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Borane−THF: New Solutions with Improved Thermal Properties and Stability[†]

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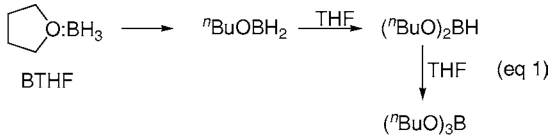
Abstract:

A new generation of borane−THF solutions stabilized with 0.005 M of 1,2,2,6,6-pentamethylpiperidine or *N*-isopropyl-*N*-methyl-*tert*-butylamine have been developed. These BTHF solutions show superior stability and reactivity at ambient temperatures when compared to BTHF complex unstabilized or stabilized with 0.005 M $NaBH_4$.

Diborane (B_2H_6) is a versatile reagent with a multitude of applications in organic and inorganic syntheses. Being a pyrophoric gas, diborane is routinely used as borane−Lewis base complexes, as they are safer and more convenient to handle. Numerous applications of these borane complexes in the synthesis of pharmaceuticals and in other industrial processes have been reported.[1] Borane−tetrahydrofuran complex (also referred to as "BTHF" or "BTHF complex") is one of the most widely used borane−Lewis base complexes for synthetic applications, such as the hydroboration of carbon−carbon double and triple bonds, and the reduction of various functional groups.[2] While several other borane reagents are available, BTHF continues to be the reagent of choice for such applications.[1,3]

Although effective in synthetic applications, BTHF suffers a few disadvantages. As a weak Lewis base, THF can complex with borane to form only up to 2.5 M BTHF solution under normal pressures.[4] At high diborane pressures, solutions of 5 M BTHF in THF have been reported.[4b] Even at low concentrations, such as 1.0 M, BTHF loses its hydride activity over time when stored at room temperature.[5] It is known that THF forms a weak complex with borane and is subject to dissociation to reach a dynamic equilibrium between borane and THF in BTHF solution.[4] This equilibrium in borane−THF solutions, at normal pressures results in the formation of free diborane. The borane complexed to THF can ring-open the THF to produce dibutoxyborane or tributoxyborane (eq 1).



This ring opening is minimal or absent below 5 °C. However, it is facile at and above room temperature. This is most likely due to the recomplexation of borane with THF, which is exothermic and may result in localized heating.[6]

Previously, this problem was partially addressed by stabilizing these BTHF solutions with a small amount of $NaBH_4$.[7] While $NaBH_4$-stabilized BTHF solutions lose very little hydride activity when stored and used at 0 °C, these BTHF solutions lose activity over time when kept at ambient temperatures, creating both safety and stability concerns.[7,8,10] Under the United States Department of Transportation (DOT) regulations, shipment of a package (at ambient temperature) containing a material which is likely to decompose with a self-accelerated decomposition temperature (SADT) of less than or equal to 50 °C, with an evolution of a dangerous quantity of heat or gas when decomposing, is prohibited unless the material is sufficiently stabilized or inhibited.[9] BTHF solutions having concentrations in excess of about 1 mole per liter generally cannot meet the SADT mandated by the DOT.[10]

The stabilizer, $NaBH_4$, is sparingly soluble in borane−THF solution and forms complexes with borane to produce

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[†] Dedicated to the late Prof. Herbert C. Brown, a great mentor and pioneer in boron chemistry.

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(1) (a) Brown, H. C.; Zaidlewicz, M. *Organic Synthesis via Boranes*; Aldrich Chemical: Milwaukee, 2001; Vol. 2. Product Number Z40,095-5. (b) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London, 1988. (c) Yardley, J. P.; Fletcher, H., III;, Russell, P. B. *Experientia* **1978**, *34*, 1124. (d) Renn, O.; Meatres, C. F. *Bioconjugate Chem.* **1992**, *3*, 563. (e) Follet, M. *Chem. Ind.* **1986**, 123.

(2) Zaidlewicz, M.; Brown, H. C. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; J. Wiley: New York, 1995; Vol. 1, p 638.

(3) For a review on amine−boranes, see: Kanth, J. V. B. *Aldrichimica Acta* **2002**, *35*, 57.

(4) (a) Wirth, H. E.; Massoth, F. E.; Gilbert, D. X. *J. Phys. Chem.* **1958**, *52*, 870. (b) Elliott Roth, W. L.; Roedel, G. F.; Boldebuck, E. M. *J. Am. Chem. Soc.* **1952**, *74*, 5211.

(5) (a) Lane, C. F. *Chem. Rev.* **1976**, *76*, 773. (b) Brown, H. C.; Heim, P.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 1637. (c) Prasad, A. S. B.; Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1992**, *48*, 4623.

(6) (a) When borane gas is passed into anhydrous THF at room temperature, a 5−10 °C temperature rise is generally observed. Accordingly, it is always a practice to cool the THF to 10 °C (ice water) to control the heat of reaction, to avoid undesired side products. (b) During stability testing, when BTHF solutions were heated without stirring, the decomposition was found to be more rapid than with stirring. This may have been from hot spots that were created where the immersion heating coil contacts the solution.

(7) (a) Brown, H. C. U.S. Patent 3,634,277, 1972. (b) When 0.005% $NaBH_4$ stabilizer was used, all of the $NaBH_4$ stayed in the THF solution. However, when more than 0.01% $NaBH_4$ stabilizer was used, some precipitation was observed, and the ^{11}B NMR indicated signals due to $NaBH_4 \cdot BH_3$ (δ: −24 ppm) in addition to $NaBH_4$ (δ: −40 ppm).

(8) Nettles, S. M.; Matos, K.; Burkhardt, E. R.; Rouda, D. R.; Corella, J. A. *J. Org. Chem.* **2002**, *67*, 2970.

(9) For requirements and testing details, see: Code of Federal Regulations 49 CFR 173.21 (f), 10-1-03 edition, U.S. Government Printing Office, p 417. A link to this reference can be found at: http://www.access.gpo.gov/nara/cfr/waisidx_03/49cfr173_03.html. Some experimental details are given in the Supporting Information.

(10) (a) SADT testing of 1.0 M BTHF stabilized with 0.005 M $NaBH_4$, using the procedure described in ref 9, resulted in a self-accelerating temperature of 42 °C. (b) For an industrial incident involving 2 M THF in a 400-L cylinder, please see *Chem. Eng. News*, July 1, 2002, and Safety Highlights in *Org. Process. Res. Dev.* **2003**, *7*, 1029.

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Table 1. **Sealed NMR tube studies at 50 °C using 1.0 M BTHF: percent of remaining BTHF complex by ^{11}B NMR**

entry	stabilizer with concentration	24 h (%)	48 h (%)	72 h (%)
1	unstabilized	82	59	39
2	0.005 M Me_2S	83	57	37
3	0.01 M $^{n}BuNEt_2$	83	58	39
4	0.005 M $^{n}BuNEt_2$	81	55	36
5	0.005 M $^{t}BuN^{i}BuEt$	83	59	43
6	0.005 M $LiBH_4$	89	64	43
7	**0.005 M $NaBH_4$**	**90**	**66**	**45**
8	0.01 M $NaBH_4$	91	69	47
9	0.005 M $PhN^{i}PrEt$	83	65	48
10	0.005 M $^{i}Pr_2N^{i}Bu$	85	65	49
11	0.005 M $Et_2N^{t}Oct$	88	73	59
12	0.0025 M NIMBA	87	74	61
13	**0.005 M PMP**	**92**	**78**	**64**
14	**0.005 M NIMBA**	**89**	**79**	**67**
15	**0.01 M NIMBA**	**92**	**77**	**72**

$NaBH_4$:BH_3 or NaB_2H_7 species as observed by ^{11}B NMR, which may precipitate out on long standing, reducing the stability of the solution.[7b] Consequently, the exact amount of stabilizer in a given solution is not consistent, leading to inconsistent performance during applications.[8,11] As a majority of BTHF applications, such as hydroboration, carboxylic acid, aldehyde, and ketone reductions are carried out at or below 25 °C,[5,12] for high-temperature synthetic applications such as reduction of nitriles the loss of hydride activity directly results in the usage of more reagent.[3,5]

In order to develop a safer and more stable BTHF for applications in organic syntheses, we have undertaken a study to explore new stabilizers for BTHF that minimize or reduce the above-mentioned problems. Such solutions would both improve safety and stability, and hence could reduce the requirement of using excess reagent.

Results and Discussion

A suitable borane scavenger must be freely miscible with BTHF solution and should be able to complex weakly with the free borane. Also, the stability effect must be achieved with a minimum amount of this stabilizer, in order not to contaminate products or complicate reaction workup. With this in mind, several Lewis bases with varying steric and electronic factors were screened as potential stabilizers.

The initial screening was carried out by ^{11}B NMR studies, placing 0.8 mL of BTHF of a given concentration and the stabilizer in a NMR tube and sealing the tube. The tube was then heated in a uniform temperature-controlled bath. Using ^{11}B NMR, the progress of the decomposition was monitored. The results obtained using 1.0 M BTHF solutions with selected stabilizers, are described in Table 1.

From the data in Table 1, it is clearly evident that some amines (entries 11, 13 and 14) show significant stabilization of the BTHF solution when compared to unstabilized borane−THF as well as $NaBH_4$-stabilized BTHF. Also, there is a marginal change by increasing the stabilizer concentration to 0.01 M (entry 15), or reducing it to 0.0025 M (entry 12). From these variations, we decided to keep the stabilizer at 0.005 M in 1.0 M BTHF to achieve optimal results with a minimum concentration of the stabilizer.

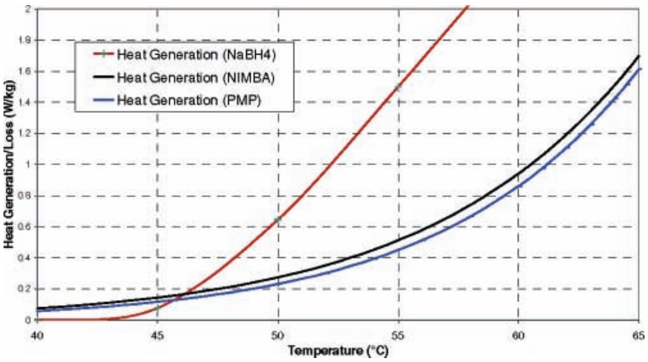

Figure 1. **Heat generation for decomposition of 1.0 M BTHF with selected stabilizers at 50 °C.**

Table 2. **Sealed NMR tube studies at 50 °C using 1.5 M BTHF: percent of remaining BTHF complex by ^{11}B NMR**

entry	stabilizer with concentration	24 h (%)	48 h (%)	72 h (%)
1	unstabilized	71	38	19
2	0.01 M NIMBA	87	68	49
3	0.01 M PMP	85	63	45

The two selected stabilizers were further studied at 0.01 M stabilizer in 1.5 M BTHF solutions. Results obtained from the sealed ^{11}B NMR studies in 1.5 M BTHF are presented in Table 2. Here also, the additives stabilize the BTHF solution to a considerable extent.[13]

Using larger sample sizes in a sealed autoclave reactor, the ^{11}B NMR integration was directly correlated to the active hydride content. The active hydride content was measured by hydrolyzing the resulting solution and measuring the hydrogen evolved.[14]

Finally, these selected candidates were subjected to the United Nations recommended testing protocol for shipment of dangerous goods.[9,13] The test for 1.0 M BTHF stabilized with 0.005 M $NaBH_4$ showed that this material is capable of undergoing self-accelerating decomposition from 42 °C (SADT: 45 °C), which fails to meet the threshold for ambient temperature shipping. On the other hand 1.0 M BTHF stabilized with *N*-isopropyl-*N*-methyl-butylamine (NIMBA) or 1,2,2,6,6-pentamethylpiperidine (PMP) showed higher critical ambient temperatures resulting in higher SADT, making it much safer to ship and handle at ambient temperature. For example, 1 M BTHF stabilized with 0.005 M PMP, has a critical ambient temperature of >45 °C with SADT of 50 °C.[13] Figure 1 depicts the heat generation pattern of 1 M BTHF stabilized with $NaBH_4$, NIMBA or PMP, under adiabatic conditions at 50 °C. The rate of heat generation is relatively slow for the amine-stabilized BTHF, when com-

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(11) (a) Fu, X;, McAllister, T. L.; Thiruvengadam, T. K.; Tann, C-H.; Su, D. *Tetrahedron Lett.* **2003**, *44*, 801. (b) Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* **2003**, *68*, 10146.

(12) Lobben, P. C.; Leung, S. S-W.; Tummala, S. *Org. Process Res. Dev.* **2004**, *8*, 1072.

(13) For details, please see the Supporting Information

(14) (a) See Supporting Information section for details. (b) The hydride estimations were carried out using the procedures described in: Brown, H. C. *Organic Syntheses via Boranes*; Aldrich Chemical Co., Inc.: Milwaukee, WI, 1997; Vol. 1.

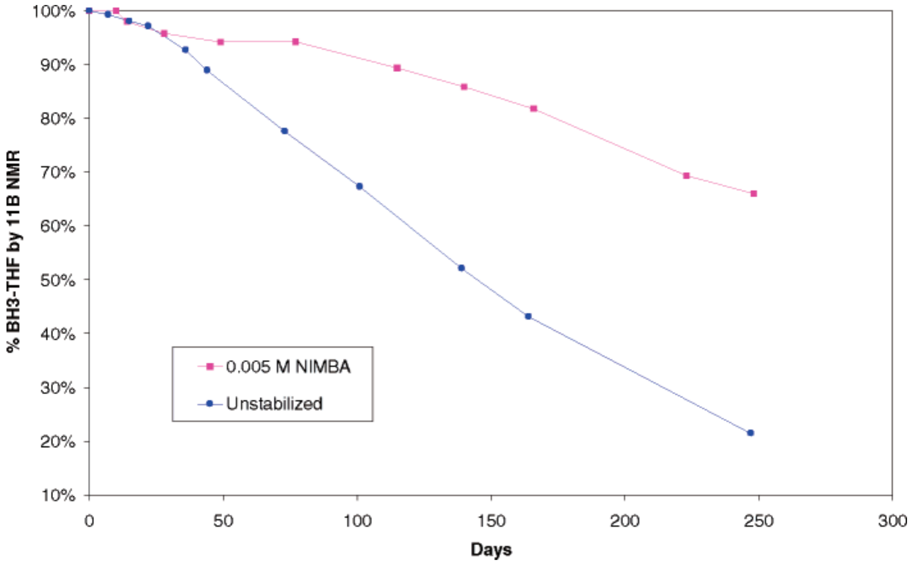


Figure 2. **Stability studies of 1.0 M BTHF at 22 °C.**

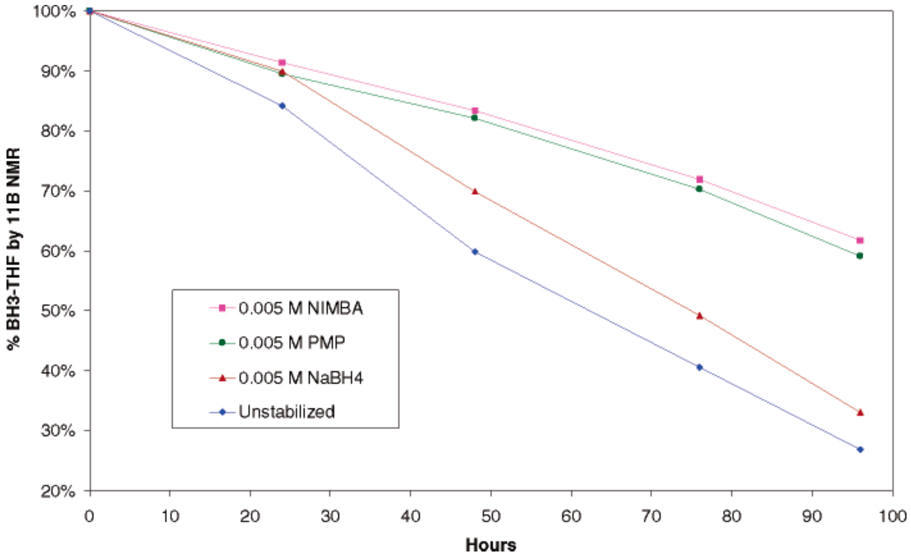


Figure 3. **Stability studies of 1.0 M BTHF at 50 °C.**

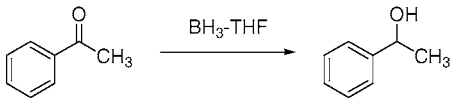
pared to that for BTHF stabilized with $NaBH_4$, directly resulting in higher SADT.

The stability of BTHF at 0 °C is well established.[7a,8] However, when stored at room temperature, degradation is rapid for unstabilized BTHF. Fortunately, our studies indicated superior stability of 1.0 M BTHF stabilized with 0.005 M NIMBA. Figure 2 depicts the stability study results of 1 M BTHF with and without stabilizer, observed in ^{11}B NMR, in a sealed NMR tube.

Encouraged by the improved stability of 1.0 M BTHF containing 0.005 M NIMBA, we have also carried out similar sealed NMR tube experiments at 50 °C. Since, borane−THF dissociates rapidly at higher temperatures, it was always used in excess or other borane−Lewis base complexes such as BMS and amine−borane complexes were used for high-temperature synthetic applications.[3,5b] Surprisingly, the 1.0 M BTHF stabilized with 0.005 M NIMBA showed superior stability, even at 50 °C, when compared to unstabilized or stabilized with 0.005 M $NaBH_4$.[13] For example, after 96 h heating at 50 °C, the ^{11}B NMR of 1.0 M BTHF stabilized with 0.005 M NIMBA indicated the presence of 58% active BTHF as compared to 24% in unstabilized BTHF (Figure 3). Also, the ^{11}B NMR study indicated the dissociation pathway of BTHF stabilized with NIMBA, PMP is considerably different from BTHF unstabilized or stabilized with $NaBH_4$. In the case of amine-stabilized BTHF solutions, some higher borane species were observed, whereas with BTHF unstabilized or stabilized with $NaBH_4$, THF-cleaved products are the major impurities. Further studies on understanding this dissociation pathway are in progress and will be the subject of further reports in this area. The higher thermal stability of BTHF containing 0.005 M NIMBA should not only make this more safe for shipping, but should also make the reagent more desirable for application at elevated temperatures.

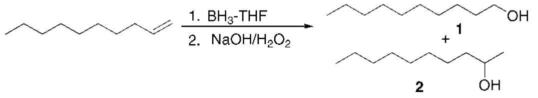
In order to establish the utility of these new amine-stabilized BTHF solutions, representative hydroboration and reduction reactions were carried out with 1-decene and acetophenone, respectively. For comparison, reactions were also carried out with 1.0 M BTHF solution stabilized with

Table 3. **Reduction of acetophenone**



1.0 M BTHF with stabilizer (0.005 M)	GC yield (%)	isolated yield (%)
$NaBH_4$	98	94
PMP	99	95
NIMBA	98	94

Table 4. **Hydroboration−oxidation of 1-decene**



1.0 M BTHF with stabilizer (0.005 M)	GC yield (%)	isolated yield (%)	regioselectivity (**1**:**2**)
$NaBH_4$	96	92	94:6
PMP	94	90	94:6
NIMBA	97	93	94:6

0.005 M $NaBH_4$. In this comparative study, both amine-stabilized BTHF solutions performed similarly to those stabilized with $NaBH_4$ (Tables 3 and 4).

In both the cases, usual workup provided essentially pure alcohol product. Simple HCl wash removed the amine stabilizer effectively providing analytically pure samples, which were cross-compared to the literature reports.[15]

In conclusion, we report new amine-stabilized borane−THF solutions for applications in organic syntheses. Though 1 M BTHF stabilized with $NaBH_4$ is still a viable option for synthetic application if handled with caution, this new generation of BTHF solutions is significantly more stable than the previously available BTHF reagents, whilst retaining the qualities of high reactivity and simple workup. In addition, these new reagents enable safer shipping and use in organic synthesis involving borane−THF at temperatures higher than ambient. For both $NaBH_4$-stabilized as well as amine-stabilized BTHF reagents, keeping them in a temperature-controlled environment (2−8 °C) for long-term storage is necessary for optimal utility and safety.[16] Further studies on understanding the mechanism of this stability effect and other synthetic applications are underway and will be the subject of future reports.

Experimental Section

Typical Procedure for Sealed NMR Tube Studies at 50 °C Using 1.0 M BTHF. Unstabilized BTHF solutions were prepared by passing diborane gas into THF solution as described in the literature.[1] This stock solution was transferred to a nitrogen-flushed, oven-dried vessel, and then a calculated amount of the stabilizer was added. This solution was diluted to the required concentration with additional anhydrous THF, and 0.8 mL portions of the solution were removed by nitrogen-flushed syringes to nitrogen-flushed, oven-dried NMR tubes. The NMR tubes were sealed and placed in a temperature-controlled bath, heated for a fixed time, and then removed for evaluation by ^{11}B NMR.

Typical Procedure for Autoclave Reactor Studies at 50 °C Using 1.0 M BTHF. Stabilized solutions were prepared as above, and 25 mL portions of the solution were removed by nitrogen-flushed syringes to oven-dried, nitrogen-flushed glass vessels in a 1 L pressure reactor. The reactor was sealed and heated with an oil bath. After the desired reaction time the apparatus was cooled to room temperature. Samples were removed for evaluation by ^{11}B NMR and hydrogen evolution.

Typical Experimental Procedure for the Racemic Reduction of Acetophenone. In an oven-dried round-bottom flask, the stabilized borane solution (Aldrich 176192, 650412, or 630390, ca. 1 M in THF, 13.3 mmol) was diluted with 2 volumes of anhydrous THF. The diluted solution was cooled to 0 °C. Acetophenone (10 mmol) was added over 5 min. The reaction mixture was stirred with a magnetic stirrer at room temperature for 2 h. The reaction was quenched by addition of H_2O (10 mL). Ether (10 mL) was added. The mixture was washed with 3 M HCl (10 mL). The organic phase was washed with H_2O (10 mL) and brine (10 mL), dried over magnesium sulfate, and filtered. The solvent was removed to record the crude yield and for GC quantification. The clear liquid was passed through a silica gel plug (2 cm × 4 cm i.d.) with ether (100 mL). After the solvent was removed, the yield of isolated product was obtained by GC and weighing.

(i) Reduction of acetophenone using BTHF stabilized with $NaBH_4$: yield (98% by GC; isolated 1.15 g (94%)). GC was run on HP5890 and an RTx-50 column with retention time 3.994 min (100 °C (1 min), then 100 °C to 180 °C @10 °C/min; splitless, Inj. 200 °C, Det. 250 °C).

(ii) Reduction of acetophenone using BTHF stabilized with PMP: yield (99% by GC; isolated 1.16 g (95%)). GC was run on HP5890 and an RTx-50 column with retention time 4.012 min.

(iii) Reduction of acetophenone using BTHF stabilized with NIMBA: yield (98% by GC; isolated 1.15 g (95%)). GC was run on HP5890 and an RTx-50 column with retention time 3.998 min.

Typical Experimental Procedure for the Hydroboration−Oxidation of 1-Decene. In an oven-dried round-bottom flask, the stabilized borane solution (Aldrich 176192, 650412, or 630390, ca. 1 M in THF, 7.5 mmol) was diluted with 1.5 volumes of anhydrous THF. The diluted solution was cooled to 0 °C. 1-Decene (D1807, 15 mmol) was added over 5 min. The reaction mixture was stirred with a magnetic stirrer at room temperature for 2 h. The reaction was cooled to 10 °C. NaOH solution (3 M, 9 mL) was then added. Hydrogen peroxide (216763, 30 wt % in water, 3 mL) was added at 10 °C. The reaction mixture was stirred at 50 °C for 2 h and then cooled to room temperature. Ether (20 mL) was added.

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(15) Brown, H. C.; Kanth, J. V. B.; Dalvi, P. V.; Zaidlewicz, M. *J. Org. Chem.* **2000**, *65*, 4655.

(16) For further details about the safe handling of new amine-stabilized BTHF solutions, please see Aldrich Technical Bulletin 218, which can be requested by e-mail (aldrich@sial.com) or can be accessed on the web: http://www.sigmaaldrich.com/aldrich/bulletin/al_techbull_al218.pdf .

The organic phase was washed with H_2O (20 mL) and brine (20 mL), dried over magnesium sulfate, and filtered. Solvent was removed to record the crude yield and for GC quantification of regioisomers 1- and 2-decanol. The clear liquid was passed through a silica gel plug (3 cm × 5 cm i.d.) with ether (150 mL) to give an isolated yield. GC was used to quantify the ratios of the regioisomers in the isolated product.

(i) Hydroboration of 1-decene using BTHF stabilized with $NaBH_4$: yield (96% by GC; isolated 2.18 g (92%)). GC was run on HP5890 and an RTx-50 column with retention times 5.34 min (1-decanol) 4.22 (2-decanol); isomeric ratio 1-decanol:2-decanol = 93.9:6.1 (100 °C (1 min), then 100 °C to 250 °C @10 °C/min; Inj. 200 °C, Det. 250 °C).

(ii) Hydroboration of 1-decene using BTHF stabilized with PMP: yield (94% by GC; isolated 2.13 g (90%)). GC was run on HP5890 and an RTx-50 column with retention times 5.54 min (1-decanol) 4.30 (2-decanol); isomeric ratio 1-decanol:2-decanol = 94.4:5.6.

(iii) Hydroboration of 1-decene using BTHF stabilized with NIMBA: yield (97% by GC; isolated 2.21 g (93%)). GC was run on HP5890 and an RTx-50 column with retention times 5.28 min (1-decanol) 4.21 (2-decanol); isomeric ratio 1-decanol:2-decanol = 94.1:5.9.

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Supporting Information Available

Details of the compound stability data, accelerating calorimetry, and adiabatic Dewar calorimetry data. This material is available free of charge via the Internet at http://pubs.acs.org.

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