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Lewis Base Activation of Lewis Acids – Group 13. In Situ Generation and Reaction of Borenium Ions

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Abstract

A variety of Lewis bases were combined with 9-BBN-NTf_2 to establish the requirements for the generation of borenium cations. Five different types of behavior were found, but the most interesting was the combination of Et_3N, DABCO, 2,6-lutidine, or $Ph_3P{=}S$ which formed borenium ions exclusively even in sub- or superstoichiometric quantities. The 9-BBN borenium ion complex of 2,6-lutidine was found to rapidly catalyze the hydrosilylation of a variety of ketones in the presence of Et_3SiH. Preliminary mechanistic experiments suggest that the reduction involves borenium ion activation of Et_3SiH and not the ketone.

Foregoing studies from these laboratories have provided extensive preparative and mechanistic illustration of the counterintuitive concept of Lewis base activation of Lewis acids.[1] The majority of the early investigations focused on the activation of silicon tetrachloride with chiral bisphosphoramides to generate a highly reactive, chiral trichlorosiliconium ion complex that catalyzed the diastereo- and enantioselective aldol additions of enoxysilanes derived from aldehydes, ketones, esters, amides, and nitriles.[2] In recent years, our attention has turned to the Lewis base activation of Lewis acidic reagents in Group 16 (selenium[3] and sulfur[4]) as well as Group 17 (bromine[5] and chlorine[6]) to effect enantioselective cyclofunctionalizations of unactivated alkenes. Despite the dramatic difference in the chemical transformations involved, the underlying principle of catalysis is the same, namely the electronic redistribution in donor–acceptor complexes first articulated by Gutmann, Figure 1.[7] To date, all of our mechanistic studies have demonstrated that the ionization of the dative complexes into highly electrophilic, cationic species is required for catalysis.

In continuation of these investigations, we were drawn to the possibility of activating Lewis acids in Group 13 in view of the recent interest in the chemistry of tricoordinate cationic boron species (borenium ions).[8] Many different methods for borenium ion generation are on record[9] and these highly reactive species have been used as stoichiometric reagents (e.g. in arene and alkane borylation).[10] On the other hand, the main focus in borenium cation catalysis has been the development of oxazaborolidine catalysts and other application methods are very rare.[11] Very recently, borenium ion catalyzed hydrogenation and hydroboration have been reported. In 2012, Crudden and co-workers reported a novel, metal-free, catalytic method for the reduction of imines using air-stable, nonhazardous boranes. The catalysts for this process are discrete, well-characterized borenium salts derived from pinacolborane.[12a] In addition, Curran, Vedejs and co-workers reported a

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Notes
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Supporting Information
Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

borenium ion catalyzed hydroboration of alkenes with *N*-heterocyclic carbene-boranes,[12b] Stephan and co-workers described hydrogenation of imines with 9-BBN–NHC borenium ion complexes,[12c] and Jäckle recently described the preparation of chiral borenium ions that effected asymmetric hydrosilylation of a ketone.[12d]

To develop a *catalytic* method for the generation of borenium ions presented far greater challenges than those encountered with Group 14, 16, and 17 elements in previous endeavors such as: (1) the design features for Lewis base activation are entirely different in view of the high affinity of the Lewis acidic elements in this group, (2) the intrinsic Lewis acidity of any precursors presents a major problem for suppression of background reactions, (3) ionization of a labile ligand is essential (at least for boron) to provide the coordinative unsaturation needed for catalysis, and (4) the lack of an established suite of known reactions of borenium ions for which (asymmetric) catalysis would be useful. Thus, we viewed this exercise as an exploratory investigation to learn the rules for the catalytic generation of borenium ions to enable the discovery of new reaction chemistry of these novel species.

The first phase of the study required the identification of a suitable boron precursor and its behavior in the presence of a wide range of Lewis bases. The structures of the possible adducts in Scheme 1 could be identified by ^{11}B-, ^{19}F-, and ^{31}P-NMR spectroscopy. From the pioneering work of Vedejs, we chose 9-borabicyclo[3.3.1]nonane bistriflimide (9-BBN-NTf_2, **1**). Vedejs demonstrated that **1** was effective for the generation of borenium and boronium cations with amine Lewis bases owing to the excellent nucleofugality of the bistriflimide group.[13]

Initially, ^{11}B and ^{19}F NMR spectroscopic analysis of isolated, purified **1** was performed in CH_2Cl_2 (0.1 M) at room temperature and sharp singlets were observed at 58.9 ppm and −70.0 ppm, respectively. To assay the potential of Lewis bases to generate borenium cations from **1**, 0.5, 1.0, and 2.0 equiv of each Lewis base were titrated to the 0.1 M solution of **1** and analyzed by NMR spectroscopy (Table 1). The ^{19}F NMR resonance at ca. −80.0 ppm is characteristic of bistriflimide anion,[13] and thus allowed the assignment of the boron-containing fragment as a cation. With this information in hand, DABCO, pyridine, 2,4-lutidine, 2,6-lutidine, HMPA, Ph_3P=O, *n*-Bu_3P=O, Ph_3P=S, $(Me_2N)_3P$=S, pyridine-*N*-oxide, DMSO, *n*-Bu_3P, and benzophenone were used as Lewis bases and the structures of the 9-BBN-Lewis base complexes were assigned by ^{11}B and ^{19}F NMR spectroscopy titration experiments. Analysis of the results revealed that these Lewis bases could be broadly classified into five different groups: (1) Type I in which weak coordination formed a boronate complex only at all loadings of Lewis base (benzophenone), (2) Type II in which strong coordination formed a boronate complex which spontaneously ionized and bound a second Lewis base to form a boronium ion at all loadings of Lewis base (2,4-lutidine, *n*-Bu_3P), (3) Type III in which strong coordination led to ionization to form borenium ions at all loadings of Lewis base (Et_3N, DABCO, 2,6-lutidine, Ph_3P=S), (4) Type IV in which strong coordination led to ionization to form borenium ions with 1.0 equiv and then boronium ions with 2.0 equiv of Lewis base (HMPA, Ph_3P=O, *n*-Bu_3P=O, $(Me_2N)_3P$=S, pyridine-*N*-oxide, DMSO), and (5) Type V in which strong coordination led to ionization to form only boronium ions at all loadings of Lewis base (pyridine, proton sponge). Notably, for Type III Lewis bases, boronium cations were not formed even with 2.0 equiv of Lewis base. Furthermore, with 1.0 equiv of Type IV Lewis bases, a borenium cation was formed predominantly together with a small amount of the boronium cation.

With a reliable method for the efficient, in situ generation of borenium-Lewis base complexes, the next phase involved the identification of a reaction to evaluate the catalytic potential of these species. The hydrosilylation reaction of ketones was selected as a model reaction inspired by the imine hydrosilylation by Crudden et al.[12a] By analogy to their

proposed catalytic cycle, ketones would be activated by the borenium complex to give the corresponding boronium complex **A**. Subsequent hydride transfer from triethylsilane would afford borinate complex **B** that could be exchanged by Et_3SiNTf_2 to regenerate the borenium-Lewis base complex catalyst (Mechanism I) (Scheme 2).

Initial experiments to probe this hypothesis were conducted by treating 4-methylbenzophenone (**5a**) with Et_3SiH (1.5 equiv) in the presence of various boron reagents. It was first established that Et_3SiH does not reduce **5a** at room temperature after 6 h (Table 2, entry 1). However, in the presence of 9-BBN-NTf_2 **1** (0.1 equiv) only over-reduced product **6a** was obtained in 69% yield in 10 min (entry 2). Whereas no reaction took place in the presence of 0.1 equiv of complex **3b** (entry 3), 0.1 equiv of complex **3e** afforded the expected reduction product **7a** in 95% yield (entry 4). Remarkably, lowering the loading of 2,6-lutidine to 0.05 equiv in the presence of 0.05 equiv of **1** still afforded exclusively **7a** albeit much more slowly such that after 20 h only a 69% yield was obtained (entry 5). Clearly, two different mechanisms are operative for the different catalysts, **1** and **3e**.

The scope of the borenium cation catalyzed hydrosilylation was explored with various ketones **5** and the results are summarized in Table 3. Generally, the use of 0.1 equiv of **3e** and 1.5 equivalents of triethylsilane was sufficient for a smooth reaction and, after treatment of the mixture with catalytic amounts of $FeCl_3$ in methanol to remove silyl-protecting group, alcohols **8** were obtained in high yield. Both electron-deficient and electron-rich aryl ketones were compatible with the reduction conditions (entries 1–4). In addition, fused- and heteroaromatic substituents had no negative influence (entries 5 and 7). A secondary alkyl group was also nicely accommodated (entry 8).

Although **3e** functioned as a catalyst for the hydrosilylation of ketones as described above, the reaction mechanism remained unclear. Several control experiments were carried out to provide mechanistic insight. First, the operation of Mechanism I (Scheme 2) was probed by the attempted generation of intermediates **A** and **B** and subjecting them to the reaction conditions. However, the combination of **3e** and benzophenone in CH_2Cl_2 revealed no interaction by ^{11}B NMR spectroscopic analysis of the mixture.

The preparation of intermediate **B** was attempted by treatment of boronate **9a**[15] with *N*-(trimethylsilyl)bis(trifluoromethanesulfonyl) imide ($TMSNTf_2$) and 2,6-lutidine. However, **9a** was not converted to either silyl ether **7a** or over-reduced product **6a** instead, it slowly converted to the corresponding lutidinium salt **10a**. In addition, **10a** was also observed in presence of Et_3SiH (Scheme 3). These experiments suggest that the hydrosilylation reaction catalyzed by **3e** does not proceed via Mechanism I.[16]

In a different mechanism for the borenium ion catalyzed ketone hydrosilylation reaction, hydride abstraction from Et_3SiH by the borenium cation could generate 9-BBN-hydride-2,6-lutidine complex **11** as the active reducing reagent (Scheme 4). To investigate this possibility required the independent preparation of **11.** However, **11** did not form from 9-BBN-dimer and 2,6-lutidine.[17] Instead, the existence of **11** was probed indirectly by a ^{11}B NMR experiment between **3e** and Et_3SiH. Although **11** was not detected via ^{11}B NMR spectroscopy, **3e** was slowly converted to 9-BBN-H dimer. Furthermore, on mixing 9-BBN-H dimer with $TMSNTf_2$ in the presence of 2,6-lutidine, 9-BBN-H dimer was also slowly converted to **3e**. Thus, the equilibrium between **3e** and 9-BBN-H dimer, as well as the ability of **3e** to activate triethylsilane toward hydrogen transfer were confirmed (Scheme 4).

With this information in hand, two plausible catalytic cycles can be constructed; one catalyzed by borenium ion **3e** (Mechanism II) and one catalyzed by Et_3SiNTf_2 (Mechanism III) (Scheme 5). Mechanism II (borenium ion activation of Et_3SiH followed by carbonyl

activation via silyl transfer (path **a**) to form silyloxycarbenium ion **D** and consummated by hydride transfer to regenerate **3e**) finds excellent precedent in the Piers mechanism for $(C_6F_5)_3B$ catalyzed hydrosilylation of ketones which has been thoroughly investigated.[18] Mechanism III involves the Tf_2N^- assisted activation of Et_3SiH to form Et_3SiNTf_2 (path **b**) that in turn forms ion **D** which is reduced by Et_3SiH.

To differentiate between these two catalytic cycles, control experiments were conducted. Mechanism III posits that the reduction involves Et_3SiNTf_2 as the activator and Et_3SiH as the reducing agent but does not require 9-BBN-H. Accordingly, **5a**, Et_3SiH, and 0.1 equiv each of $TMSNTf_2$ and 2,6-lutidine were combined in CH_2Cl_2 at room temperature. The reaction required 6 h to reach full conversion and afforded **7a** in 92% yield. In contrast, an identical reaction containing 0.1 equiv of 9-BBN-H dimer was complete within 10 min to afford **7a** in 96% yield (Scheme 6). Thus, although Mechanism III is viable, it does not compete with Mechanism II under the established reaction conditions.

In a final set of experiments, the stability of silyl ether **7a** in the presence of Et_3SiH and both catalysts was tested. Treatment of **7a** with **1** resulted in the formation of **6a** in 99% yield after 10 min. However, **7a** did not react with borenium cation **3e** even after in 24 h. These results further support the operation of Mechanism II and also explain the formation of the reduced product **6a** in reaction without 2,6-lutidine (Scheme 7).

In conclusion, the interaction of various Lewis bases with 9-BBN-NTf_2 has been investigated. The stable borenium cation complex **3e** catalyzed the hydrosilylation of ketones. Mechanistic studies have revealed that this reaction takes place via a hydride abstraction pathway similar to the Piers mechanism for $(C_6F_5)_3B$ catalyzed hydrosilylation of ketones. Further studies on this concept, including the development of other activation modes and asymmetric reactions, will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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15. Boronate**9a**was prepared by reaction of 9-BBN-H with authentic carbinol**8a**; see the Supporting Information.
16. Hydrosilylation of imines with neutral boranes proceeds by a differnt mechanism than by borenium ions. Mewald M, Oestreich M. Chem Eur J. 2012; 18:14079–14084. [PubMed: 22996207]
17. 9-BBN-H Dimer was treated with 2,6-lutidine in CH_2Cl_2 at room temperature. After 24 h, ^{11}B NMR analysis showed no change.
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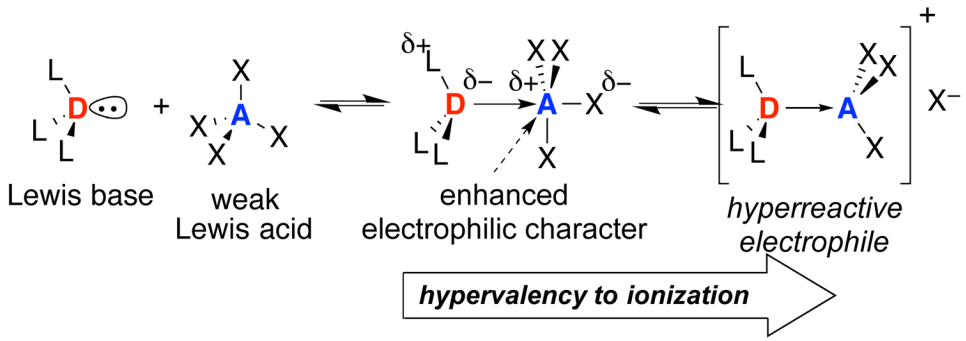
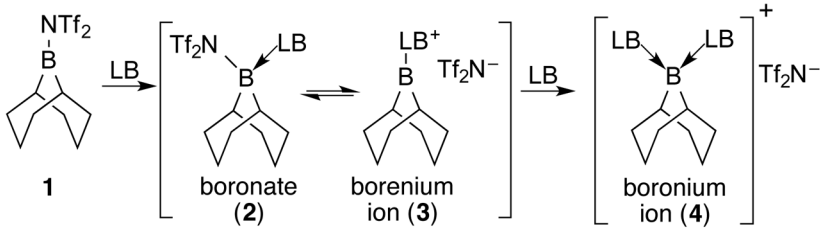
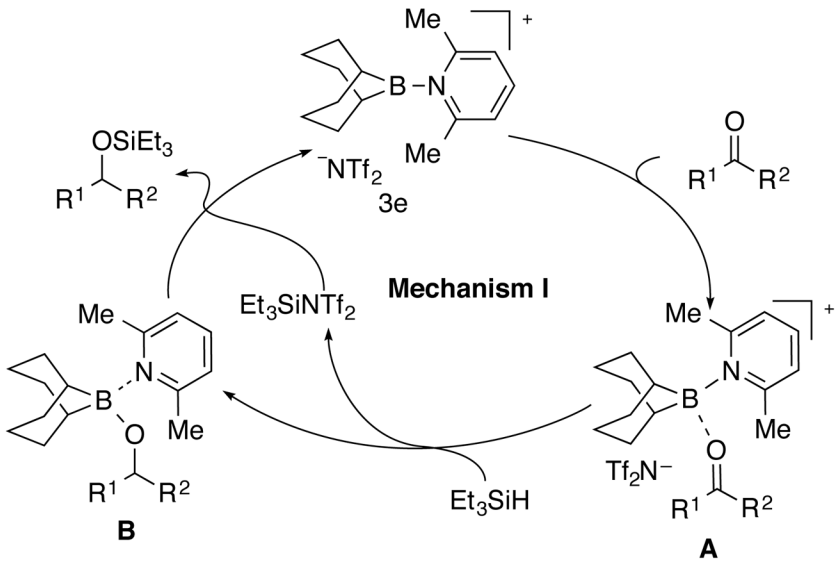


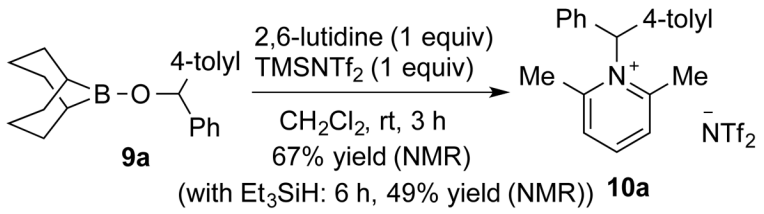
Figure 1.
Gutmann formulation of Lewis base activation of Lewis acids.



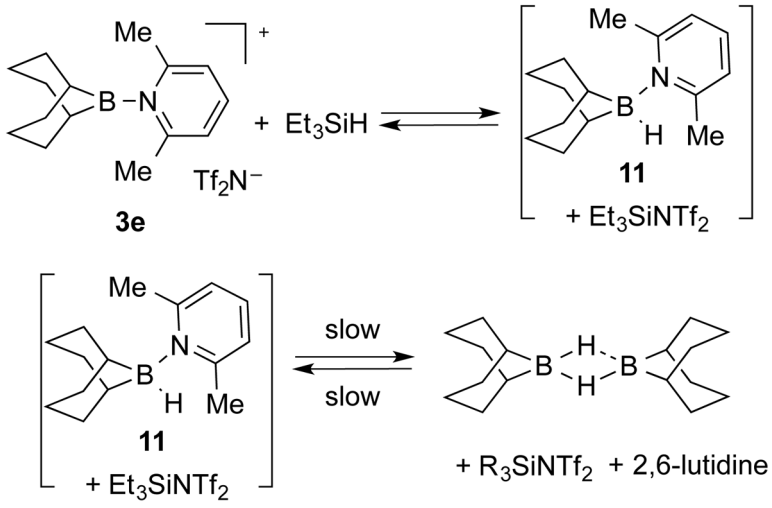
Scheme 1.



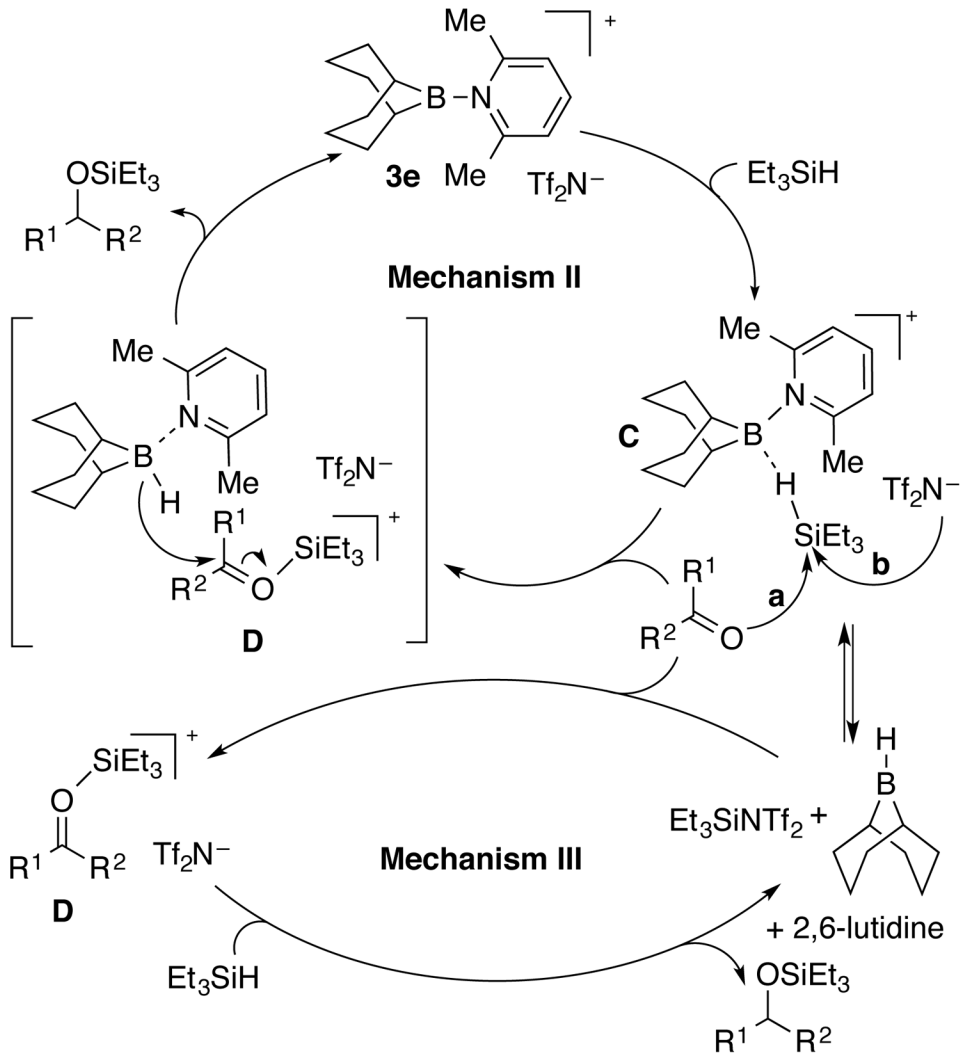
Scheme 2.



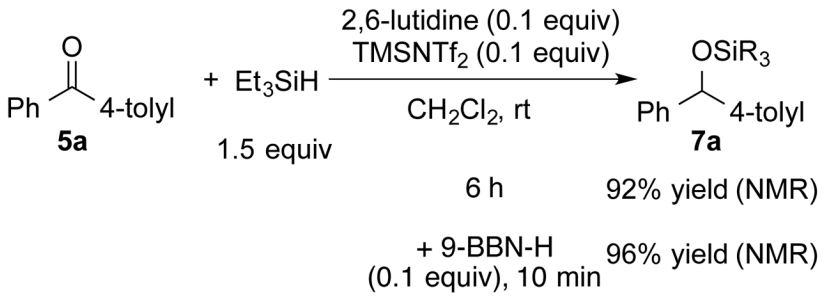
Scheme 3.



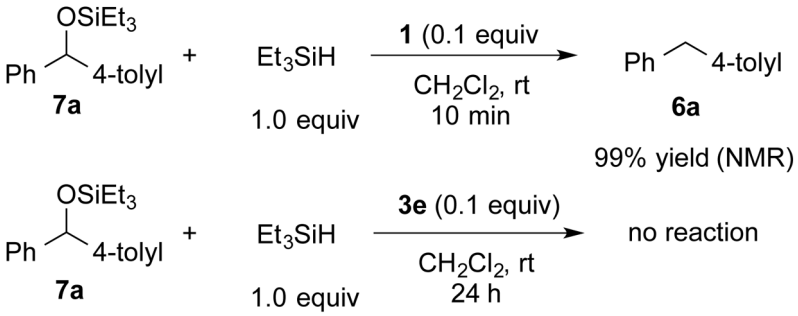
Scheme 4.



Scheme 5.



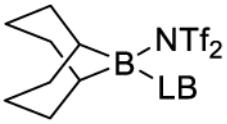
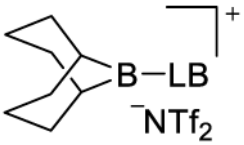
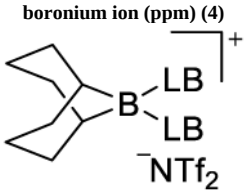
Scheme 6.



Scheme 7.

Table 1

Titration Experiments with 1 and Various Lewis Bases. ^{11}B-NMR Data.[a]

Lewis base	boronate complex (ppm) (2) 	borenium ion (ppm) (3) 	boronium ion (ppm) (4) 
Et_3N (**a**)		84.8 (85.1)[b]	
DABCO (**b**)		56.9	
pyridine (**c**)			5.2
2,4-lutidine (**d**)	39.4		9.7
2,6-lutidine (**e**)		84.4	
DMAP (**f**)		(66.5)[b]	(3)[b]
proton sponge (**g**)[c]			(16.2)[b]
HMPA (**h**)		64.9	17.8
$Ph_3P{=}O$ (**i**)		67.4	17.3
n-$Bu_3P{=}O$ (**j**)		65.1	14.5
$Ph_3P{=}S$ (**k**)		80.4	
$(Me_2N)_3P{=}S$ (**l**)		80.9	46.9
pyridine-*N*-oxide (**m**)		64.2	14.4
DMSO (**n**)		66.1	15
n-Bu_3P (**o**)	33.1		−5.4
benzophenone (**p**)	35.6[d]		

[a] ^{11}B NMR spectra were recorded at 128 MHz (CH_2Cl_2) with proton decoupling. Chemical shifts are reported in ppm from $BF_3{\cdot}OEt_2$ (0.0 ppm) as the external standard.

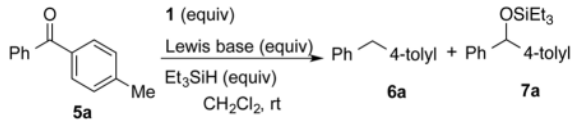
[b] Data in parentheses are from ref. 13.

[c] 1,8-bis(dimethylamino)naphthalene.

[d] 2.0 equiv of Lewis base.

Table 2

Hydrosilylation of Ketones Catalyzed by Various Boron Reagents.[a]



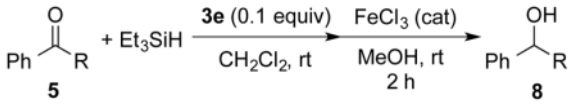
entry	1 (equiv)	Lewis base (equiv)	Et_3SiH (equiv)	time	yield[b] 6a (%)	yield[b] 7a (%)
1	0	–	1.5	6 h	0	0
2	0.1	–	1.5	10 min	69	0
3	0.1	DABCO (0.1)	1.0	12 h	0	0
4	0.1	2,6-lutidine (0.1)	1.5	30 min	<5	95
5	0.05	2,6-lutidine (0.05)	1.5	20 h	<5	69

[a] Reactions were performed at room temperature in an NMR tube (see Supporting Information for details).

[b] Yields determined by integration of product signals versus Cl_3CCH_2Cl as an internal standard.

Table 3

Substrate Scope.[a]



entry	R	ketone	time (min)	yield[b] (%)	alcohol
1	4-Me–C_6H_4	**5a**	30	92	**8a**
2	3-Me–C_6H_4	**5b**	10	90	**8b**
3	4-MeO–C_6H_4	**5c**	180	91	**8c**
4	4-Br–C_6H_4	**5d**	10	93	**8d**
5	1-naphthyl	**5e**	60	86	**8e**
6	2-furyl	**5f**	10	82	**8f**
7	2-thiophen	**5g**	60	83	**8g**
8[c]	isopropyl	**5h**	60	77	**8h**

[a] Unless otherwise noted, reactions were performed on 0.1 mmol scale with 1.5 equiv of Et_3SiH in dichloromethane (1.0 mL).

[b] Yield of isolated, purified product.

[c] 0.2 equiv of **3e** was used as catalyst.