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Taking the F out of FLP: Simple Lewis Acid–Base Pairs for Mild Reductions with Neutral Boranes via Borenium Ion Catalysis

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Supporting Information

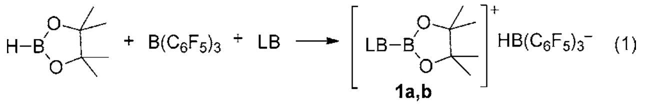
ABSTRACT: Discrete three-coordinate borenium salts **1c** and **1d** are accessed by cooperative Lewis acid–base pair-mediated heterolytic splitting of the B–H bond in pinacolborane by $B(C_6F_5)_3$·DABCO and Ph_3C^+/DABCO, respectively. The resulting salts are competent catalysts in the reduction of a broad range of imines and can be generated in situ. Moreover, a mechanistic framework for borenium catalysis based on experimental evidence is proposed. The reaction is suggested to proceed by borenium activation of the imine substrate followed by counterintuitive hydride delivery from HBPin (with the assistance of DABCO) rather than from the $HB(C_6F_5)_3^-$ anion, contrary to typical mechanisms of reduction in FLP systems.

Electrophilic boron cations are interesting alternatives to expensive, potentially toxic, high-molecular-weight metal-based Lewis acids. In particular, three-coordinate boron cations (borenium ions) were rarities a decade ago but are now readily accessible reagents.[1−3] Despite this fact, until recently, virtually the only application of these reactive species was as proposed intermediates in oxazaborolidene reductions.[4] However, in the last two years, work has appeared that illustrates the significant potential for discrete borenium intermediates to participate in the synthesis of boron-containing organic compounds. For example, electrophilic aromatic substitution reactions mediated by electrophilic borenium ions have been reported by the Ingleson group,[5,6] and Vedejs has studied the stoichiometric, intramolecular $C(sp^3)$–H insertions of these species.[7] Vedejs and Curran recently reported the use of NHC·BH_3 complexes in the generation of borenium ion equivalents that are able to catalyze hydroborations using the parent NHC·BH_3 complex as the stoichiometric reductant.[8]

Herein we report the generation and isolation of stable borenium salts and the first example of their use as catalysts for metal-free reductions with stable, neutral boranes.[9] Isotopic labeling studies and kinetic experiments provide evidence for true borenium catalysis rather than frustrated Lewis pair (FLP) chemistry, leading to the interesting conclusion that the 1,4-diazabicyclo[2.2.2]octane (DABCO) complex of the neutral borane pinacolborane (HBPin) is a better reducing agent than the anionic borohydride $HB(C_6F_5)_3^-$.[10]

Significant advances have been made in the last five years in the area of FLP chemistry.[11] Typically, highly sterically hindered and reactive Lewis acids and bases are used in concert to activate small molecules such as silanes[12−15] and H_2.[16,17] These systems can be used catalytically in the presence of suitable receptors for the heterolytically cleaved E–H bonds as long as the regeneration of the Lewis acid catalyst (which is almost exclusively $B(C_6F_5)_3$) is suitably efficient.[18,13,15]

Recently, our group proposed the formation of borenium ion **1a** in the reaction between $B(C_6F_5)_3$ and HBPin in the presence of a Lewis base by an FLP-type mechanism (eq 1).[19] In the presence of an acceptor olefin and a Rh complex, this resulted in a dramatically improved system for the hydroboration of olefins as a result of accelerated cleavage of the B–H bond.[19] Expanding on this concept, we speculated that borenium ions such as **1a** and **1b** could act as unique catalysts for the reduction of organic species under mild, metal-free conditions because they combine a strongly acidic borenium ion and a borohydride anion in the same salt.

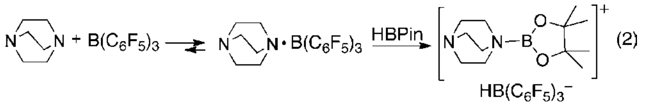


1a,b

1a, LB = THF
1b, LB = $PhNMe_2$

Borenium ion generation. As a starting point, we began by investigating the ability of various Lewis acid–base pairs to effect heterolytic splitting of the B–H bond of shelf-stable borane reagents, such as catecholborane (HBCat) and HBPin. Because of the propensity for tetrahydrofuran to polymerize when exposed to strongly acidic catalysts,[19,20] we focused on DABCO as the Lewis base.

As shown in eq 2, mixing equimolar amounts of $B(C_6F_5)_3$ and DABCO resulted in the formation of an insoluble Lewis acid–base adduct since DABCO, unlike typical bulky FLP-type bases, is sterically unhindered. Interestingly, exposure of this DABCO·$B(C_6F_5)_3$ complex to an equimolar amount of HBPin resulted in the clean, high-yielding formation of borenium ion **1c** (eq 2), illustrating that even this *classical* Lewis base pair is capable of cleaving nonpolar bonds such as the H–B bond in HBPin.[21,22]



1c

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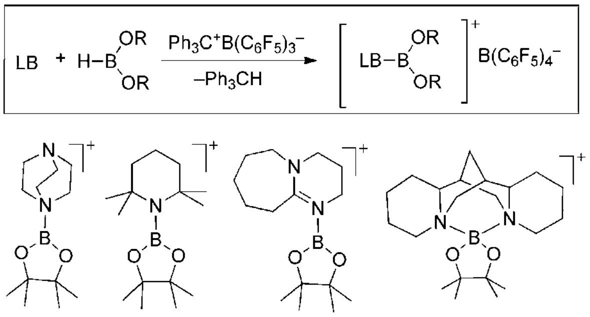
Borenium ion **1c** is characterized by two signals in the ^{11}B NMR spectrum, one at 25.4 ppm due to the borenium ion and one at −25.0 ppm due to the borohydride counterion ($^{1}J_{B,H}$ = 89.3 Hz). This outcome parallels that of the FLP $B(C_6F_5)_3$/tBu$_3$P, which is known to split the B−H bond of HBCat to form a related phosphaborenium hydridoborate salt.[23]

However, all attempts to isolate **1c** were unsuccessful. Since trityl salts are isoelectronic with $B(C_6F_5)_3$ and have similar hydride affinities,[24] we examined the formation of borenium ions using $Ph_3C^+B(C_6F_5)_4^-$.[25] When the reaction between this salt and HBPin was carried out in the presence of DABCO, the closely related borenium complex **1d** was obtained (Chart 1).[26]

Chart 1. Borenium and Boronium Ions Prepared by Hydride Abstraction with Trityl Salts



1d **2** **3** **4**

Using this procedure, we were consistently able to isolate **1d** in >90% yield by concentration, precipitation with pentanes, and repeated extraction of the resulting solid with pentanes to remove Ph_3CH. The NMR data for the borenium fragment of **1d** matched those of **1c**.

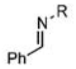
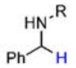
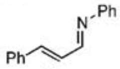
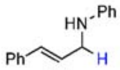
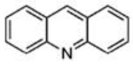
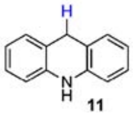
Other Lewis bases were also investigated (Chart 1). For example, the reaction of 2,2,6,6-tetramethylpyridine and 1,8-diazabicyclo[5.4.0]undec-7-ene with HBPin and $Ph_3C^+B(C_6F_5)_4^-$ led to the clean generation of borenium ions **2** and **3**, respectively, as determined by NMR spectroscopy, although neither of these was isolated in pure form.[27] The chelating chiral amine (−)-sparteine led to the corresponding four-coordinate boronium ion **4**.

Catalytic reductions. As previously noted, when generated by FLP chemistry, salts **1a**−**c** combine a highly electrophilic borenium cation with a reactive borohydride (eqs 1 and 2) and thus should be well-suited to catalyze mild, metal-free reductions of unsaturated organic molecules. In the event, exposing *N*-benzylidene-2-methylpropan-2-amine (**5a**) to 1 equiv of HBPin and 5 mol % $B(C_6F_5)_3$·DABCO (to generate **1c** in situ) in $PhCF_3$ resulted in clean reduction to the corresponding pinacolboramide **6a** (δ_B = 24.7 ppm) after 45 min in full conversion. As shown in Table 1, this catalyst system effectively hydroborates a range of *N*-alkyl and *N*-aryl aldimines.[26]

These results stand in contrast to related FLP-based hydrogenation reactions of aldimines, where the nature of the N-substituent is highly restricted because release of the Lewis acid from the reduced product is the proposed turnover-limiting step.[16,28] In addition to aldimines, nitriles and N-heterocycles such as acridine were also cleanly reduced to give the N-protected primary amine and the 1,4 addition product, respectively.

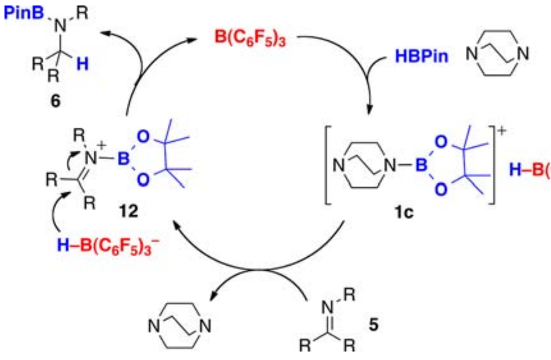
Mechanism. With some idea of the scope and limitations in hand, we speculated on the mechanism of the reaction (Scheme 1). In a typical FLP mechanism, $B(C_6F_5)_3$ acts as the catalyst and splits the H−B bond in HBPin, with DABCO acting as the Lewis base. The reaction of the resulting borenium ion **1c** with imine **5** gives activated iminium ion **12**, which has a borohydride as its counterion. By analogy with FLP chemistry, this borohydride would then reduce the activated iminium **12**, regenerating the $B(C_6F_5)_3$ catalyst.

Table 1. $B(C_6F_5)_3$·DABCO-Catalyzed Reduction of C═N Double Bonds

Entry	Substrate	Product	Time	Yield^a 1c	Yield^a 1d
1	 **5a** R = *t*Bu, **5b** R = Bn, **5c** R = Ph		45 min	**7a**, 100% (70%)^b	100% (71%)^b
2			3 h	**7b**, 89% (80%)	100% (90%)
3			1 h	**7c**, 91% (86%)^c	100% (96%)
4	 **5d**	 **7d**	2 h	(40%)^d	(79%)^e
5	$PhCN$ **8**	$PhCH_2NH_2$ **9**	24 h^f	79% (54%)^g	24% (18%)^g
6	 **10**	 **11**	1 h	(95%)	(96%)

^{a}Yields relative to substrate; isolated yields are given in parentheses. ^{b}Isolated as the trifluoroacetamide. ^{c}8 h reaction time. ^{d}20 h reaction time, the product was isolated along with hydrocinnamaldehyde in a 6:1 ratio. ^{e}Only trace hydrocinnamaldehyde was observed. ^{f}100 °C. ^{g}The product was isolated as the pivalylamide.

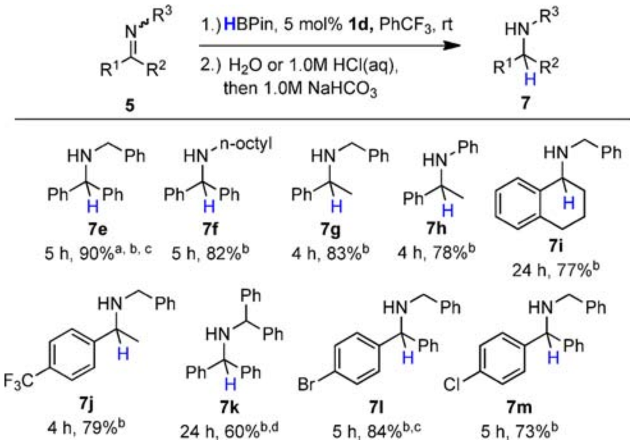
Scheme 1. Potential Mechanism for Reduction by Borenium Borohydride Salts in Analogy to FLP Hydrogenations



Remarkably, however, we found that borenium ions **1d** prepared with unreactive (non-hydridic) counterions such as $B(C_6F_5)_4^-$ were also highly active catalysts for the reduction of C═N bonds in the presence of HBPin (Table 1, final column). In all cases, except when elevated temperatures were employed, borenium ion **1d** *with no apparent hydride source* outperformed **1c**.[29] Thus, the mechanism of reduction under these conditions must be different from that proposed for FLP reductions with H_2. In addition to its high reactivity in the reduction of regular aldimines, **1d** reduced *α*,*β*-unsaturated aldimines such as **5d** more cleanly than **1c** did, and it also proved to be highly competent in the reduction of a variety of ketimines (Table 2).

To provide a direct comparison of the catalytic efficiency of $B(C_6F_5)_3$ in an FLP-type mechanism with that of borenium ions bearing unreactive counterions, we examined the kinetics of the reduction of imine **5e** with HBPin using catalytic quantities of

Table 2. Borenium-Catalyzed Reduction of Ketimines



7e	5 h	90%[a, b, c]
7f	5 h	82%[b]
7g	4 h	83%[b]
7h	4 h	78%[b]
7i	24 h	77%[b]
7j	4 h	79%[b]
7k	24 h	60%[b,d]
7l	5 h	84%[b,c]
7m	5 h	73%[b]

[a] Average of two independent experiments. [b] Isolated yield. [c] Acid–base treatment was required to cleave the N–B bond completely. [d] The solvent was 2:1 $PhCF_3$:CH_2Cl_2.

borenium ions **1d** [DABCO–$BPin^+$]$B(C_6F_5)_4^-$ and **1c** [DABCO–$BPin^+$]$HB(C_6F_5)_3$, the latter generated in situ from $B(C_6F_5)_3$·DABCO and HBPin. The reaction rates for the two systems were on the same order of magnitude, with the nonhydridic system **1d** actually reacting somewhat faster than the borohydride-containing Lewis acid–base pair **1c** (Figure 1). Thus, borenium ion **1d** is clearly kinetically competent to catalyze the hydroboration of imines.

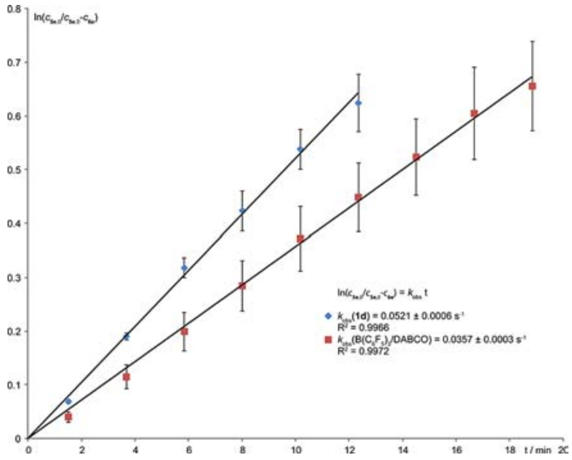
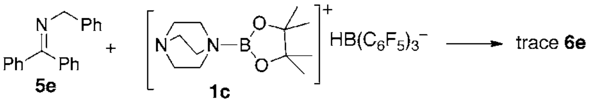


Figure 1. Initial rates of reduction of **5e** by HBPin catalyzed by 7.5 mol % **1d** (blue) and 7.5 mol % $B(C_6F_5)_3$·DABCO (red).

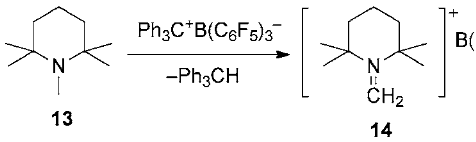
When **1c** was employed stoichiometrically in the reduction of imine **5e**, only traces of product **6e** were observed after 4 h at room temperature (eq 3). This illustrates clearly that the hydridoborate $HB(C_6F_5)_3^-$ is considerably slower at reducing imine **5e** compared with the combination of **1d** and HBPin under the reaction conditions.



(3)

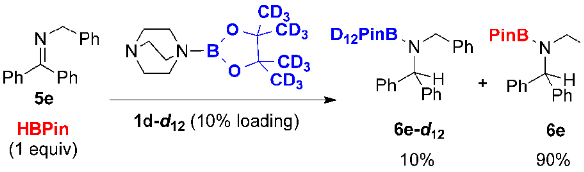
Competition experiments in which the rates of reduction with HBPin and DBPin were compared gave a high primary kinetic isotope effect of $k_H/k_D = 6.7 \pm 0.1$, clearly showing that cleavage of the B–H bond in HBPin takes place in the turnover-limiting step. Consistent with this, the reaction was found to be first order in HBPin over certain concentration ranges [see the Supporting Information (SI)]. Since the direct reduction of a borenium-activated iminium ion with HBPin would result in the unlikely generation of the highly unstable borinium ion $PinB^+$, we then examined the role of DABCO in the reaction.

Kinetic analysis of the role of DABCO was complicated since 1 equiv of DABCO was always present in the medium as a stabilizing group for the borenium ion and the addition of excess DABCO inhibited the reduction, likely by preventing borenium transfer to the less Lewis basic imine.[29a] However, we were able to prepare iminium ion **14** as a model for a borenium-activated iminium ion (eq 4). Treatment of **14** with excess HBPin gave no reaction, but in the presence of DABCO, **14** was fully consumed. When DBPin was employed, deuterium incorporation in the product was observed. When DABCO was replaced with imine **5e** to probe the Lewis basicity of this species, we observed no consumption of **14**, indicating that the imine itself is not Lewis basic enough to activate HBPin. In addition, low-temperature NMR studies revealed an interaction between HBPin and DABCO, while there was no observable interaction between HBPin and imine **5e** (see the SI). Taken together, these data indicate that the strong Lewis base DABCO is required in the hydride delivery step of the reduction.[29b]



13 **14** (4)

As a final test of the mechanism of reduction, we employed perdeuterated borenium **1d**-d_{12} (prepared from HBPin-d_{12}) at 10 mol % loading in the catalytic reduction of **5e** by HBPin (eq 5).



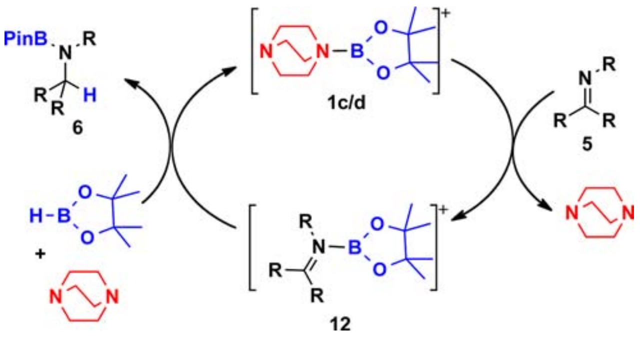
(5)

The corresponding d_{12}-labeled product was observed together with the regular protio product by electron impact/time of flight mass spectroscopy in a ratio of ca. 1:10 based on signal intensities. Thus, the BPin group from the initial borenium ion is incorporated into the product and then regenerated after transfer of the hydride of HBPin to the active iminium ion.

A mechanism consistent with all of these observations is shown in Scheme 2. The reaction begins with the transfer of a borenium ion from catalyst **1c** or **1d** to imine **5**. The resulting boron-activated iminium ion **12** is then reduced by HBPin with assistance from the Lewis base DABCO, likely by formation of a precomplex as implied by the low-temperature NMR studies. Reduction of **12** regenerates the borenium ion catalyst, which then reenters the catalytic cycle. In the case where $B(C_6F_5)_3$ is employed to generate the borenium ion by FLP-type hydride abstraction from HBPin, $B(C_6F_5)_3$ acts only as an initiator and is not itself involved in the catalytic cycle.

In conclusion, we have developed 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 based on pinacolborane.

Scheme 2. Revised Mechanism of Borenium-Catalyzed Imine Reduction



Mechanistic studies have revealed that this reaction constitutes the first intermolecular process catalyzed by an isolated borenium ion. This mode of reaction constitutes an attractive alternative that avoids stoichiometric borohydride salts or explosive hydrogen gas in the synthesis of bulky 2° amines. Further work on the chemistry of these and related borenium ions, including the development of an enantioselective process, is underway in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, NMR spectra, kinetic data, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) During review of this manuscript, the use of 9BBN·NHC adducts as precursors for borenium-based catalysts for FLP-type hydrogenations was reported. See: Farrell, J. M.; Hatnean, J. A.; Stephan, D. W. *J. Am. Chem. Soc.* **2012**, *134*, 15728.

(10) In recent work, the Organ group has shown that the same is true for $HSnBu_3$-mediated reductions, namely, that the stannane itself, rather than $HB(C_6F_5)_3^-$, is the true reducing agent in FLP-type hydrostannylations of alkynes. See: Oderinde, M. S.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 9834.

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(21) Non-FLP combinations have been shown to activate H_2. See: (a) Geier, S. J.; Stephan, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 3476. (b) Binding, S. C.; Zaher, H.; Chadwick, F. M.; O'Hare, D. *Dalton Trans.* **2012**, *41*, 9061. However, increasing the steric bulk in one of the components (particularly the Lewis acid) resulted in remarkable, increased functional group tolerance (e.g., see ref 22).

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(26) Replacing the noncoordinating perfluorophenylborate by tetrafluoroborate under identical conditions resulted in the slow formation of a four-coordinate F-bridged boronium salt, as indicated by signals with chemical shifts close to 0 ppm in the ^{11}B NMR spectrum. The signals for the borenium cations in **1c** and **1d** exhibited the same chemical shift in the ^{11}B NMR spectrum, indicating absence of a bridging μ-H interaction with the electrophilic boron center and $HB(C_6F_5)_3^-$ in **1c**.

(27) The reaction generated only the borenium ions as drawn, but for **2** and **3**, remaining starting material complicated the isolation of the pure borenium salts, so we focused on **1d**.

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(29) (a) HBPin was unable to reduce the imine in the absence of $B(C_6F_5)_3$·DABCO. Similarly, DABCO alone or HBpin and DABCO in the absence of the borenium catalyst under otherwise identical conditions showed no reactivity. (b) Query, I. P.; Squier, P. A.; Larson, E. M.; Isley, N. A.; Clark, T. B. *J. Org. Chem.* **2011**, *76*, 6452.