Molecular Addition Compounds. 11. *N*-Ethyl-*N*-isopropylaniline−Borane, A Superior Reagent for Hydroborations and Reductions

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Hydroboration studies with a new, highly reactive amine−borane adduct, H_3B−NPhEtPr^i, and representative olefins, such as 1-hexene, styrene, β-pinene, cyclopentene, norbornene, cyclohexene, 2-methyl-2-butene, α-pinene, and 2,3-dimethyl-2-butene, in tetrahydrofuran, dioxane, *tert*-butyl methyl ether, *n*-pentane, and dichloromethane, at room temperature (22 ± 3 °C) were carried out. The reactions are faster in dioxane, requiring 0.5−1 h for the hydroboration of simple, unhindered olefins to the trialkylborane stage. Moderately hindered olefins, such as cyclohexene and 2-methyl-2-butene, give the corresponding dialkylboranes rapidly, with further hydroboration slow. However, the hindered α-pinene and 2,3-dimethyl-2-butene structures give stable monoalkylboranes very rapidly, with further hydroboration proceeding relatively slowly. The hydroborations can also be carried out in other solvents, such as THF, *tert*-butyl methyl ether, and *n*-pentane. A significant rate retardation is observed in dichloromethane. Regioselectivity studies in the hydroboration of 1-hexene, styrene, and allyl chloride with H_3B−NPhEtPr^i in selected solvents were made. The selectivities are similar to those reported for BH_3−THF with 1-hexene and styrene, whereas some differences were noted for allyl chloride. The alkylboranes obtained after hydroboration were oxidized with hydrogen peroxide/sodium hydroxide, and the product alcohols were obtained in quantitative yields, as established by GC analysis. The rates and stoichiometry of the reaction of H_3B−NPhEtPr^i in tetrahydrofuran with selected organic compounds containing representative functional groups were examined at room temperature. Simple aldehydes, ketones, carboxylic acids, and aliphatic esters were reduced to the alcohol stage. Acid chlorides, anhydrides, and aromatic carboxylic esters were unreactive under similar conditions. Imines, tertiary amides, and nitriles were reduced to the corresponding amines. However, primary and secondary amides and nitro compounds were not reduced under these conditions. The reduction of esters, amides, and nitriles, which exhibit a sluggish reaction at room temperature, proceeds readily under reflux conditions in tetrahydrofuran and dioxane and also without solvent (at 85−90 °C). The carrier amine was recovered by simple acid−base manipulations in good yield and can be readily recycled to make the borane adduct.

Borane−Lewis base complexes are finding an increasing role as hydroborating and reducing agents in organic synthesis.[2] Numerous applications for the synthesis of pharmaceuticals and other industrial applications have been reported.[3−5] Well-established borane−Lewis base complexes, such as borane−tetrahydrofuran (BH_3−THF) and borane−dimethyl sulfide (BMS), are largely catering to these needs.[6,7] However, these important reagents are not free from certain disadvantages. For example, the low concentration of borane in the commercial BH_3−THF limits its applications to only one solvent, moreover the complex is not stable over long periods.[8] Though BMS does not possess these disadvantages, the volatility, flammability, and unpleasant odor of the dimethyl sulfide creates problems from the environmental point of view. Amines as borane carriers are free of these problems.[3] However, from the first preparation of the borane−amine adduct with trimethylamine in 1937,[9] many amine−borane adducts have been prepared, but all of them have been found to be less reactive than BH_3−THF and BMS.[10−12] As a result, the applicability of these amine−borane adducts has been limited to their reducing properties at higher operating temperatures.[3] A detailed study of the reducing and hydroborating properties of these amine−borane adducts was carried out from this laboratory earlier, and it was found that the borane adducts of *N*-phenylmorpholine and *N*,*N*-diethylaniline hydroborate 1-octene in 2−3 h at room temperature.[12] However, these adducts fail to reduce ketones at room

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(1) Postdoctoral associate with support from the Aldrich Chemical Co..
(2) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London, 1988.
(3) Lane, C. F. *Aldrichemica Acta* **1973**, *6*, 51.
(4) Follet, M. *Chem. Ind.* **1986**, 123.
(5) Ren, O.; Meatres, C. F. *Bioconjugate Chem.* **1992**, *3*, 563.
(6) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975, p 18. A reprinted edition is currently available: *Organic Syntheses via Boranes*; Aldrich Chemical Co., Inc.: Milwaukee, WI 1997; Vol. 1.
(7) Lane, C. F. *Aldrichemica Acta* **1973**, *6*, 21.
(8) Kollonitsch, J. *J. Am. Chem. Soc.* **1961**, *83*, 1515.
(9) Burg, A. B.; Schlesinger, H. I. *J. Am. Chem. Soc.* **1937**, *59*, 780.
(10) Long, L. H.; Mellor, W. J. In *A Comprehensive Treatise on Inorganic and Theoretical Chemistry;* Longman: London 1981; Supplement Vol. 5, Part B1, p 1.
(11) Mueller, A. In *Gmelin Handbook of Inorganic and Organometallic Chemistry*, Springer: Berlin, 1992; 4th Supplement, Vol. 3, p 1.
(12) (a) Brown, H. C.; Murray, L. T. *Inorg. Chem.* **1984**, *23*, 2746. (b) Hutchins, R. O.; Learn, K.; Nazer, B.; Pytlewski, D.; Pelter, A. *Org. Prep. Proced. Int.* **1884**, *16*, 335.

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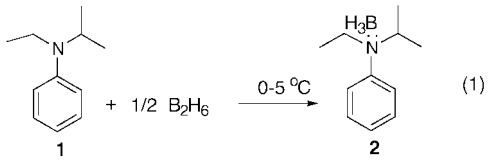
temperature (22 ± 3 °C) even when used for prolonged periods of time. Very recently, after we completed our present study, a report appeared on the synthetic utility of *N*,*N*-diethylaniline−borane as a reducing agent.[13]

Relatively recently a detailed study aimed at developing highly reactive, environmentally benign borane carriers utilizing new amine−borane adducts incorporating steric and electronic modifications was conducted in the hope of finding improved reagents.[14−16] To further explore their synthetic utility and reactivity, it was decided to study their hydroborating and reducing properties in more detail. Among the various new *N*,*N*-dialkylaniline derivatives, the most promising, *N*-ethyl-*N*-isopropylaniline, was selected for the present study, and the results are described here.

Results and Discussion

Preparation and Stability. The borane adduct of *N*-ethyl-*N*-isopropylaniline (**1**) was prepared by passing a slight excess of diborane gas into the neat amine at 0−5 °C (eq 1). The concentration of the adsorbed borane



(1)

was established to be 5.0 M by hydrolysis of an aliquot, using a 2 M HCl−glycerol−water mixture, measuring the hydrogen evolved.

The adduct thus obtained, maintained under nitrogen, is stable at room temperature indefinitely. In ^{11}B NMR the adduct showed a peak at −14.4 (CCl_4, $_qJ_{B-H}$ 98.6 Hz). The stability of solutions of this adduct in THF, *tert*-butyl methyl ether, and dioxane was also studied. Solutions of the adduct in solvents (2 M in BH_3) were sealed in NMR tubes and monitored using ^{11}B NMR at intervals. No new peaks in the ^{11}B NMR spectra other than that given by the adduct appeared during six months of observation.

Hydroboration of Olefins in Tetrahydrofuran. Hydroboration of representative mono-, di-, tri-, and tetrasubstituted olefins with **2** was conducted in THF at room temperature. To establish the rate and stoichiometry, the reactions were carried out in solutions that were 0.5 M in BH_3 and 1.5 M in olefin. The procedure followed was to add the THF solution of the olefin (3 equiv) to the amine−borane (1 equiv) in THF at 0 °C, stirring the mixture further at room temperature (22 ± 3 °C). The progress of the hydroboration was conveniently followed by taking out aliquots at intervals, hydrolyzing with 3 M HCl−glycerol−THF (2:1:0.2), and measuring the hydrogen evolved. The reactions were also followed by ^{11}B NMR, monitoring a decreasing amine−borane signal and an increasing alkylborane signal.

N-Ethyl-*N*-isopropylaniline−borane (**2**) hydroborates 1-hexene in THF in less than 30 min, forming the trihexylborane. Hydrolysis of the reaction mixture does not evolve any hydrogen indicating complete utilization of borane. Disubstituted olefins, such as *β*-pinene and cyclopentene, are also hydroborated to the trialkylborane stage in 1 h. The moderately hindered 2-methyl-2-butene gave disiamylborane after 45 min (^{11}B NMR, *δ* ppm, +31.2), and further hydroboration is slower. Cyclohexene forms dicyclohexylborane rapidly in 45 min (^{11}B NMR, *δ*, ppm, +51.2 after methanolysis), and 2.95 hydride equiv is utilized in 24 h (^{11}B NMR, *δ*, ppm, +81.5 after methanolysis corresponding to the formation of tricyclohexylborane). However, the more hindered α-pinene consumes one hydride rapidly, giving $IpcBH_2$ in 30 min, and then the reaction continues slowly, with the hydride utilization increasing to 1.93 in 24 h at room temperature, indicating incomplete formation of Ipc_2BH. This is also confirmed by ^{11}B NMR, which gives two peaks after methanolysis, at +32.26 (minor, due to $IpcB(OMe)_2$) and +52.79 (major, due to Ipc_2BOMe). Further substitution on the olefin, that is, the tetrasubstituted 2,3-dimethyl-2-butene, results in further lowering of the hydride uptake. Here also, addition of the first hydride is very fast, giving thexylborane (^{11}B NMR *δ* ppm +24.6), and the olefin−BH_3 ratio then rises to 1.76 after 24 h (^{11}B NMR *δ* ppm +23.71 and +80.83, after methanolysis +31.01 and +52.83).

Table 1. Hydroboration of Representative Olefins with BH_3−THF and H_3B−NPhEtPr^i in Molar Ratio 3:1 in THF at Room Temperature

	BH_3−THF[a]		H_3B−NPhEtPr^i [b]	
olefin	time (h)	hydrides used	time (h)	hydrides used
1-hexene	<0.50	3.00	<0.50	3.00
styrene	0.50	3.00	0.50	3.00
β-pinene	1.00	3.00	1.00	3.00
cyclopentene	1.00	3.00	1.00	3.00
norbornene	1.00	3.00	1.50	3.00
cyclohexene	24	2.97	24	2.95
	0.58	2.00	0.75	2.00
2-methyl-2-butene	24	2.94	24	2.90
	0.75	2.00	0.75	2.00
α-pinene	24	1.96	24	1.93
	0.33	1.00	0.33	1.00
2,3-dimethyl-2-butene	24	1.79	24	1.76
	0.33	1.00	0.33	1.00

[a] Reactions were carried out using BH_3−THF (5 mmol) and an olefin (15 mmol) in THF (total volume 10 mL). [b] Reactions were carried out using H_3B−NPhEtPr^i (5 mmol) and an olefin (15 mmol) in THF (total volume 10 mL).

The reactivity of **2** toward these representative olefins compares with that of BH_3−THF. Hydroborations using BH_3−THF were conducted under identical conditions, and the results are included in Table 1.

Hydroboration of Olefins in Other Solvents. Hydroborations with **2** were also conducted in solvents such as dioxane, *tert*-butyl methyl ether, *n*-pentane, and dichloromethane. In dioxane, **2** shows an enhanced reactivity when compared to solutions of **2** in tetrahydrofuran. Thus, in dioxane **2** hydroborates unhindered mono- and disubstituted olefins to the corresponding trialkylborane stage within 1 h. Enhanced reactivity is also observed for hindered olefins. For example, α-pinene is cleanly hydroborated to the Ipc_2BH stage. This is also confirmed by ^{11}B NMR observation, which reveals the exclusive presence of Ipc_2BOMe after methanolysis (*δ* ppm +53.2). Figure 1 illustrates the plots of hydroboration of hindered olefins with time in dioxane.

In *tert*-butyl methyl ether the reactivity of the borane−amine adduct **2** is very similar to that observed in THF. In *n*-pentane, the hydroborations are slightly slower than

(13) Salunkhe, A. M.; Burkhardt, E. R. *Tetrahedron Lett.* **1997**, *38*, 1519.
(14) Brown, H. C.; Zaidlewicz, M.; Dalvi, P. V. *Organometallics*, in press.
(15) Brown, H. C.; Zaidlewicz, M.; Dalvi, P. V.; Narasimhan, S.; Mukhopadyay, A., manuscript in preparation.
(16) Brown, H. C.; Zaidlewicz, M.; Dalvi, P. V., manuscript in preparation.

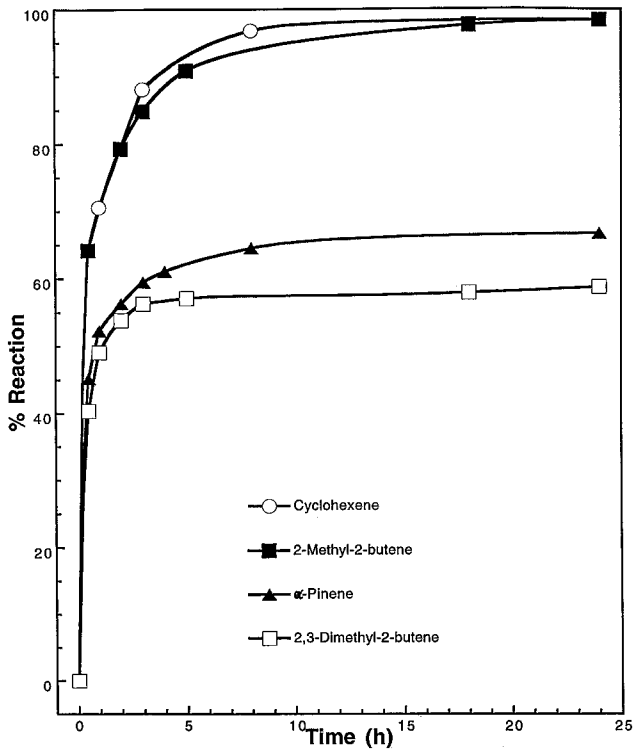


Figure 1. Hydroboration of hindered olefins with $H_3B-NPh-EtPr^i$ in dioxane at room temperature.

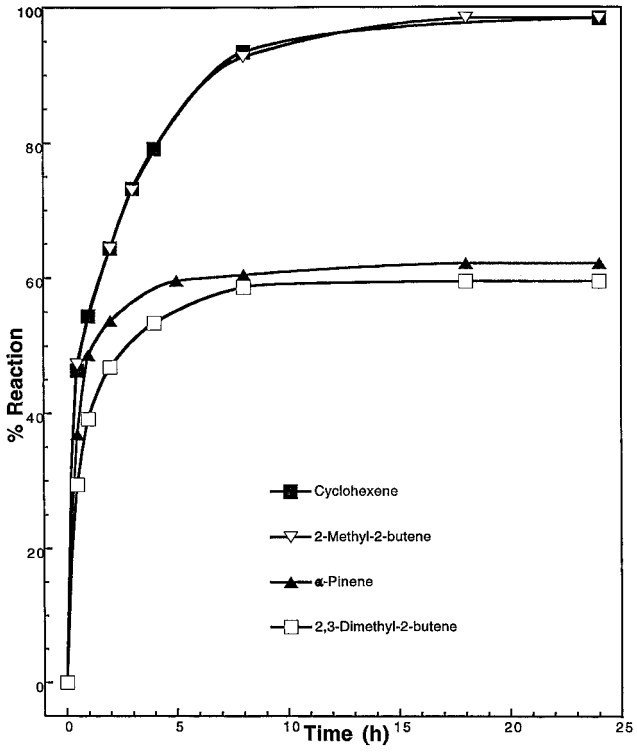


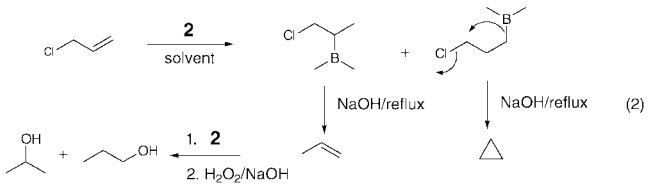
Figure 2. Hydroboration of hindered olefins with $H_3B-NPh-EtPr^i$ in dichloromethane at room temperature.

those in THF or dioxane, but they could be carried out with no difficulties. For unhindered olefins the hydroboration is complete in less than 1 h. Hindered olefins react slower and require 24 h for complete reaction. α-Pinene takes less than two hydride equiv in 24 h. In dichloromethane, an appreciable retardation of the rates of hydroboration is observed (Figure 2). Thus, 3 h is required for the hydroboration of 1-hexene to the trialkylborane stage (^{11}B NMR δ ppm, +86.3).

Summarizing all the solvents, the following order of reactivity with change of solvent in the hydroboration of representative olefins with **2** was noted: dioxane > tetrahydrofuran > *tert*-butyl methyl ether > *n*-pentane ≫ dichloromethane. Table 2 summarizes the results in various solvents.

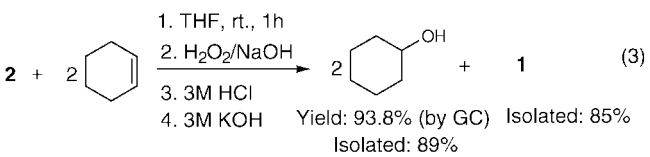
Regioselectivity of Hydroboration. Regioselectivity studies for 1-hexene, styrene, and allyl chloride with **2** in THF, dioxane, *tert*-butyl methyl ether, diethyl ether, diglyme, monoglyme, *n*-pentane, and toluene were undertaken. 1-Hexene and styrene were hydroborated in a 3:1 ratio, whereas allyl chloride was hydroborated in a 1:1 molar ratio as reported for BH_3-THF.[17] All the reactions were followed by ^{11}B NMR. The intermediate organoboranes were oxidized with H_2O_2-NaOH, and the product alcohols were analyzed by GC.

As follows from the results presented in Table 3, the regioselectivity of hydroboration of 1-hexene and styrene with **2** in most solvents is similar to that reported for BH_3-THF,[17] but is a little lower in *tert*-butyl methyl ether (92:8). However, for allyl chloride significant deviations from the 60:40 reported for BH_3-THF are observed.[18] Thus, in THF and dioxane the ratio is ~70:30. For other solvents the ratio is 65−55:35−45. The higher ratio of terminal:internal addition in THF and dioxane is also observed in the ^{11}B NMR spectra. Thus, for organoboranes obtained from allyl chloride in THF and dioxane, the R_3B signal, which reflects the elimination and rehydroboration of propene formed from the internal boron addition product of allyl chloride, is smaller, compared to results in other solvents. The extent of internal addition is obtained from the combined yield of 1- and 2-propanols (eq 2). Hydroboration of



1-propene in THF using **2** under similar conditions revealed that the amine−borane adds to the terminal double bond to give terminal versus internal in the ratio 94:6.

Hydroboration−Oxidation of Olefins. To further establish the synthetic applicability of this new highly reactive amine−borane adduct, hydroboration−oxidation of olefins was also studied. Hydroboration−oxidation of cyclohexene with **2** in THF gave cyclohexanol in quantitative yields (~99% by GC, 90% isolated, eq 3). The



recovered amine using acid−base manipulations can be used again for the preparation of borane adducts.

(17) Brown, H. C. *Hydroboration*; Benzamin: New York, 1962.
(18) Brown, H. C.; Keblys, K. A. *J. Am. Chem. Soc.* **1964**, 86, 1971.

Table 2. Hydroboration of Representative Olefins With 2 in Various Solvents at Room Temperature[a]

	dioxane		THF		*tert*-butyl methyl ether		*n*-pentane		dichloromethane	
olefin	time (h)	hydrides utilized	time (h)	hydrides utilized	time (h)	hydrides utilized	time (h)	hydrides utilized	time (h)	hydrides utilized
1-hexene	0.50	3.00	0.50	3.00	0.50	3.00	1.00	3.00	3.00	3.00
									1.00	2.12
styrene	0.50	3.00	0.50	3.00	0.50	3.00	1.00	3.00	3.00	3.00
									1.00	2.22
β-pinene	0.50	3.00	1.00	3.00	1.00	3.00	1.00	3.00	3.00	3.00
									1.00	2.19
cyclopentene	1.00	3.00	1.00	3.00	1.00	3.00	1.00	3.00	3.00	3.00
									1.00	2.37
norbornene	1.00	3.00	1.50	3.00	1.00	3.00	1.00	3.00	3.00	3.00
									1.00	2.51
cyclohexene	24	2.95	24	2.95	24	2.93	24	2.95	24	2.95
	0.58	2.00	0.75	2.00	0.91	2.00	1.00	2.00	2.33	2.00
2-methyl-2-butene	24	2.95	24	2.90	24	2.85	24	2.95	24	2.90
	0.58	2.00	0.75	2.00	0.83	2.00	1.00	2.00	2.60	2.00
α-pinene	24	2.00	24	1.93	24	1.85	24	1.77	24	1.86
	0.33	1.00	0.33	1.00	0.33	1.00	0.33	1.00	0.33	1.00
2,3-dimethyl-2-butene	24	1.76	24	1.76	24	1.81	24	1.79	24	1.78
	0.33	1.00	0.33	1.00	0.66	1.00	0.33	1.00	0.66	1.00

[a] Reactions were carried out using amine−borane **2** (5 mmol) and an olefin (15 mmol) in a total solution volume of 10 mL.

Table 3. Regioselectivity of Hydroborations with H_3B−NPhEtPr^i Adduct in Various Solvents at Room Temperature[a]

solvent	1-hexene (1-hexanol− 2-hexanol)	styrene (1-phenylethanol− 2-phenylethanol)	allyl chloride (boron addition to terminal vs internal)[b]
n-pentane	95.6:4.4	87.8:12.2	58:42
toluene	95.8:4.2	85.4:14.6	57:43
diethyl ether	95.7:4.3	86.6:13.4	62:38
t-Bu-*O*-Me	92.0:8.0	86.6:13.4	65:35
THF	96.0:4.0	85.6:14.4	72:28
monoglyme	96.0:4.0	85.8:14.2	55:45
diglyme	94.6:5.4	85.0:15.0	57:43
dioxane	95.8:4.2	85.6:14.4	72:28

[a] In the case of 1-hexene and styrene, the reactions were carried out by adding 15 mmol of olefin to 5 mmol of amine−borane in solvent (total solution 10 mL). In the case of allyl chloride 20 mmol of olefin was added to 20 mmol of amine−borane in a solvent (total solution 20 mL). [b] The internal addition is based on the combined yield of 1- and 2-propanols obtained after oxidation.

Since the basic amine **1** was present in the reaction mixture after hydroboration, oxidation of the organoborane with hydrogen peroxide was also examined without the usual addition of sodium hydroxide. The oxidation was instantaneous; however the yield of cyclohexanol was slightly lower (~91% by GC). In the case of 1-hexene, the yield of 1- and 2-hexanols was even less (80% by GC) and the isomeric ratio was 89:11. Apparently, the oxidation is not complete. The hydroboration can be conveniently carried out in a variety of solvents. However, for water immiscible solvents, such as *n*-pentane, ethyl ether, and *tert*-butyl methyl ether, either ethanol or THF should be added to facilitate oxidation.

Selective Reductions

Amine−boranes have wide applicability as reducing agents.[3] Earlier studies on reducing properties of known amine−borane adducts are limited to high-temperature reductions and reductions under acidic conditions.[3,12] The amine−boranes reported in the literature so far fail to reduce ketones at room temperature. However, the presence of Lewis acids, such as BF_3−OEt_2, facilitates the reduction of ketones at room temperature.[3,19] Recently, asymmetric reduction of aromatic ketones with *N*,*N*-diethylaniline−borane in the presence of catalytic amounts of oxazaborolidine prepared from α,α-diphenylpyrrolidinemethanol is reported.[20,21] Fortunately, the amine−borane **2** reduced acetophenone to the corresponding alcohol in 2 h at room temperature. Figure 3 illustrates rates of reduction of acetophenone with various amine−borane adducts at room temperatures. Encouraged by this observation, a detailed study on the reducing properties of selected functional groups in

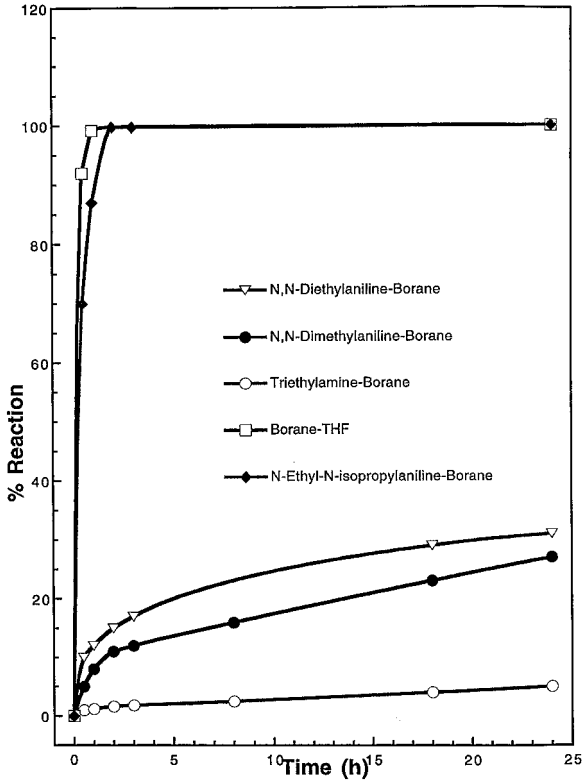


Figure 3. Reduction of acetophenone with various borane reagents in THF at room temperature.

(19) Periasamy, M.; Kanth, J. V. B.; Reddy, C. K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 427.
(20) Salunkhe, A. M.; Burkhardt, E. R. *Tetrahedron Lett.* **1997**, *38*, 1523.
(21) Periasamy, M.; Kanth, J. V. B.; Prasad, A. S. B. *Tetrahedron* **1994**, *50*, 6411.

organic compounds using *N*-ethyl-*N*-isopropylaniline−borane adduct (**2**) was also carried out.

Rate and Stoichiometric Studies. The procedure adopted was to add 6.25 mmol of the organic compound to 8.3 mmol of amine−borane in sufficient THF to give 25 mL of solution. This makes the reaction mixture 0.33 M in BH_3 (1 M in hydride) and 0.25 M in compound. The compound was added at 0 °C and stirred further at room temperature (contents maintained at room temperature ~20 °C). Aliquots are removed at appropriate intervals and analyzed for residual hydride by hydrolysis using glycerol−3N HCl−THF (1:1:0.2) and by measuring the hydrogen evolved. This establishes both the rate and the stoichiometry of the reaction. The reactions are also cross-checked by either ^{11}B NMR analysis or GC analysis.

Alcohols. Alcohols reacted with **2** rapidly and liberated hydrogen quantitatively. No further reaction was observed. The rate of hydrogen evolution for the alcohols decreases in the following order: primary > secondary > tertiary. This is in agreement with the usual interpretation that the acidity of the hydroxylic hydrogen in these alcohols decreases in this order.[22] However, the relatively slow reactivity of phenol may be attributed to the weaker basic character of the oxygen atom which may retard the formation of a prior addition complex (eq 4).

$$\mathrm{ROH} + \mathrm{BH_3} \longrightarrow \mathrm{R\text{-}O{:}B{:}H}\ (\mathrm{H,H,H}) \longrightarrow \mathrm{R\text{-}OBH_2} + \mathrm{H_2} \qquad (4)$$

To further understand the reactivity of these alcohols toward amine−boranes, another set of experiments was carried out by using 3 equiv of alcohol for 1 equiv of amine−borane.

Reaction of **2** with 3 equiv of simple unhindered hydroxy compounds such as 1-butanol and benzyl alcohol was very fast and gave trialkoxyborane (^{11}B NMR, +19, singlet). Moderately hindered 2-pentanol required a longer time to react completely. Hindered tertiary alcohols formed only dialkoxyborane (^{11}B NMR, +26.2, doublet), with further reaction proceeding only very slowly.

Aldehydes and Ketones. The aldehydes and ketones examined all consumed one hydride, indicating reduction to the alcohol stage. Caproaldehyde, benzaldehyde, and 2-hexanone were reduced rapidly within 1 h. In the case of acetophenone and benzophenone the reactions were slower, attributed to the combined steric and electronic effects of the phenyl group. The results are summarized in Table 4.

For better synthetic utility, reductions were also tried using 2 equiv of compound for 1 equiv of amine−borane. However, under these molarity conditions the reactions require more time to go to completion than observed above. For example, using adduct **2**, benzaldehyde took 2 h for complete reaction and acetophenone 18 h. The reduction of benzaldehyde with **2** under these conditions was carried out on a preparative scale, and the benzyl alcohol was isolated in 82% yield, while the amine was recovered in 91% yield. Similarly, the reduction of acetophenone gave 1-phenylethanol in 86% yield, and *N*-ethyl-*N*-isopropylaniline was recovered in 90% yield.

Carboxylic Acids, Anhydrides, and Acid Chlorides. The reaction with caproic acid is very fast, whereas the reaction with benzoic acid is somewhat slower. Both reactions consume ~3 hydride equiv, 1 for hydrogen evolution and 2 for the reduction to the alcohol stage. ^{11}B NMR studies for the reduction of caproic acid with **2** show a peak at +19.5, and traces of unreacted amine−borane are also indicated. Among the other acyl derivatives, only acetic anhydride was reduced to a considerable extent, taking 3.4 hydride equiv from **2** out of the expected 4 for complete reduction.[23] Also, the ^{11}B NMR analysis shows trialkoxyborane (+18.1, singlet) as a major peak with trace amounts of amine−borane. The other anhydrides, such as succinic anhydride and phthalic anhydride, formed precipitate which did not dissolve even after 48 h. Hydride analysis revealed very little hydride uptake. The ^{11}B NMR of the THF solution showed only the presence of amine−borane in solution. Hydrolysis with water and the usual workup of the reaction mixture gives unreacted anhydride in major amounts. Under the standard conditions both the aliphatic and aromatic acid chlorides, capropyl chloride and benzoyl chloride, fail to react even after prolonged periods of time (Table 5). This may provide an opportunity to reduce selectively carboxylic acids in the presence of acid chlorides.

Esters. Aliphatic esters react very slowly with **2** and require 72 h for the uptake of two hydrides required for reduction to the alcohol stage. However, the aromatic

Table 4. Reaction of H_3B−NPhEtPr^i with Representative Aldehydes and Ketones at Molar Ratio 1.33:1 in THF at Room Temperature

	H_3B−NPhEtPr^i	
compound[a]	time (h)	hydride equiv used for reduction[b]
caproaldehyde	0.75	1.00
benzaldehyde	0.50	1.00
2-hexanone	1.00	1.00
acetophenone	0.50	0.70
	1.00	0.87
	2.50	1.00
benzophenone	0.50	0.02
	3.00	0.32
	6.00	0.68
	12	0.97
	15	1.00

[a] Compound (6.25 mmol) was added to 8.3 mmol of amine−borane (25 mmol of hydride) in 25 mL of solution 0.25 M in compound and 1.00 M in hydride. [b] No hydrogen evolution noted.

Table 5. Reaction of H_3B−NPhEtPr^i with Representative Carboxylic Acid and Acyl Derivatives at Molar Ratio 1.33:1 in THF at Room Temperature

	H_3B−NPhEtPr^i			
compound[a]	time (h)	hydrogen equiv evolved	hydride equiv used	hydride equiv for reduction
caproic acid	0.50	1.00	3.00	2.00
benzoic acid	0.25	1.00	1.23	0.23
	5.00	1.00	3.00	2.00
acetic anhydride	0.25	0.00	1.71	1.71
	2.00	0.00	3.11	3.11
	6.00	0.00	3.37	3.37
	24	0.00	3.40	3.40
succinic anhydride	precipitate formed			
phthalic anhydride	precipitate formed			
caproyl chloride	24	0.00	0.29	0.29
benzoyl chloride	24	0.00	0.26	0.26

[a] Compound (6.25 mmol) was added to 8.3 mmol of amine−borane (25 mmol of hydride) in 25 mL of solution 0.25 M in compound and 1.00 M in hydride.

(22) House, H. O. *Modern Synthetic Methods*; Benzamin Inc.: New York, 1965; Chapter 7.

(23) Brown, H. C.; Heim, P.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 1637.

Table 6. Reaction of H_3B−NPhEtPr^i with Representative Esters at Molar Ratio 1.33:1 in THF at Room Temperature

	H_3B−NPhEtPr^i	
compound[a]	time (h)	hydride equiv used for reduction[b]
ethyl butyrate	0.50	0.26
	1.00	0.32
	4.00	0.78
	24	1.29
	72	2.00
methyl caproate	0.50	0.20
	2.00	0.46
	8.00	1.07
	24	1.26
	48	1.87
	72	2.00
methyl benzoate	0.50	0.09
	1.00	0.09
	2.00	0.13
	20	0.20
	48	0.20

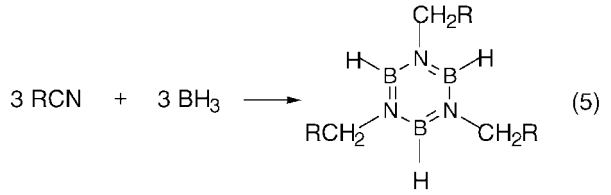
[a] Compound (6.25 mmol) was added to 8.3 mmol of amine−borane (25 mmol of hydride) in 25 mL of solution 0.25 M in compound and 1.00 M in hydride. [b] No hydride evolution noted.

ester, methyl benzoate, does not show any appreciable uptake even after longer hours (>72 h). The following Table 6 summarizes the results.

Amines, Imines, and Amides. *n*-Hexylamine liberates only 0.12 equiv of hydrogen upon the reaction with **2** over 24 h. The resulting solution, after 24 h, was found to contain *n*-hexylamine−borane (60%), reagent amine−borane (29%), and borane−THF (10%) complexes as revealed by ^{11}B NMR (δ −19.9, −15.1, and −1.1 respectively), indicating the presence of an equilibrium mixture. Imines, such as N-benzylidene−butylamine, are reduced to the corresponding amines rapidly with the uptake of one hydride, and the resulting amine−boranes were in equilibrium with the reagent amine−borane. *N*-Benzylidene−aniline takes a relatively longer time (4−8 h) which may be attributed to the presence of phenyl groups on both sides of the imine functionality.

Primary amides are reduced very slowly, exhibiting only about 50% reduction even after long hours. The reactions evolve hydrogen (~1.3 equiv) rapidly, with further reduction slow, though the presence of unreacted amine−borane in the reaction medium is observed by ^{11}B NMR. In the case of the secondary amide, *N*-methylbenzamide, rapid hydrogen (~0.83 equiv) evolution is also observed, with the formation of a white precipitate and only slow further reaction. On the other hand, the rates of reaction of tertiary amides are considerably faster, exhibiting hydride uptake of two required for reduction to the amine stage.[23] The following Table 7 summarizes the results.

Nitriles and Nitro Compounds. Nitriles react very slowly with **2**, but the reaction proceeds slowly to completion with the uptake of two hydrides required for reduction to the amine stage.[23] The reduction of nitriles produces the corresponding 1,3,5-trialkylborazines (^{11}B NMR, broad signal around +1). Consequently, isolation of the amine requires hydrolysis of the intermediate borazine (eq 5).[24]



(5)

Table 7. Reaction of H_3B−NPhEtPr^i with Representative Amines, Imines, and Amides at Molar Ratio 1.33:1 in THF at Room Temperature

	H_3B−NPhEtPr^i			
compound[a]	time (h)	hydrogen equiv evolved	hydride equiv used	hydride equiv for reduction
n-hexylamine	0.50	0.04	0.04	0.00
	1.00	0.10	0.10	0.00
	24	0.12	0.12	0.00
N-benzylidene−butylamine	0.50	0.00	1.00	1.00
	1.00	0.00	1.00	1.00
N-benzylidene−aniline	0.50	0.00	0.36	0.36
	1.00	0.00	0.72	0.72
	2.00	0.00	0.85	0.85
	4.00	0.00	1.00	1.00
caproamide	0.50	1.32	1.42	0.10
	1.00	1.32	1.62	0.30
	18	1.32	2.45	1.13
	24	1.32	2.55	1.23
	48	1.32	2.55	1.23
benzamide	0.50	1.31	1.41	0.10
	1.00	1.35	1.59	0.24
	4.00	1.35	2.04	0.69
	18	1.35	2.24	0.89
	36	1.35	2.43	1.08
	72	1.35	2.76	1.41
N-methylbenzamide	0.50	0.52	0.53	0.01
	1.00	0.67	0.82	0.15
	4.00	0.78	1.28	0.50
	18	0.83	2.36	1.53
	24	0.83	2.66	1.83
	48	0.83	2.69	1.86
N,*N*-dimethylcaproamide	0.50	0.00	0.89	0.89
	1.00	0.00	1.70	1.70
	2.00	0.00	2.00	2.00
N,*N*-dimethylbenzamide	0.50	0.00	0.31	0.31
	1.00	0.00	0.57	0.57
	4.00	0.00	1.53	1.53
	8.00	0.00	2.00	2.00

[a] Compound (6.25 mmol) was added to 8.3 mmol of amine−borane (25 mmol of hydride) in 25 mL of solution 0.25 M in compound and 1.00 M in hydride.

Table 8. Reaction of H_3B−NPhEtPr^i with Representative Nitriles and Nitro Compounds at Molar Ratio 1.33:1 in THF at Room Temperature

	H_3B−NPhEtPr^i	
compound[a]	time (h)	Hydride equiv used for reduction[b]
heptanenitrile	2.00	0.00
	12	0.33
	24	1.03
	36	1.89
	48	2.00
benzonitrile	2.00	0.32
	12	0.98
	24	1.26
	48	1.58
	72	1.94
	96	1.98
nitromethane	1.00	0.00
	24	0.00
nitrobenzene	24	0.00

[a] Compound (6.25 mmol) was added to 8.3 mmol of amine−borane (25 mmol of hydride) in 25 mL of solution 0.25 M in compound and 1.00 M in hydride. [b] No hydride evolution noted.

A detailed account of more rapid reductions at higher temperatures, with isolation of the products, is discussed subsequently.

Nitro compounds such as nitromethane and nitrobenzene failed to react under the present conditions. This inertness of borane toward the nitro group is presumably due to the very weakly basic properties of the group. The reduction studies with the nitriles and the nitro compounds are presented in Table 8.

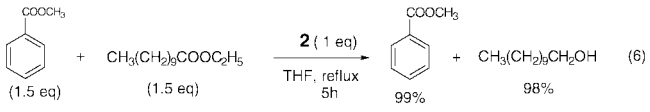
Epoxides. The reaction of epoxides is slow. With simple 1,2-propylene oxide, the hydride uptake is almost one after 24 h, but the usual workup and GC analysis reveals only 30% of propanols. Similar results are realized with styrene oxide also. It consumes 2 hydride equiv after 24 h, though only one hydride is required for reduction, and the usual workup gave only small amounts of 1- or 2-phenylethanols. These observations were similar to those reported for BH_3−THF, and it was also known that presence of sodium borohydride or boron trifluoride markedly changes the reaction of epoxides with diborane.[25] However, in the present study, no further efforts were made to improve the reactivity of epoxides with **2**.

Reaction of 2 with Esters, Amides, and Nitriles at Reflux Temperatures. The reduction of some functional groups, such as esters, amides, nitriles, etc., are sluggish at room temperature. However, BH_3−THF[26] and BMS[27] have proven to be the reagents of choice for these reductions over any complex metal hydride.[28−31] To further establish the potential of this new, reactive amine−borane adduct and in a bid to find an alternative for BH_3−THF and BMS, it was decided to examine whether a modest increase in the temperature would facilitate the reduction. Thus reductions with **2** toward esters, amides, and nitriles were also examined in tetrahydrofuran and dioxane at reflux temperature and also without solvent at 85−90 °C.

Esters. The reductions of ethyl undecanoate, methyl caproate, and methyl benzoate with **2** in THF and dioxane at reflux temperatures were studied. It was established from previous experiments at room temperature that esters require 2 hydride equiv for the reduction to the alcohol stage. Accordingly, reductions were carried out in 1:1.5 amine−borane/ester molar ratio using 10% excess hydride to ensure complete reaction. The procedure adopted was to add 12.5 mmol of ester to a solution of 9 mmol of amine−borane in 21.6 mL of the solvent, reacting the mixture under reflux. Aliquots were taken out at intervals, worked up, and checked for the presence of the starting ester by GC analysis. The reactions were also cross-checked by ^{11}B NMR analysis. The results are presented in Table 9.

In dioxane, the reductions are very fast. Aliphatic esters are reduced in 15 min, and methyl benzoate is reduced in 30 min. In THF, the reductions are relatively slower, probably because of the somewhat lower refluxing temperature. Thus, **2** reduced ethyl undecanoate to 1-undecanol in 2 h.

Reductions without solvent were carried out by mixing the amine−borane adduct **2** with esters and heating to 85−90 °C. Under these conditions aliphatic esters reduce rapidly within 15 min. However, methyl benzoate reacts much slower and some loss of diborane was observed leading to incomplete reduction. This was also confirmed by ^{11}B NMR which showed the presence of only trialkoxyborane, with absence of amine−borane, confirmed by GC analysis which showed the presence of unreacted ester. The reactions could be forced to completion by taking an excess of **2**. Advantage was taken of the difference in reactivity between aromatic and aliphatic esters in THF to achieve the selective reduction of ethyl undecanoate in the presence of methyl benzoate (eq 6).



(6)

Table 9. Reduction of Representative Esters, Nitriles, and Amides with H_3B−NPhEtPr^i in Tetrahydrofuran and Dioxane at Reflux and without Solvent

	H_3B−NPhEtPr^i time (h)		
compound	THF	dioxane	neat[a,b]
ethyl undecanoate[c]	2.00	0.25	0.25
methyl caproate[c]	2.00	0.25	0.25
methyl benzoate[c]	12.00	0.50	10
n-heptanenitrile[d]	2.00	0.50	
benzonitrile[d]	6.00	0.50	
caproamide[e]	10.00	2.00	
benzamide[e]	12.00	2.00	
N-methylbenzamide[f]	10.00	1.00	
N,*N*-dimethylcaproamide[g]	0.25	0.25	
N,*N*-dimethylbenzamide[g]	0.50	0.25	

[a] Amine−borane in 30% excess was taken to compensate the loss of diborane in heating. [b] At 85−90 °C. [c] Compound (12.5 mmol) was added to 9.1 mmol of amine−borane (10% excess of hydride) in 25 mL of solution (0.5 M in compound). [d] Compound (6.25 mmol) was added to 8.3 mmol of amine−borane (25 mmol of hydride) in 25 mL of solution 0.25 M in compound and 1.00 M in hydride. [e] Compound (6.25 mmol) was added to 9 mmol of amine−borane (10% excess) in 25 mL of solution in THF or dioxane. [f] Compound (6.25 mmol) was added to 13.7 mmol of amine−borane (10% excess) in 25 mL of solution of THF or dioxane. [g] Compound (6.25 mmol) was added to 11.6 mmol of amine−borane (10% excess) in 25 mL of solution of THF or dioxane.

Nitriles. Reductions of *n*-heptanenitrile and benzonitrile were carried out with **2**. From studies at room temperature, it was established that nitriles consume 2 hydride equiv to give the corresponding borazine derivative which can be hydrolyzed to the product amine. Accordingly, reactions were carried out by adding 9 mmol of amine−borane (10% excess) and 8.3 mmol of nitrile to THF or dioxane and refluxing the mixture. The reactions were followed by taking aliquots at intervals and GC analysis for the remaining nitrile after workup. The results are presented in Table 9. As follows from the results, in THF the aliphatic nitrile is reduced faster than the aromatic one. In dioxane, the reductions are faster, being complete in 30 min for both nitriles. Reductions of nitrile in neat condition were not studied because loss of diborane during the reaction was observed leading to incomplete reduction.

Amides. Reductions of primary, secondary, and tertiary amides using **2** in THF and dioxane at reflux temperature were followed by ^{11}B NMR, hydrolysis of aliquots at intervals, and GC examination for unreacted amide. The product of the reduction is an amine which forms a relatively stable borane−amine, so that one mole of borane reagent is required per mole of amine product. Accordingly, tertiary amides require 5 hydrides, second-

(24) Emeleus, H. J.; Wade, K. *J. Chem. Soc.* **1960**, 2614.
(25) Brown, H. C.; Yoon, N. M. *J. Chem. Soc., Chem. Commun.* **1968**, 1549.
(26) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912.
(27) Lane, C. F. *Aldrichemica Acta* **1975**, *8*, 20.
(28) Gaylord, N. G. *Reductions with Complex Metal Hydrides*; Interscience: New York, 1956; p 544.
(29) Zabicky, J. *The Chemistry of Amides*; Interscience: New York, 1970; p 795.
(30) Brown, H. C.; Weissman, P. M.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1458.
(31) Lane, C. F. *Aldrichemica Acta* **1977**, *10*, 49.

ary 6 hydrides, and primary 4 hydrides.[32] The reductions gave quantitative yields of amine products (by GC). The results are presented in Table 9.

In refluxing THF, reactions with primary amides evolve hydrogen (2 equiv) rapidly and further reduction is slow. *N*-Methylbenzamide, a secondary amide, evolves hydrogen (1 equiv) rapidly; here also further reaction is slow. Tertiary amides are reduced rapidly, giving the corresponding borane adducts as products. In dioxane, the reductions are faster, being complete in 2 h for the slowest reacting primary amides and in only 15 min for the tertiary amides.

Isolation of the Product Amine. In case of reduction of aldehydes, ketones, acids, esters, etc., the product alcohols are readily separated by simple acid−base manipulations. When the product is a water-soluble alcohol, it can be easily isolated by either distillation or column chromatography.

Two procedures for the isolation of product amines obtained from imines, nitriles, and amides can be used. The first procedure is used when the product amine and the carrier amine differ in boiling points or polarities. The reduction product, the amine−borane, is hydrolyzed with 6 M hydrochloric acid, and the mixture of both amines obtained by treatment of the acidic phase with sodium hydroxide is separated by distillation or column chromatography. The second procedure is applied when the product amine is strongly complexed with borane (as in the case with less-hindered amines, for example, *N*-methylbenzylamine and *N*,*N*-dimethylbenzylamine); the reaction product is treated with dilute hydrochloric acid. Under these conditions the product borane−amine complex is stable. The more hindered carrier amine is extracted into the acidic aqueous phase, separated, and recovered by alkalization. The product amine can be liberated from its borane adduct by the addition of boron trifluoride-etherate.

Conclusions

The present study demonstrates the synthetic potential of the new, highly reactive amine−borane adduct *N*-ethyl-*N*-isopropylaniline-borane (**2**). Simple unhindered olefins can be hydroborated to the trialkylborane stage, whereas hindered olefins can be partially hydroborated to the mono- or dialkylborane stage. The hydroborations can be carried out conveniently in a variety of solvents. The amine−borane adduct shows enhanced reactivity in dioxane but low reactivity in dichloromethane. The present study also indicates that the reactivity of **2** toward representative olefins is similar to that of BH_3−THF and BMS, so the accumulated data on the rates and stoichiometry of hydroboration with these reagents can be used to predict the hydroboration results with **2**. However, in the case of allyl chloride, some deviations were observed. Possibly the presence of the amine favors the elimination of >B−Cl from the product. In the great majority of cases, the hydroboration products were oxidized using hydrogen peroxide−sodium hydroxide to give the corresponding alcohols in quantitative yields, without any interference by the amine.

This study also demonstrates that **2** can substitute for borane−dimethyl sulfide (BMS) in the reduction of various functional groups. Aldehydes, ketones, carboxylic acids, imines, and tertiary amides are reduced conveniently at room temperature. Functional groups which show sluggish reactivity at room temperature, such as esters, primary and secondary amides, and nitriles, can be readily reduced in tetrahydrofuran or dioxane under reflux conditions.

In refluxing dioxane the reductions of esters, amides, and nitriles are complete in 15 min−2 h. The reductions are faster than with BMS in refluxing THF, even when dimethyl sulfide is removed from the reaction mixture.[32] In refluxing tetrahydrofuran, the reduction of esters, amides, and nitriles is slower and differences in reactivity made possible certain selective reductions, such as the reduction with **2** of aliphatic esters in the presence of aromatic esters.

The borane carrier amine **1** can be readily recovered from the hydroboration or reduction products by simple acid−base manipulations, distillation, or column chromatography and can be easily recycled for the preparation of the borane adduct. Consequently, **2** described in the present study can serve as an eco-friendly substitute for the currently popular hydroborating agents, such as borane−dimethyl sulfide and borane−tetrahydrofuran.

Experimental Section

Methods. All manipulations and reactions with air-sensitive compounds were carried out in an atmosphere of dry nitrogen. The special techniques employed in handling air-sensitive materials are described elsewhere.[6] Glassware parts were oven-dried for several hours, assembled while hot, and cooled in a stream of dry nitrogen gas. ^{11}B NMR spectra were recorded at 96 MHz and were referenced relative to BF_3−OEt_2. ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively. GC analyses were carried out either on a chromatograph equipped with SPB-5 (0.25 μm × 30 m) capillary column or with a chromatograph provided with FID and a CI-100A integrator. The following columns were used: 6 ft × 0.125 in., 15% Carbowax 20M on Chromosorb W, 9 ft × 0.125 in., 3% OV-17 on Chromosorb-G. Optical rotations were measured on a polarimeter. Hydride analysis studies were carried out using the gasimeter.[6]

Materials. *N*-Ethyl-*N*-isopropylaniline and its borane adduct were prepared following the procedure reported earlier.[14] All solvents were purified according to literature procedures and stored under nitrogen. Tetrahydrofuran and dioxane were freshly distilled from benzophenone ketyl before use. All olefins were distilled from a small amount of lithium aluminum hydride and stored under nitrogen. All compounds except amides were commercial samples and were used as obtained. Amides used in this study were prepared following literature procedures[33] and were fully analyzed before use.

Hydroboration of Representative Olefins with 2. General Procedure. An oven-dried, 50 mL hydroboration flask, provided with a septum inlet to introduce and remove compounds, a stirring bar, and a stopper, was cooled to 0 °C under nitrogen. The flask was charged with an amine borane adduct (5 mmol) and a solvent. A solution of an olefin (15 mmol, 6 M, 2.5 mL) was added at 0 °C, and the contents were further stirred at room temperature (19−25 °C). The contents of the reactions were always maintained in the temperature range. Aliquots (1 mL) were taken out at intervals and hydrolyzed using 3M HCl−glycerol−THF (2:1:0.2) hydrolysis solvent. The hydrogen evolved was measured using Brown's gasimeter to establish the presence of active hydride. The reactions were simultaneously followed by ^{11}B NMR, observing the relative

(32) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.

(33) Vogel, A. I. *Practical Organic Chemistry*, 5th ed.; Longman: Essex, 1989.

ratio of an amine−borane signal and the signals due to the hydroboration product.

Regioselectivity Studies. Regioselectivity studies in hydroborations of 1-hexene, styrene, and allyl chloride using **2** were carried out. To study the solvent effect, reactions were carried out in tetrahydrofuran, dioxane, monoglyme, diglyme, toluene, diethyl ether, *tert*-butyl methyl ether, and *n*-pentane. The procedure followed for tetrahydrofuran is representative for water miscible solvents. For water immiscible solvents, 5 mL of ethanol or THF was added to facilitate hydrogen peroxide oxidation.

Hydroboration of 1-Hexene with 2 in Tetrahydrofuran. An oven-dried hydroboration flask was cooled to 0 °C under a stream of nitrogen gas. In the flask was placed **2** (1.00 mL, 5.00 M, 5 mmol) in freshly distilled THF (7.5 mL) and undecane (7.5 mmol, GC standard). 1-Hexene (15 mmol, 1.26 g) was added slowly for 5 min at 0 °C. The contents were further stirred for 2 h at room temperature. The reaction was quenched with careful addition of water. The reaction mixture was cooled to 10 °C, and 3 mL of 3.00 N NaOH was added, followed by the slow addition of 2 mL of 30% hydrogen peroxide for 10 min. The contents were further stirred at 50 °C for 2 h to ensure completion of oxidation. The reaction mixture was cooled to room temperature, and the organic layer was separated. The aqueous layer was saturated with potassium carbonate and extracted with ether, and the combined organic extract was washed with brine and dried over anhydrous magnesium sulfate. The combined yield of 1- and 2-hexanols was 98% (by GC using OV-17 column). The ratio of 1-hexanol−2-hexanol is 96:4.

Hydroboration of Allyl Chloride with 2 in Tetrahydrofuran. An oven-dried hydroboration flask was cooled under a stream of nitrogen. In the flask was placed **2** (4.0 mL, 5.00 M, 20 mmol) in dry THF (14.5 mL) at 0 °C, and allyl chloride (20 mmol, 1.53 g) was added slowly for 5 min. The contents were further stirred for 4 h at 25 °C. After excess hydride was destroyed with water, 3 M NaOH (12 mL) was added at 10 °C and the reaction mixture was refluxed for 3 h at 64 °C to remove gaseous products, which were collected in a cold trap attached. The reaction mixture was cooled to 10 °C, and 2 mL of 30% hydrogen peroxide was added slowly. The contents were stirred for 2 h at room temperature and 1 h at 50 °C to ensure complete oxidation. After separation of the layers, the aqueous phase was saturated with potassium carbonate and extracted with ether. The combined organic extract was dried over anhydrous magnesium sulfate and analyzed by GC using the Carbowax column. The combined yield of 1- and 2-propanols was 28%, with a ratio of 1-propanol−2-propanol of 92:8.

Hydroboration−Oxidation of Cyclohexene with 2 in Tetrahydrofuran. Into an oven- dried hydroboration flask was placed **2** (1.00 mL, 5.00 M, 5 mmol) in freshly distilled THF (7.5 mL). Cyclohexene (10 mmol, 0.82 g) was added slowly for 5 min at 0 °C. The contents were further stirred for 1 h at room temperature. The reaction was quenched with careful addition of water. The reaction mixture was cooled to 10 °C, and 3 mL of 3 N NaOH was added followed by the slow addition of 1 mL of 30% hydrogen peroxide. The contents were further stirred at 50 °C for 2 h. The reaction mixture was cooled to room temperature, and the organic layer was separated. The aqueous layer was saturated with potassium carbonate and extracted with ether. The combined organic layer was washed with 3 N HCl, then with brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave essentially pure cyclohexanol, which was further purified by passing through a small silica gel pad, providing a yield of 1.06 g (89%).

The aqueous layer was neutralized with 3 N KOH solution and extracted with ether. The combined organic extract was washed with brine and dried over anhydrous magnesium sulfate. GC analysis of the crude product showed the presence of cyclohexanol (2%) in addition to **1** (98%). Amine was recovered in pure form by column chromatography using hexane−ethyl acetate (95:5) as eluent in 85% (0.75 g) yield.

Reduction of Organic Functional Groups with 2 At Room Temperature in THF. General Procedure. All reductions were carried out under a dry nitrogen atmosphere. In a 50 mL flask, fitted with a sidearm capped by a rubber septum (to permit introduction and removal of material with a hypodermic syringe), was placed amine−borane **2** (5.00 M, 8.3 mmol) in freshly distilled THF (20 mL). To this solution was slowly added the compound to be reduced in THF (5.00 mL, 6.25 mmol) for 5 min. The final solution is 0.25 M in reducible compound and 1 M in hydride. At appropriate time intervals, samples were withdrawn and hydrolyzed using glycerol−2 N HCl−THF (1:3:1) and the hydrogen evolved was measured using the Brown gasimeter to determine the amount of residual hydride. Progress of the reaction was also checked by ^{11}B NMR and GC analysis. In a separate run using the same quantities and conditions, the reaction flask was attached to a gasimeter to measure the hydrogen evolved.

In a number of cases, the reduction was carried out as described above to establish yield and stoichiometry. However, the reaction mixtures were then worked up to isolate and characterize the reduction products. A few representative examples are described below for isolation of the reduced product and recovery of borane carrier amine.

Reduction of Benzaldehyde (2 equiv) with 2 (1 equiv) in THF at Room Temperature. An oven-dried two-necked RB flask, provided with a condenser, septum inlet, and stirring bar, was cooled to 0 °C under nitrogen. Into the flask was placed freshly distilled THF (21.80 mL) and **2** (1.66 mL, 5.00 M, 8.3 mmol). Benzaldehyde (1.68 mL, 16.6 mmol) was added slowly for 5 min, and the contents were further stirred at room temperature for 2 h. The reaction was quenched with water (2 mL), and the organic layer was separated. The aqueous layer was extracted with ether, and the combined organic extract was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed on a rotary evaporator, and the crude product was subjected to column chromatography on silica gel. Amine, eluted using 2% ethyl acetate in hexane and alcohol, eluted with 10% ethyl acetate in hexane, were compared with authentic samples. The yield of benzyl alcohol was 1.47 g (82%), and that of the amine was 1.23 g (91%)

Reduction of Acetophenone (2 equiv) with 2 (1 equiv) in THF at Room Temperature. An oven-dried two-necked RB flask, provided with a condenser, septum inlet, and stirring bar, was cooled to 0 °C under nitrogen. Into the flask was placed freshly distilled THF (21.3 mL) and **2** (1.66 mL, 5.00 M, 8.3 mmol). Acetophenone (1.99 g, 16.6 mmol) was added slowly for 5 min, and the contents were further stirred at room temperature for 18 h. The reaction was quenched with water, and diethyl ether was added. The organic layer was separated, washed with 3 N HCl, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave essentially pure 1-phenylethanol which was further purified by passing through a small silica gel pad. The yield of 1-phenylethanol was 1.72 g (86%).

The combined aqueous layer was neutralized using aqueous KOH and extracted with ether. The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator, and the GC analysis of crude product on the OV-17 column revealed the presence of **1** in a purity of 97%. The yield of recovered amine was 1.21 g (90%).

Reduction of Representative Esters with 2 in THF and Dioxane at Reflux. Amine−borane adduct **2** in THF or dioxane was treated with representative esters such as ethyl undecanoate, methyl caproate, and methyl benzoate. The procedure followed for methyl benzoate in THF is representative.

An oven-dried, RB flask (50 mL), provided with a condenser, septum inlet, and a stirring bar, was cooled under a flow of nitrogen. Into the flask was placed freshly distilled THF (21.6 mL) and **2** (1.80 mL, 5 M, 9 mmol) at room temperature. Methyl benzoate (1.55 mL, 12.5 mmol) was added, and the reaction mixture was stirred under reflux. Aliquots of the reaction mixture were removed at appropriate intervals, hydrolyzed, and tested for the remaining unreacted ester on

GC using the OV-17 column. Thus the progress of reaction was monitored. After 12 h no residual ester was detected and the exclusive formation of benzyl alcohol noted in addition to **1**.

In a separate run, the contents were refluxed for 12 h and cooled, the reaction was then quenched with water, and aqueous NaOH (3 N) was added. The organic layer was separated, and the aqueous layer was saturated with K_2CO_3 and extracted with ether. The combined organic extract was dried over anhydrous magnesium sulfate, the solvent was evaporated, and the residue was subjected to column chromatography using silica gel. Amine was eluted using hexane−ethyl acetate (95:5) and benzyl alcohol using hexane−ethyl acetate (80:20).

In the case of water−insoluble alcohol products, such as 1-undecanol (reduction of ethyl undecanoate), the workup procedure can be simplified as follows. After completion of the reduction, the reaction mixture was quenched with water, ether was added, and amine was extracted into the aqueous layer using HCl (3 N). The organic layer was dried over anhydrous $MgSO_4$, and evaporation of the solvent provided essentially pure 1-undecanol (99% by GC). The aqueous layer was neutralized with NaOH to liberate amine (97% pure by GC).

^{1}H NMR of 1-undecanol (200 MHz, $CDCl_3$) δ ppm: 0.86 (t, 3H), 1.25 (m, 16H), 1.54 (m, 2H), 1.74 (s, 1H), 3.61 (t, 2H).

Reduction of Representative Nitriles with 2 in THF and Dioxane at Reflux. Reduction studies of heptanenitrile and benzonitrile using amine−borane adduct **2** in THF and dioxane under reflux conditions were carried out. The procedure followed for benzonitrile in THF is representative.

An oven-dried RB flask (50 mL), provided with a reflux condenser, a septum inlet, and a stirring bar, was cooled under a flow of nitrogen. Into the flask was placed freshly distilled THF (22.3 mL) and **2** (1.80 mL, 5 M, 9 mmol). Benzonitrile (0.85 mL, 8.3 mmol) was added, and the reaction mixture was stirred under reflux. Aliquots were removed at appropriate intervals and, after hydrolysis, tested for the presence of residual benzonitrile using GC analysis on the OV-17 column. After refluxing for 6 h, no residual nitrile was found. In a separate experiment, after refluxing for 6 h, the reaction mixture was cooled and quenched with water, and HCl (6 N) was added. The contents were refluxed further for 1 h, cooled, and neutralized by the addition of solid NaOH. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extract was dried over anhydrous $MgSO_4$. Analysis (by GC) of the reaction mixture revealed a quantitative yield of benzylamine.

Reduction of Representative Amides with 2 in THF and Dioxane Under Reflux. Reduction studies of caproamide, benzamide, *N*-methylbenzamide, *N*,*N*-dimethylcaproamide, and *N*,*N*-dimethylbenzamide using **2** in dioxane and THF were carried out under reflux conditions. The course of the reaction was followed by GC analysis of the reaction mixture after hydrolysis. The reactions were quenched as soon as the starting amide was fully consumed. The reduction of *N*,*N*-dimethylbenzamide with **2** in dioxane is representative.

Reduction of *N*,*N*-Dimethylbenzamide with 2. An oven-dried 50 mL RB flask, provided with reflux condenser, septum inlet, and a stirring bar, was cooled under a flow of nitrogen. The outlet of the condenser was connected to a mercury bubbler. Into the flask was placed *N*,*N*-dimethylbenzamide (1.76 g, 12.5 mmol) in dry dioxane (20.6 mL), and **2** (4.4 mL, 22 mmol) was added. The contents were heated under reflux for 15 min. by which time no starting amide was present (by GC analysis). The reaction was quenched with water, 6 N HCl (18 mL) was added, and the contents were heated to reflux for 1 h. The reaction mixture was cooled to 0 °C, and solid NaOH was added until the mixture became basic. The organic compounds were extracted with ether, and the combined organic extracts were dried over $MgSO_4$. GC analysis of the mixture revealed the quantitative conversion. Distillation under reduced pressure gave **2** (2.31 g, 89% yield (isolated), 94% pure by GC) and *N*,*N*-dimethylbenzylamine (1.26 g, 75%, 99% pure by GC).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 2.50 (s, 6H), 3.98 (s, 2H), 7.38 (m, 5H).

An alternate procedure can also be used to isolate the amines. In an experiment similar to that outlined above, after the reduction was complete the excess active hydride was destroyed by the addition of water. The reaction mixture was taken in ether (20 mL) and washed with dilute HCl (3 N), and the organic layer was dried over anhydrous $MgSO_4$. Evaporation of the solvent provided essentially pure *N*,*N*-dimethylbenzylamine−borane (^{11}B NMR δ −8.3, quartet, in THF) adduct from which the amine was liberated by the addition of BF_3−OEt_2. The combined aqueous layer was neutralized with base to obtain *N*-ethyl-*N*-isopropylaniline in 90% pure form (by GC).

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