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Solvent and Temperature Effects on the Reduction and Amination Reactions of Electrophiles by Lithium Dialkylaminoborohydrides

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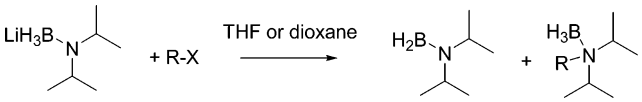

The influence of temperature and solvent effects on the reduction and amination mechanisms of iodomethane by lithium *N*,*N*-diisopropylaminoborohydride (*i*Pr-LAB) was examined in varying concentrations of THF and dioxane. The reactions of benzyl chloride and trimethylsilyl chloride with *i*Pr-LAB in THF were also studied. The amination of iodomethane is favored over reduction at low and room temperatures in pure THF and with increasing the amount of dioxane in THF. At higher temperatures, the reduction reaction appears to compete with the amination. In dioxane solvent, however, iodomethane yields exclusively the amination product regardless of temperature. On the other hand, reduction by *i*Pr-LAB to the aminoborane is the only product observed in THF when benzyl chloride and trimethylsilyl chloride are used. To understand the solvent effects on the product distribution, ab initio and density functional theory (DFT) calculations were used to examine the mechanisms of reduction and amination of chloromethane and bromomethane by lithium dimethylaminoborohydride (LAB) in THF and dioxane. The results of these calculations show that the relative reaction barrier heights are significantly affected by the nature of the coordinated solvent molecule and thus lend support to the experimental observations.

Introduction

Lithium aminoborohydrides (LABs) are powerful, selective, and air-stable reducing agents comparable in reducing power to $LiAlH_4$ and $LiEt_3BH$. LABs can be prepared as solids, as 1−2 M THF solutions, or generated in situ for immediate use. Since LABs can be synthesized from any primary or secondary amines, the steric and electronic environment of these reagents can be easily controlled. THF solutions of LABs retain their chemical activity for at least 9 months when stored at 25 °C under nitrogen. LABs are capable of reducing a variety of functional groups, and their use as reducing agents has been the subject of several reviews.[1]

In 1992, during our initial work with lithium dialkylaminoborohydrides (LABs), we observed exothermic reaction of LABs with methyl iodide.[2] Analysis of this reaction using ^{11}B NMR showed the exclusive formation of the reduction product, that is, the corresponding aminoboranes ($R_1R_2N-BH_2$), in high purity (Scheme 1).[3]

Aminoboranes are well-known in material science as precursors of BN-based ceramics.[4] However, the reactions of ami-

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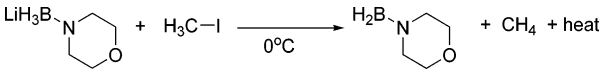
SCHEME 1. Reaction of LAB with Methyl Iodide



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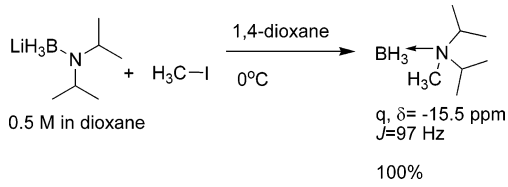
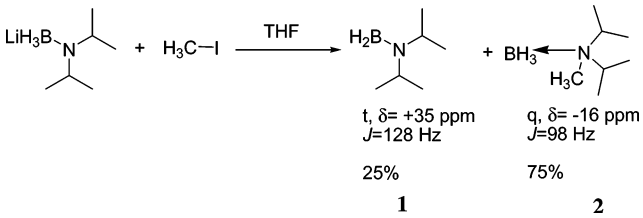


noboranes in organic chemistry have been scarcely studied. The methods to synthesize aminoboranes include reduction of corresponding (amino)dihaloboranes[5] and thermally induced dehydrogenation of secondary amine−borane adducts (R_1R_2-HN:BH_3).[6] It was recently shown, however, that monomeric (dialkylamino)boranes ($R_1R_2N-BH_2$) can be used as an inexpensive boron source in palladium-catalyzed carbon−boron bond formation from aryl halides.[7] Thus, we decided to return to a topic we have not studied since 1992 (see ref 3) and reexamine our in situ synthesis of aminoboranes from lithium aminoborohydrides (LABs) under ambient reaction conditions. Hydride transfer from LAB reagents to an alkyl halide, resulting in the formation of aminoboranes, is a general reaction of sterically hindered LAB reagents, including those derived from diisopropyalmine and morpholine.

We were interested in using this reaction for the synthesis of monomeric diisopropylaminoborane from the corresponding aminoborohydride. The reported procedure[7] for synthesis of boronic acids with aminoboranes required use of 1,4-dioxane as a solvent. Consequently, we prepared lithium *N*,*N*-diisopropylaminoborohydride (*i*Pr-LAB) 0.5 M in 1,4-dioxane[8] and reacted it with methyl iodide. To our surprise, only the amination product was obtained and no reduction product, diisopropylaminoborane, was detected in the reaction (Scheme 2).

In the past, we have reported that product distribution in the reactions of LABs with benzyl halides in THF could be controlled by temperature.[9] However, since the above reaction in dioxane afforded only the amination product regardless of the temperature, the solvent, 1,4-dioxane, appears to have a major effect on the reaction mechanism. The mechanism of these reactions is not yet well understood but could possibly occur via either the monomeric or dimeric form of lithium dialkylaminoborohydrides.[10] In this paper, we report the results of our investigation of the nucleophilic substitution and reduction reactions of *i*Pr-LAB with alkyl halides. Ab initio and density functional theory (DFT) calculations were performed to better understand the observed solvent effects and to shed light on the reaction mechanisms.

SCHEME 3



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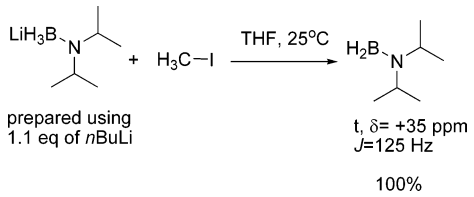

Discussion of Experimental Results

We first checked our original procedure[3] for the preparation of diisopropyl aminoborane. Thus, lithium diisopropylaminoborohydride (*i*Pr-LAB) 1 M in THF was reacted with methyl iodide at 0 °C. When the reaction mixture was analyzed by ^{11}B NMR spectroscopy, we found that there are two products in the reaction mixture: the desired aminoborane (t, $\delta = +35$ ppm, $J = 128$ Hz) and amine−borane (q, $\delta = -16$ ppm, $J = 98$ Hz). The latter is the product of the amination reaction (Scheme 3).

Unfortunately, the amination product **2** was dominant in this reaction. This was puzzling, since previously we obtained aminoborane **1** exclusively from a reduction reaction.[3] Investigating further, we discovered that since 1992, the experimental procedure for the synthesis of LABs has changed a little. When the exclusive formation of aminoborane was reported earlier, LAB reagents were routinely prepared from the corresponding amine−boranes using 1.1 equiv of *n*BuLi.[3] Since then, the standard procedure for preparation of LAB reagents has made use of exactly 1 equiv of *n*BuLi.[11,12] We were surprised that such a small variation in the amount of *n*BuLi in preparation of LAB reagents could make such a remarkable difference in the reactivity of the LAB reagents. The difference in reactivity may be the result of mixed aggregate formation, Lewis acid effects from excess butyllithium, or a combination of the two. Investigating this sensitive dependence of LAB reactivity on the method of its preparation is beyond the scope of the present paper but will be examined in the near future. We speculate that the excess nBuLi present in the earlier method of preparing LABs may have an influence on the aggregation state of the reagent and, thus, its reactivity. We have, of course, confirmed our observation that LAB reagents, 1 M in THF, prepared from one equivalent of *n*BuLi, with methyl iodide gave a mixture of aminoborane **1** and amine−borane **2** (Scheme 3), whereas LAB reagents, 1 M in THF, prepared from 1.1 equiv of *n*BuLi, produced only aminoborane (Scheme 4).

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(8) Usually LAB reagents are prepared 1 M in THF. Because of the solubility issues, LAB was prepared 0.5 M in dioxane.
(9) Collins, C. J.; Lanz, M.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1999**, *64*, 2574.
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(12) The earlier procedure would use, for example, 22 mmols of *n*BuLi, 20 mmols of $BH_3{\cdot}SMe_2$, 20 mmols of diisopropylamine, and sufficient amount of THF to make a 1 M solution. The more recent procedure would use only 20 mmols of *n*BuLi.
(13) The initial concentrations are comparable to those in the trials in Table 1 with 1:1 THF:dioxane.

TABLE 1. Reactions of LAB (1 M in THF) with Various Halides and in Different Solvents[a]

entry	alkyl halide	solvent	T (°C)	$BH_2-N(iPr)_2$ (%)[b]	BH_3:$NMe(iPr)_2$ (%)[b]
1	CH_3I	THF	0	25	75[c]
2	CH_3I	THF	25	25	75
3	CH_3I	THF	65	50	50
4	CH_3I	dioxane/THF 1:9[d]	25	25	75
5	CH_3I	dioxane/THF 2:3[d]	25	13	87
6	CH_3I	dioxane/THF 1:1[d]	0	0	100
7	CH_3I	dioxane/THF 1:1[d]	25	0	100
8	TMS−Cl	THF	0	100	0
9	TMS−Cl	THF	25	100	0
10	$PhCH_2Cl$	THF	0	100[e]	0
11	$PhCH_2Cl$	THF	25	100[e]	0

[a] LAB reagent was prepared with 1 equiv of *n*BuLi. [b] Ratios were obtained by integration of ^{11}B NMR spectra. In ^{11}B NMR spectra, areas of the peaks with different widths cannot be compared by integration. However, comparisons between the same species (e.g., BH_3-NMeR_2) of two different reactions can be made (e.g., entries 8 and 9). [c] When LAB reagent is prepared with 1.1 equiv of *n*BuLi, only the reduction is observed, as previously reported in ref 3. [d] The ratios of the solvents correspond to the solvent in the LAB reagent and additional solvent added to the reaction. [e] LAB reagents with less sterically demanding amine (e.g., LiH_3BPyrr) reduce benzylhalides to hydrocarbons at 25 °C; at 0 °C S_N2 reaction is favored.[9]

To further examine the product distributions resulting from *i*Pr-LAB, 1 M in THF, prepared from 1 equiv of *n*BuLi (Scheme 3), a series of reactions of *i*Pr-LAB were performed, varying halides, temperatures, and solvents. The LAB reagent was prepared in THF and varying amounts of dioxane were added to check the effect of dioxane on the product distribution. Results are summarized in Table 1.

The reaction of *i*Pr-LAB (1 M in THF) with methyl iodide produces a mixture of aminoborane ($BH_2-N(iPr)_2$) and amine−borane ($BH_3-NMe(iPr)_2$). At 0 °C, amination by S_N2 mechanism is the major reaction and as the temperature increased to 65 °C, reduction reaction competed favorably with amination reaction (Table 1, entries 1−3). We also found that the above reaction favors amination product ($BH_3-NMe(iPr)_2$) as the amount of dioxane is increased (Table 1, entries 4−7). On the other hand, *i*Pr-LAB, 1 M in THF, when treated with either TMS−Cl or benzyl chloride at 0 °C and 25 °C, produces exclusively the aminoborane ($BH_2-N(iPr)_2$), the reduction product (Table 1, entries 4−7). These results indicate that the reaction of *i*Pr-LAB with halides can proceed by at least two different mechanisms: conventional S_N2 amination reaction and reduction of alkyl halide by hydride. Apparently with methyl iodide, the amination reaction is favored over the reduction pathway at lower temperatures and in solvents containing increasing amounts of dioxane. However, with TMS−Cl or benzyl chloride, *i*Pr-LAB gives exclusively reduction product, $BH_2-N(iPr)_2$.

The reaction of lithium dimethylaminoborohydride (1 M in THF, prepared using 1 equiv of *n*BuLi) with methyl iodide, bromocyclohexane, or 1-iodooctane generates only the amination product.

To investigate the influence of dioxane on product distribution even further, we prepared *i*Pr-LAB 0.5 M in dioxane[7] from the corresponding amine−borane using 1 equiv of *n*BuLi and treated it with methyl iodide at 0 °C. The analysis of the reaction mixture by ^{11}B NMR showed that amine−borane (q, $\delta = -16$ ppm, $J = 98$ Hz) was the exclusive product (Table 2, entry 1).

The same result was obtained when temperature was increased to 25 °C and 80 °C (Table 2, entries 2 and 3). In the past, we reported that product distribution in the reactions of LAB reagents prepared in THF with benzyl halides could be controlled by temperature.[9] In contrast, LAB reagents prepared in dioxane provided only the amine−borane product regardless of the temperature. To obtain insight into the detailed reaction mechanisms and the effect of the two solvents, the activation free energies were calculated for the reaction of lithium dimethylaminoborohydride with chloro- and bromomethane.

TABLE 2. Reactions of LAB 0.5 M in Dioxane with Methyl Iodide at Various Temperatures[13]

entry	alkyl halide	solvent	T (°C)	$BH_2-N(iPr)_2$	$BH_3-NMe(iPr)_2$
1	CH_3I	dioxane	0	0	100
2	CH_3I	dioxane	25	0	100
3	CH_3I	dioxane	80	0	100

Computational Methods

All geometry optimizations, transition structure searches, and frequency calculations were performed with the Gaussian 98 or Gaussian 03 programs.[14] Transition structures were located with either the QST3 method or by further optimization of a previously located transition structure at a different level of theory using the Opt=TS keyword. Geometry optimizations were performed at the HF/6-31+G(*d*), B3LYP/6-31+G(*d*), and MP2/6-31+G(*d*) levels of theory for both the reactants and transition structures. Harmonic frequencies of the reactants and transition structures were calculated at the HF/6-31+G(*d*) level. The thermal corrections to the free energies at 298.15 K were taken from the frequency calculations

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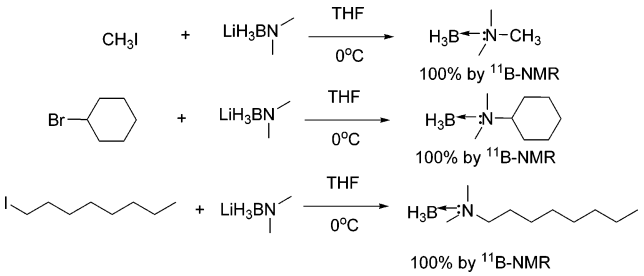
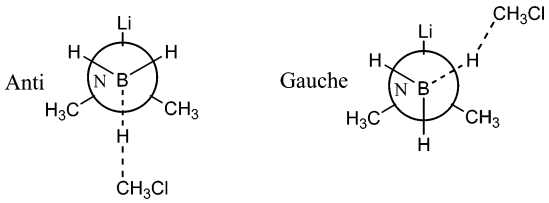
SCHEME 5



SCHEME 6. Newman Projections of the Anti and Gauche Reductions of Chloromethane by Lithium Dimethylaminoborohydride



and were added to the electronic energies at each level of theory to obtain approximate free energies of each reactant and transition structure.

Solvent effects were modeled by placing explicit THF or dioxane ligands on the lithium atoms. In each LAB molecule or transition structure, two THF or one bidentate dioxane ligand was used on each lithium atom. Such an approach to modeling solvation effects on organolithium compounds has been used in other studies[15,16] and generally gives results in agreement with available experimental results.

Discussion of Computational Results

Four reactions were considered in analogy to those previously examined[10] in the gas phase: reduction of chloromethane by the borane hydrogen anti to the lithium, reduction of chloromethane by the borane hydrogen gauche to the lithium (Scheme 6), a conventional S_N2 reaction by the nitrogen atom, and an unusual front-side attack on chloromethane by the nitrogen atom, resulting in an S_N2-like product. The transition-state structures for these reactions are shown in Figure 1.

The data in Table 3 show the calculated activation free energies of reduction and amination of chloromethane by lithium dimethylaminoborohydride. The Hartree−Fock barrier heights are considerably higher than those predicted by the B3LYP method in almost all cases, while the only correlated ab initio method practical for these reactions, the MP2, predicts values that lie in-between but close to the DFT results. The gauche arrangement of the reactive hydride and the LAB lithium atom is energetically favored over the anti conformation with both THF and dioxane solvation. The predominant reaction is predicted to be amination by the S_N2 mechanism, which has a lower activation barrier than the reduction reactions by more than 7 kcal/mol in THF and by about 11 kcal/mol in dioxane.

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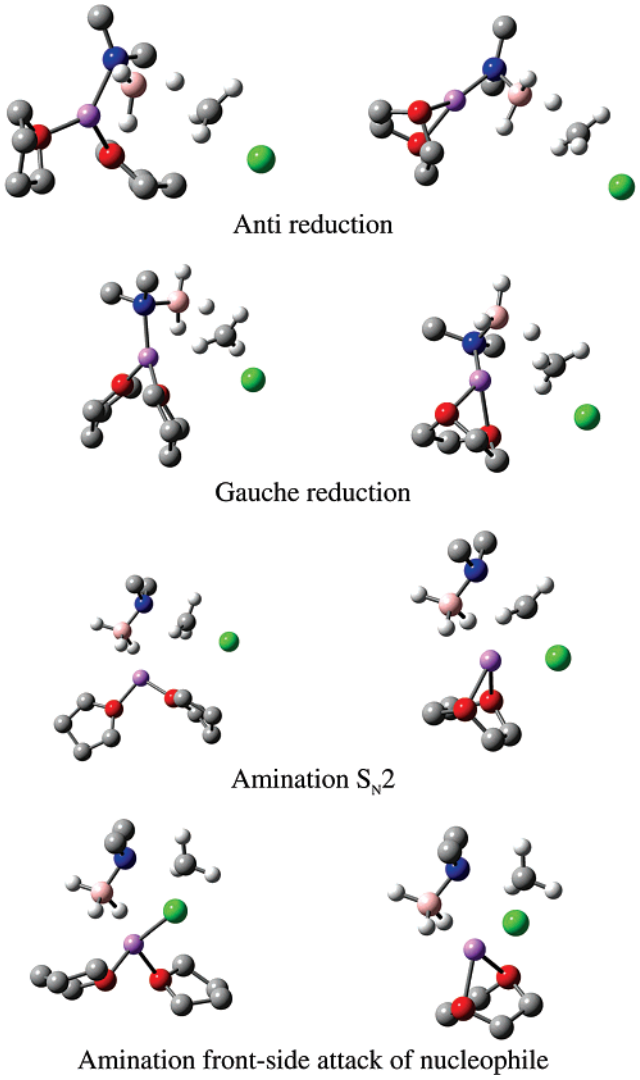

FIGURE 1. Transition states for the reaction of lithium dimethylamineborohydride with chloromethane with explicitly coordinated solvent molecules. Left column: THF; right column: dioxane. Gray: carbon; white: hydrogen; pink: boron; green: chlorine; blue: nitrogen; red: oxygen; violet: lithium.

TABLE 3. Calculated Activation Free Energies for Reaction (in kcal/mol) of Dimethyl LAB with Chloromethane

reaction	solvent	HF	B3LYP	MP2
reduction anti	THF	41.8	32.0	39.8
reduction gauche	THF	41.8	32.3	36.2
S_N2 backside	THF	33.9	25.3	26.9
S_N2 frontside	THF	66.0	48.9	49.3
reduction anti	dioxane	45.1	35.1	44.1
reduction gauche	dioxane	45.3	35.7	39.5
S_N2 backside	dioxane	39.9	29.7	28.3
S_N2 frontside	dioxane	62.6	46.2	48.2

As in the previously reported gas-phase calculations, the front-side amination reaction was a high-energy pathway and will not be considered further in this paper.

The reduction and amination reactions of lithium diisopropylaminoborohydride (*i*Pr-LAB) were modeled with chloromethane and bromomethane. The calculated activation free energies are shown in Tables 4 and 5, respectively. In most cases, B3LYP predicts lower barrier heights relative to the MP2; however, in a few cases, the B3LYP calculations resulted in

TABLE 4. Calculated Activation Free Energies for Reaction (in kcal/mol) of *i*Pr-LAB with Chloromethane

reaction	solvent	HF	B3LYP	MP2
reduction anti	THF	40.5	30.1	38.2
reduction gauche	THF	43.1	32.8	35.6
S_N2	THF	38.6	29.1	31.2
reduction anti	dioxane	43.8	33.6	41.8
reduction gauche	dioxane	46.1	35.8	40.0
S_N2	dioxane	43.6	32.5	30.9

TABLE 5. Calculated Activation Free Energies for Reaction (in kcal/mol) of *i*Pr-LAB with Bromomethane

reaction	solvent	HF	B3LYP	MP2
reduction anti	THF	34.2	25.3	29.2
reduction gauche	THF	34.7	25.1	23.6
S_N2	THF	30.1	21.5	18.2
reduction anti	dioxane	37.5	28.5	32.7
reduction gauche	dioxane	39.4	30.2	30.7
S_N2	dioxane	35.7	25.3	22.0

TABLE 6. Calculated Differences ($\Delta G_{red}^{\ddagger} - \Delta G_{S_N2}^{\ddagger}$) in MP2 Activation Barriers (in kcal/mol) between the Gauche Reduction and Amination Reactions

LAB	CH_3X	THF	dioxane
$LiBH_3N(Me)_2$	CH_3Cl	9.3	11.2
$LiBH_3NiPr_2$	CH_3Cl	4.4	9.1
$LiBH_3NiPr_2$	CH_3Br	5.4	8.7

higher activation barriers. In each case, the Hartree−Fock barriers are higher, considerably so in some cases.

In both THF and dioxane, the most favorable reduction pathways of the alkyl halides were via the gauche conformation. In the gas phase, this was attributed to coordination of the halide leaving group to the lithium atom.[16] In the solvated systems, that coordination is prevented by the steric effects of the coordinated THF and dioxane ligands, and the difference between the anti and gauche activation barriers is correspondingly less. Comparing the data in Tables 3 and 4, we see that increasing the steric bulk from lithium dimethylaminoborohydride to lithium diisopropylaminoborohydride has a minimal effect on the activation free energy of hydride reduction but increases the barrier of the S_N2 reaction by 4.3 and 2.6 kcal/mol in THF and dioxane, respectively. Thus, the net effect of increasing steric strain is to favor the hydride reduction reaction over amination.

The leaving group effect is apparent from comparison of Tables 4 and 5. The bromine leaving group resulted in lower activation free energies between 7 and 13 kcal/mol, compared to the reactions with chloromethane. The leaving group effect was larger in THF than in dioxane by about 3−6 kcal/mol.

Considering that experimentally, the reactions of LAB with organic halides result in nearly 100% yield, the absolute free-energy barriers predicted by all of the calculations appear to be rather high. However, it is sufficient for our purposes to determine the relative barrier heights for reduction versus amination. Thus, in Table 6, the differences in activation barrier heights at the MP2 level of theory for the more favorable gauche reduction pathway and the amination are summarized. This shows that the S_N2 amination is the lowest energy pathway in both solvents, but it becomes significantly more favorable in dioxane compared to THF. This is in qualitative agreement with the experimental data, as further discussed below.

Lithium dimethylaminoborohydride is expected to yield only the amination product in both THF and dioxane because of the much lower (by 9.3 and 11.2 kcal/mol, respectively) activation free energies compared to the reduction pathway. This result is corroborated by the experimental data (Scheme 5), which shows that this LAB (1 M in THF prepared using 1 equiv of *n*BuLi) exclusively yields the amination product with methyl iodide, bromocyclohexane, or 1-iodooctane.

The preference for amination over reduction is less dramatic for the more hindered *i*Pr-LAB in THF and, while the calculations still predict the amination product to be preferred, a small amount of the reduction product cannot be ruled out. This was, in fact, the case with iodomethane (Table 1, entry 1). In dioxane, the difference in barrier heights remains large for *i*Pr-LAB, and only the amination product was found experimentally in dioxane solution (Table 2) and even in THF−dioxane mixtures when the dioxane content is increased (Table 1, entries 4, 5, and 7).

The calculations also lend support to the widely accepted mechanism by which LABs achieve reduction, hydride migration to the halide from the boron. To verify whether an electron-deficient boron atom would indeed allow a negatively charged hydride to migrate, we examined both the Mulliken charges and the charges obtained by fitting the electrostatic potential at points selected by the CHelpG algorithm of Breneman and Wiberg[17] for the TS structures of both gauche and anti reductions of MeCl using *i*Pr-LAB. In each case, both methods of calculating partial charges yield negative charges for the hydrogens attached to the boron. The migrating hydride in the gauche TS is predicted to have a partial charge of −0.13 by both Mulliken and CHelpG methods and −0.05 (Mulliken) and −0.08 (CHelpG) in the anti TS. In contrast, the H atoms attached to the methyl group have charges of +0.30 (Mulliken) and +0.20 (CHelpG) for the gauche, and +0.28 (Mulliken) and +0.16 (CHelpG) for the anti transition states.

Conclusion

The experiments described in this paper show that reduction or amination of alkyl halides by LAB reagents can be regulated by reaction conditions. The amination of methyl iodide is favored over the reduction pathway at lower temperatures and in solvents containing increasing amounts of dioxane. The latter observation is supported by quantum chemistry calculations, which predict that in dioxane, the activation barrier for amination is significantly smaller than that for reduction whereas the difference is less dramatic in THF, and a small amount of the reduction product cannot be ruled out. The reduction product can be exclusively obtained with trimethylsilyl chloride or benzyl chloride regardless of the temperature. The calculations lend support to the hydride transfer mechanism that has been generally accepted as the means by which LABs achieve the reduction of organic halides. In spite of the electron-deficient nature of the boron, a partial negative charge is predicted for the migrating hydrogen in the transition states of both reduction pathways examined (see Figure 1). The controlled reactivity of LAB reagents toward alkyl halides demonstrates, once again, their dual properties as both hydride and amine transfer reagents.

Experimental

General Methods. All reactions were performed in oven-dried, nitrogen-cooled glassware. All air- and moisture-sensitive compounds were introduced via syringes or cannula through a rubber septum. THF was distilled from sodium-benzophenone. Compounds

(17) Breneman, C. M; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.

were not isolated. All reactions were analyzed by ^{11}B NMR. ^{11}B NMR spectra were recorded neat. Chemical shifts are reported relative to external standard BF_3*Et_2O (δ = 0 ppm).

General Procedure for the Preparation of LAB Reagent 1 M Solution in THF/Hexanes. Diisopropylamine (5.06 g, 7 mL, 50 mmol, 1 equiv) was mixed with anhydrous THF (18 mL) in a serum vial. The solution was cooled to 0 °C (ice bath), and borane dimethylsulfide (5 mL, 10 M, 50 mmol, 1eq) was added dropwise via syringe and was stirred for 1 h at 0 °C and was analyzed by ^{11}B NMR. The analysis showed the solution to be diisopropylamine−borane = −21.08 (q, J = 95.3 Hz). Then, *n*-butyllithium in hexanes (20 mL, 2.5 M, 50 mmol, 1 equiv) was measured in oven-dried graduated cylinder and was added dropwise via cannula needle to the solution of amine−borane at 0 °C. After stirring at 0 °C for 1 h, an aliquot was taken and analyzed by ^{11}B NMR (80.25 MHz, THF) which showed the solution to be lithium diisopropylaminoborohydride = −23.64 (q, J = 83.4 Hz). LAB reagent was transferred to an oven-dried, nitrogen-cooled ampule via a cannula needle.

Although the chemical shift of the corresponding amine−borane complex is virtually identical to that of the LAB, the *J*-values of the amine−borane complex is different and range from 95 to 98 Hz.

General Procedure for the Reaction of LAB Reagent with Alkyl Halides. The following procedure for reaction of *i*Pr-LAB reagent with methyl iodide (Table 1, entry 1) is representative. A 50-mL, round-bottom flask equipped with magnetic stirring bar and fitted with rubber septa was charged with lithium diisopropylaminoborohydride (1 M in THF, 5 mL, 5 mmol, 1 equiv) and 5 mL of anhydrous THF. The reaction was cooled to 0 °C (ice bath) and methyl iodide (0.31 mL, 5 mmol, 1 eq) was added slowly dropwise (caution: v. exothermic rxn). After all methyl iodide was added, the ice bath was removed and reaction was stirred at room temperature for 1 h. After 1 h, the ^{11}B NMR (80.25 MHz, THF) showed formation of diisopropyl aminoborane complex (δ= 35.33 ppm, t, J = 125.11 Hz) and *N*,*N*,*N*-diisopropylmethyl amine borane (δ = −15.61 ppm (q, J = 98.31 Hz).

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Supporting Information Available: Complete experimental procedures and data on compounds are provided (PDF). Tables of MP2 optimized geometries and energies of all reactants and transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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