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Aminoborohydrides. 14. Lithium Aminoborohydrides in the Selective Reduction *or* Amination of Alkyl Methanesulfonate Esters

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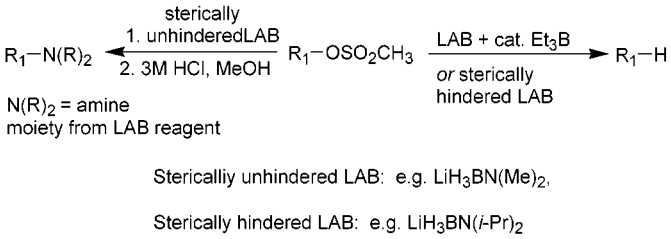
ABSTRACT



Lithium aminoborohydride (LAB) 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 using a hindered LAB reagent or by forming the highly reactive Super-Hydride reagent in situ using LAB and a catalytic amount of triethylborane. The reduction methodology disclosed herein is a safe and convenient alternative to existing synthetic methods.

Alkyl and aryl methanesulfonate esters are important reagents in organic synthesis.[1] They have excellent leaving group properties, are readily available, and are common intermediates for the deoxygenation of alcohols to their parent alkanes.[2] Deoxygenation of alcohols to alkanes is a common synthetic transformation that is usually achieved by reducing the sulfonate ester derivatives with lithium aluminum hydride (LAH).[3] LAH reductions of primary alkyl sulfonates generally proceed with satisfactory results, whereas sterically hindered alkyl sulfonates treated with LAH suffer from unfavorable side reactions (elimination and sulfer−oxygen bond cleavage).[3] For reactions where LAH cannot be used, lithium triethylborohydride ($LiEt_3BH$ or Super-Hydride) is an excellent alternative.[4] However, for complete reduction, 2 equiv of the highly reactive $LiEt_3BH$ is required and oxidation of the resulting trialkylborane complicates the workup procedure in a large-scale reaction.

Lithium aminoborohydride (LAB) reagents have recently emerged as a new class of powerful and selective reducing agents[5] that could potentially carry out the deoxygenation of alcohols to their alkanes. However, under certain circumstances, LABs preferentially transfer their amine functionality over a hydride. For example, both unsubstituted and substituted benzyl halides treated with LAB reagents at 0 °C give the corresponding tertiary amine−borane complexes, whereas the same reaction at 65 °C affords toluene products.[6] There is thus a difference in the reactivity of LAB reagents toward

(1) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.
(2) March, J. *Advanced Organic Chemisty*, 4th ed; Wiley and Sons: New York, 1992; pp 441−442.
(3) Gaylord, N. G. *Reduction with Complex Metal Hydrides*; Interscience Publishers: New York, 1956; pp 855−875.
(4) (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064. (b) Super-Hydride is a registered trademark of Sigma-Aldrich Chemical Co.
(5) Fisher, G. B.; Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1992**, *33*, 4533.
(6) Collins, C. J.; Lanz, M.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1999**, *64*, 2574.

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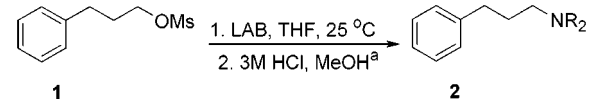
alkyl halides with temperature. Additionally, LAB reagents undergo a unique reaction with 2-halobenzonitriles.[7] During this reaction, reduction of the nitrile is accompanied by amination at the carbon bearing the halogen, and 2-aminobenzylamines are obtained. Clearly, LAB reagents are capable of mediating the transfer of both their amine and hydride functionalities; exploring and ultimately controlling this dual reactivity is desired. Herein we report the controlled reactivity of LABs toward alkyl sulfonates as modulated by temperature, steric bulk, and the in situ generation of Super-Hydride.

Primary alkyl methanesulfonates treated with unhindered LAB reagents at 0 and 25 °C provide only the corresponding tertiary amines; no reduction products are observed by GC analysis. Under these reaction conditions, LABs are exclusively amine transfer agents. For example, 3-phenylpropyl methanesulfonate **1** provides tertiary amines **2** in excellent yield with a variety of LAB reagents after an acidic methanolic workup procedure (Table 1). However, when the same reaction is performed at 65 °C, reduction to the corresponding alkane is a competitive reaction.

Table 1. Amination Reactions of Primary Alkyl Sulfonates with Various Lithium Aminoborohydride Reagents[a]



LiH_3BNR_2[b]	Time	Product	Yield[c]
$LiH_3BN(Me)_2$	30 min.	**2a**	92 %
$LiH_3BN(Et)_2$	30 min.	**2b**	75 %
$LiH_3BPyrr.$	30 min.	**2c**	94 %
$LiH_3BMorph.$	30 min.	**2d**	87 %
$LiH_3BHomopip.$	30 min.	**2e**	99 %

[a] 10 mmol of **1**, 2.5 equiv of LAB, acidic methonolic workup liberates borane from originally formed amine−borane, providing amine products (**CAUTION!** *hydrogen evolution!*). See ref 6 for further experimental details. Compounds identified by proton and carbon NMR. [b] Prepared from corresponding amine−borane, see ref 5 for a detailed procedure. [c] Isolated yield. No other products observed by GC analysis.

^{11}B NMR identifies the boron species that are generated during the reaction, and temperature dependent differences are detected. At 0 °C, only the residual LAB reagent (δ −16, q) and the amine−borane complex of the tertiary amine product (δ −14, q) are evident.[8] At reflux temperature, in addition to these two species, $LiBH_4$ (δ −43, quin.) and H_2BNR_2 (δ 0, t) are present. This difference in boron species with temperature can be accounted for by the more efficient metal hydride transfer reaction at 65 °C between the more Lewis acidic boron of the tertiary amine−borane and the less Lewis acidic boron of the LAB reagent.[9] In this way, $LiBH_4$ is generated along with the amino−borane side product for reactions run at high temperature (Figure 1). Such

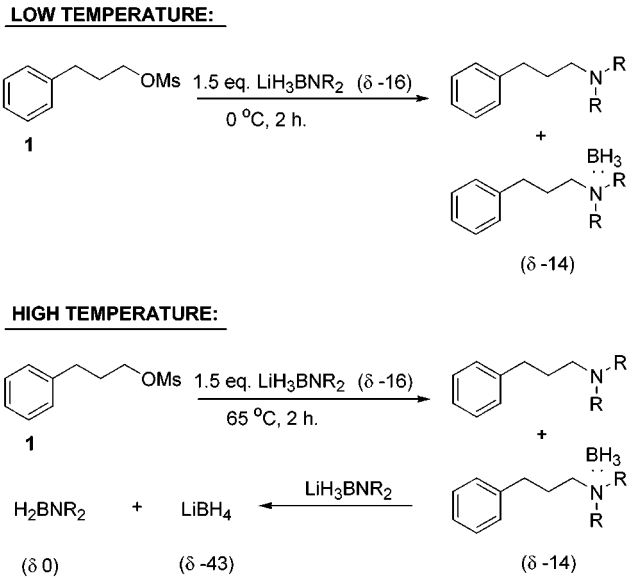


Figure 1. Temperature dependent differences in boron species generated during the reaction of **1** with LAB. Species characterized by coupled and decoupled ^{11}B NMR spectra.

differences in reactivity with temperature have previously been reported for metal hydride transfer reactions.[10]

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. However, to make reduction the dominant reaction, the ability of the LAB reagent to transfer its amine moiety must be suppressed. A sterically hindered LAB reagent (lithium diisopropylaminoborohydride) should be less likely to transfer its amine functionality in an S_N2 fashion, and hydride transfer would thus be expected. Indeed, even at 25 °C, primary alkyl sulfonates undergo only reduction with a sterically hindered LAB reagent.

Although lithium diisopropylaminoborohydride initiates reduction for primary alkyl sulfonates, it is not suitable for secondary alkyl sulfonates, which are recovered unchanged after prolonged exposure at reflux temperature. For example, 3-phenylpropyl methanesulfonate **1** treated with lithium diisopropylaminoborohydride is reduced to 3-phenylpropane **3** in 30 min at 25 °C, but cyclohexylmesylate **4** is not

(7) Thomas, S.; Collins, C. J.; Cuzens, J. R.; Spiciarich, D.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **2001**, *66*, 1999.

(8) Aliquots were removed from the reaction flask via canunula needle, were run neat, and were referenced to BF_3:OEt_2 (δ = 0) for ^{11}B NMR spectra.

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

(10) Brown, H. C.; Singaram, B.; Singaram, S. *J. Organomet. Chem.* **1982**, *239*, 43.

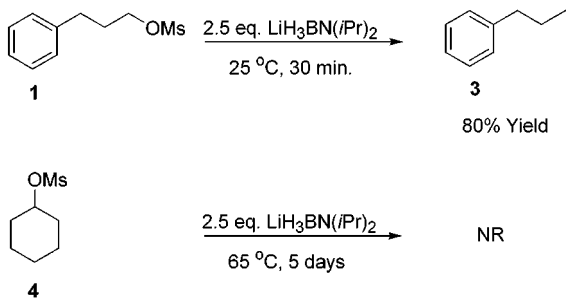


Figure 2. Representative reduction of primary alkyl sulfonates with lithium diisopropylaminoborohydride. Analysis by GC; yield reported was determined using a suitable internal standard and authentic product sample. No other products were detected.

susceptible to reduction (Figure 2). To achieve reduction for secondary mesylates, a more powerful reducing agent is necessary.

$LiEt_3BH$ is an exceptionally powerful nucleophilic reducing agent capable of reducing even hindered alkyl sulfonates.[11] However, it is not without its disadvantages, which are 2-fold: The original procedure requires 2 equiv of $LiEt_3BH$, presumably due to the formation of the unreactive complex $Et_6B_2H^-Li^+$,[12] and an oxidation step in the workup procedure is required.[13] Generating $LiEt_3BH$ in situ eliminates the disadvantages that are associated with this reagent, yet maintains the advantages inherent in using such a powerful, nucleophilic reducing agent.

Since lithium hydride transfer has been reported between LAB reagents and hindered trialkylorganoboranes, producing lithium trialkylborohydrides,[9] conceivably a similar exchange reaction between LAB and Et_3B should generate $LiEt_3BH$. The LAB reagent would act as a lithium hydride transfer reagent with Et_3B, producing $LiEt_3BH$, with aminoborane as a side product. The newly formed $LiEt_3BH$ would then become the reducing species. Since Et_3B is regenerated during reduction of the alkyl sulfonate, theoretically only a catalytic amount of Et_3B is required. In this way, the primary hydride source is from LAB reagent, which is nonpyrophoric.

LAB reagents are an ideal lithium hydride source for the proposed generation of $LiEt_3BH$. They are simple to prepare, are easily handled, and can be stored in an ampule for prolonged periods of time without undergoing decomposition. Unlike LiH, LABs would provide a homogeneous reaction environment, and the reduction product could easily be obtained by performing a simple workup procedure.[14] Additionally, LAH is not suitable for such a metal hydride exchange reaction with Et_3B as it suffers from practical complications resulting from gel formations due to the required addition of triethylenediamine (TED), which precipitates aluminum hydride as TED·AlH_3.[10]

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

(12) Holder, R. W.; Mattuno, M. G. *J. Org. Chem.* **1977**, *42*, 2166.

(13) CAUTION! Trialkylboranes are known to be extremely pyrophoric. $LiEt_3BH$ generates triethyl borane upon loss of a hydride. Using a catalytic amount of Et_3B for the in situ generation of $LiEt_3BH$ substantially decreases the amount of pyrophoric material for a given reduction.

The in situ generation of $LiEt_3BH$ for the reduction of alkyl methanesulfonates proved to be quite successful. Using 1.5 equiv of LAB 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 **1** is treated with 20 mol % of Et_3B and 1.5 equiv of $LiH_3BN(Me)_2$, 3-phenylpropane **3** is the only observable product (Figure 3). After only 15 min at reflux

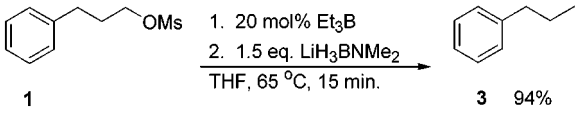
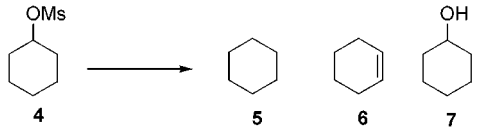


Figure 3. Reduction of primary alkylsulfonic ester with LiH_3BNMe_2 and 20 mol % of Et_3B.

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 **4** with our hindered LAB reagent. However, after subjecting cyclohexylmesylate **4** to the modified procedure of generating $LiEt_3BH$ via LAB, cyclohexane **5** was generated in 95% yield. This new reduction methodology provides results comparable with those of the original methodology.[4,11] Using our methodology, cyclohexylmesylate **4** is reduced to cyclohexane **5** in 95% yield, with only a trace amount of cylcohexene **6** present in the reaction mixture and no cyclohexanol **7** detected by GC analysis. With the original methodology, a 68% yield of cyclohexane **5** was reported, with a 12% yield of the elimination product cyclohexene **6** (Table 2). Generating $LiEt_3BH$ in situ using LAB and a

Table 2. Reduction of Cyclohexyl Sulfonates with Various Hydride Reducing Agents



Substrate	Reagent	Temp. °C	Products % 5	6	7
4	$LiH_3BN(Me)_2$, cat. Et_3B, THF[a]	65	95	5	0
4	$LiEt_3BH$, THF[b]	60	68	12	0

[a] 1.5 equiv of LAB, 20 mol % of Et_3B. Precent study, solutions were 0.1 M in sulfonate, reaction time 4 h. Analysis by GC using internal standard. [b] 2.1 equiv of $LiEt_3BH$, reaction time 4 h. Reference 12.

catalytic amount of Et_3B is thus a new and useful methodology that is complimentary to existing synthetic methods.

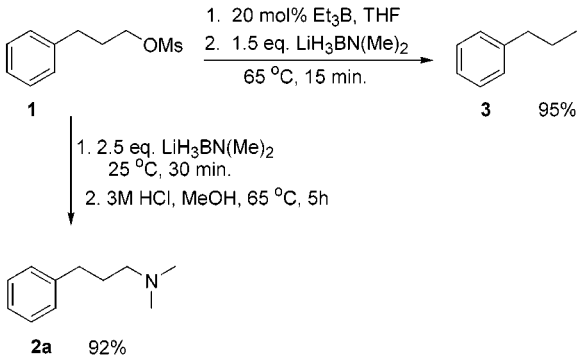


Figure 4. Representative selective reduction *or* amination of alkyl sulfonate 1-mesyl-3-phenylpropane **1** as mediated by lithium dimethylaminoborohydride. Analysis by GC; yield reported was determined using a suitable internal standard and authentic product samples.

The dual properties of LAB reagents are governed by reaction conditions in their reactivity toward alkyl methanesulfonate esters, providing control over reduction vs amination of the title compounds. By treating the alkyl sulfonate **1** with both LAB and a catalytic amount of Et_3B, or by employing a sterically hindered LAB reagent, reduction to the alkane **3** is accomplished. Alternatively, using a sterically unhindered LAB in the absence of Et_3B, LABs mediate the transfer of their amine functionality and tertiary amines **2** are obtained in excellent yield (Figure 4).

The reduction methodology reported herein highlights the synthetic advantages $LiEt_3BH$ offers. Moreover, the controlled reactivity of LAB reagents toward alkyl methanesulfonate esters demonstrates their dual properties as both hydride and amine transfer reagents.

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Supporting Information Available: Proton and carbon spectra for compounds **2a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) **Procedure for the preparation of 3-phenylpropane 3 from 3-phenylpropyl methanesulfonate 1 is representative.** An oven-dried 50 mL round-bottom flask with a sidearm is equipped with a magnetic stir bar and reflux condenser. The apparatus is assembled while hot and cooled under a stream of nitrogen. The sidearm and reflux condenser are fitted with rubber septum and secured with copper wire. The apparatus is kept under a stream of nitrogen run through an oil bubbler. The flask is charged with 10 mL of dry THF (distilled from sodium−benzophenone), followed by 1 mmol of 3-phenylpropyl methanesulfonate **1**, 1 mmol of internal standard (mesitylene), and 0.2 mmol of Et_3B. The solution is allowed to reach reflux temperature, at which time 1.5 mmol of 1 M LiH_3BNMe_2 is added *dropwise*. See refs 5, 6, or 7 for a more detailed description of LAB handling and quenching. (CAUTION!, if quenched with 3 M HCl, *hydrogen evolution!*) After 15 min, a 0.1 mL aliquot is removed from the reaction mixture and placed in 1 mL of pentane (LAB and amine−boranes are insoluble in pentane). The sample is filtered through a syringe filter and analyzed by GC. Yields reported are GC yields, utilizing an internal standard and corrected for detector response.