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

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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 B₂H₆ with several substrates including benzene (100 °C) and methane (180 °C), and found evidence for the formation of phenylboron compounds and, indirectly, of 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 4-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 insertion 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 a hindered amine borane complex **1** with 50 mol% of the strong electrophile Tr[B(C₆F₅)₄] predictably resulted in formation of an *H*-bridged cationic boron intermediate **2**, $\delta^{11}\text{B} = -1.1$ ppm in C₆D₅Br (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 $\delta +69.3$ ppm in the ¹¹B NMR spectrum within 10 minutes at room temperature.¹² Over the same timescale, the ¹H NMR spectrum showed disappearance of the *t*-Bu singlet of **2** ($\delta^1\text{H} = 0.86$ ppm), while two new singlets appeared ($\delta^1\text{H} = 0.64$ and 1.27 ppm; 6:2 integral ratio). Together with the substantial down-field shift of the broad B–H resonance ($\delta^1\text{H} = 4.8$ ppm) and liberation of H₂, these and other spectroscopic data (see Supporting Information) 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

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

the uncommon B–H borenium ion class; only a few such compounds have been reported to date.^{4,14} Hydride quench with *n*-Bu₄NBH₄ converted **4** to the isolable amine borane **5** (82% yield), readily identified by the broad CH₂B ¹H and ¹³C NMR signals (δ 0.75 ppm and 31 ppm, respectively, in CDCl₃), and an *H*-coupled triplet at δ –4.2 ppm in the ¹¹B NMR spectrum.

Seeking further improvement of the protocol, Tf₂NH was evaluated as the “hydridophile” (Scheme 2). The composition of activated intermediates was greatly influenced by the solvent and by the ratio between **1** and Tf₂NH. 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% of Tf₂NH for activation, but the *H*-bridged cation **7** was also detected as the activated species in CD₂Cl₂. Subsequent events were also influenced by the ratio of Tf₂NH and **1**. Using 5 mol% of Tf₂NH in toluene, clean catalytic cyclization to **5** and H₂ 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 good solubility of its derivatives in aromatic solvents allowed developing a simple catalytic procedure that could be used with a range of substrates (Scheme 3; Table 1). The same 5% loading of the catalyst Tf₂NH was used in most cases, and the reactions were performed in sealed vials at 160 °C without attempting to define the threshold temperatures for each example. After quenching with *n*-Bu₄NBH₄ to convert borenium equivalents derived from the 5% Tf₂NH 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 HRMS (Supporting Information).

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

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. Due to difficulties in isomer separation, the minor product **14** was characterized as an enriched mixture.

To further address regioselectivity, substrate **15** was tested under the catalytic conditions (entry 7). The aromatic borylation product **16** predominated, although an aliphatic borylation product **17** was also detected.^{16,17} The cyclization of a related substrate **18** was more complex (entry 8), although the major product **19** reflects a similar preference for borylation at methyl over 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 due to a second borylation event with loss of H₂. As evidenced by *in situ* NMR spectroscopy between 120–160 °C, the formation of **20** begins only after most of **18** has 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 borylation⁴ affords a markedly different 1:1.3 ratio of **23:24**, 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 events after 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 may be limited by slow regeneration of the *H*-bridged intermediate **2** (Scheme 2), corresponding to the reaction of borenium salt **4** with the amine borane **1** in the stoichiometric reaction. However, when a solution of **4** in C₆D₅Br was treated with 2 equiv of Me₃N·BH₃ at rt, the symmetrical *H*-bridged cation **25**¹¹ was detected by NMR assay among other products. This observation supports facile intermolecular hydride transfer from Me₃N·BH₃ 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 Scheme 4 discussion, below).

To confirm the assignment, **25** was prepared independently by treating Me₃N·BH₃ with 0.5 equiv of Tr[B(C₆F₅)₄] in dry benzene (eq. 1), and the structure was established by X-ray crystallography (Fig. 1).¹⁹ Prior studies have proposed related structures based on NMR evidence or theoretical considerations.^{11,20,21}

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 pre-catalyst *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 referred to 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 BH₃ complexes using either stoichiometric or catalytic activation by strong electrophiles. When performed using stoichiometric Tr[B(C₆F₅)₄], cyclization of **1** proceeds at ambient temperature, generating a 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 Tf₂NH activation requires temperatures above 120 °C for catalyst turnover on a practical timescale, the borylation products are formed cleanly. According to several examples in Scheme 3, insertion into methyl C–H is strongly favored vs. methylene C–H. Further experimental and computational investigations on this unusual transformation are ongoing and will be reported separately.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- (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 δ 120.5, 120.2 and 119.6 ppm; ^{19}F : three signals, 0.74:1:1 ratio at δ -69.2, -76.7 and -78.8 ppm; ^{11}B : two signals at δ 0.6 and -4.6 ppm), and the presence of a stereogenic S atom in one of the isomers is evident from the ^1H and ^{13}C NMR spectra. See Supporting Information for additional details.
- (16). A related aromatic borylation using catalytic $\text{Tr}[\text{B}(\text{C}_6\text{F}_5)_4]$ was briefly mentioned in ref. 4, but TF_2NH gives a cleaner reaction.
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- (18). The following data exclude differences in solvent and activating agent vs. ref. 4: (a) **22** + 0.9 eq $\text{Tr}[\text{B}(\text{C}_6\text{F}_5)_4]/\text{PhF}$, 4h (rt); **23:24** 1.1:1. (b) **22** + 5 mol% $\text{Tr}[\text{B}(\text{C}_6\text{F}_5)_4]/\text{PhF}$, 24h (160 °C); **23:24** 17:1.
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- (22). The simplest example **25** generated *in situ* using 30 mol% $\text{Tr}[\text{B}(\text{C}_6\text{F}_5)_4]$ in $\text{C}_6\text{D}_5\text{Br}$ decomposed at >120 °C. After 19 h at 160 °C ^{11}B NMR assay showed new proton-coupled signals at δ 3.2, -2.4, 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 low conversion from **10** to **11**.

Figure 1.

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

Scheme 1.

Scheme 2.

Scheme 3. Catalytic C–H borylation using Tf_2NH activation

Scheme 4.

Table 1
Catalytic C-H borylation using Tf₂NH activation ^a

entry	substrate	solvent	products (isomer ratio; % isol)
1	1	C ₆ H ₅ F	5 (75%)
2	8	C ₆ H ₆	9 (96%)
3	10 ^b	C ₆ H ₅ F	11 (14%) 10 (63%) ^c
4 ^d	10 ^e	C ₆ H ₅ F	11 (13%) 10 (45%)
5 ^f	10 ^e	C ₆ H ₅ F	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 5 mol% Tf₂NH, sealed tube, 160 °C, 14 h unless noted, quenched with *n*-Bu₄NBH₄

^b 1:1 dr or single diastereomer

^c 20% conversion, NMR assay

^d 10 mol% Tf₂NH, 60 h

^e single diastereomer

^f 10 mol% Tf₂NH, 60 h, pressure vented 4 times during thermolysis

^g 24h