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Superelectrophilic Intermediates in Nitrogen-Directed Aromatic Borylation

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Abstract: The first examples of borylation under conditions of borenium ion generation from hydrogen-bridged boron cations are described. The observable H-bridged cations are generated by hydride abstraction from *N,N*-dimethylamine boranes $Ar(CH_2)_nNMe_2BH_3$ using Ph_3C^+ $(C_6F_5)_4B^-$ (TrTPFPB) as the hydride acceptor. In the presence of excess TrTPFPB, the hydrogen-bridged cations undergo internal borylation to afford cyclic amine borane derivatives with $n = 1-3$. The products are formed as the corresponding cyclic borenium ions according to reductive quenching experiments and ^{11}B and ^1H NMR spectroscopy in the case with $Ar = C_6H_5$ and $n = 1$. The same cyclic borenium cation is also formed from the substrate with $Ar = o\text{-}C_6H_4SiMe_3$ via desilylation, but the analogous system with $Ar = o\text{-}C_6H_4CMe_3$ affords a unique cyclization product that retains the *tert*-butyl substituent. An *ortho*-deuterated substrate undergoes cyclization with a product-determining isotope effect of k_H/k_D 2.8. Potential cationic intermediates have been evaluated using B3LYP/6-31G* methods. The computations indicate that internal borylation from **14a** occurs via a C−H insertion transition state that is accessible from either the borenium π complex or from a Wheland intermediate having nearly identical energy. The $Ar = o\text{-}C_6H_4SiMe_3$ example strongly favors formation of the Wheland intermediate, and desilylation occurs via internal $SiMe_3$ migration from carbon to one of the hydrides attached to boron.

Introduction

The structural chemistry of cationic, trivalent boron environments ("borenium" ions according to the Nöth terminology)[1] has attracted interest over many years because of the similarity with the isoelectronic carbenium ions in terms of orbital occupancy, electron count, and net charge. In an early investigation, Ryschkewitsch and Miller reported NMR evidence that the cation **2** is in equilibrium with the picoline−BCl_3 complex **1** in the presence of excess aluminum chloride (Figure 1).[2a] More recently, Fujio et al. found that the pyridine−diphenylchloroborane adduct **3** is converted into **4** using $SbCl_5$ as the chloride abstracting agent.[2b] According to the analogies initially recognized by Olah et al.[3] and also noted by Nöth in his excellent review,[1] salt **4** is isoelectronic with trityl cation, while **2** is analogous to dichlorobenzyl cation. By the same analogy, borenium ions have been included in Olah's classification of superelectrophiles, along with several other monocationic species that have a positively charged heteroatom adjacent to an unoccupied *p*-orbital.[3] Several *O*- and/or *N*-substituted borenium species have been detected in structural studies using spectroscopic[1,2,4] and crystallographic techniques,[5,6] as summarized in the review literature.[1,7]

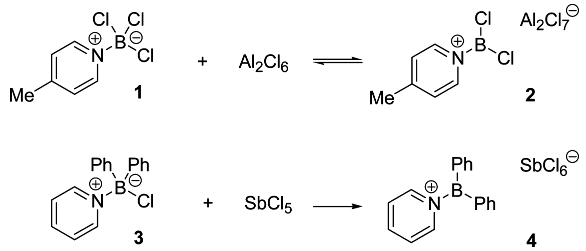

Figure 1. Generation of borenium ions in solution.

According to prior work, borenium ions are potent electrophiles that may approach the more familiar carbenium[8] or

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(3) (a) Olah, G. A. *Angew. Chem., Int. Ed.* **1993**, *32*, 767. (b) The definition of "superelectrophile" stated in the Olah review specifies that dicationic species are superelectrophiles, but the discussion also identifies several factors that enhance the electrophilicity of neutral or monocationic species. Explicit examples in Olah's review include Lewis acid complexes of boric acid, trimethyl borate, and boron trichloride. In this usage, "superelectrophilicity" may be understood more broadly as a qualitative comparison between an exceptionally enhanced electrophile and the unenhanced parent electrophile. (c) *Superelectrophiles and Their Chemistry*; Olah, G. A., Klumpp, D. A., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2008.

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10.1021/ja905369n CCC: $40.75

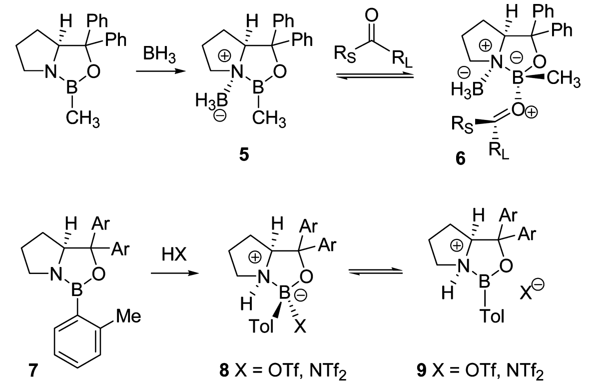

Figure 2. Oxazaborolidines as borenium ion precursors.

silylium[9] cations in terms of reactivity. Indeed, the challenge of obtaining X-ray quality crystals of a structure related to **4** was met only recently[6] and required highly hindered B-aryl groups to prevent boron coordination by external electron donors. Borenium species containing nitrogen or oxygen electron pair donors are more stable because delocalization partially satisfies electron demand at boron, but they retain substantial Lewis acidity and act as catalysts in several important applications. The best known example is the enantioselective Corey−Bakshi−Shibata reduction of ketones via the intermediate **5**, generated *in situ* from an oxazaborolidine and a borane source (Figure 2).[10] Although **5** does not carry a net positive charge, a borenium subunit can be recognized along the N−B−O segment due to the formally positive nitrogen. Structurally similar but far more potent borenium electrophiles **9** can be generated from neutral precursors **7** by protonation at nitrogen.[11] In this case, **9** does carry a net positive charge and serves as a highly reactive Lewis acid catalyst despite the moderating influence of oxygen electron pairs and the tendency of triflate to form a covalent adduct at boron (**8**). In other applications, related *O*- or *N*-substituted (stabilized) borenium ion intermediates may be involved in the epimerization at boron in several families of chiral heterocycles,[12] while nonstabilized borenium species may play a role in C−F bond cleavage reactions,[13] the abstraction of hydride from amine boranes using trityl or diarylmethyl cations,[14] and perhaps also some of the hydroboration chemistry of iodoborane complexes.[15] Given the complexity and debatable information content of formal charges in structures related to species such as **5**, **6**, or **9**, we omit the charges at individual atoms in most of the subsequent drawings to allow focus on the far more important net charge.

In the absence of stabilizing heteroatom electron pairs or hindered aryl substituents at boron, borenium ions should be exceptionally reactive electrophiles. Furthermore, the structural analogy with carbenium ions resulting from the net positive charge and vacant *p*-orbital at boron suggests potentially important applications for the formation of C−B bonds. Isolated examples of relevant electrophilic borylation chemistry have been encountered over the years, usually under relatively drastic conditions (boron halide/aluminum trichloride),[16] but the possible involvement of borenium species has been largely overlooked.[17]

Given the intensive current interest in transition metal catalyzed applications of aryl and alkyl boranes and boronic acids,[18,19] it is time to revisit mechanistic options available to electrophilic boron for C−B bond formation. Little is known regarding the reactivity of borenium cations with carbon nucleophiles. We were especially interested to learn whether the tendency of trivalent boron to form three-center two-electron (3c2e) bonds would enable or impede the Friedel−Crafts electrophilic substitution pathway in an intramolecular context, but the mechanistic analogy with carbenium ion chemistry was a larger consideration. Therefore, our work began with the investigation of a borenium ion analogy for the classical Friedel−Crafts cyclization using benzylic amine boranes as the substrates. The study detailed below has demonstrated a series of relevant cyclizations and has encountered evidence for a mechanism that has implications for electrophilic borylation chemistry beyond the nitrogen-directed examples described herein.

Methods and Results

A prior study in our laboratory generated the nonstabilized borenium ion **11** from triethylamine borane **10** by hydride abstraction with trityl cation and found that **11** is trapped efficiently by the starting complex **10** to form the hydride-bridged cation **12** (Figure 3).[20] The 3c2e bond in **12** increases the electron density at boron compared to the borenium ion **11**, but **12** is a capable electrophile nevertheless and undergoes bonding interactions with weak nucleophiles including triflate and bistriflimidate anions, trialkylsilanes, and dichloromethane.

The above observations indicate that **12** acts as an *in situ* source of borenium species equivalent to **11**. We therefore performed the analogous activation of *N*,*N*-dimethylbenzylamine borane **13a** while monitoring intermediates by NMR spectroscopy (Scheme 1).

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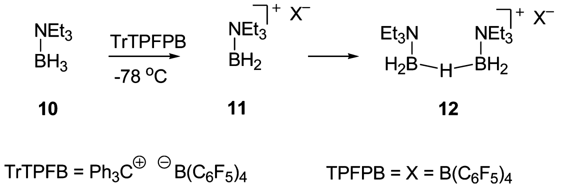
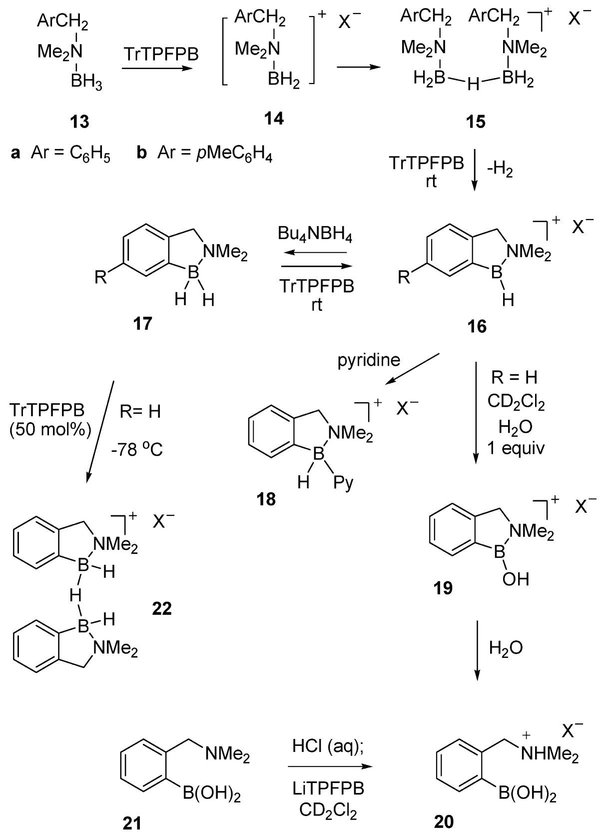


Figure 3. Hydride-bridged borenium species.

Scheme 1



Treatment of **13a** with trityl tetrakis(pentafluorophenyl)borate (TrTPFPB) at −78 °C in CD_2Cl_2 and assay by ^1H NMR at −20 °C showed the expected conversion of **13a** to **15a**, according to an upfield peak at δ $^1H = -1.9$ ppm and a ^{11}B chemical shift at δ 0.0 ppm. No signals for trivalent boron species such as **14a** were detected. However, a highly deshielded peak did appear in the range expected for trivalent boron (δ $^{11}B = 59$ ppm) when a similar experiment was performed in the more robust solvent C_6D_5Br at room temperature. The new boron signal was not consistent with the 1:2:1 triplet expected for **14a** but could be interpreted as a barely resolved, broad doublet (*J* ca. 150 Hz) by comparing proton-coupled and -decoupled spectra. This magnitude of B−H splitting would be consistent with the sp^2 environment in a free borenium ion, but the multiplicity requires a single proton at boron. Capture of **14a** by an external or an internal nucleophile followed by a second hydride abstraction would satisfy the multiplicity requirement and suggested several possible structures, but the question of cation identity was quickly resolved when addition of Bu_4NBH_4 to quench the reaction mixture produced the known benzazaborolidine **17a**[21] (72% isolated). The δ $^{11}B = 59$ ppm signal must therefore be due to the trivalent boron cation **16a**, stabilized by "bora-benzylic" delocalization between the formally unoccupied boron *p*-orbital and the aromatic π-electrons. Structure **16a** also helps to understand an unusually broad, strongly deshielded signal at δ $^1H = 5.9$ ppm that is coupled to boron and integrates to 1H and can, therefore, be assigned as the B−H proton.

An earlier encounter with cation **16a** has been reported from our laboratory, starting from the benzazaborolidine **17a**.[13] Hydride abstraction using trityl tetrafluoroborate in the presence of pyridine readily afforded the pyridine adduct **18** (as the tetrafluoroborate salt), but attempts to detect intermediates by NMR initially gave complex results. Using TrTPFPB as the hydride acceptor at −78 °C converted **17a** into species having unidentified broad NMR signals, including a transient signal at δ $^{11}B = 38.7$ ppm that disappeared upon adding pyridine at −50 °C or warming to room temperature. The δ 38.7 ppm signal was tentatively attributed to **16a**, but anomalies were noted that could not be explained, including partial recovery of **17a** after the pyridine quench. In the current study, the δ 38.7 ppm signal was detected at δ 39 ppm as a minor peak in experiments starting from either **13a** or **17a** (conditions designed to minimize contamination by water) while the major signal was observed at δ $^{11}B = 59$ ppm. However, the δ 39 ppm signal (broad singlet; no proton coupling) became major if 1 equiv of water was added to the solution obtained from **17a** with TrTPFPB in CD_2Cl_2 at room temperature and was, therefore, assigned as the hydroxyborenium ion **19**. In support of this assignment, addition of a second equivalent of water produced the protonated boronic acid **20** (δ $^{11}B = 29$ ppm; δ $^1H = 5.29$ (2H, br s, OH), 4.28 (2H, d, benzylic CH_2), 2.89 (6H, d, NMe_2) ppm), identical to the salt formed by protonation of known boronic acid **21** followed by anion metathesis and extraction into CD_2Cl_2.

Having clarified the identity of the signal at δ $^{11}B = 39$ ppm, we returned briefly to the NMR experiment from **17a** using TrTPFPB activation, but under conditions expected to favor the formation of hydride-bridged cations (50 mol % TrTPFPB). The dominant species formed in C_6D_5Br was assigned as the hydride-bridged structure **22**, based on δ $^{11}B = 11$ ppm. This signal is downfield compared to neutral **17a** but far upfield from the signals of *B*-hydroxyborenium cation **19** or the borenium ion **16a**. In the cleanest experiments, the only other ^{11}B NMR signal detected was that due to the TPFPB anion. However, distinct maxima for **16a** or **17a** were present in addition to the 11 ppm signal of **22** if the amount of TrTPFPB used for activation of **17a** was adjusted to 83 mol % or 33 mol %, respectively. The proton chemical shifts were less characteristic, but the shift values varied as the mol % of TrTPFPB used for cation generation was changed. This behavior is consistent with an equilibrium between **22** and **17a** + **16a** that is fast on the ^1H NMR time scale but slow on the ^{11}B NMR time scale. Quenching cation **22** with pyridine generates the adduct **18** previously isolated as well as recovered **17a**. Thus, the hydride bridged cation **22** apparently was present as a latent source of **16a** in the original experiment starting from **17a**,[13] while a different species (the hydroxyborenium ion **19**) was responsible for the trivalent boron chemical shift observed (δ ^{11}B 39 ppm) in the complex NMR spectra resulting from water contamination. We note that structure **16a** as redefined in the current study remains as the only borenium ion detected to date that contains a B−H bond, but it is now clear that **16a** has the δ $^{11}B = 59$ ppm chemical shift.

To establish the scope of conversion from substituted benzylamine boranes into cyclic amine boranes, several experiments were conducted with modified substrates (Table 1). A comparison of solvents for the cyclizations showed that bromobenzene (or other halobenzenes) gives higher conversion and better isolated yield of **17a** (72%) compared to toluene (48%) or dichloromethane (27%), so the conditions developed for the bromobenzene NMR experiments were used for the other entries of Table 1 without optimization of individual examples,[22] followed by Bu_4NBH_4 reductive workup. A slurry of $NaBH_4$ in diglyme also gave an acceptable

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(21) For characterization of **17a**, see ref 13.

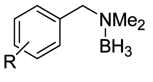
(22) The bromobenzene experiments are also more convenient because activation with TrTPFPB can be performed at room temperature, in contrast to dichloromethane. In the latter solvent, solvent-assisted degradation of triphenylmethane occurs via Friedel−Crafts alkylation as discussed in ref 20.

Table 1. Nitrogen-Directed Borylation[a]

entry	substrate	R	*n*	time (h)	product (%)[b]
1	**13a**	H	1	4	**17a** (72%)
2	**13b**	*p*-Me	1	4	**17b** (41%)
3	**13c**	*m*-Me	1	4	**17c** (79%)[c]
4	**13d**	*o*-Me	1	4	**17d** (76%)
5	**13e**	*p*-Br	1	8	**17e** (53%)
6	**13f**	*p*-Cl	1	8	**17f** (73%)
7	**13g**	*m*-Cl	1	4	**17g** (67%)[d]
8	**13h**	*p*-F	1	16	**17h** (59%)
9	**13i**	*m*-F	1	4	**17i** (67%)[e]
10	**13j**	*o*-Br	1	16	**17j** (55%)
11	**13k**	*o*-Cl	1	16	**17k** (55%)
12	**13l**	*o*-F	1	16	**17l** (39%)
13	**23**	H	2	4	**24** (74%)
14	**25**	H	3	16	**26**[f]

[a] Reactions at room temperature in C_6H_5Br, 90 mol % TrTPFPB, followed by quench with Bu_4NBH_4. [b] Yields based on TrTPFPB as limiting reagent. [c] 3:1 mixture of inseparable regioisomers. [d] 1:1.3 mixture of regioisomers. [e] 4:1 mixture of regioisomers. [f] ca. 30% (major product) + ca. 10% contaminants

yield in the case of **17a** (63%). Reductively quenched reaction mixtures were loaded directly onto silica gel for FC purification even though the borohydride caused cracking of the silica column. This resulted in poor separation for some cases, but the simple technique allowed convenient solvent removal and reasonable recoveries of **17** in addition to 10−20% unreacted **13** in typical experiments. Overall, the conversions were modest for some examples, but cyclized products were easily obtained over a range of aromatic substitutuents. Halogen substituents required longer reaction times for conversion to **17** (entries 5, 6, 8), especially in the case of the *ortho*-halogen derivatives (entries 10−12) by comparison with the *para*-isomers, suggesting the possibility of nonproductive formation of a B−X bond between electrophilic boron and the *ortho*-halogen. Longer tethers were also tolerated (entries 13, 14), although activation of **25** resulted in slower cyclization (30−40% **25** recovered after 16 h) and formed **26** along with degradation products that could not be separated from **26**.



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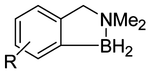

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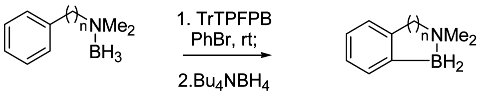
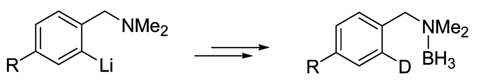


23 n= 2
25 n= 3

24 n= 2
26 n= 3

To gain further insight into events leading to **16**, the product-determining step was probed by a deuterium labeling study. The monodeuterated substrates **13a**-D_1 and **13b**-D_1 were prepared by D_2O quench of the corresponding *ortho*-lithiated *N*,*N*-dimethylbenzylamines **27**[23] and borane complexation, giving 95% deuterium incorporation (eq 1). The directed borylation of these substrates can occur with either loss or retention of deuterium in the product, so the ratio of **17**-D_1 to **17** corresponds to k_H/k_D. Substrate **13b**-D_1 proved more suitable for this study compared to **13a**-D_1 because the ^{1}H NMR signal for the *ortho*-C−H of **17a**-D_1 overlaps with another aromatic proton signal while all aromatic proton signals for **13b**-D_1 are fully resolved in the 500 MHz ^{1}H NMR spectrum. Accordingly, **13b**-D_1 was treated with TrTPFPB as usual, and the product **17b** (41% obtained after Bu_4NBH_4 quench) was assayed using ^{1}H NMR. Based on the ratio of deuterium-free vs deuterated products, the magnitude of the kinetic isotope effect (KIE) was found to be $k_H/k_D = 2.8$. This result indicates that the C−H(D) bond at which boron substitution occurs is broken during or before the regioselectivity-determining step (see Discussion).



27

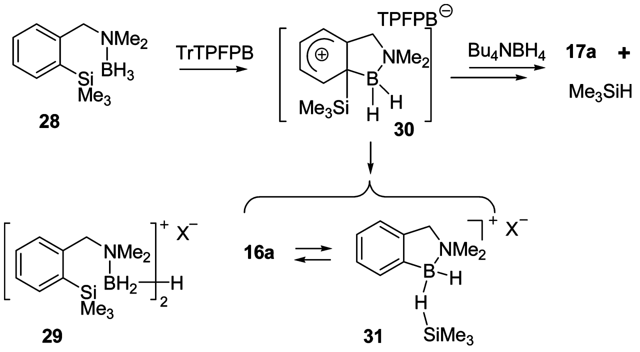
13-D_1

a R = H **b** R = Me

(1)

Given that proton removal plays a unique role in conversion to products, we investigated additional substrates designed to provide insight regarding mechanistic details of the electrophilic borylations. In the first series, the aryllithium reagent **27a** was trapped with TMSCl, followed by conversion into the amine borane **28** as usual. Treatment of **28** with TrTPFPB at room temperature resulted in efficient conversion to desilylated cyclization products, and reductive quenching with Bu_4NBH_4 gave **17a** in 96% isolated yield (Scheme 2). Even 10 mol % of the trityl salt was sufficient for 91% conversion of **28** to cyclization products within 1 h at room temperature, in striking contrast to the behavior of **13a**. In the latter case, the only product observed under similar conditions was the hydrogen-bridged dimer **15a**, and no cyclization occurred at room temperature unless >50 mol % of TrTPFPB was used for the activation as in Table 1 (ca. 40 mol % TrTPFPB is present in addition to the amount needed to generate **15**). Evidently, the TrTPFPB activates **15a** for cyclization by promoting the release of the more reactive borenium ion **14a**. However, no hydrogen-bridged intermediate analogous to **15a** could be detected starting from **28** and TrTPFPB, and additional TrTPFPB was not required to effect the cyclization. According to this evidence, the hydrogen-bridged structure **29** would have to be considerably more reactive than **15** due to the presence of silicon, sufficient to undergo spontaneous cyclization via **30**.

Scheme 2



When an experiment from **28** and equimolar TrTPFPB was monitored by ^{11}B NMR spectroscopy, we were surprised to find that the chemical shift for the cationic cyclization product does not match the δ 59 ppm value found for **16a**. Instead, the observed value was $\delta\ ^{11}B = 42$ ppm. We attribute the chemical shift difference to an equilibrium involving the 3c2e hydrogen-bridged silane adduct **31**, formally corresponding to the interaction of **16a** with Me_3SiH formed during the electrophilic borylation. Control experiments in bromobenzene-D_5 support this premise and indicate that the chemical shift of the equilibrating mixture of **16a** + **31** moves upfield as the proportion of added silane increases.[24] Both

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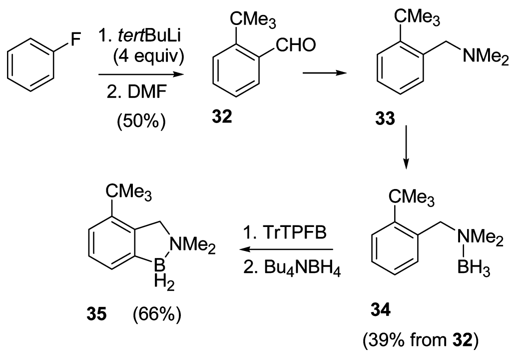
(24) Borenium cation **16a** was generated in bromobenzene and was treated with progressively increasing amounts of *i*Pr_3SiH. The following relationship between mol % of added *i*Pr_3SiH vs ^{11}B chemical shift was observed: 0 mol %, 59 ppm; 10 mol %, 57 ppm; 50 mol %, 48 ppm; 300 mol %, 45 ppm.

Scheme 3

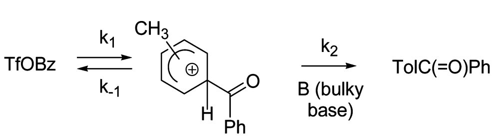


16a and **31** are converted into **17a** by the borohydride quench according to this interpretation.

The last series of experiments compared the above cyclizations with the analogous reaction starting from the *o*-*tert*-butyl substrate **34**, available from the benzyne-derived *o*-*tert*-butylbenzaldehyde **32** via reductive amination as shown in Scheme 3. The standard activation procedure from **34** was performed in bromobenzene at room temperature, and reductive workup provided the cyclization product **35** in 66% yield. Loss of the *tert*-butyl group had been anticipated as a possible outcome in this reaction given the behavior of the silicon analogue **28**, but no such products were detected (<2% of **17a**).

Discussion; Evaluation of Potential Reactive Intermediates

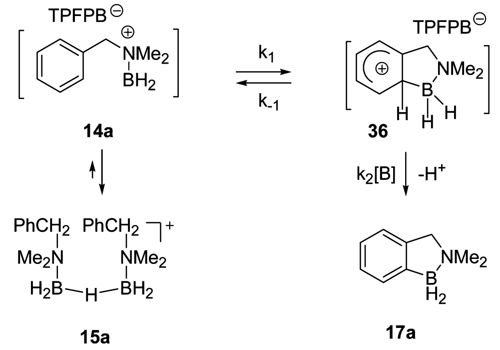
Most electrophilic aromatic substitution reactions proceed with no KIE,[25,26] although many exceptions are known.[25c,27] Negligible KIE has been taken as evidence not only that a σ-bonded cationic (Wheland) intermediate is involved in the reaction but also that its formation is rate-limiting. On the other hand, the interpretation of a significant KIE can be more challenging. In a recent example, the acylation of toluene using the mixed anhydride $PhCO_2Tf$ was characterized by $k_H/k_D = 1.14$ in the presence of the hindered base 2,4,6-tri-*tert*-butylpyridine, but a substantially larger value of 1.85 was observed in the presence of TfOH.[27h] Under the conditions with base added, $k_2[B]$ is much greater than k_{-1} and k_1 is the rate-determining step (eq 2). However, with TfOH added, $k_2[B]$ decreases relative to k_{-1} and deprotonation becomes rate limiting.



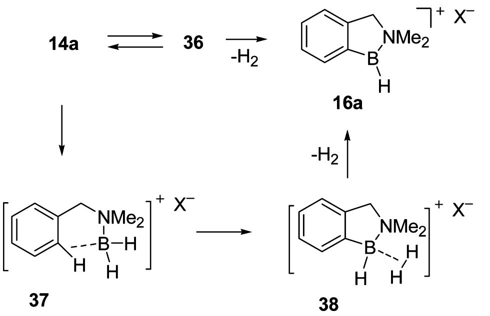
(2)

For the electrophilic borylations, a small modification of the above argument would explain the value of KIE = 2.8 observed for conversion from **13a** to **17a**. In contrast to typical electrophilic aromatic substitutions, this process is conducted under exceptionally nonbasic conditions because the conjugate acid of the TPFPB anion would correspond to a superacid that is known only as the etherate complex.[28] In this situation, the bromobenzene solvent is one candidate for the "strongest" external base, while various boron bonds, internal as well as external, constitute the alternative choices. Hydridic B−H bonds in amine boranes do have basic properties, although direct protonation of the B−N σ-bond is competitive under some conditions.[29] In any event, C−H bond breaking could well be rate limiting in the absence of adequate external base, resulting in $k_2[B] \ll k_{-1}$ in Scheme 4. The sequence of events might then proceed from the observable H-bridged **15a** via transient intermediates including the borenium ion **14a** and the Wheland intermediate **36**, followed by slow proton transfer and aromatization.[30]

Scheme 4



Scheme 5



(3)

If no external base "B" is capable of removing the proton from **36**, then $k_2[B]$ will be too small to account for facile product formation at room temperature. In this scenario, conversion from **36** directly to the observed intermediate **16a** may occur by evolution of hydrogen as the slow step and without the intermediacy of **17a** (Scheme 5; eq 3). Another

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(25) (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; pp 623−640. (b) March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 2001; pp 675−758. (c) Melander, L. C. S. *Isotope Effects on Reaction Rates*; Roland Press: New York, 1960; pp 107−122.

(26) (a) Melander, L. *Ark. Kemi* **1950**, *2*, 211. (b) Lauer, W. M.; Noland, W. E. *J. Am. Chem. Soc.* **1953**, *75*, 3689. (c) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1961**, *83*, 4571. (d) Ehrlich, A.; Berliner, E. *J. Org. Chem.* **1972**, *37*, 4186. (e) Zhang, B.-L.; Pionnier, S. *J. Phys. Org. Chem.* **2001**, *14*, 239.

(27) (a) Zollinger, H. *Helv. Chim. Acta* **1955**, *38*, 1617. (b) Grovenstein, E.; Kilby, D. C. *J. Am. Chem. Soc.* **1957**, *79*, 2972. (c) Berliner, E. *J. Am. Chem. Soc.* **1960**, *82*, 5435. (d) Olah, G. A.; Kuhn, S. J.; Flood, S. H.; Hardie, B. A. *J. Am. Chem. Soc.* **1964**, *86*, 2203. (e) Kresge, A. J.; Brennan, J. F. *J. Org. Chem.* **1967**, *32*, 752. (f) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3505. (g) Perrin, C. L. *J. Org. Chem.* **1971**, *36*, 420. (h) Effenberger, F.; Maier, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 3429. (i) Dzudza, A.; Marks, T. J. *J. Org. Chem.* **2008**, *73*, 4004.

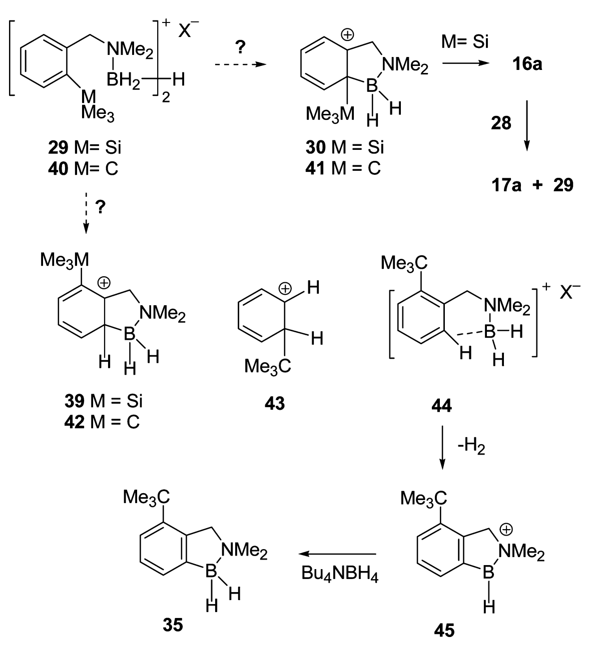
(28) Jutzi, P.; Müller, C.; Stammler, A.; Stammler, H.-G. *Organometallics* **2000**, *19*, 1442.

(29) (a) Kelly, H. C.; Marchello, F. R.; Giusto, M. B. *Inorg. Chem.* **1964**, *3*, 431. (b) Kelly, H. C.; Marriott, V. B. *Inorg. Chem.* **1979**, *18*, 2875. (c) Kelly, H. C.; Giusto, M. B.; Marchello, F. R. *J. Am. Chem. Soc.* **1964**, *86*, 3882.

(30) (a) Hubig, S. M.; Kochi, J. K. *J. Org. Chem.* **2000**, *65*, 6807. (b) Reed, C. A.; Kim, K.-C.; Stoyanov, E. S.; Stasko, D.; Tham, F. S.; Mueller, F. J.; Boyd, P. D. W. *J. Am. Chem. Soc.* **2003**, *125*, 1796.

possible explanation for the observed KIE is that **36** is not on the pathway leading to products (i.e., negligible contributions from k_2[B], Scheme 4, and eq 3, Scheme 5). Instead, conversion from **14a** to the initial product **16a** might take place by a C−H insertion process involving the 3c2e interactions represented by structures **37** and **38** (eq 3b). In some respects, this sequence is reminiscent of mechanisms proposed for transition metal C−H insertions involving aromatic substrates,[31] but the 3c2e bonding interaction between the mostly vacant borenium *p*-orbital of **14a** and the arene C−H σ bond leads to a cationic borenium−hydrogen complex **38**. Related hypervalent species may be involved in high temperature hydrogen transfer reactions catalyzed by trialkyl boranes,[32] the recent hydrogen activation experiments of Stephan et al. and related studies,[33] and gas phase equilibria involving $BH_2(+)$, H_2, and $BH_4(+)$.[34] The relationship between **38** and **16a** has a close parallel in the cationic ammonia borane derivatives $[H_3N{\bullet}BH_4]^+$ (borenium ion hydrogen adduct) and $[H_3N{\bullet}BH_2]^+$ (borenium ion), structures that have been evaluated computationally.[35]

Scheme 6



The contrasting behavior of the trimethylsilyl (**28**) and *tert*-butyl (**34**) substrates is especially interesting in the mechanistic context. The simplest interpretation in the silicon case invokes formation of a transient hydrogen-bridged cation **29** followed by spontaneous cyclization to the Wheland intermediate **30** and desilylation (Scheme 6). Facile conversion to **30** is due to stabilization by the well-known beta effect of silicon in the *ipso* substitution.[36] According to the extensive studies of Lambert et al. and Reed et al.,[9a,b] the naked cation $Me_3Si(+)$ cannot simply “fall off”, but the solvents used in our study (bromobenzene, toluene) would be sufficiently nucleophilic to assist in the desilylation step from **30** by coordination at silicon.[27g] Alternatively, desilylation from **30** might occur via bonding between silicon and an adjacent (nucleophilic) H−B bond to give **31** followed by formation of **16a** upon loss of Me_3SiH. This alternative pathway reverses the order of events after generation of the Wheland intermediate **30** but does not change the overall result, namely the facile conversion to **16a** using stoichiometric trityl activation or to **17a** using 10 mol % of TrTPFPB. No silicon-containing products were detected that might have been formed via proton removal from the isomeric Wheland intermediate **39**. This observation is consistent with exclusive formation of the more stabilized **30** in the cyclization step or reversible formation of both **30** and **39**, followed by product determining desilylation.

For somewhat different reasons, an equally simple scenario might have been expected in the *tert*-butyl case. Activation of **34** with TrTPFPB would generate **40** as usual, and conversion to Wheland intermediates **41** and **42** is feasible in principle. However, in contrast to the silicon analogy, loss of the cation $Me_3C(+)$ from **41** *should not* require nucleophilic assistance by solvent. Protonated *tert*-butylbenzene **43** is known to fragment to benzene and $Me_3C(+)$ in superacid solution at temperatures well below −30 °C.[37] These conditions rule out assistance by nucleophiles or by base, and the analogy argues that **41** would undergo unassisted fragmentation to the amine borane **17a** and $Me_3C(+)$. Because this was not observed, we conclude that **41** was never formed. Without the stabilizing beta effect of silicon, it is easy to believe that **41** would not be formed, but similar logic suggests that **42** may also not be formed if an alternative, lower energy pathway is available to explain the conversion from **34** into **35**. We have therefore explored the possibility that a C−H insertion pathway may be

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(31) (a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754. (b) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (c) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (d) Harvey, J. N.; Aggarwal, V. K.; Bathelt, C. M.; Carreón-Macedo, J.-L.; Gallagher, T.; Holzmann, N.; Mulholland, A. J.; Robiette, R. *J. Phys. Org. Chem.* **2006**, *19*, 608. (e) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879.

(32) (a) DeWitt, E. J.; Ramp, F. L.; Trapasso, L. E. *J. Am. Chem. Soc.* **1961**, *83*, 4672. (b) Ramp, F. L.; DeWitt, E. J.; Trapasso, L. E. *J. Org. Chem.* **1962**, *27*, 4368. (c) Köster, R.; Bruno, G.; Binger, P. *Ann.* **1961**, *644*, 1.

(33) (a) Welch, G. C.; San Juan, R. R.; Masuda, J. D.; Stephan, D. W. *Science* **2006**, *314*, 1124. Geier, S. J.; Gilbert, T. M.; Stephan, D. W. *J. Am. Chem. Soc.* **2008**, *130*, 12632. Chase, P. A.; Stephan, D. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7433. Geier, S. J.; Stephan, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 3476. (b) Review: Stephan, D. W. *Dalton Trans.* **2009**, 3129, and references therein. (c) Sumerin, V.; Schulz, F.; Atsumi, M.; Wang, C.; Nieger, M.; Leskelä, M.; Repo, T.; Pyykkö, P.; Rieger, B. *J. Am. Chem. Soc.* **2008**, *130*, 14117. Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5997. Sumerin, V.; Schulz, F.; Nieger, M.; Leskelä, M.; Repo, T.; Rieger, B *Angew. Chem., Int. Ed.* **2008**, *47*, 6001. Spies, P.; Schwendemann, S.; Lange, S.; Kehr, G.; Fröhlich, R.; Erker, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7543. Axenov, K. V.; Kehr, G.; Frohlich, R.; Erker, G. *J. Am. Chem. Soc.* **2009**, 3454. Rokob, T. A.; Hamza, A.; Stirling, A.; Pápai, I. *J. Am. Chem. Soc.* **2009**, *131*, 2029. (d) Privalov, T. *Chem.—Eur. J.* **2009**, *15*, 1825. (e) The current view of hydrogen activation invokes simultaneous action by an amine or phosphine *in addition* to $B(C_6F_5)_3$ as the electrophile. No such additives are present in our deuterium exchange experiment, although assistance by internal B−H bonds in deuterium activation may play a similar role.

(34) (a) DePuy, C. H.; Gareyev, R.; Hankin, J.; Davico, G. E.; Damrauer, R. *J. Am. Chem. Soc.* **1997**, *199*, 427. (b) DePuy, C. H.; Gareyev, R.; Hankin, J.; Davico, G. E.; Krempp, M.; Damrauer, R. *J. Am. Chem. Soc.* **1998**, *120*, 5086.

(35) (a) Protonated ammonia borane $[H_3N{\bullet}BH_4]^+$ is more stable than $[H_3N{\bullet}BH_2]^+ + H_2$ by 5.7 kcal/mol (ref 35b). However, the analogous comparison between **38** and **16a** plus hydrogen would have to take into account the effect of borabenzylic delocalization that would help stabilize **16a**. (b) Rasul, G.; Prakash, G. K.; Olah, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 13387. (c) Zeng, X.; Davico, G. E. *J. Phys. Chem.* **2003**, *107*, 11565.

(36) (a) Bennetau, B.; Dunogues, J. *Synlett.* **1993**, 171. (b) Kaufmann, D. *Chem. Ber.* **1987**, *120*, 853. (c) For a general review of the silicon β-effect, see: Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.

(37) Olah, G. A.; Schlosberg, R. H.; Porter, R. D.; Mo, Y. K.; Kelly, D. P.; Mateescu, G. D. *J. Am. Chem. Soc.* **1972**, *94*, 2034.

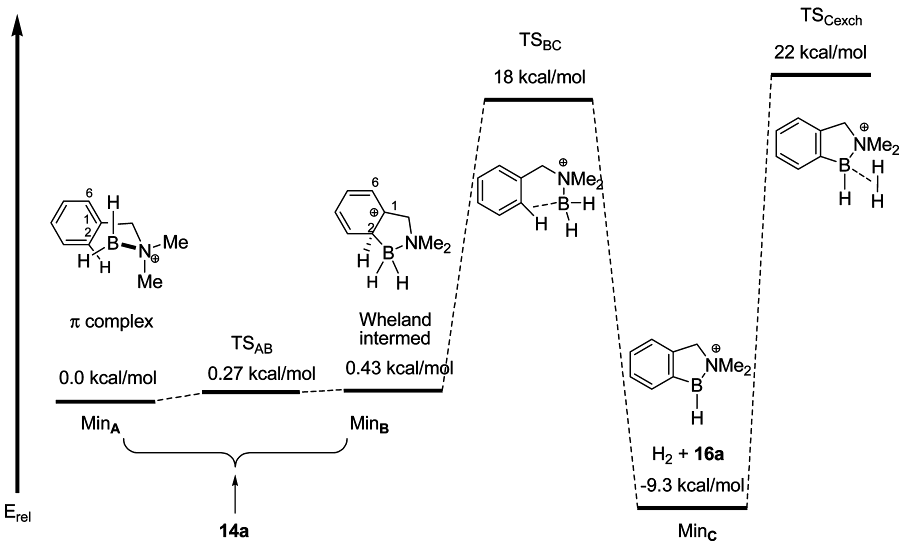
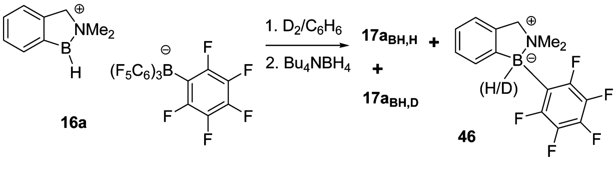


Figure 4. B3LYP/6-31G* energies for cationic structures from **14a** to **16a**.

a viable alternative for this conversion as well as for the related events shown in Scheme 5.

The geometry and energy of potential cationic intermediates, starting with the presumed borenium ion **14a**, was evaluated using B3LYP/6-31G* calculations performed using the Gaussian 03 program package.[38] An energy minimum ($E_{rel} = 0.0$ kcal/mol) was found for a π-complex (Min$_A$, Figure 4), showing interaction between the benzene ring and the empty *p* orbital at boron with two short r_{CB} contacts at 2.38 Å for C(1) and 2.55 Å for C(2), respectively. A second local minimum ($E_{rel} = 0.43$ kcal, corrected for zero-point energy) was assigned as the Wheland intermediate **36** = Min$_B$ based on the shorter r_{CB} contacts compared to Min$_A$, 2.31 Å for C(1) and 2.01 Å for C(2). The transition structure TS$_{AB}$ ($E_{rel} = 0.27$ kcal/mol) was also identified along the relatively flat energy surface from Min$_A$ to Min$_B$, similar structures that lead to TS$_{BC}$ ($E_{rel} = 18$ kcal/mol; Figure 4). Subsequent exchange between products and H$_2$ can occur through an isomeric transition state TS$_{Cexch}$ ($E_{rel} = 22$ kcal/mol). MP2 calculations with the cc-pVTZ basis confirm the results obtained with B3LYP to within a few kcal/mol, suggesting that the broad features of the potential energy surfaces are correct.[39]

In the context of Scheme 5, TS$_{BC}$ corresponds to the 3c2e transition structure **37** for the C−H insertion pathway and the energy barrier relative to the π-complex (Min$_A$) is consistent with cyclization at room temperature. For the reverse reaction from **16a** + H$_2$, the relatively high enthalpic barrier (ca. 27 kcal/mol, corresponding to somewhat higher $\Delta G^{\ddagger}$) suggests that the exchange reaction between **16a** and molecular hydrogen should be too slow to be detected, but the possibility was explored experimentally (eq 4). Thus, **16a** was generated independently by reaction of **17a** with TrTPFPB, and the suspension in benzene was stirred under D$_2$ (ca. 2−3 atm). After 15−30 days, the heterogeneous mixture was quenched with Bu$_4$NBH$_4$ and ca. 20% of **17a** was recovered with variable deuterium incorporation (MS assay). However, extensive decomposition of **16a** was evident and resulted in the formation of borane complex **46** (eq 4; ca. 20%) as one component of precipitated material that could not be dispersed reproducibly during the deuterium incorporation attempts. Formation of **46** was confirmed in control experiments in the absence of deuterium (46% isolated after 24 h reflux in benzene; 10% after 12 d at rt). Faster decomposition was observed in bromobenzene (>90% conversion within 24 h at rt), but other significant decomposition products were formed in addition to **46**. In the best deuterium experiment, ca. 40% D$_1$ incorporation was measured in both **46** and recovered **17a**. These results exceed reaction rate expectations based on the calculated value of TS$_{BC}$, depending on the precision of the computations, but cautious interpretation is appropriate in any event, given the uncertainties regarding mechanism under the highly dilute, heterogeneous reaction conditions used for the deuterium incorporation studies. Among other concerns, decomposition from **16a** to **46** presumably also generates (C$_6$F$_5$)$_3$B, a potent electrophile that may play a role in the deuterium exchange in view of its known interaction with molecular hydrogen.[33]



(4)

Byproduct **46** was not formed in substantial amounts in the stoichiometric cyclization experiments from **13a** and TrTPFPB under the usual conditions (4 h, rt), although traces of **46** were observed by NMR assay after 9 h. On the other hand, no sign of **46** or other decomposition products was detected when **13a** was activated using 5% TrTPFPB in early attempts to achieve catalytic conversion to **17a**, even at toluene reflux temperatures. These experiments encouraged the investigation of more forcing conditions. Remarkably, heating **13a** with 5% TrTPFPB in toluene (160 °C bath, sealed tube) followed by quenching with Bu$_4$NBH$_4$ resulted in efficient conversion to **17a** (90% isolated). Evidently, the presence of excess amine borane ensures hydride transfer to the cation **16a** and suppresses formation of the byproduct **46** in the catalytic procedure.

Attention was now turned to the cationic trimethylsilyl-containing structures generated starting from **28** (Figure 5).

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(38) Frisch, M. J. *Gaussian 03*, rev. C.02; Gaussian, Inc: Wallingford, CT, 2004; see Supporting Information for details.

(39) Details of these calculations, carried out using the MOLPRO software (MOLPRO, version 2008.1, Werner H.-J. et al.), are in the Supporting Information.

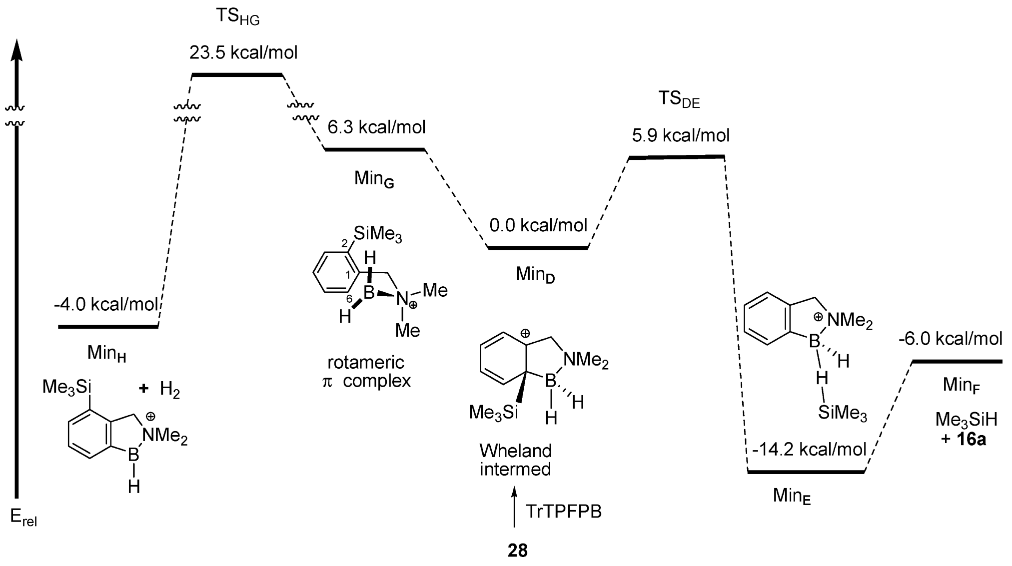

Figure 5. B3LYP/6-31G* energies for cationic structures from **28** to **16a**.

Attempted optimization of a presumed π-complex analogous to $Min_{\mathbf{A}}$ (Figure 4) having the BH_2 subunit placed near the $Me_3SiC(2)-C(1)$ segment resulted instead in the Wheland intermediate $Min_{\mathbf{D}}$ = **30** (E_{rel} = 0.0 kcal/mol, Figure 5). The structure is clear from the almost fully formed B−C(2) bond (1.67 Å) with boron nearly in the plane of the aromatic ring and a somewhat elongated C(2)−Si bond (2.19 Å) at an angle of 105° relative to the ring. A low-lying $TS_{\mathbf{DE}}$ was found just 5.9 kcal/mol above $Min_{\mathbf{D}}$ that leads to formal migration of $Me_3Si(+)$ from carbon to the adjacent boron-bound hydride. The result is conversion to $Min_{\mathbf{E}}$ = **31** (E_{rel} = −14.2 kcal/mol) with a hydride bridge linking boron (r_{BH} = 1.41 Å) and silicon (r_{SiH} = 1.61 Å), followed by B−H−Si dissociation ($Min_{\mathbf{F}}$). On the other hand, when the initial optimization was performed with the BH_2 subunit rotated to be near the benzene C(1)−C(6) segment, a local minimum corresponding to a π-complex $Min_{\mathbf{G}}$ was found (E_{rel} = 6.3 kcal/mol). The higher energy path for loss of hydrogen from $Min_{\mathbf{G}}$ via $TS_{\mathbf{GH}}$ (E_{rel} = 23.5 kcal/mol) is analogous to the sequence of Figure 4, but it does not compete with the more facile Si migration pathway from $Min_{\mathbf{D}}$ to $Min_{\mathbf{E}}$. These results reflect substantial cation stabilization by the β-silyl group in $Min_{\mathbf{D}}$ compared to the regioisomeric Wheland intermediate derived from borylation at benzene C(6). Furthermore, the computations reveal a low-energy mechanism for aromatization from $Min_{\mathbf{D}}$ via $TS_{\mathbf{DE}}$ that does not require participation by an external nucleophile or base.

The remaining stages of the conversion from $Min_{\mathbf{E}}$ to **16a** (stoichiometric) or **17a** (catalytic) are not fully depicted in Figure 5 because dissociation of a B−H bond into Me_3SiH and **16a** ($Min_{\mathbf{F}}$, E_{rel} = −6.0 kcal/mol) or dissociation of a Si−H bond into $Me_3Si(+)$ and **17a** (E_{rel} = +32 kcal/mol) would be followed by adduct formation involving the high energy borenium or silylium cations and various external electron donors. The specific details would include interactions between **16a** and solvent (stoichiometric conditions via $Min_{\mathbf{F}}$) or between $Me_3Si(+)$ and potentially bridging B−H bonds from unreacted **28** or with solvent (catalytic conditions). No attempt was made to evaluate the relevant energy profiles, but the latter pathway formally involving Si−H dissociation followed by intermolecular hydride transfer from **28** to $Me_3Si(+)$ would nicely explain the facile catalytic conversion from **28** to **17a** using 10% TrTPFPB. For similar reasons, the details of the reverse reaction from Me_3SiH and **16a** ($Min_{\mathbf{F}}$) were also not evaluated in detail. However, a transition state was found (E_{rel} = −2.3 kcal/mol; $TS_{\mathbf{E}\mathit{ent}\mathbf{E}}$, not illustrated) for the reversible migration of Me_3Si between the two B−H hydrogens in $Min_{\mathbf{E}}$ (**31**). The activation barrier from $Min_{\mathbf{E}}$ is quite small (11.9 kcal/mol) and meets one of the requirements for facile isotopic exchange with an external Si−D bond. Accordingly, independently generated **16a** was stirred with excess Et_3SiD in benzene at room temperature. After 10 min, **16a** was isolated by precipitation with hexane and was assayed by ^1H NMR spectroscopy. Only 8% of residual B−H signal intensity was found in recovered **16a**, as expected for the reverse reaction from $Min_{\mathbf{F}}$ (**16a** + R_3SiH) followed by fast H/D exchange[20] at the stage of $Min_{\mathbf{E}}$. This decisive experiment provides qualitative confirmation for the relative energies deduced by the computational method. It is also consistent with the observed change in the ^{11}B chemical shift of **16a** upon addition of R_3SiH as mentioned earlier.

Finally, the computations were used to evaluate cationic intermediates in the *tert*-butyl series starting from **34**. Most features of the pathway leading to **35** were found to be analogous to those shown in Figure 4 from cation **14a** to **16a**. However, attempted optimization of a π-complex with boron interacting with C(2) resulted in a local energy minimum corresponding to the less hindered π-complex rotamer where boron interacts with the unsubstituted C(6). Constrained optimization indicates that the more hindered rotamer would be ca. 10 kcal/mol less stable, suggesting that simple steric repulsions are the reason why intermediate **41** is never formed. Subsequent events from the π-complex to structures **44** and **45** resemble those of Figure 4, but the local minimum corresponding to the Wheland intermediate **42** was not found (see Supporting Information for details).

Summary

Our findings support the involvement of borenium species or hydrogen-bridged cations such as **15** and **29** in the borylations, and they raise the intriguing prospect of C−H insertion mechanisms via borenium ion intermediates at room temperature.[40,41] According to the B3LYP/6-31G* computations, the rate-determining step can be described as a C−H insertion at the stage of the intermediate borenium π-complex or the corresponding Wheland intermediate. In the case of **14a**, the two cations (π-complex or Wheland) have essentially identical energies and similar geometries. We did not attempt to evaluate transition states for potentially competing intermolecular proton removal at the stage of the Wheland intermediates, partly because external bases were not added in these experiments, and partly because simpler benzenium ions are remarkably stable if the counterion is noninteractive (neither basic nor nucleophilic).[30b] In the present study, the tetrakis(pentafluorophenyl)borate (TPFPB) anion is sufficiently nucleophilic to react with sextet boron in the dearylation process shown in eq 4,[42] but there is no evidence to suggest that TPFPB functions as a base.

The detection of hydrogen bridged cationic intermediates related to **15a** with representative substrates not containing *ortho*-silicon indicates that hydrogen bridging is a stabilizing factor that somewhat impedes intramolecular borylation. Although we have not revisited intermolecular or intramolecular electrophilic borylations described in earlier literature reports,[17,43] we note that borenium intermediates would explain the isolated reports of surprisingly facile oxygen-directed aromatic borylations of biaryl phenols and related structures because these reactions are conducted in the presence of the oxophilic Lewis acid $AlCl_3$.[44] It may be rewarding to re-examine this chemistry under reaction conditions chosen to promote more specific generation of borenium intermediates.[45] If borenium electrophiles can be accessed in the absence of potentially bridging (and, therefore, stabilizing) ligands at boron, reactions should be faster and it may be possible to develop new methodology for low temperature borylation and C−H insertion chemistry.

Acknowledgment. This work was supported by the National Institute of General Medical Sciences, NIH (GM067146).

Supporting Information Available: Experimental procedures and characterization data. Full computational details including optimized Cartesian coordinates. Complete refs 38 and 39. This material is available free of charge via the Internet at at http://pubs.acs.org.

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(40) At higher temperatures, intramolecular aryl borylation is also known in the case of neutral, trivalent borane intermediates: (a) Köster, R.; Reinert, K. *Angew. Chem.* **1959**, *71*, 521. (b) Laaziri, H.; Bromm, L. O.; Lhermitte, F.; Gschwind, R. M.; Knochel, P. *J. Am. Chem. Soc.* **1999**, *121*, 6940. Varela, J. A.; Peña, D.; Goldfuss, B.; Denisenko, D.; Polborn, K.; Knochel, P. *Chem.—Eur. J.* **2004**, *10*, 4252, and references therein.

(41) Similar transition state geometries have been identified for the thermal cyclizations of neutral boranes (ref 40) and have been discussed using the terminology of C−H activation and 4-center dehydrogenation: Goldfuss, B.; Knochel, P.; Bromm, L. O.; Knapp, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 4136. Varela, J. A.; Peña, D.; Goldfuss, B.; Polborn, K.; Knochel, P. *Org. Lett.* **2001**, 2395.

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(44) In principle, the oxophilic Lewis acid can promote borylation of phenols HOAr by reversibly forming intermediates $Cl_3AlO(Ar)BX_2$ that contain a borenium subunit. This chemistry warrants re-investigation under reaction conditions designed to promote more specific generation of borenium species.

(45) In a qualitative comparison of relative electrophilicities, the B3LYP/6-31G* bond energies were calculated for the hypothetical gas phase reactions of H_3B, Me_3C^+, $Me_3N^+BH_2$, and H_3C^+ with the representative nucleophiles H_3N and H_3P. The sum of the bond energies (B−N + B−P) for each electrophile provides a rough measure of electrophilicity: H_3B (54 kcal/mol), Me_3C^+ (79 kcal/mol), $Me_3N^+BH_2$ (87 kcal/mol), and H_3C^+ (224 kcal/mol); these data indicate that the borenium ion is much more electrophilic than borane but does not approach the most electrophilic cation H_3C^+ in this series.