Reduction of ethyl cinnamate**



Scheme 15. **Reduction of *N*-alkoxyamine ester**



Reduction of Tertiary Amides. LAB reagents do not reduce primary and secondary amides even in refluxing THF. Conversely, a wide variety of aromatic and aliphatic tertiary amides are reduced in excellent yield in dry air with LABs.[6c,d] The reduction of unhindered tertiary amides, such as *N*,*N*-dimethylbenzamide, gave benzyl alcohol regardless of the LAB used. However, for more sterically demanding tertiary amides, selective C−O or C−N bond cleavage[15] was achieved by varying the steric environment of the amine

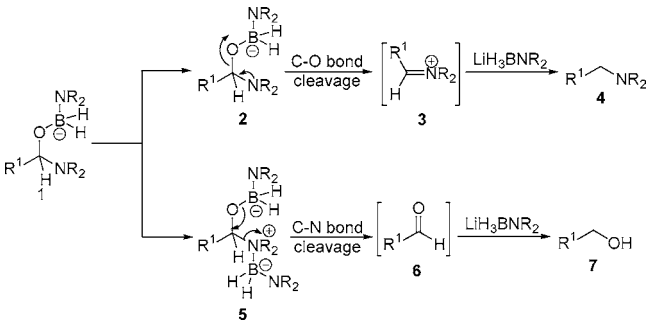
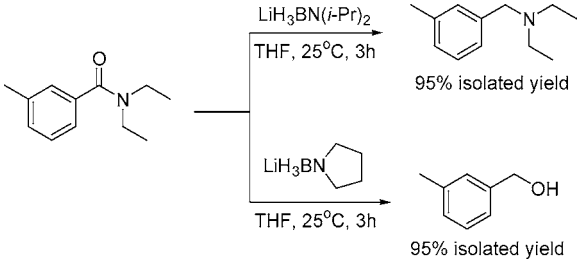


Figure 2. **Mechanism of the reduction of 1-pyrrolidinooctanamide leading to amine or alcohol.**

Scheme 16. **Reduction of 1-pyrrolidinooctanamide to tertiary amine or alcohol**



moiety of the LAB. For example, reduction of 1-pyrrolidinooctanamide with $LiPyrrBH_3$ gave 1-octanol in 77% isolated yield. When the reduction of 1-pyrrolidinooctanamide was carried out with the significantly more sterically demanding LAB, $LiH_3BN(i\text{-}Pr)_2$, 1-octylpyrrolidine was obtained in 95% isolated yield. Similarly, reduction of *N*,*N*-diethyl-*m*-toluamide with LiH_3 $BN(i\text{-}Pr)_2$ gave 3-methyl-*N*,*N*-diethylbenzylamine in 95% isolated yield, whereas reduction of this amide with $LiPyrrBH_3$ gave 3-methylbenzyl alcohol in 95% isolated yield (Scheme 16).

The selectivity of this reduction appears to involve a common intermediate, **1**, obtained as the initial reduction product of the amide (Figure 2).[6d,11k]

From the intermediate **1**, two different pathways lead to the corresponding amine or alcohol. In the first, the iminium species, **3**, is formed by the expulsion of the lithium dihydridoaminoborinate, **2**. LAB then rapidly reduces the iminium group to the corresponding amine, **4**. In the second pathway, the complexation of an aminoborane to the nitrogen of **1** converts the amine to an ammonium moiety, **5**, making it a better leaving group. Expulsion of the diaminodihydridoborohydride moiety results in the formation of an aldehyde, **6**, which is rapidly reduced to the corresponding alcohol, **7**. We found that the outcome of these reductions depends on the sterics of the amide as well as of the LAB reagent. As the groups bonded to the amide or LAB nitrogen are made more sterically demanding, amine formation through C−O bond cleavage is favored. This is probably due to the unfavorable steric interactions between the LAB and the amide nitrogen. Whereas reductions performed with $LiAlH_4$ give mainly C−O bond cleavage and those carried out with $LiEt_3BH$[11k] give C−N bond cleavage, LABs offer selective C−O or C−N bond cleavage by simply altering the steric environment of the amine moiety of the LAB.

Myers et al. described a practical synthesis of chiral alcohols that employed pseudoephedrine as a chiral auxiliary.[16a] An amide of pseudoephedrine is first deprotonated with LDA and then alkylated with the appropriate alkyl halide to give the substituted amide with 97−99% de. The amide is then reduced to the alcohol with lithium pyrrolidinoborohydride to give the desired chiral alcohol in high chemical yield and greater than 97−99% ee (Scheme 17, Table 1).

Although the reduction was problematic for R = Ph and R′ = Et, the use of LiH_3BNH_2 in THF gave the desired primary alcohol in 80% yield and 88% ee. In the last entry of Table 1, it is noted that the reduction had to be done with lithium amidoborohydride (LiH_3BNH_2).

Lithium amidoborohydride is now widely used for the removal of Evans' chiral auxiliary and for reduction of amides to the corresponding alcohols. For example, Theodorakis and co-workers successfully employed lithium amidoborohydride (LiH_3BNH_2) to reduce an amide to the corresponding alcohol in their synthesis of borelledin (Scheme 18).[17]

Reduction of Lactams. Various five- and six-membered *N*-alkyl lactams were reduced to the corresponding cyclic amines using lithium dimethylaminoborohydride.[18] Most of the reductions were complete after refluxing in THF for 2 h. The cyclic amine products were easily isolated after an aqueous workup in very good to excellent yields. For example, 1-dodecyl-2-pyrrolidinone was reduced to the corresponding amine in 96% isolated yield (Scheme 19).

It is possible to selectively reduce sensitive functionalities with LAB reagent in the presence of a lactam. Stirring with 1.1 equiv of LiH_3BNMe_2 at −10 °C reduces the ester in methyl 1-benzyl-2-oxopyrrolidine-4-carboxylate without affecting the lactam, thus giving the alcohol product (Scheme 20).[18]

Reduction of Epoxides. Epoxides were readily reduced to the corresponding alcohols with $LiPyrrBH_3$. Unlike sodium borohydrides, LAB reagents do not transfer their amine moiety in the reaction with epoxides; therefore, no amino alcohols were formed in this reduction. Styrene oxide gave predominantly 1-phenylethanol. Additionally, cyclohexene oxide was reduced to cyclohexanol (Scheme 21).

Reduction of Azides. Synthesis of primary amines by the reduction of azides is an important transformation in organic synthesis.[19] Azides are commonly reduced either by

(15) $LiAlH_4$: (a) Uffer, H.; Schlitter, E. *Helv. Chim. Acta* **1948**, *31*, 1397. (b) Gaylord, N. G. *Reductions With Complex Metal Hydrides*; Wiley-Interscience: New York, 1956; pp 544−592. (c) Zabicky, J., Ed. *The Chemistry of Amides*; Wiley-Interscience: New York, 1970; pp 795−801. Borane: (d) Brown, H. C.; Heim, P. *J. Am. Chem. Soc.* **1964**, *86*, 3566. (e) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912. (f) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 441. (g) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 996. $NaBH_4$. (h) Borch, R. F. *Tetrahedron Lett.* **1968**, 61. (i) Satoh, T.; Suzuki, S. *Tetrahedron Lett.* **1969**, 4555. (j) Rahman, A. U.; Basha, A.; Waheed, N. *Tetrahedron Lett.* **1969**, 219. $LiEt_3BH$: (k) Brown, H. C.; Kim, S. C. *Synthesis* **1977**, 635. This paper also reported the first observation of competing C−O vs C−N bond cleavage in the reduction of tertiary amides. However, $LiEt_3BH$ gives predominantly C−N bond cleavage only for aromatic *N*,*N*-dimethylamides.

(16) (a) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361. (b) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623.

(17) Vong, B. G.; Abraham, S.; Xiang, A. X.; Theodorakis, E. A. *Org. Lett.* **2003**, *5*, 1620.

(18) Flankien, J. M.; Collins, C. J.; Lanz, M.; Singaram, B. *Org. Lett.* **1999**, *1*, 799.

(19) Sheradsky, T. *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley-Interscience: New York, 1971; Chapter 6.

Scheme 17. **Reduction of amide to remove chiral auxiliary**

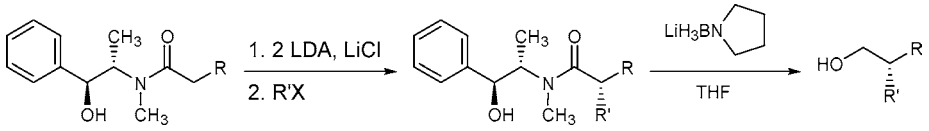
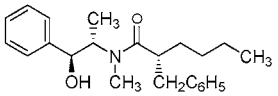
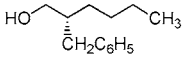
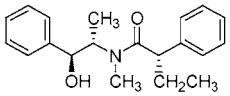
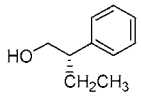
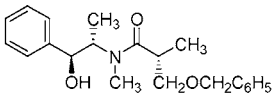
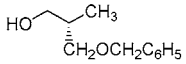
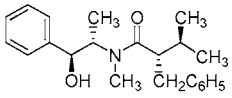
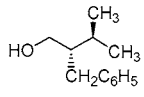
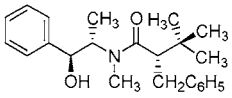
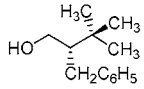
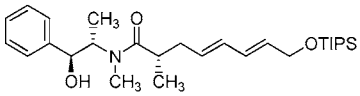
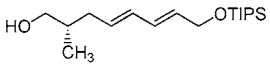


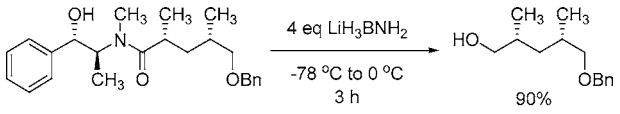
Table 1. **Reduction[a] of amides: synthesis of chiral alcohols**

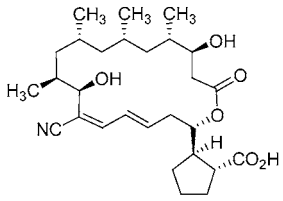
Amide	de, %	Alcohol	Yield, %	ee, %
	99		92	³95
	99		90	90
	98		88	93
	99		88	³95
	99		91	³95
	95		84	94

Reactions run with LiH_3BNH_2 (4.0-4.5 equiv) generated in situ at 0 °C.

[a] Reactions run with LiH_3BNH_2 (4.0−4.5 equiv) generated in situ at 0 °C.

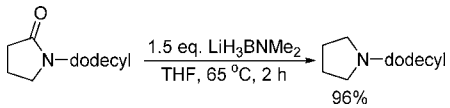
Scheme 18. **Removal of Evans' chiral auxiliary**





borelledin

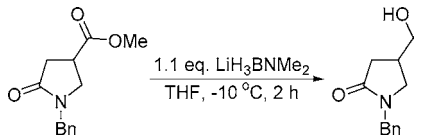
Scheme 19. **Reduction of 1-dodecyl-2-pyrrolidinone**



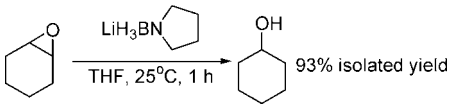
using an excess of $LiAlH_4$[20] or by catalytic hydrogenation,[21] although other methods have been developed.[22]

Lithium dimethylaminoborohydride ($LiH_3BN(Me)_2$) was employed for azide reductions to facilitate separation of the amine generated during workup from the primary amine

Scheme 20. **Reduction of ester in the presence of lactam**



Scheme 21. **Reduction of cyclohexene oxide**



reduction product. Aliphatic and aromatic azides were reduced to the corresponding primary amines with 1.5 equiv of $LiH_3BN(Me)_2$[23a] at 25 °C in THF. The reductions were complete within 2 to 5 h, depending on the electronic and steric environment of the azide. For example, the reduction of benzyl azide gave benzylamine in 85% isolated yield (Scheme 22).

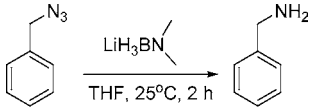
(20) (a) Boyer, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 5865. (b) Boyer, J. H.; Canter, F. C. *Chem. Rev.* **1954**, *54*, 1. (c) Hojo, H.; Kobayashi, S.; Soai, J.; Ikeda, S.; Mukaiyama, T. *Chem. Lett.* **1977**, 635. (d) Kyba, E. P.; John, A. M. *Tetrahedron Lett.* **1977**, 2737.

(21) Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590.

(22) (a) Pei, Y.; Wickham, B. O. S. *Tetrahedron Lett.* **1993**, *34*, 7509. (b) Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763. (c) Rolla, F. *J. Org. Chem.* **1982**, *47*, 4327. (d) Samano, M. C.; Robins, M. J. *Tetrahedron Lett.* **1991**, *32*, 6293. (e) Sarma, J. C.; Sharma, R. P. *Chem. Ind.* **1987**, *21*, 764. (f) Bayley, H.; Standring, D. N.; Knowles, J. R. *Tetrahedron Lett.* **1978**, 3633.

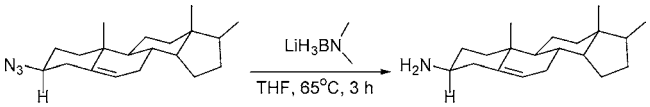
(23) (a) Alvarez, S. G.; Fisher, G. B. Singaram, B. *Tetrahedron Lett.* **1995**, *36*, 2567. (b) Pei, Y.; Wickham, B. O. S. *Tetrahedron Lett.* **1993**, *34*, 7509, footnotes 1 and 2. (c) Pei, Y.; Wickham, B. O. S. *Tetrahedron Lett.* **1993**, *34*, 7509, footnote 3.

Scheme 22. **Reduction of benzyl azide**



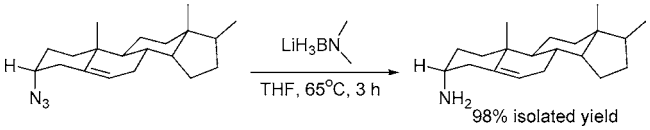
85% isolated yield

Scheme 23. **Reduction of azides**



98% isolated yield

Scheme 24. **Reduction of azides**



98% isolated yield

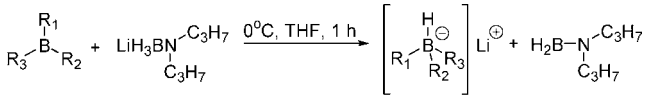
Furthermore, we used this methodology during the course of our studies of the nicotinic acetycholine receptor (AchR),[21a,b] a cell membrane protein. 3α-Azidocholest-5-ene and 3*β*-azidocholest-5-ene were reduced with LiH_3BNMe_2 to the corresponding cholestene amines in 98% isolated yield (Schemes 23 and 24).[21a] Previously, these azides were reduced to corresponding amines with 12−25 equiv of $LiAlH_4$ under an inert atmosphere.[21c] Cholestene amines were used as non-radiolabeled cell membrane photoaffinity tags.[21b]

Three aspects of these reductions are particularly noteworthy; first, only 1.5 equiv of $LiH_3BN(Me)_2$ are required to obtain a 98% isolated yield of both the 3α-aminocholest-5-ene and 3*β*-aminocholest-5-ene; second, the reductions are complete in 2−3 h; and, finally, the reductions of both 3α-azidocholest-5-ene and 3*β*-azidocholest-5-ene were carried out *in air*.

Reactions of Trialkylboranes: A General Synthesis of Alkyl-Substituted Borohydrides. Trialkylboranes react with LAB reagents to form lithium trialkylborohydrides. Lithium trialkylborohyrides are powerful and selective reducing agents.[24] Because of their synthetic utility as reducing agents, several synthetic routes to lithium trialkylborohydrides have been explored.[25] Trialkylborohydrides can be synthesized by addition of lithium hydride (LiH) to unhindered trialkyboranes.[26] However, this procedure is not suitable for the synthesis of hindered trialkylborohydrides. This has led to the development of a number of reactive LiH equivalents, such as *tert*-butyllithium and $LiAlH_4$.[27,28]

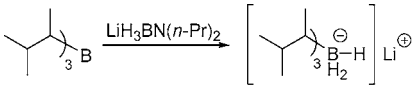
We envisioned LABs to be ether-soluble sources of activated LiH, much like $LiAlH_4$. This in turn suggested that LABs would be excellent sources of LiH for transfer of these elements to alkylboranes. Results from our laboratories have confirmed that LABs readily add LiH to borane, monoalkyl-

Scheme 25. **General reaction of trialkylboranes with LAB**



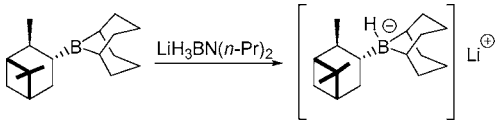
R_1, R_2, R_3 = Alkyl, H

Scheme 26. **Reaction of tri-isoamylborane with LAB**



^{11}B-NMR: δ -13.5 (d, *J* = 78 Hz)

Scheme 27. **Reaction of *B*-isopinocampheyl-9-borabicyclo(3.3.1)nonane with LAB**



^{11}B-NMR: δ - 6.6 (d, *J* = 75 Hz)

boranes, dialkylboranes, and hindered trialkylboranes to form the corresponding lithium alkylborohydrides (Scheme 25).[29]

The exchange of LiH from LABs to the trialkylboranes indicates that the aminoboranes are less Lewis acidic than these alkylboranes. Even highly hindered trialkylboranes, such as tri-isoamylborane and *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane, reacted readily with lithium di-*n*-propylaminoborohydride in THF to afford the corresponding lithium trialkylborohydrides (Schemes 26 and 27).[27]

Generally, due to incomplete reaction between LiH and trialkylboranes, lithium trialkylborohydrides give broad undefined peaks in their ^{11}B NMR spectra.[30] However, the ^{11}B NMR spectra of the trialkylborohydrides obtained by the above transfer reaction showed sharp splitting patterns, indicative of a complete transfer of LiH from LAB to the trialkylboranes.

The transfer of LiH converts the LAB to a dihydridoaminoborane (R_2NBH_2), which remains in the reaction mixture (Scheme 25). Since R_2NBH_2 compounds are relatively unreactive and are poor reducing agents,[7b] the presence of the R_2NBH_2 in the final product does not influence the reactivity of the lithium alkylborohydride.

Lithium tri-isoamylborohydride is known to react with 4-*tert*-butylcyclohexanone to yield the corresponding *cis*-alcohol.[31] Lithium tri-isoamylborohydride produced by the exchange reaction also reduces 4-*tert*-butylcyclohexanone in the presence of the aminoborane byproduct to offer only the *cis*-alcohol (Scheme 28).

We next sought to determine the generality of this reaction. Further studies of the exchange reaction showed that LABs transfer LiH to dialkylboranes, such as di-isopinocampheylborane (Scheme 29).

In addition to forming di- and trialkylborohydrides, we also tested the exchange reaction on monoisopinocampheyl-

(24) (a) Krishnamurthy, S. *Aldrichimica Acta* **1974**, *7*, 55. (b) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064. (c) Brown, H. C.; Kim, S. C. *Synthesis* **1977**, 635.

(25) (a) Brown, H. C.; Krishnamurthy, S.; Hubbard, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 3343. (b) Brown, C. A.; Krishnamurthy, S. *J. Organomet. Chem.* **1978**, *156*, 111. (c) Brown, H. C.; Krishnamurthy, S.; Hubbard, J. L. *J. Organomet. Chem.* **1979**, *166*, 271.

(26) Brown, H. C.; Moerikofer, A. W. *J. Am. Chem. Soc.* **1962**, *84*, 1478.

(27) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1491.

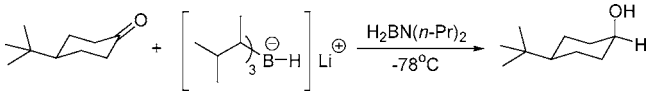
(28) (a) Brown, H. C.; Hubbard, J. L.; Singaram, B. *J. Org. Chem.* **1979**, *44*, 5004. (b) Brown, H. C.; Hubbard, J. L.; Singaram, B. *Tetrahedron* **1981**, *37*, 2359.

(29) Harrison, J.; Alvarez, S. G.; Godjoian, G.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 7193.

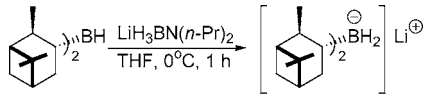
(30) Brown, H. C.; Khuri, A.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1977**, *99*, 6237.

(31) Krishnamurthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 3383.

Scheme 28. **Reduction of 4-*tert*-butylcyclohexanone with lithium tri-isoamylborohydride**

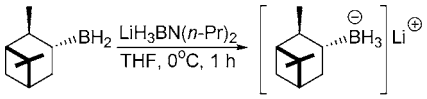


Scheme 29. **Reaction of di-isopinocampheylborane with LAB**



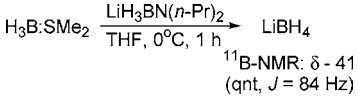
^{11}B-NMR: δ - 5.8 (t, *J* = 67 Hz)

Scheme 30. **Reaction of monoisopinocampheylborane with LAB**



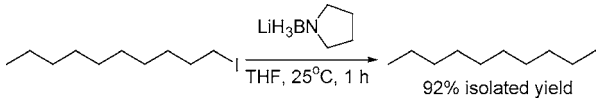
^{11}B-NMR: δ - 21.1 (q, *J* = 75Hz)

Scheme 31. **Reaction of borane with LAB**



^{11}B-NMR: δ - 41 (qnt, *J* = 84 Hz)

Scheme 32. **Reduction of alkyl halides**



borane, a monoalkylborane. The exchange reaction afforded the corresponding monoalkylborohydride (Scheme 30).

The exchange reaction also works with borane and affords lithium borohydride in essentially quantitative yield (Scheme 31).

The dihydridoaminoborane byproduct is much less Lewis acidic than borane or alkylboranes. Consequently, the exchange reaction is the result of the thermodynamically favorable exchange of lithium hydride. Thus, trialkyl-, dialkyl-, and monoalkylboranes can be converted into the corresponding lithium alkylborohydrides by this simple exchange reaction. The mild reaction conditions and the generality of the reaction make this procedure attractive for the synthesis of a wide variety of substituted borohydrides.

Reduction of Alkyl Halides. The reduction of alkyl halides with LAB reagent provided the corresponding alkanes in excellent yields. Thus, 1-iododecane was cleanly reduced to decane (Scheme 32).

In contrast to lithium aminoborohydrides, when sodium aminoborohydrides[32] were reacted with alkyl iodides, the dimethylamine portion of the reagent was transferred to give the corresponding tertiary amine (Scheme 33). This result suggests an S_N2 reaction of sodium aminoborohydride with 1-iododecane.

Reduction of Alkyl Methanesulfonate Esters. Primary alkyl sulfonates undergo reduction to corresponding hydrocarbons with a sterically hindered LAB reagent.[33] Unfortunately, the same LAB reagent is not suitable for secondary alkyl sulfonates, which are recovered unchanged even after prolonged exposure at reflux temperature (Scheme 34).

Surprisingly, when primary alkyl methanesulfonates were treated with sterically unhindered LAB reagents at 0 and 25 °C no reduction products were formed; the corresponding tertiary amines were observed by GC analysis. Unexpectedly, under these reaction conditions, LABs are exclusively amine transfer agents. For example, 3-phenylpropyl methanesulfonate provides tertiary amines in excellent yield with a variety of LAB reagents after an acidic methanolic workup procedure (Scheme 35).

The reduction of alkyl methanesulfonates with unhindered LAB reagents is also possible in the presence of Et_3B. Under these reaction conditions $LiEt_3BH$ is generated in situ. Using 1.5 equiv of lithium dimethylaminoborohydride and 20 mol % of Et_3B, reduction of both primary and secondary alkyl mesylates is accomplished in very high yield. For example, when 3-phenylpropyl methanesulfonate is treated with 20 mol % of Et_3B and 1.5 equiv of $LiH_3BN(Me)_2$, 1-phenylpropane is the only observable product (Scheme 35). After only 15 min at reflux temperature, a 94% yield of the reduction product is obtained, with no other observable products by GC analysis.

Not only is the methodology for generating $LiEt_3BH$ in situ using LAB successful, but it is also applicable to secondary and alicyclic methanesulfonate esters. These hindered mesylates are typically more difficult to reduce, as we had experienced with the unsuccessful reduction of cyclohexylmesylate (**8**) with our hindered LAB reagent. However, after subjecting cyclohexylmesylate (**8**) to the modified procedure of generating $LiEt_3BH$ via LAB, cyclohexane (**9**) was generated in 95% yield. This new reduction methodology provides results comparable with those of the original methodology[34,35] Using our methodology, cyclohexylmesylate (**8**) is reduced to cyclohexane (**9**) in 95% yield, with only a trace amount of cyclohexene (**10**) present in the reaction mixture and no cyclohexanol detected by GC analysis. With the original methodology, a 68% yield of cyclohexane (**9**) was reported, with a 12% yield of the elimination product cyclohexene (**10**) (Table 2).

Temperature, steric bulk, and in situ generation of Super-Hydride using LAB and a catalytic amount of triethylborane can also control the reactivity of LABs towards alkyl sulfonates. However, when the same reaction is performed at 65 °C, reduction to the corresponding alkane is a competitive reaction. Controlling the competitive reduction vs amination reactivity of LAB reagents toward alkyl sulfonates is particularly appealing, considering the current methods for reducing alkyl sulfonate esters to alkanes.

Reduction of Nitriles. Reaction of lithium dimethylaminoborohydride with a series of phenylacetonitriles demonstrated that LABs can function as bases.[36] Treatment of phenylacetonitrile with $LiH_3BN(CH_3)_2$ in THF followed by quenching with D_2O gave no benzylamine, but monodeuterated phenylacetonitrile was obtained in 81% yield (Scheme

(32) Hutchins, R. O.; Learn, K.; El-Telbany, F.; Stercho, Y.P. *J. Org. Chem.* **1984**, *49*, 2438.

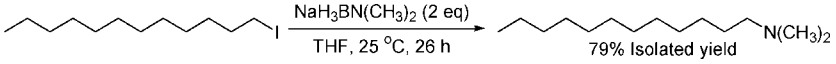
(33) Thomas, S.; Huynh, T.; Enriquez-Rios, V.; Singaram, B. *Org. Lett.* **2001**, *3*, 3915.

(34) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.

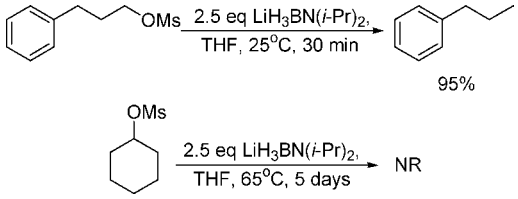
(35) (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064. (b) Super-Hydride is a registered trademark of Sigma-Aldrich Chemical Co.

(36) Goralski, C. T.; Singaram, B. Unpublished results.

Scheme 33. **Reaction of sodium aminoborohydride with 1-iodododecane**



Scheme 34. **Reduction of methanesulfonate esters**



Scheme 35. **Amination or reduction of primary alkyl methanesulfonates**

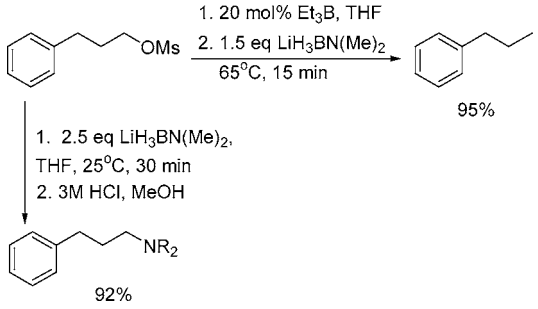
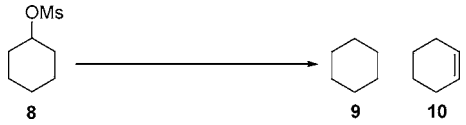
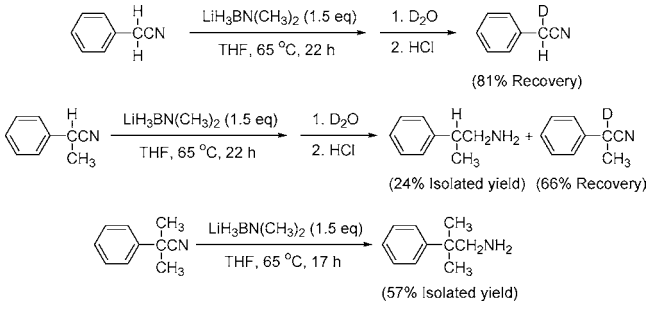


Table 2. **Reduction of cyclohexyl mesylate with various hydride reducing agents**



reagent	temp (°C)	products 9	products 10
$LiH_3BN(Me)_2$, cat Et_3B, THF	65	95	5
$LiEt_3BH$, THF	60	68	12

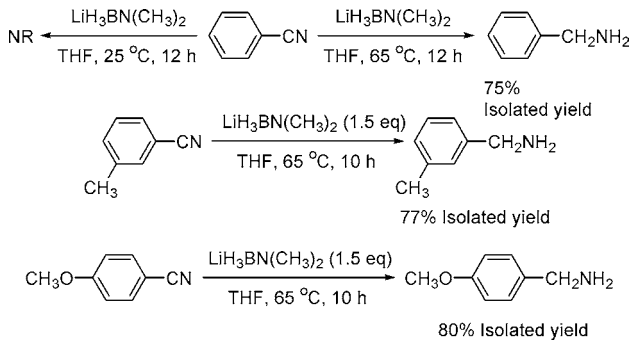
Scheme 36. **LABs can function as bases or reduce nitriles**



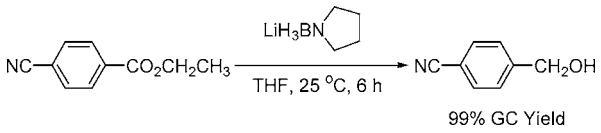
35). Treatment of 2-phenylpropionitrile with $LiH_3BN(CH_3)_2$ under the same conditions gave a 24% isolated yield of 2-phenylpropylamine and a 66% recovery of 2-deuterio-2-phenylpropionitrile. Reduction of 2-methyl-2-phenylpropionitrile (which contains no hydrogen alpha to the nitrile group) with $LiH_3BN(CH_3)_2$ gave a 57% isolated yield of 2-methyl-2-phenylpropylamine. These reactions are summarized in Scheme 36.

Simple aliphatic nitriles are not reduced with LAB—the substrates are recovered in high yield.[37] In fact, it is possible to reduce the following functional groups in the presence of a nitrile group: aldehyde, ketone, ester, and epoxide. The situation is different for aromatic nitriles.[38] Benzonitrile does not react with lithium dimethylaminoborohydride in THF at room temperature. However, increasing the temperature to 65 °C affords benzylamine in 75% isolated yield. Simple, nonreactive functional groups, such as alkyl groups or alkoxy groups, are well tolerated, and excellent isolated yields of the corresponding benzylamines were obtained (Scheme 37).

Scheme 37. **Reduction of aromatic nitriles**



Scheme 38. **Reduction of ester in the presence of the nitrile**



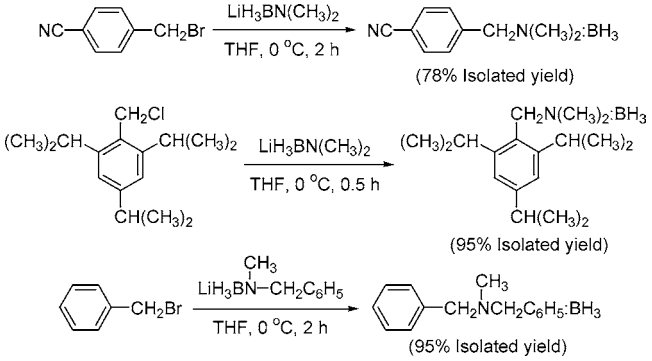
The temperature sensitivity of this reaction allows the selective reduction of more reactive functional groups in the presence of the nitrile. Thus, treatment of ethyl 4-cyanobenzoate with lithium pyrrolidinoborohydride in THF at room temperature afforded a 99% GC yield of 4-cyanobenzyl alcohol (Scheme 38).

Surprisingly, similar treatment of 4-cyanobenzyl bromide with lithium dimethylaminoborohydride afforded 78% yield of the nitrogen transfer product 4-cyanodimethylbenzylamine—borane complex. This was an unexpected result because neither nitrile nor benzyl halide was reduced; the only isolated product came from the amine transfer reaction. The fact that the amination occurred is quite intriguing since LAB reagents are known to reduce benzyl halides to hydrocarbons at 25 °C. Obviously, LAB reagents react with benzyl halides via a different pathway at 0 °C. We found that LAB reagents can react with various benzyl and alkyl halides to produce tertiary amine—boranes at 0 °C (Scheme 39).[39] No quaternary ammonium salts were obtained in the reaction due to the interaction of the amine lone pair with the borane moiety.

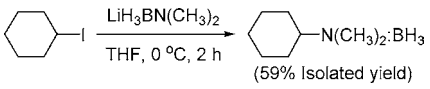
This chemistry also has been extended to the preparation of simple aliphatic amines (Scheme 40) and complex diamines (Scheme 41). Great interest has been shown in this

(37) Collins, C. J.; Fisher, G. B.; Reem, A.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1997**, *38*, 529.
(38) Collins, C. J.; Lanz, M.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1999**, *64*, 2574.
(39) Collins, C. J.; Lanz, M.; Goralski, C. T. *J. Org. Chem.* **1999**, *64*, 2574.

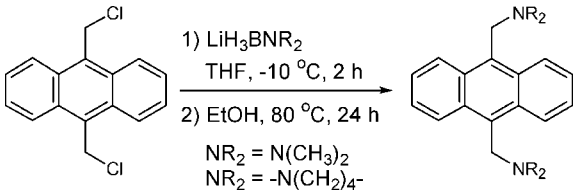
Scheme 39. **Amination of benzyl halides**



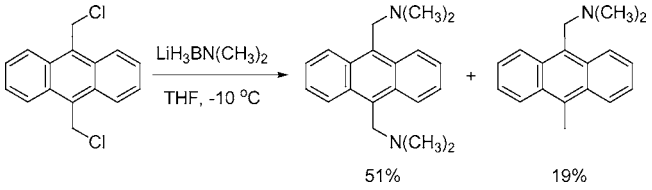
Scheme 40. **Preparation of aliphatic amines**



Scheme 41. **Preparation of complex diamines**



Scheme 42. **Synthesis of precursors for PET systems**

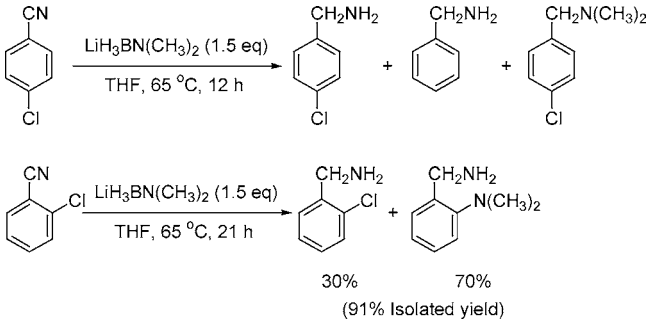


class of amines for sensing sugars in combination with boronic acids.

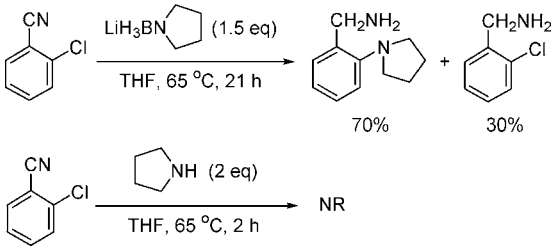
These amination reactions indicate that LAB reagents, which can be viewed as borane complexes of lithium *N*,*N*-dialkylamides, react in a S_N2 fashion. On the other hand, carbene, radical, and carbanion pathways are operating in the case of lithium *N*,*N*-dialkylamides.[40] Tertiary amine products are not formed in these reactions. Lodeiro and co-workers[41] synthesized precursors for the new fluorescence PET (photoinduced electron transfer) systems by this method (Scheme 42). However, some reduction product was formed along with the expected product.

Tandem Reduction/Amination Reactions. The reaction of benzonitriles containing halogens has provided some very interesting results. Treatment of 4-chlorobenzonitrile with lithium dimethylaminoborohydride in refluxing THF afforded a 55% yield of a mixture of 4-chlorobenzylamine (the expected product), benzylamine (the result of dechlorination and reduction), and 4-chloro-*N*,*N*-dimethylbenzylamine. In contrast, reaction of 2-chlorobenzonitrile with lithium dimethylaminoborohydride under the same conditions gave a

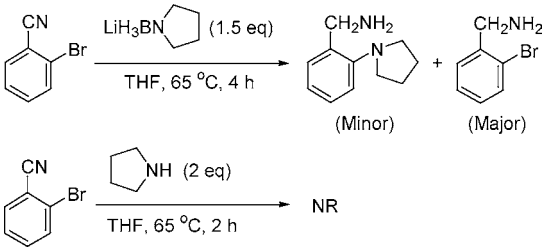
Scheme 43. **Reactions of LAB with 4- and 2-chlorobenzonitriles**



Scheme 44. **Reactions of 2-chlorobenzonitrile with lithium pyrrolidinoborohydride and pyrrolidine**



Scheme 45. **Reactions of 2-bromobenzonitrile with lithium pyrrolidinoborohydride and pyrrolidine**



91% isolated yield of a 70/30 mixture of 2-(dimethylamino)-benzylamine (the result of nucleophilic aromatic substitution of the chlorine by the dimethylamino group, another example of nitrogen transfer, followed by reduction of the nitrile group) and 2-chlorobenzylamine (Scheme 43).

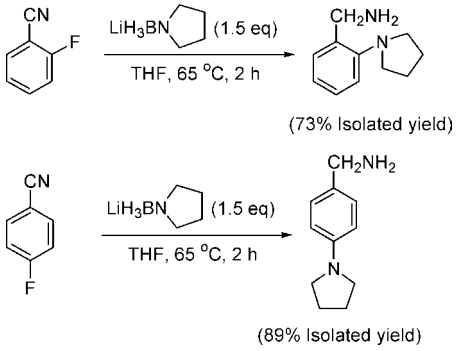
Reaction of 2-chlorobenzonitrrile with lithium pyrrolidinoborohydride under similar conditions gave analogous results to those obtained with lithium dimethylaminoborohydride — a 70/30 mixture of 2-(pyrrolidino)benzylamine and 2-chlorobenzylamine. Treatment of 2-chlorobenzonitrile with pyrrolidine under similar conditions gave only recovered starting material (Scheme 44).

We have nominated this displacement/reduction sequence as tandem amination/reduction. The tandem amination/reduction was further studied with other halogenated benzonitriles. Reaction of 2-bromobenzonitrile with lithium pyrrolidinoborohydride gave 2-bromobenzylamine as the major product, with the tandem reduction product becoming the minor product. Treatment of 2-bromobenzonitrile with pyrrolidine under similar conditions afforded only recovered starting material (Scheme 45).

Treatment of 2-fluorobenzonitrile and 4-fluorobenzonitrile with lithium pyrrolidinoborohydride in THF at reflux afforded 73% and 89% yields, respectively, of the corresponding pyrrolidinobenzylamines (Scheme 46).

(40) (a) Creary, X. *J. Am. Chem. Soc.* **1977**, *99*, 7632. (b) Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, *58*, 424.
(41) Tamayo, A.; Lodeiro, C.; Escriche, L.; Berta, J. C.; González, C. P. *Inorg. Chem.* **2005**, *44*, 8105.

Scheme 46. **Reactions of 4- and 2-fluorobenzonitrile with lithium pyrrolidinoborohydride**



These results indicated that a novel reaction was taking place. In particular, a one-pot tandem reaction seemed to occur, wherein amination at the carbon bearing the halogen was accompanied by reduction of the nitrile.[42a,b]

The reaction of 2-bromobenzonitrile with various LAB reagents affords primarily the reduction product, 2-bromobenzylamine (Figure 3). 2-(*N*,*N*-Dialkylamino)benzylamine is obtained as a minor product, while the reaction of 2-chlorobenzonitrile with various LAB reagents provides primarily the tandem reaction product, 2-(*N*,*N*-dialkylamino)-benzylamine. Finally, when 2-fluorobenzonitrile is treated with LAB reagent, the tandem reaction product is exclusively obtained. The S_NAr tandem amination/reduction reaction of 2-halobenzonitriles with lithium aminoborohydrides is a one-pot procedure and an attractive synthetic tool for the aromatic substitution of less nucleophilic amines.[43]

The generality of the reactions of fluorobenzonitriles with various lithium *N*,*N*-dialkylaminoborohydrides was investigated. Through this screening, a particularly interesting feature of the LAB-induced tandem amination/reduction reaction of halobenzonitriles is demonstrated. Specifically, LAB reagents containing a less nucleophilic amine were able to undergo amine substitution as well as reduction of the nitrile (Table 3). In contrast, the free amine failed to induce amine substitution. In this case, the nitrile moiety does not activate the aromatic ring for nucleophilic attack by the free amine, and the starting material is recovered unchanged. For example, lithium morpholinoborohydride reacts with 2-fluorobenzonitrile via the tandem amination/reduction reaction pathway to provide 2-(4-morpholino)benzylamine in 81% yield. In comparison, free morpholine does not give any S_N-Ar reaction with the same substrate under reflux conditions, and the starting material is recovered unchanged.

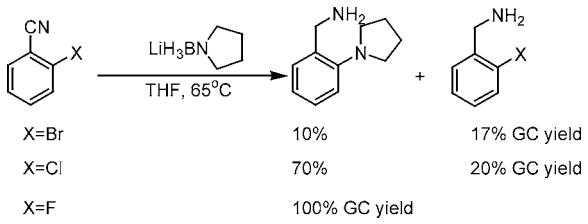
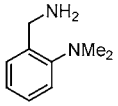
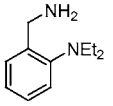
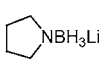
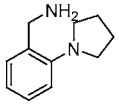
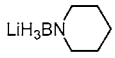
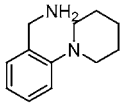
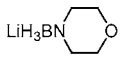
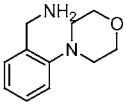
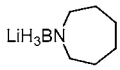
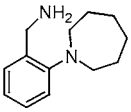


Figure 3. **Reactions of 2-halobenzonitriles with lithium pyrrolidinoborohydride.**

Table 3. **Tandem S_NAr amination/reduction products from the reaction of 2-fluorobenzonitrile with various lithium aminoborohydrides**

entry	LiH_3BNR_2	product	yield(%)
1	LiH_3BNMe_2		81
2	LiH_3BNEt_2		70
3			84
4			94
5			81
6			75

The reactions of 2-fluorobenzonitrile with various lithium *N*,*N*-dialkylaminoborohydrides are fairly general and give the corresponding 2-(*N*,*N*-dialkylamino)benzylamines in very good yield (Table 3). Thus, a wide variety of amines from the very nucleophilic, such as pyrrolidine, to the less nucleophilic, such as morpholine, are able to undergo substitution with 2-fluorobenzonitriles via LAB reagents.

Computer Calculations on LABs. Pratt and co-workers have carried out computer calculations that indicated that lithium dimethylaminoborohydride exists largely as a hydrogen-bridged dimer (Figure 4) in the gas phase.[44]

The calculations also suggested that the dimer might coexist with the monomer (Figure 5) in tetrahydrofuran (THF), particularly in the case of more sterically hindered lithium aminoborohydrides.

More recently, this group performed density functional theory (DFT) calculations to determine the effects of ethereal

(42) (a) Thomas, S.; Collins, C. J.; Goralski, C. T.; Singaram, B. *Chem. Innovation* **2000,** *30*, 31. (b) Thomas, S.; Collins, C. J.; Cuzens, J. R.; Spiciarich, D.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **2001**, *66*, 1999.

(43) One of the reviewers suggested that the halogen replacement by the amine portion of the LAB reagent occurs via an addition−elimination mechanism rather than via an S_NAr mechanism. The order of reactivity of the halogenated benzonitriles (F > Br > Cl) is in accord with that normally observed with S_NAR substitution (Smith, M.B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: New York, 2001; pp 850−853 and references cited therein). Further, the formation of a deep red color in the reactions of LABs with 2-halobenzonitriles is characteristic of the formation of Meisenheimer complexes as intermediates. Studies conducted with 2-fluoropyridine and LAB reagents showed similar results (Thomas, S.; Roberts, S.; Pasumansky, L.; Gamsey, S.; Singaram, B. *Org. Lett.* **2003**, *5*, 3867). These results are not discussed here, since this review was intended to focus on the reduction properties of LAB reagents. Additional discussion on the work with 2-fluoropyridine can be found in the following review: Pasumansky, L.; Singaram, B.; Goralski, C. T. *Aldrichimica Acta* **2005**, *38*, 61.

(44) Mogali, S.; Darville, K.; Pratt, L. M. *J. Org. Chem.* **2001**, *66*, 2368.

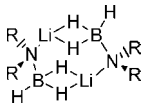


Figure 4. **Hydrogen-bridged dimer of LAB.**

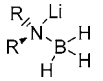


Figure 5. **Monomer of LAB.**

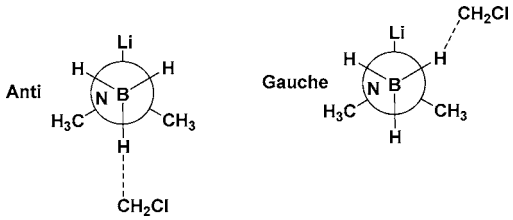


Figure 6. **Transition structure geometries for chloromethane reduction by the LAB monomer.**

solvents on the aggregation state of lithium dialkylaminoborohydrides (LABs). On the basis of DFT calculations, Pratt and co-workers concluded that solvation of lithium dialkylaminoborohydrides is best represented by a combination of microsolvation with coordinating ligands and a continuum solvation model. The combined model predicts a monomer−dimer equilibrium for lithium dimethylaminoborohydride and predicts more hindered lithium dialkylaminoborohydrides to exist primarily as monomers.[45]

In the gas phase, LABs can reduce alkyl halides by three possible pathways. The most favorable mechanism is a backside attack by the hydride nucleophile with a gauche conformation of the H−B−N−Li dihedral angle (Figure 6). This conformation allows the lithium atom to assist the departure of the chloride leaving group.

The lithium atom also assisted the departure of the chloride ion in the amination reaction, and the more favorable geometry of the LAB dimer transition structure makes the dimer mechanism the most energetically favorable pathway in the gas phase. The calculated activation free energies show that LAB reagents reduce alkyl halides much more readily than borane, diborane, borane/ether, or borane/dimethyl sulfide complexes. This appears to result both from the ability of the lithium amide fragment to release electrons onto boron and from the ability of the lithium atom to assist the departure of the leaving group. Although the B3LYP DFT method often underestimates activation barriers, sometimes severely, it produced reasonable qualitative results for the compounds of this investigation.[46]

Conclusion

Lithium aminoborohydrides are a new class of powerful, yet selective, reducing agents that reproduce, in air, virtually all of the transformations for which $LiAlH_4$ is now used and more (Figure 7).

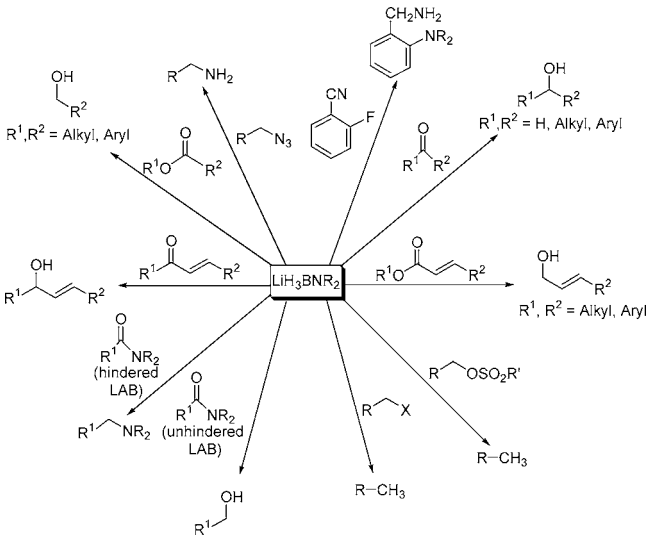


Figure 7. **Reactions of LAB reagents.**

The reactivity of LABs is comparable to that of both $LiAlH_4$ and Vitride. LABs are air-stable, non-pyrophoric, thermally stable, and liberate hydrogen only slowly with protic solvents above pH 4. LABs, whether solid or as THF solutions, retain their chemical activity for at least 6 months when stored under nitrogen at 25 °C. LABs can be synthesized from any primary or secondary amine, thus allowing precise control of the steric and electronic environment of these reagents.

The spectrum of the reactions of LABs is not limited to their reducing properties. Lithium aminoborohydrides are reagents with multiple personalities. First and foremost, LABs are reducing agents. Both hydride and amine can be transferred in tandem amination/reduction reactions of halobenzonitriles. Also, amination or reduction properties of LABs can be fine-tuned to ultimately control their dual personality.

The future use of these new reducing agents in both industry and academia appears to be quite promising. Lithium aminoborohydrides are already finding useful applications in organic synthesis. In undergraduate teaching laboratories, transformations that would seldom be attempted due to the need to use $LiAlH_4$ or borane, such as the reduction of tertiary amides or esters, may become routine experiments with the use of LABs. For example, for the past 4 years, students in the U.C. Santa Cruz introductory organic chemistry laboratory class have employed 1 M THF solutions of LABs to reduce aliphatic, aromatic, and α,β-unsaturated esters to the corresponding aliphatic, aromatic, and allylic alcohols, in air, in 70−98% isolated yields without incident or difficulty. In academic research laboratories, the short reaction times, ease of generation and handling, and simple workup procedures for performing reductions with LABs make these new reagents attractive alternatives to $LiAlH_4$ or lithium triethylborohydride ("SuperHydride") reductions.

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(45) Pratt, L. M.; Mogali, S.; Glinton, K. *J. Org. Chem.* **2003**, *68*, 6484.
(46) Pratt, L. M.; Nguyen, N. V. *J. Org. Chem.* **2005**, *70*, 10561.