JOC Article

Reductions of Aliphatic and Aromatic Nitriles to Primary Amines with Diisopropylaminoborane

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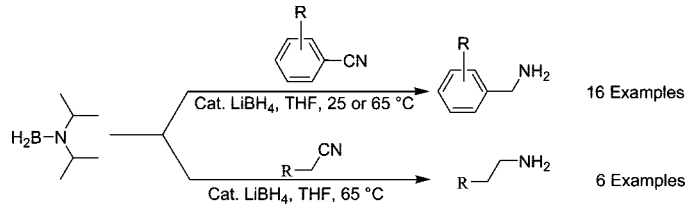

Diisopropylaminoborane [$BH_2N(iPr)_2$] in the presence of a catalytic amount of lithium borohydride ($LiBH_4$) reduces a large variety of aliphatic and aromatic nitriles in excellent yields. $BH_2N(iPr)_2$ can be prepared by two methods: first by reacting diisopropylamineborane [$(iPr)_2N:BH_3$] with 1.1 equiv of *n*-butyllithium (*n*-BuLi) followed by methyl iodide (MeI), or reacting *i*PrN:BH_3 with 1 equiv of *n*-BuLi followed by trimethylsilyl chloride (TMSCl). $BH_2N(iPr)_2$ prepared with MeI was found to reduce benzonitriles to the corresponding benzylamines at ambient temperatures, whereas diisopropylaminoborane prepared with TMSCl does not reduce nitriles unless a catalytic amount of a lithium ion source, such as $LiBH_4$ or lithium tetraphenylborate ($LiBPh_4$), is added to the reaction. The reductions of benzonitriles with one or more electron-withdrawing groups on the aromatic ring generally occur much faster with higher yields. For example, 2,4-dichlorobenzonitrile was successfully reduced to 2,4-dichlorobenzylamine in 99% yield after 5 h at 25 °C. On the other hand, benzonitriles containing electron-donating groups on the aromatic ring require refluxing in tetrahydrofuran (THF) for complete reduction. For instance, 4-methoxybenzonitrile was successfully reduced to 4-methoxybenzylamine in 80% yield. Aliphatic nitriles can also be reduced by the $BH_2N(iPr)_2$/cat. $LiBH_4$ reducing system. Benzyl cyanide was reduced to phenethylamine in 83% yield. $BH_2N(iPr)_2$ can also reduce nitriles in the presence of unconjugated alkenes and alkynes such as the reduction of 2-hexynenitrile to hex-5-yn-1-amine in 80% yield. Unfortunately, selective reduction of a nitrile in the presence of an aldehyde is not possible as aldehydes are reduced along with the nitrile. However, selective reduction of the nitrile group at 25 °C in the presence of an ester is possible as long as the nitrile group is activated by an electron-withdrawing substituent. It should be pointed out that lithium aminoborohydrides (LABs) do not reduce nitriles under ambient conditions and behave as bases with aliphatic nitriles as well as nitriles containing acidic α-protons. Consequently, both LABs and $BH_2N(iPr)_2$ are complementary to each other and offer methods for the selective reductions of multifunctional compounds.

Introduction

Aliphatic amines are among the most important organic intermediates in the chemical industry with a worldwide production in the year 2000 of several 100 000 tons per annum.[1] These compounds are important in a variety of industries including agrochemicals, dyes, drugs, surfactants, and plastics; as auxiliaries for the rubber, textile, and paper industries; and as anticorrosion agents and process chemicals for gas scrubbing.[1] Examples of compounds with aliphatic amines that are used in these industries are shown in Figure 1.

Due to their interesting physiological properties, amines are extremely important functionalities in numerous biologically active pharmaceuticals used worldwide. For example, central

(1) Aliphatic Amines In *Ullmann's Encyclopedia of Industrial Chemistry*, 7th ed.; Wiley-VCH: Weinheim, Germany, 2008; Vol. A2, p 2.

10.1021/jo8023329 CCC: $40.75
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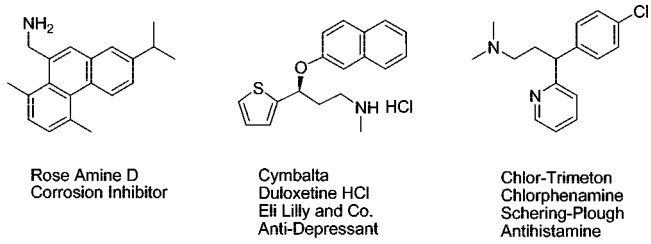


FIGURE 1. Examples of aliphatic amines used in industry.

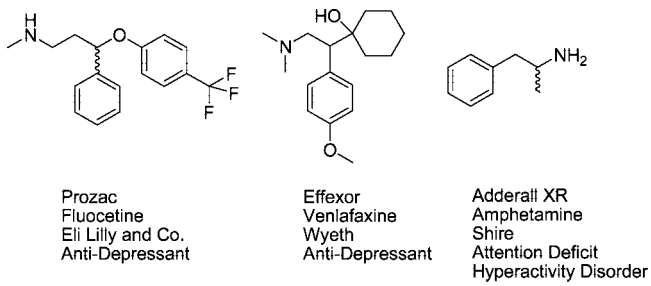
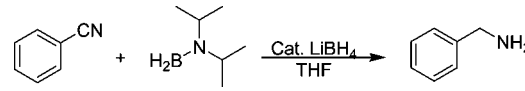


FIGURE 2. Example of CNS drugs with amine side chains.

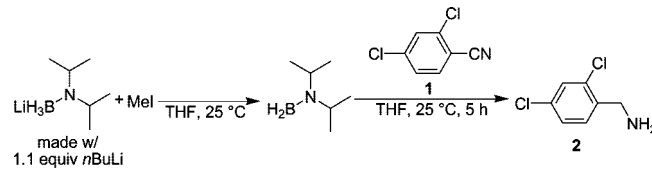
nervous system (CNS) drugs make up the largest sector of pharmaceuticals sold worldwide. It is interesting to look at some of the structures of successful CNS drugs as they contain amine side chains (Figure 2).[2]

With the growing repertoire of biologically relevant nitrogenous molecules, there is an emerging need for efficient synthetic methods to prepare amines.[3,4] A frequently applied process in the pharmaceutical industry is the heterogeneous catalytic hydrogenation of nitriles.[4] Nitriles can also be reduced utilizing a variety of hydride reducing agents which often require transition metal salts as catalysts.[5−8] However, these methods suffer from harsh reaction conditions such as high temperatures, pressures, use of toxic transition metal catalysts, or pyrophoric reducing agents. Recently, we have discovered the synthesis of the nonpyrophoric diisopropylaminoborane [$BH_2N(iPr)_2$] from the corresponding lithium diisopropylaminoborohydride (*i*PrLAB).[9−11] Herein we report the reduction of various nitriles to the corresponding amines by $BH_2N(iPr)_2$ in the presence of a catalytic amount of a lithium salt, such as lithium borohydride ($LiBH_4$) (Scheme 1).

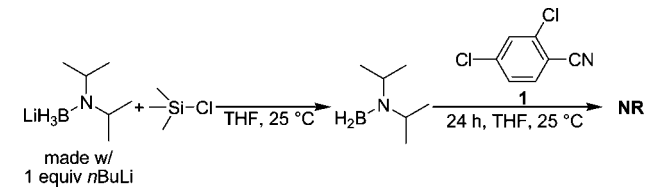
SCHEME 1. Reduction of a Nitrile by the $BH_2N(iPr)_2$/cat. $LiBH_4$ Reducing System



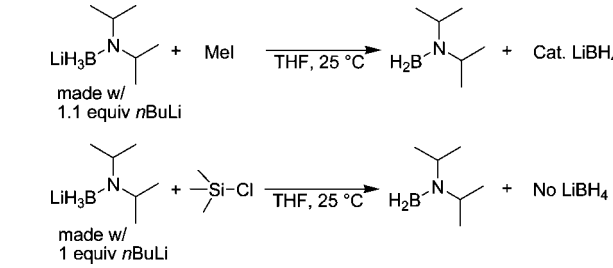
SCHEME 2. Reduction of 2,4-Dichlorobenzonitrile with $BH_2N(iPr)_2$ Made with 1.1 equiv of *n*-BuLi and MeI



SCHEME 3. Reduction of 2,4-Dichlorobenzonitrile with $BH_2N(iPr)_2$ Made with TMSCl



SCHEME 4. Differences in the Reactivity of Aminoboranes



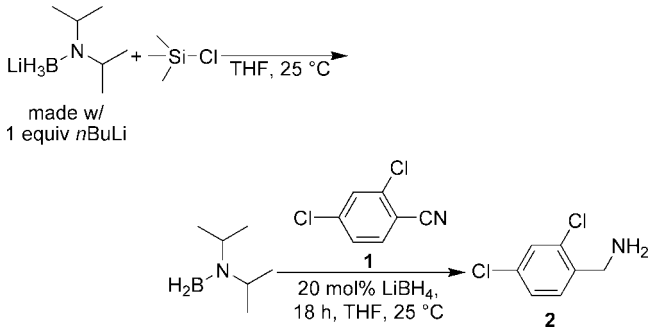
Results and Discussion

Reductions of Nitriles by $BH_2N(iPr)_2$. During our exploratory investigations of the properties of $BH_2N(iPr)_2$, we have discovered that $BH_2N(iPr)_2$, generated in situ by reacting diisopropylamineborane [$(iPr)_2N{:}BH_3$] with 1.1 equiv of *n*-butyllithium (*n*-BuLi) followed by methyl iodide (MeI), reduced nitriles to their corresponding amines.[10,11] The reduction of 2,4-dichlorobenzonitrile **1** by 2 equiv of $BH_2N(iPr)_2$ was complete after 5 h of stirring at 25 °C yielding 99% of the corresponding benzyl amine **2** after a simple acid−base workup. When this reaction was performed with 1 equiv of $BH_2N(iPr)_2$, only 49% of the corresponding amine was obtained even after 24 h. It was apparent that this reaction requires 2 equiv of $BH_2N(iPr)_2$ for complete reduction (Scheme 2).

We have previously shown that $BH_2N(iPr)_2$ can be synthesized by other routes.[10] It was of interest to see if $BH_2N(iPr)_2$ prepared by other methods could also be used in the reduction of nitriles. Consequently, $BH_2N(iPr)_2$ was synthesized by reacting *i*PrN:BH_3 with 1 equiv of *n*-BuLi followed by trimethylsilyl chloride (TMSCl), which was then reacted with **1** (Scheme 3).[11] We were surprised that there was no reduction even after 24 h and **1** was recovered unchanged. Since aminoboranes are not isolated but prepared in situ, it is clear

(2) Barton, C. *CNS Drug Discoveries: what the future holds*; Espicom Business Intelligence: West Sussex, UK, 2006; p 1.
(3) (a) Buehler, C. A.; Pearson, D. E. *Survey of Organic Synthesis*; Wiley-Interscience: New York, 1970; Vol. 1, pp 413−512. (b) Mitsunobu, O. *Comprehensive Organic Synthesis*; Trost, R. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 6, p 65.
(4) (a) Rappoport, Z. *The Chemistry of the Cyano Group*; Wiley Interscience: New York, 1970; pp 307−340. (b) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th ed.; Wiley: Toronto, Canada, 1992; p 1276.
(5) (a) Wade, R. C. *J. Mol. Catal.* **1983**, *18*, 273. (b) Satoh, S. *Tetrahedron Lett.* **1969**, *10*, 4555. (c) Egli, R. A. *Helv. Chim. Acta* **1970**, *53*, 47. (d) Khurana, J. M.; Kukreja, G. *Synth. Commun.* **2002**, *32*, 1265.
(6) (a) Nystrom, F.; Brown, W. G. *J. Am. Chem. Soc.* **1948**, *70*, 3738. (b) Amundsen, L. H.; Nelson, L. S. *J. Am. Chem. Soc.* **1951**, *73*, 242. (c) Brown, H. C.; Weissman, P. M.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1458. (d) Soffer, L. M.; Parrotta, E. W. *J. Am. Chem. Soc.* **1954**, *76*, 3580.
(7) (a) Hudlicky, M. *Reductions in Organic Chemistry*, 2nd ed.; ACS Monograph 188; American Chemical Society: Washington, DC, 1996. (b) Yoon, N. M.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 2927. (c) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1960**, *82*, 681. (d) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464.
(8) Pasumansky, L.; Goralski, C. T.; Singaram, B. *Org. Process Res. Dev.* **2006**, *10*, 959.
(9) Fisher, G. B.; Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1992**, *33*, 4533.
(10) Pasumansky, L.; Haddenham, D.; Clary, J. W.; Fisher, G. B.; Goralki, C. T.; Singaram, B. *J. Org. Chem.* **2008**, *73*, 1898–1905.
(11) Pasumansky, L.; Collins, C. J.; Pratt, L. M.; Nguyen, N. V.; Ramachandran, B.; Singaram, B. *J. Org. Chem.* **2007**, *72*, 971–976.

SCHEME 5. Reduction of 2,4-Dichlorobenzonitrile with $BH_2N(iPr)_2$, Prepared from *i*PrLAB and TMSCl, in the Presence of a Catalytic Amount of $LiBH_4$



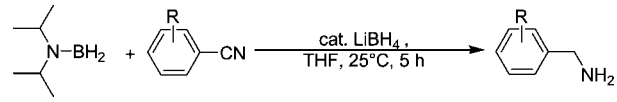
that the source of the aminoborane plays an important role in this reaction. We postulated that $BH_2N(iPr)_2$ prepared from 1.1 equiv of *n*-BuLi and MeI may have a different reactivity than $BH_2N(iPr)_2$ prepared from 1 equiv of *n*-BuLi and TMSCl. Upon re-examining the ^{11}B NMR spectra of $BH_2N(iPr)_2$ prepared by both methods, it was observed that $BH_2N(iPr)_2$ made from 1.1 equiv of *n*-BuLi and MeI contained a trace amount of $LiBH_4$. However, $BH_2N(iPr)_2$ prepared with 1 equiv of *n*-BuLi and TMSCl did not contain any $LiBH_4$ (Scheme 4).[12] This observation led us to formulate the hypothesis that $LiBH_4$ is acting as a catalyst in the reduction of nitriles with $BH_2N(iPr)_2$.

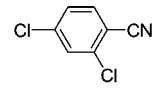
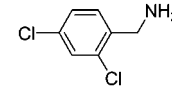
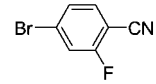
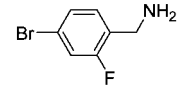
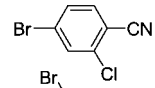
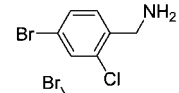
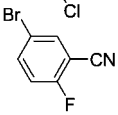
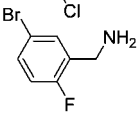
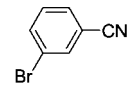
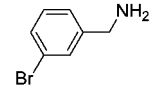
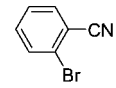
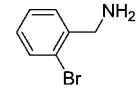
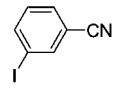
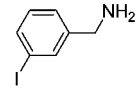
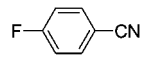
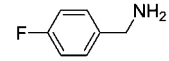
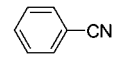
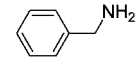
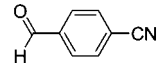
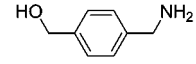
We have tested this hypothesis by reacting pure $BH_2N(iPr)_2$ prepared from 1 equiv of *n*-BuLi and TMSCl with **1** in the presence of 10 mol % of $LiBH_4$.[12] The nitrile was completely reduced after 18 h at 25 °C and the corresponding benzyl amine was isolated in 90% yield (Scheme 5). These results clearly indicate that $LiBH_4$ is effective in catalyzing the reduction of nitriles by $BH_2N(iPr)_2$. It should be noted that $LiBH_4$ alone does not reduce nitriles in THF even at 65 °C.[13] This catalysis is most likely promoted through lithium ion coordinating to the nitrogen atom of the nitrile, thus activating the nitrile group for reduction by $BH_2N(iPr)_2$.

The generality of this reaction was investigated by reducing a series of benzonitriles with $BH_2N(iPr)_2$ at 25 °C to obtain the corresponding benzyl amines. Substituted benzonitriles reduced by $BH_2N(iPr)_2$ at 25 °C furnished the corresponding benzyl amine products in very good to excellent isolated yields (Table 1).

Reductions of benzonitriles with one or more electron-withdrawing groups on the aromatic ring are generally faster and result in higher yields (Table 1, entries 1−8). For example, 2,4-dichlorobenzonitrile was successfully reduced to 2,4-dichlorobenzylamine in 99% yield (Table 1, entry 1). Similarly, 4-bromo-2-chlorobenzonitrile was reduced to 4-bromo-2-chlorobenzylamine in almost quantitative 99% yield (Table 1, entry 3). Unfortunately, selective reduction of a nitrile in the presence of an aldehyde was not successful. During the reduction of 4-cyanobenaldehyde both the nitrile and the aldehyde were reduced to yield [4-(aminomethyl)phenyl]methanol in 80% yield (Table 1, entry 10). We should point out that in the case of the *o*-fluorobenzonitriles the corresponding benzylamine is obtained during the reaction with aminoboranes (Table 1, entries 2 and 4), whereas lithium aminoborohydride (LAB) reagents predominately afford the tandem displacement/reduction product, 2-(dialkylamino)benzylamine.[14] Thus, the aminoborane reduction methodology is complementary to the LAB tandem displacement/reduction reaction (Scheme 6).

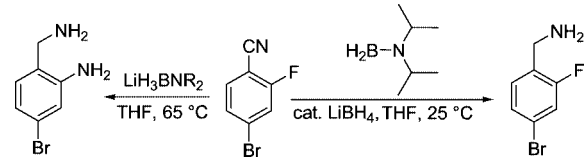
TABLE 1. $BH_2N(iPr)_2$ Reduction of Benzonitriles at 25 °C[a]



Entry	Nitrile	Benzyl Amine	Isolated Yield
1			99
2			90
3			99
4			95
5			94
6			94
7			95
8			97
9			60
10			80

[a] Reactions were carried out on 5 mmol scale with 1 equiv of nitrile and 2 equiv of aminoborane made with 1.1 equiv of *n*-BuLi and MeI.

SCHEME 6. Reduction or Tandem Displacement/Reduction of 4-Bromo-2-fluorobenzonitrile



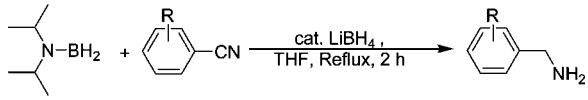
During our investigation on the generality of the reduction of nitriles with the $BH_2N(iPr)_2$/cat. $LiBH_4$ system, we found that benzonitriles with a sterically crowded nitrile or electron-donating groups required higher temperatures for complete reduction. Consequently, a series of nitriles were reduced by

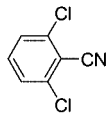
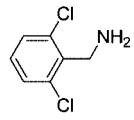
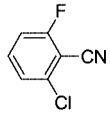
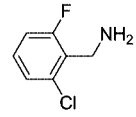
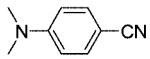
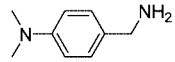
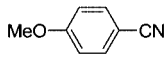
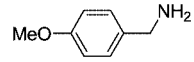
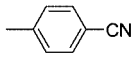
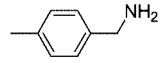
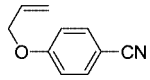
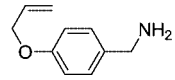
(12) It should be noted that $BH_2N(iPr)_2$ can be prepared from *i*PrLAB and TMSCl by using a slight excess of *n*-BuLi so that it contains a catalytic amount of $LiBH_4$. $BH_2N(iPr)_2$ prepared in this manner is also able to reduce nitriles with no additives.

(13) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702.

(14) (a) Thomas, S.; Collins, C. J.; Cuzens, J. R.; Spiciarich, D.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **2001**, *66*, 1999–2004. (b) Thomas, S.; Collins, C. J.; Goralski, C. T.; Singaram, B. *Chem. Innovation* **2000**, *30*, 31.

TABLE 2. Diisopropylaminoborane Reduction of Benzonitriles in Refluxing THF[a]



Entry	Nitrile	Benzyl Amine	Isolated Yield
1			77
2			70
3			93
4			80
5			80
6			85

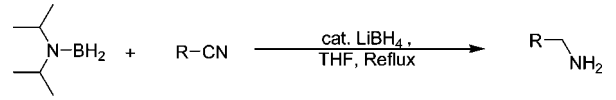
[a] Reactions were carried out on 5 mmol scale with 1 equiv of nitrile and 2 equiv of aminoborane made with 1.1 equiv of *n*-BuLi and MeI.

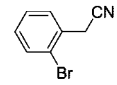
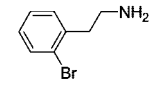
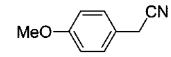
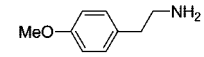
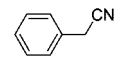
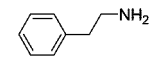
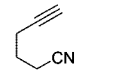
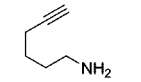
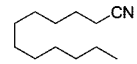
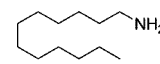
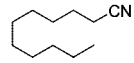
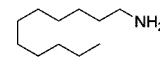
$BH_2N(iPr)_2$ in refluxing THF producing the corresponding benzylamine products in very good to excellent yields (Table 2).

Reductions of benzonitriles with electron-donating groups on the aromatic ring require heating to 65 °C in order to go to completion (Table 2, entries 3−6). For example, 4-methoxybenzonitrile was successfully reduced to 4-methoxybenzylamine in 80% yield after 2 h of refluxing in THF (Table 2, entry 4). Benzonitriles containing an alkene that is not conjugated with the nitrile group can also be reduced selectively without affecting the C−C multiple bond (Table 2, entry 6). For example, 4-(allyloxy)benzonitrile is reduced to corresponding (4-(allyloxy)phenyl)methanamine in 85% yield after 2 h of reflux in THF. Additionally, 2,6-dichlorobenzonitrile was reduced to the corresponding amine in 77% yield after 2 h of refluxing in THF (Table 2, entry 2). The lower yield and requirement for increased temperature is attributed to the steric hindrance around the reduction site.

Aliphatic nitriles can also be reduced by the $BH_2N(iPr)_2$/cat. $LiBH_4$ system. It should be pointed out that many of the current methods cannot reduce aliphatic nitriles even under extended reflux.[6,15,16] The reductions do not occur because the hydrogen α to the nitrile is acidic and is deprotonated by these reagents, thus halting the reduction. The $BH_2N(iPr)_2$/cat. $LiBH_4$ reducing system does not suffer from this problem and a series of aliphatic nitriles were reduced to their corresponding amines in refluxing THF in excellent yields (Table 3).

TABLE 3. Diisopropylaminoborane Reduction of Aliphatic Nitriles in Refluxing THF[a]



Entry	Nitrile	Aliphatic Amine	Time (h)	Isolated Yield
1			18	80
2			18	94
3			24	83[b]
4			12	80[c]
5			18	99
6			12	95

[a] Reactions were carried out on 5 mmol scale with 1 equiv of nitrile and 2 equiv of aminoborane made with 1.1 equiv of *n*-BuLi and MeI. [b] Crude yield. See ref 17. [c] Isolated as a benzamide.

A variety of aliphatic nitriles can be reduced by the $BH_2N(iPr)_2$/cat. $LiBH_4$ reducing system in refluxing THF (Table 3). Benzyl cyanides are notoriously hard nitriles to reduce because of the extreme acidity of the protons α to the nitrile. This acidity leads to deprotonation instead of reduction with most reducing agents. In contrast, the $BH_2N(iPr)_2$/cat. $LiBH_4$ reducing system reduces a variety of benzyl cyanides to their corresponding phenethylamines in excellent yields.[17] The reduction of benzyl cyanides allows for the easy preparation of a variety of biologically active compounds to be made from similar benzyl nitriles (Figure 2). Aliphatic nitriles that contain an alkyne that is not conjugated with the nitrile group can be reduced selectively without affecting the C−C multiple bond (Table 3, entry 4). For example, 2-hexynenitrile is reduced to the corresponding hex-5-yn-1-amine in 80% yield after 18 h of reflux in THF. These results demonstrate that it is possible to reduce a wide variety of nitriles to the corresponding amines in very high yields with this $BH_2N(iPr)_2$/cat. $LiBH_4$ reducing system, which complements the reduction of nitriles by BH_3:THF.

Catalysis of $BH_2N(iPr)_2$ Reduction of Nitriles with Other Lithium Ion Sources. In the previous section, we have shown that various nitriles can be reduced by $BH_2N(iPr)_2$ in the presence of a catalytic amount of $LiBH_4$. The $LiBH_4$ is thought to activate the nitrile for reduction by $BH_2N(iPr)_2$ through lithium ion coordination. If this reduction is indeed promoted through lithium ion coordination, then other sources of lithium ions should also promote the reduction. In an effort to test this hypothesis, the reduction of **1** was attempted with pure $BH_2N(iPr)_2$, prepared from *i*PrLAB made with 1 equiv of *n*-BuLi

(15) Collins, C. J.; Fisher, G. B.; Reem, A.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1997**, *38*, 529.
(16) (a) Brown, H. C.; Kim, K. C.; Krishnamurthy, S. J. *J. Org. Chem.* **1980**, *45*, 1. (b) Malek, J. *Tetrahedron Lett.* **1968**, *9*, 3303.

(17) The crude yield of phenethylamine is reported. A small amount of the crude phenethylamine was purified by forming the oxalate salt and then recrystalizing from methanol.

SCHEME 7. Reduction of 2,4-Dichlorobenzonitrile with $BH_2N(iPr)_2$, Prepared from 1 equiv of *n*-BuLi and TMSCl, in the Presence of a Catalytic Amount of a Lithium Ion Additive

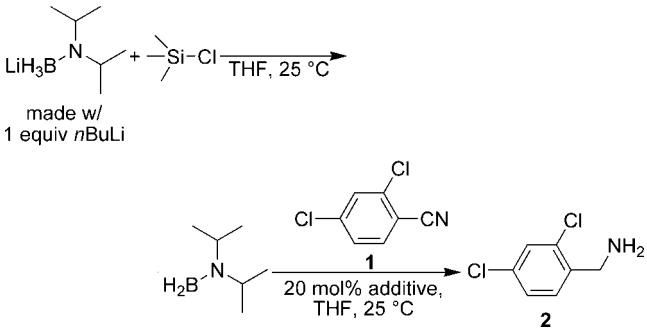
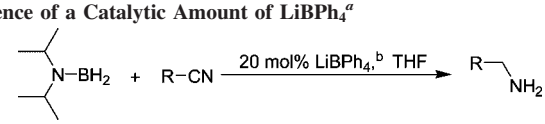
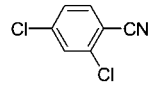
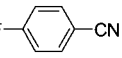
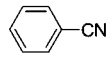
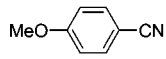
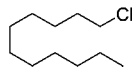


TABLE 4. Reduction of Nitriles by Pure $BH_2N(iPr)_2$ in the Presence of a Catalytic Amount of $LiBPh_4$[a]



Entry	Nitrile	Temp (°C)	Time (h)[c]	Yield[d]
1		25	5	91
2		25	5	98
3		25	5	98
4		65	2	86
5		65	18	94

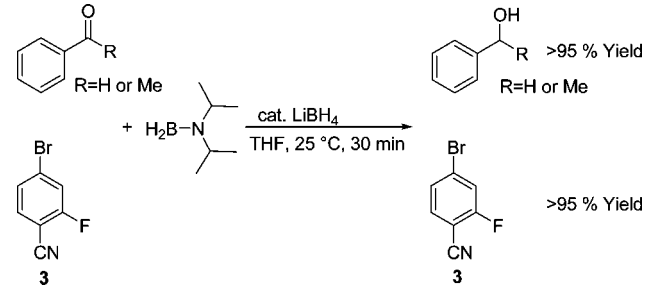
[a] Reactions were carried out on 3 mmol scale with 1 equiv of nitrile, 2 equiv of aminoborane, and 20 mol % of $LiBPh_4$. Reaction progress was monitored via TCL (2:1 hexanes/ethyl acetate) and IR. [b] See ref 18. [c] Time for complete reduction to occur. [d] Determined by NMR.

and TMSCl, in the presence of a catalytic amount of various lithium ion additives (Scheme 7).

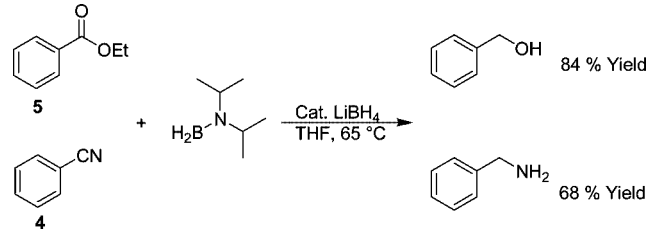
Lithium salts, such as LiCl, LiBr, LiI, and $LiBF_4$, did not catalyze this reduction. Fortunately, lithium tetraphenylborate ($LiBPh_4$)[18] promotes the reduction of a nitrile by $BH_2N(iPr)_2$. We believe that the lithium ions in the other sources are bound too tightly by their counterions, interfering with their ability to catalyze the reduction. We also tried boron trifluoride etherate (BF_3:Et_2O) and phenyllithium (PhLi), the precursors of $LiBPh_4$, to check their catalytic activity in this reaction. We discovered that neither of these precursors alone promoted the reduction of nitriles with $BH_2N(iPr)_2$. We then tested whether $LiBPh_4$ can catalyze the reduction of other nitriles. A representative set of nitriles was reduced with pure $BH_2N(iPr)_2$ in the presence of a catalytic amount of $LiBPh_4$ (Table 4).

(18) The lithum tetraphenylborate ($LiBPh_4$) was synthesized by reacting 4 equiv of phenyllithium (PhLi) with 1 equiv of trifluoroborane etherate (BF_3:Et_2O) in tetrahydrofuran (THF) under an inert atmosphere.

SCHEME 8. Competitive Reduction of 4-Bromo-2-fluorobenzonitrile and Benzaldehyde at 25 °C



SCHEME 9. Competitive Reduction of Benzonitrile and Ethyl Benzoate at 65 °C



We have found that various nitriles can be reduced by pure $BH_2N(iPr)_2$, made with 1 equiv of *n*-BuLi and TMSCl, using $LiBPh_4$ as a catalyst (Table 4). These results further support the hypothesis that nitriles are activated for the reduction by $BH_2N(iPr)_2$ through lithium ion coordination.

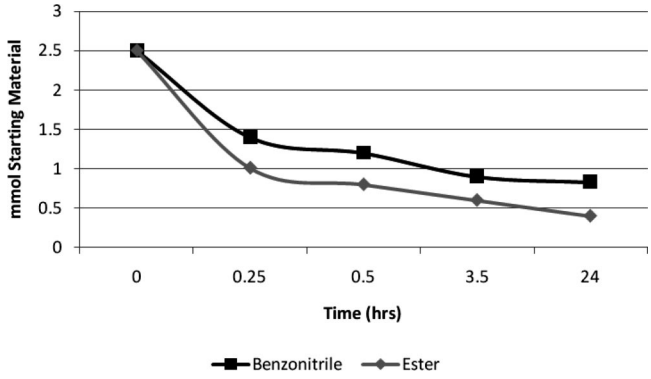
Chemoselective Reductions of Nitriles. The development and use of reagents that will selectively transform a given functional group in a multifunctional compound is highly desirable, especially in reductive transformations. To determine the chemoselectivity in the reduction of nitriles with the $BH_2N(iPr)_2/LiBH_4$ system in the presence of other functional groups, several experiments were conducted.

As observed with 4-cyanobenzaldehyde (Table 1, entry 10), both nitrile and aldehyde are reduced by $BH_2N(iPr)_2$ under standard reaction conditions. It should be noted that $BH_2N(iPr)_2$ cannot reduce aldehydes without lithium salt promotion.[10] To investigate if a nitrile can be reduced faster than an aldehyde in an intermolecular reaction, a competitive reduction of 4-bromo-2-fluorobenzonitrile **3** and benzaldehyde was performed. It was found that the very reactive benzaldehyde was reduced to benzyl alcohol in 30 min, leaving 4-bromo-2-fluorobenzonitrile **3** intact (Scheme 8). Ketones are also reduced selectively by the $BH_2N(iPr)_2$/cat. $LiBH_4$ system.[10]

We have previously shown that the $BH_2N(iPr)_2$/cat. $LiBH_4$ reducing system is able to reduce esters at 65 °C.[10] To determine if it is possible to reduce a nitrile in the presence of an ester at 65 °C, a competitive reaction between benzonitrile **4** and ethyl benzoate **5** was conducted (Scheme 9). Samples were collected at different intervals and analyzed on a GC with use of an internal standard (Chart 1). This demonstrated that **5** was reduced faster then **4** at 65 °C. However, the results show that nitriles without electron-withdrawing groups cannot be selectively reduced in the presence of esters.

Earlier it was established that nitriles containing electron-withdrawing groups, such as halogens, are readily reduced to primary amines at 25 °C in 5 h. Consequently, it should be possible to selectively reduce an aromatic nitrile containing an electron-withdrawing group in the presence of an ester at 25 °C. Accordingly, a competitive reaction between **3** and **5**

CHART 1. Competitive Reduction of Benzonitrile and Ethyl Benzoate at 65 °C



SCHEME 10. Competitive Reduction of 4-Bromo-2-fluorobenzonitrile and Ethyl Benzoate at 25 °C

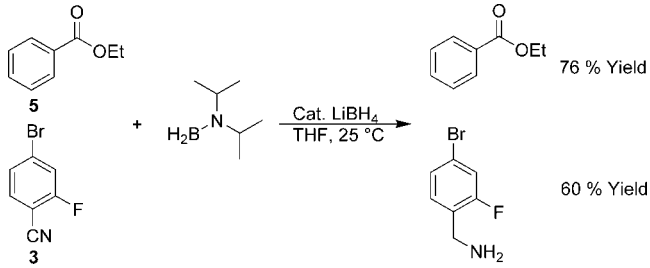
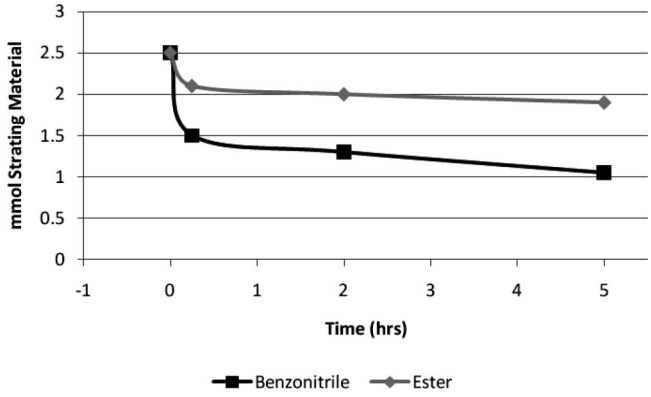


CHART 2. Competitive Reduction of 4-Bromo-2-fluorobenzonitrile and Ethyl Benzoate at 25 °C



was conducted (Scheme 10). Samples were collected at different intervals and analyzed by GC by using an internal standard (Chart 2). As expected, the reduction of **3** occurred faster than **5**, demonstrating that selective reduction of nitriles in the presence of esters is possible if the aryl nitrile contains an electron-withdrawing substituent on the aromatic ring.

Conclusion

We have shown that $BH_2N(iPr)_2$ in the presence of a catalytic amount of $LiBH_4$ reduces nitriles under exceedingly mild reaction conditions affording the corresponding primary amines in excellent yields. For example, treatment of 4-bromo-2-chlorobenzonitrile with 2 equiv of $BH_2N(iPr)_2$ for 5 h at 25 °C provides 4-bromo-2-chlorobenzylamine in 99% yield. Both aromatic and aliphatic nitriles can also be reduced by this method in high yields. Nitriles with electron-withdrawing groups are reduced faster then aromatic esters.

It is important to note that $BH_2N(iPr)_2$ shows different reactivity when prepared in situ by different methods, since a trace amount of $LiBH_4$ in the solution of $BH_2N(iPr)_2$ dramatically changes its reactivity. An addition of a catalytic amount of $LiBH_4$ or $LiBPh_4$ to pure $BH_2N(iPr)_2$, made with 1 equiv of *n*-BuLi and TMSCl, reduces nitriles to the corresponding primary amines. LAB, the precursor to aminoboranes, can reduce unactivated aromatic nitriles sluggishly at 65 °C, but gives tandem displacement/reduction with halogen activated aryl nitriles at 65 °C. It should also be pointed out that LAB reagents deprotonate the α-proton of aliphatic nitriles, preventing reduction. In summary, we have developed a mild and efficient method for the reduction of aromatic and aliphatic nitriles.

Experimental Section

General Procedure for the Reduction of a Nitrile by Pure $BH_2N(iPr)_2$ and a Catalytic Amount of $LiBH_4$. The following procedure for the reduction of 2,4-dichlorobenzonitrile by pure $BH_2N(iPr)_2$ is representative. To a 50-mL round-bottomed flask equipped with magnetic stir bar and fitted with a rubber septum was added 2,4-dichlorobenzonitrile (0.86 g, 5 mmol). The flask was charged with pure diisopropylaminoborane[10] (10 mL, 1 M in THF, 10 mmol) and $LiBH_4$ (0.5 mL, 2 M in THF, 20 mol %). The reaction was complete in 18 h at 25 °C as evidenced by TLC (Hex:EtOAc 2:1). The reaction mixture was cooled to 0 °C (ice bath) and unreacted $BH_2N(iPr)_2$ was quenched with 3 M HCl (7 mL) (**caution**: hydrogen evolution). The acidic solution was stirred for 30 min and then made basic with NaOH pellets to pH ∼10. 2,4-Dichlorobenzylamine was extracted with 1:1 Et_2O:THF (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo (25 °C, 1 Torr) to afford 2,4-dichlorobenzylamine as a light-yellow oil (90% yield).

General Procedure for the Reduction of a Nitrile by $BH_2N(iPr)_2$, Prepared from *i*PrLAB and MeI. The following procedure for the reduction of 2,4-dichlorobenzonitrile by $BH_2N(iPr)_2$ is representative. To a 50-mL round-bottomed flask equipped with magnetic stir bar and fitted with a rubber septum was added 2,4-dichlorobenzonitrile (0.86 g, 5 mmol). The flask was charged with diisopropylaminoborane (20 mL, 0.5 M in THF, 10 mmol),[10] obtained from *i*PrLAB made with 1.1 equiv of *n*-BuLi and MeI and upon addition the solution turns bright red. The reaction goes to completion in 5 h at 25 °C, as evidenced by TLC (Hex:EtOAc 2:1) analysis. The reaction mixture was cooled to 0 °C (ice bath) and unreacted $BH_2N(iPr)_2$ was quenched with 3 M HCl (7 mL) (**caution**: hydrogen evolution). The acidic solution was stirred for 30 min and then basified with NaOH pellets to pH ∼10. The aqueous layer was extracted with 1:1 Et_2O:THF (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo (25 °C, 1 Torr) to afford 2,4-dichlorobenzylamine as a light-yellow oil (99% yield).

2,4-Dichlorobenzylamine (Table 1, entry 1): yellowish oil, 99% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 2H), 3.83 (s, 2H), 7.23 (d, 1H, J = 8.75 Hz), 7.33 (d, 1H, J = 8 Hz), 7.36 (d, 1H, J = 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.1, 127.2, 129.2, 129.2, 133.5, 134.1, 138.6; exact mass *m*/*z* calcd for $C_7H_7Cl_2N$, HRMS (70 eV) *m*/*z* (M^+ + 1) calcd 174.99555, found 174.99603.

2,6-Dichlorobenzylamine (Table 2, entry 1): yellowish oil, 77% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (br s, 2H), 4.11 (s, 2H), 7.12 (t, 1H, J = 8.5 Hz), 7.29 (d, 2H, J = 8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.2, 128.3, 128.5, 128.9, 135.2, 138.1; exact mass *m*/*z* calcd for $C_7H_7Cl_2N$, HRMS (70 eV) *m*/*z* (M^+ +1) calcd 174.99555, found 174.99563.

2-(2-Bromophenyl)ethanamine (Table 3, entry 1): yellowish oil, 80% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.4 (br s, 2H), 2.88 (t, 2H, J = 7 Hz), 2.97 (t, 2H, J = 7 Hz), 7.07 (m, 1H), 7.23 (m, 2H), 7.54 (d, 1H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.3, 42.1, 124.7, 127.5, 128.0, 130.9, 133.0, 139.2; exact mass *m*/*z* calcd for $C_8H_{10}BrN$, HRMS (70 eV) *m*/*z* (M^+ + 1) calcd 200.01224, found 200.00694.

General Procedure for the Reduction of a Nitrile by Pure $BH_2N(iPr)_2$ and Catalytic $LiBPh_4$. The following procedure for the reduction of 2,4-dichlorobenzonitrile by pure $BH_2N(iPr)_2$ and catalytic $LiBPh_4$ is representative. To a 50-mL round-bottomed flask equipped with magnetic stir bar and fitted with a rubber septum was added 2,4-dichlorobenzonitrile (0.52 g, 3 mmol) and THF (3 mL). The flask was charged with pure diisopropylaminoborane[10] (6 mL, 1 M in THF, 6 mmol) and $LiBPh_4$[18] (2.4 mL, 0.25 M in THF, 20 mol %). The reaction goes to completion in 5 h at 25 °C, as evidenced by TLC (Hex:EtOAc 2:1) and IR analysis. The reaction mixture was cooled to 0 °C (ice bath) and unreacted $BH_2N(iPr)_2$ was quenched with 3 M HCl (4.5 mL) (**caution**: hydrogen evolution). The acidic solution was stirred for 30 min and then basified with NaOH pellets to pH ~10. The aqueous layer was extracted with 1:1 Et_2O:THF (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo (25 °C, 1 Torr) to afford 2,4-dichlorobenzylamine as a light-yellow oil.

Supporting Information Available: The preparation of $BH_2N(iPr)_2$ and spectroscopy data for all compounds characterized. This material is available free of charge via the Internet at http://pubs.acs.org.

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