JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

N-Directed Aliphatic C−H Borylation Using Borenium Cation Equivalents

Aleksandrs Prokofjevs and Edwin Vedejs*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States

Supporting Information

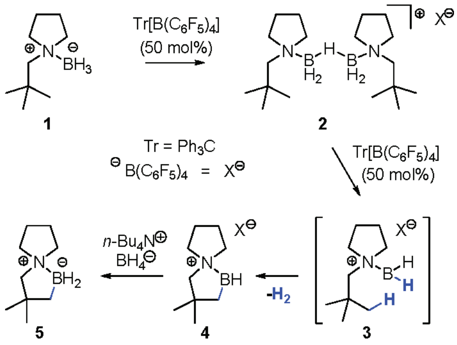
ABSTRACT: Highly electrophilic boron cations derived from hindered amine borane complexes have been shown to undergo intramolecular aliphatic C−H borylation.

Tricoordinate boron inserts into C−H bonds upon heating.[1−5] In the first report, Hurd studied the reaction of B_2H_6 with several substrates, including benzene (100 °C) and methane (180 °C), and found evidence for the formation of phenylboron compounds and, indirectly, methylboron species, respectively.[1] Related intramolecular C−H insertion reactions were subsequently identified[2,3] and were explored in depth by Köster et al.[3] However, typically extreme conditions (ca. 200−300 °C), variable regioselectivity, and substrate limitations may have discouraged further development. According to computational evaluation, the borylation of aliphatic C−H bonds involves a four-center mechanism.[5,6] Some of the relatively facile electrophilic borylations of aromatic substrates by tethered tricoordinate boron species may also follow a C−H insertion pathway,[4] but an electrophilic aromatic substitution mechanism is a plausible alternative in most cases, pending definitive evidence. Related C−H insertions may also take place in the gas-phase reactions of simple alkanes with cationic, dicoordinate boron intermediates (borinium cations) under flowing afterglow conditions.[7]

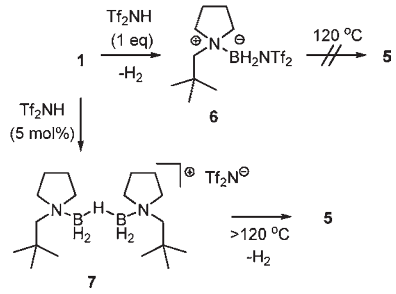
Stimulated by intensive recent interest in transition-metal-mediated borylations using C−H insertion chemistry,[8−10] we have explored the possibility that nitrogen-tethered cationic tricoordinate boron species (borenium salts) may have similar reactivity. As described below, several examples of borenium C−H insertion have now been demonstrated under more promising conditions compared to the thermal methods reported for neutral boranes.

Treating the hindered amine borane complex **1** with a 50 mol % loading of the strong electrophile $Tr[B(C_6F_5)_4]$ predictably resulted in formation of the H-bridged cationic boron intermediate **2**, with $\delta(^{11}B) = -1.1$ ppm in C_6D_5Br (Scheme 1).[11] Further addition of the electrophilic trityl salt induced rapid formation of a tricoordinate boron species, as evidenced by a broad signal at +69.3 ppm in the ^{11}B NMR spectrum within 10 min at room temperature.[12] Over the same time scale, the ^1H NMR spectrum showed the disappearance of the *t*-Bu singlet of **2** [$\delta(^1H) = 0.86$ ppm] and the appearance of two new singlets [$\delta(^1H) = 0.64$ and 1.27 ppm; 6:2 integral ratio]. Together with the substantial downfield shift of the broad B−*H* resonance [$\delta(^1H) = 4.8$ ppm] and liberation of H_2, these and other spectroscopic data [see the Supporting Information (SI)] are consistent with the spirocyclic borenium structure **4**. At no time was the open-chain borenium cation **3** detected. Interestingly, **4** constitutes a rare example of a tricoordinate boron cation lacking stabilizing n- or π-donor groups.[13] Additionally, **4** is a representative of the uncommon B−H borenium ion class; only a few such compounds have been reported to date.[4,14] A hydride quench with n-Bu_4NBH_4 converted **4** to the isolable amine borane **5** (82% yield), which was readily identified by the broad CH_2B ^1H and ^{13}C NMR signals (0.75 and 31 ppm, respectively, in $CDCl_3$) and an H-coupled triplet at −4.2 ppm in the ^{11}B NMR spectrum.

Scheme 1



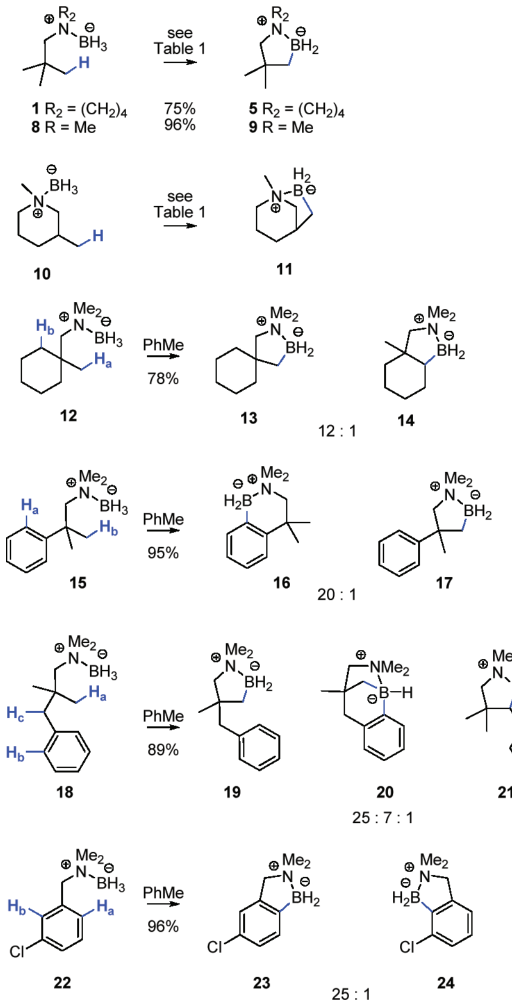
Scheme 2



In search of further improvement of the protocol, Tf_2NH was evaluated as the “hydridophile” (Scheme 2). The composition of activated intermediates was greatly influenced by the solvent and the **1**/Tf_2NH ratio. Thus, the stoichiometric reaction in toluene-d_8 afforded the covalent adduct **6**.[15] The same adduct **6** was also seen in toluene-d_8 using 5 mol % Tf_2NH for activation,

Received: August 26, 2011
Published: November 14, 2011

Scheme 3. Catalytic C—H Borylation Using Tf_2NH Activation



but the H-bridged cation **7** was also detected as the activated species in CD_2Cl_2. Subsequent events were also influenced by the **1**/Tf_2NH ratio. With 5 mol % Tf_2NH in toluene, clean catalytic cyclization to **5** and H_2 was observed above 120 °C. In contrast, heating the covalent adduct **6** under the same conditions mostly afforded decomposition products.

The high stability of the bistriflimide anion paired with the good solubility of its derivatives in aromatic solvents allowed the development of a simple catalytic procedure that could be used with a range of substrates (Scheme 3 and Table 1). The same 5% loading of the catalyst Tf_2NH was used in most cases, and the reactions were performed in sealed vials at 160 °C without attempting to define the threshold temperature for each example. After the reaction was quenched with n-Bu_4NBH_4 to convert borenium equivalents derived from the 5% Tf_2NH to amine boranes, simple filtration through silica gel to retain polar bistriflimide-containing byproducts gave clean isomer mixtures in most cases. The products were further purified by crystallization or chromatography, and structures were assigned by multinuclear NMR spectroscopy and high-resolution mass spectrometry (HRMS) (see the SI).

The intramolecular borylation method is particularly efficient for forming C—B bonds next to quaternary centers in hindered amine boranes, furnishing organoboron structures that are not available via the conventional hydroboration route. Thus, amine boranes **1** and **8** cleanly formed products **5** and **9**, respectively (Table 1, entries 1 and 2). In contrast, the usual procedure with substrate **10** gave only 20% conversion (entry 3; a 14% yield of **11** isolated), from either a single diastereomer or a 1:1 mixture. Increased catalyst loading (10%) and prolonged heating (60 h) did not improve the conversion (entry 4). The yield of **11** was higher (25%) when the hydrogen pressure was periodically vented (entry 5 vs entry 4), but the reaction stalled as before.

Table 1. Catalytic C—H Borylation Using Tf_2NH Activation[a]

entry	substrate	solvent	products (isomer ratio; % isol)
1	**1**	C_6H_5F	**5** (75%)
2	**8**	C_6H_6	**9** (96%)
3	**10**[b]	C_6H_5F	**11** (14%), **10** (63%)[c]
4[d]	**10**[e]	C_6H_5F	**11** (13%), **10** (45%)
5[f]	**10**[e]	C_6H_5F	**11** (25%), **10** (35%)
6	**12**	toluene	**13**, **14** (12:1; 78%)
7	**15**	toluene	**16**, **17** (20:1; 95%)
8	**18**	toluene	**19**, **20**, **21** (25:7:1; 89%)
9	**22**[g]	toluene	**23**, **24** (25:1; 96%)

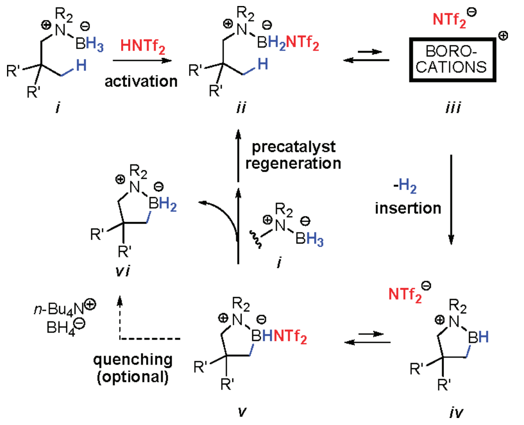
[a] Conditions: 5 mol % Tf_2NH, sealed tube, 160 °C, 14 h unless otherwise noted, quenched with n-Bu_4NBH_4. [b] 1:1 dr or single diastereomer. [c] 20% conversion, NMR assay. [d] 10 mol % Tf_2NH, 60 h. [e] Single diastereomer. [f] 10 mol % Tf_2NH, 60 h, pressure vented four times during thermolysis. [g] 24 h.

Cyclization of the aliphatic amine borane **12** afforded spirocycle **13** as the major product (entry 6), revealing the preferred C—H insertion reactivity as methyl > methylene. Because of difficulties in isomer separation, the minor product **14** was characterized as an enriched mixture.

To address the regioselectivity further, substrate **15** was tested under the catalytic conditions (entry 7). The aromatic borylation product **16** predominated, although the aliphatic borylation product **17** was also detected.[16,17] The cyclization of the related substrate **18** was more complex (entry 8), although the major product **19** reflects a similar preference for borylation at the methyl C—H over the methylene C—H, as seen with **12** (entry 6). The minor product **21** also contains a new aliphatic C—B bond, while the unusual tricyclic product **20** contains aryl as well as aliphatic C—B bonds, apparently as a result of a second borylation event with loss of H_2. As evidenced by in situ NMR spectroscopy between 120 and 160 °C, the formation of **20** began only after most of the **18** had been converted to **19**, suggesting that the aromatic borylation event leading to **20** is the slower cyclization step in this sequence. In the absence of a suitably placed aliphatic C—H bond, the same reaction conditions induced efficient aromatic borylation from **22** to a 25:1 mixture of **23** and **24** (entry 9). It is interesting that a related stoichiometric borylation[4] afforded a markedly different **23**:**24** ratio of 1:1.3, indicating a change in the product-determining steps.[18]

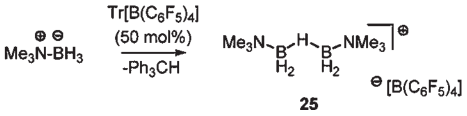
While the formation of **4** from **2** under the influence of added electrophile (Scheme 1) parallels observations in the previously reported aromatic borylation,[4] the events after the formation of **7** in the catalytic reaction remain unclear. The substantial rate difference between the stoichiometric and catalytic processes raised suspicions that perhaps the rate of the catalytic process

Scheme 4



may be limited by slow regeneration of the H-bridged intermediate **2** (Scheme 2), corresponding to the reaction of borenium salt **4** with amine borane **1** in the stoichiometric reaction. However, when a solution of **4** in C_6D_5Br was treated with 2 equiv of $Me_3N\cdot BH_3$ at room temperature, the symmetrical H-bridged cation **25**[11] was detected by NMR assay among other products. This observation provides evidence of facile intermolecular hydride transfer from $Me_3N\cdot BH_3$ to **4**, and by analogy from **1** to **4**, and suggests that other steps in the catalytic process control the rate of catalyst turnover (see the discussion of Scheme 4 below).

To confirm the assignment, **25** was prepared independently by treating $Me_3N\cdot BH_3$ with 0.5 equiv of $Tr[B(C_6F_5)_4]$ in dry benzene (eq 1), and the structure was established by X-ray crystallography (Figure 1).[19] Prior studies have proposed related structures based on NMR evidence or theoretical considerations.[11,20,21]

(1) 

$$\overset{\oplus\ \ominus}{Me_3N\text{-}BH_3} \xrightarrow[-Ph_3CH]{Tr[B(C_6F_5)_4]\ (50\ mol\%)} \left[Me_3N\text{-}\underset{H_2}{B}\text{-}H\text{-}\underset{H_2}{B}\text{-}NMe_3\right]^{\oplus}\ {}^{\ominus}[B(C_6F_5)_4]$$

25

In response to review, hypothetical catalytic cycles are drawn in Scheme 4. The activation and quenching steps are well-defined, and regeneration of the activated precatalyst *ii* via hydride transfer from the starting amine borane *i* to the initial product *v* is plausible. However, it would be too early to propose a rate-determining step. The borocations mentioned within the black box include borenium salts or their hydride-bridged equivalents, but several other cations are conceivable in view of the rich chemistry of amine boranes. The high temperature required for the catalytic method suggests that activated species other than **7** are present,[22] in contrast to the stoichiometric reaction, but a role for **7** is not excluded.

In summary, we have shown the feasibility of N-directed C−H borylation via borocations derived from hindered amine BH_3 complexes using either stoichiometric or catalytic activation by strong electrophiles. When performed using stoichiometric $Tr[B(C_6F_5)_4]$, cyclization of **1** proceeds at ambient temperature, generating the unique unstabilized B−H borenium salt **4** and hydrogen. This observation demonstrates that the inherent barrier for C−H insertion is quite low. Although the corresponding catalytic process using Tf_2NH activation requires temperatures above 120 °C for catalyst turnover on a practical time scale, the borylation products are formed cleanly. According to several examples in Scheme 3, insertion into methyl C−H bond is strongly favored over insertion into the methylene C−H bond. Further experimental and computational investigations of this unusual transformation are ongoing and will be reported separately.

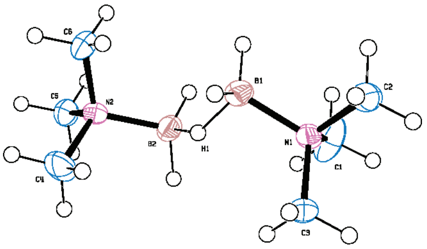


Figure 1. ORTEP plot of **25** (the counterion has been omitted for clarity). The part of the structure to the left of H1 is disordered. Selected bond lengths (Å) and angles (deg): B1−N1, 1.58; N1−C1, 1.48; N1−C2, 1.48; N1−C3, 1.48; B1−N1−C1, 112; B1−N1−C2, 106; B1−N1−C3, 112.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures, X-ray crystallography data (CIF), NMR spectra and computational results. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

edved@umich.edu

■ ACKNOWLEDGMENT

This work was supported by the National Institute of General Medical Sciences of the NIH (GM067146). The authors thank Dr. J. W. Kampf for the X-ray structure determination of **25**.

■ REFERENCES

(1) Hurd, D. T. *J. Am. Chem. Soc.* **1948**, *70*, 2053.

(2) (a) Winternitz, P. F.; Carotti, A. A. *J. Am. Chem. Soc.* **1960**, *82*, 2430. (b) Logan, T. J.; Flautt, T. J. *J. Am. Chem. Soc.* **1960**, *82*, 3446. (c) Brown, H. C.; Murray, K. J.; Müller, H.; Zweifel, G. *J. Am. Chem. Soc.* **1966**, *88*, 1443. (d) Abruscato, G. J.; Tidwell, T. T. *J. Org. Chem.* **1972**, *37*, 4151. (e) Varela, J. A.; Peña, D.; Goldfuss, B.; Denisenko, D.; Kulhanek, J.; Polborn, K.; Knochel, P. *Chem.—Eur. J.* **2004**, *10*, 4252 and references therein.

(3) (a) Köster, R.; Reinert, K. *Angew. Chem.* **1959**, *71*, 521. (b) Köster, R.; Larbig, W.; Rotermund, G. W. *Justus Liebigs Ann. Chem.* **1965**, *682*, 21. (c) Köster, R.; Benedikt, G.; Fenzl, W.; Reinert, K. *Justus Liebigs Ann. Chem.* **1967**, *702*, 197.

(4) De Vries, T. S.; Prokofjevs, A.; Harvey, J. N.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14679 and references therein.

(5) Goldfuss, B.; Knochel, P.; Bromm, L. O.; Knapp, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 4136.

(6) (a) Goldfuss, B. *Chem.—Eur. J.* **2009**, *15*, 12856. (b) Swinnen, S.; Nguyen, V. S.; Sakai, S.; Nguyen, M. T. *Phys. Chem. Chem. Phys.* **2009**, *11*, 9703.

(7) DePuy, C. H.; Gareyev, R.; Hankin, J.; Davico, G. E.; Krempp, M.; Damrauer, R. *J. Am. Chem. Soc.* **1998**, *120*, 5086.

(8) Cho, J.-Y.; Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **2000**, *122*, 12868.

(9) Vanchura, B. A., II; Preshlock, S. M.; Roosen, P. C.; Kallepalli, V. A.; Staples, R. J.; Maleczka, R. E., Jr.; Singleton, D. A.; Smith, M. R., III. *Chem. Commun.* **2010**, *46*, 7724 and references therein..

(10) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(11) De Vries, T. S.; Vedejs, E. *Organometallics* **2007**, *26*, 3079.

(12) Nöth, H.; Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; Springer: Berlin, 1978.

(13) Prokofjevs, A.; Kampf, J. W.; Vedejs, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 2098.

(14) (a) Bonnier, C.; Piers, W. E.; Parvez, M.; Sorensen, T. S. *Chem. Commun.* **2008**, 4593. (b) Bonnier, C.; Piers, W. E.; Parvez, M. *Organometallics* **2011**, *30*, 1067.

(15) Compound **6** exists as a mixture of O- and N-bound NTf_2 isomers according to multinuclear NMR data. The ^{13}C and ^{19}F signals are decisive (^{13}C: three F-coupled quartets at 120.5, 120.2, and 119.6 ppm; ^{19}F: three signals in a 0.74:1:1 ratio at −69.2, −76.7, and −78.8 ppm; ^{11}B: two signals at 0.6 and −4.6 ppm), and the presence of a stereogenic S atom in one of the isomers is evident from the ^{1}H and ^{13}C NMR spectra. See the SI for additional details.

(16) A related aromatic borylation using catalytic $Tr[B(C_6F_5)_4]$ was briefly mentioned in ref 4, but Tf_2NH gives a cleaner reaction.

(17) For recent reports of electrophilic aromatic borylation, see: (a) Del Grosso, A.; Pritchard, R. G.; Muryn, C. A.; Ingleson, M. J. *Organometallics* **2010**, *29*, 241. (b) Ishida, N.; Moriya, T.; Goya, T.; Murakami, M. *J. Org. Chem.* **2010**, *75*, 8709. (c) Del Grosso, A.; Singleton, P. J.; Muryn, C. A.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2102. Also see refs 4 and 13.

(18) The following data exclude differences in solvent and activating agent vs ref 4: (a) **22** + 0.9 equiv of $Tr[B(C_6F_5)_4]/PhF$, 4 h (rt): **23**:**24** = 1.1:1. (b) **22** + 5 mol % $Tr[B(C_6F_5)_4]/PhF$, 24 h (160 °C): **23**:**24** = 17:1.

(19) Additional X-ray crystallography data and computational analysis of **25** are available in the SI.

(20) Stephens, F. H.; Baker, R. T.; Matus, M. H.; Grant, D. J.; Dixon, D. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 746.

(21) During review of this manuscript, the X-ray structure of a more highly stabilized analogue of **25** was reported. See: Inés, B.; Patil, M.; Carreras, J.; Goddard, R.; Thiel, W.; Alcarazo, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8400.

(22) In the simplest example, **25** generated in situ using 30 mol% $Tr[B(C_6F_5)_4]$ in C_6D_5Br decomposed at >120 °C. After 19 h at 160 °C, a ^{11}B NMR assay showed new proton-coupled signals at 3.2 and −2.4 ppm and complex signals between −14 and −19 ppm. If analogous hydride-bridged cations are required intermediates in the catalytic borylations, then their decomposition may explain the low conversion from **10** to **11**.