

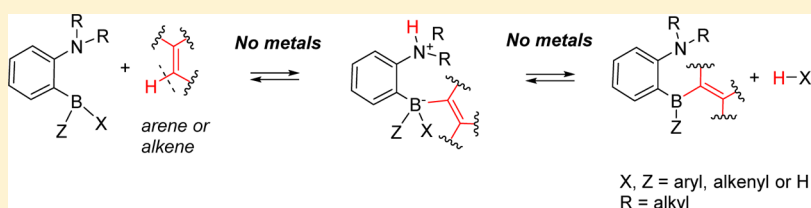
# Metal-Free $sp^2$ -C–H Borylation as a Common Reactivity Pattern of Frustrated 2-Aminophenylboranes

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**S** Supporting Information



**ABSTRACT:** C–H borylation is a powerful and atom-efficient method for converting affordable and abundant chemicals into versatile organic reagents used in the production of fine chemicals and functional materials. Herein we report a facile C–H borylation of aromatic and olefinic C–H bonds with 2-aminophenylboranes. Computational and experimental studies reveal that the metal-free C–H insertion proceeds via a frustrated Lewis pair mechanism involving heterolytic splitting of the C–H bond by cooperative action of the amine and boryl groups. The adapted geometry of the reactive B and N centers results in an unprecedentedly low kinetic barrier for both insertion into the  $sp^2$ -C–H bond and intramolecular protonation of the  $sp^2$ -C–B bond in 2-ammoniophenyl(aryl)- or -(alkenyl)borates. This common reactivity pattern serves as a platform for various catalytic reactions such as C–H borylation and hydrogenation of alkynes. In particular, we demonstrate that simple 2-aminopyridinium salts efficiently catalyze the C–H borylation of heteroarenes with catecholborane. This reaction is presumably mediated by a borenium species isoelectronic to 2-aminophenylboranes.

## INTRODUCTION

Organoboron compounds, namely, boronic acids and their esters, find wide application in synthetic transformations such as C–C cross-couplings, reductions, syntheses of alcohols and phenols, and other reactions. Classical methods for the synthesis of arylboron compounds utilize organomagnesium or -lithium reagents in stoichiometric amounts.<sup>1</sup> Metal-catalyzed C–H borylation provides an essentially more powerful and atom-efficient method for conversion of affordable and abundant chemicals into versatile organoboron reagents. Until recently, the catalysis of these reactions was dominated by complexes of Pd, Pt, Ru, Ir, and other noble metals.<sup>2</sup> For economic and toxicity reasons, there is a significant interest in the development of C–H borylations catalyzed by abundant transition metals<sup>3</sup> or metal-free methods.<sup>4</sup>

A new approach for metal-free activation of various bonds has recently been proposed. Pairs of Lewis acids and Lewis bases, so-called “frustrated Lewis pairs” (FLPs), exhibit cooperative reactivity that results in heterolytic splitting of  $\sigma$  and  $\pi$  bonds of various substrate molecules to produce the respective ionic or zwitterionic [Lewis acid]<sup>−</sup>–substrate–[Lewis base]<sup>+</sup> adducts.<sup>5</sup> Many of these reactions have been turned into catalytic processes, particularly  $H_2$  activation into hydrogenation.<sup>6</sup> Terminal acetylenes, being relatively acidic compounds with sterically accessible and highly symmetric  $sp$ -

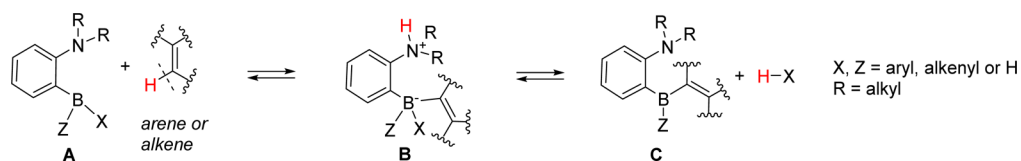
C–H bonds, undergo smooth C–H bond splitting with FLPs.<sup>7</sup> However, the splitting of  $sp^2$ -C–H and  $sp^3$ -C–H bonds is still a great challenge for FLP chemistry since only a few examples of such reactivity have been reported.<sup>8</sup>

Herein we report the results of our comprehensive study of the reactivity of 2-aminophenylboranes (2-APBs; see **A** in **Scheme 1**). We demonstrate that this particular family of *ansa*-aminoboranes (with N and B reactive centers fixed in a chelating manner) easily undergo insertion into  $sp^2$ -C–H bonds of simple arenes and alkenes, producing zwitterionic FLP adducts **B** in a reversible manner (**Scheme 1**). This reactivity is of major importance for metal-free catalysis since these elementary C–H insertion and protonation steps can be incorporated into various catalytic cycles. For instance, we have recently reported a 2-APB-catalyzed hydrogenation of alkynes to give *cis*-alkenes in which facile intramolecular protonation of the alkenyl group is crucial for the successful reaction.<sup>9</sup> In continuation of our studies of 2-APBs, we now report facile  $sp^2$ -C–H borylation of simple arenes and alkenes, including relatively unreactive benzene and hex-1-ene, with various 2-APBs, resulting in the formation of novel aminoboranes **C**.<sup>10</sup> On the basis of our findings, we propose a conceptually new

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**Scheme 1. Common Reactivity of 2-Aminophenylboranes: Facile Metal-Free  $sp^2$ -C–H Insertion into Arenes and Alkenes Forming Zwitterions B and Their Reverse Intramolecular  $sp^2$ -C–B Protonolysis**

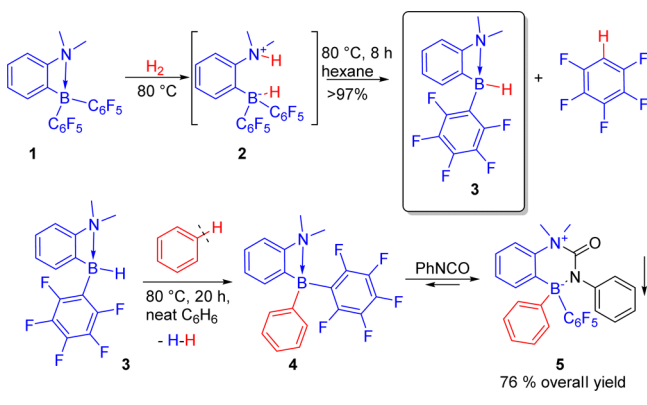


catalytic cycle for  $sp^2$ -C–H borylation of various substrates mediated by a borenium species isoelectronic to 2-APBs.

## RESULTS

**C–H Activation of Benzene.** We recently reported that 2-[bis(pentafluorophenyl)boryl]-*N,N*-dimethylaniline (**1**) reacts with  $H_2$  to produce the respective adduct, 2-(dimethylammonio)phenylborohydride **2** (Scheme 2).<sup>11</sup> This process is

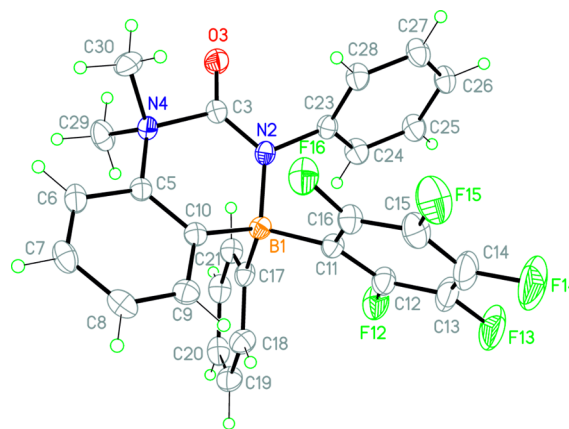
**Scheme 2. Preparation of **3** from **1** by Hydrogenolysis of the B– $C_6F_5$  Bond, C–H Borylation of Benzene by **3** To Produce Aminoborane **4**, and Isolation of Its Crystalline Phenyl Isocyanate Adduct **5****



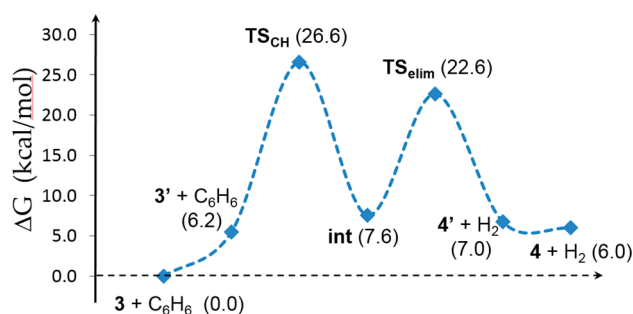
reversible at room temperature, whereas at elevated temperatures an intramolecular protonolysis of the B– $C_6F_5$  bond takes place, forming aminohydroborane **3** and pentafluorobenzene.<sup>9</sup> This reactivity was surprising since pentafluorophenyl borates are known for extreme stability, against protonolysis in particular,<sup>12</sup> securing their application as weakly coordinating anions in catalysis.<sup>13</sup> Further studies revealed that selective  $sp^2$ -C–B bond protonative cleavage is a reactivity characteristic of the 2-dimethylaminophenylboryl core.<sup>9</sup>

Preparation of **3** in benzene is accompanied by the formation of byproduct in up to 40% yield. Switching to bromobenzene suppressed byproduct formation to yields of less than 20%. A side reaction with aromatic solvents was apparent, since **1** could be converted into **3** in high yield in hexane (Scheme 2). Accordingly, aminoborane **3** was shown to furnish the C–H borylation product **4** when heated in benzene, while **1** remained intact even upon prolonged heating. The crystalline FLP adduct **5** obtained from **4** and phenyl isocyanate was isolated in 76% overall yield, and the structure was determined by the single-crystal X-ray diffraction method (Figure 1).

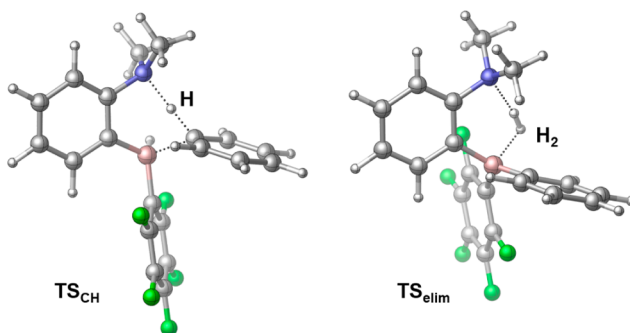
The thermodynamic and kinetic requirements of the C–H borylation of benzene with **3** were then examined computationally.<sup>14</sup> The results pointed to a two-step mechanism involving C–H bond cleavage (coupled with B–C bond formation) and subsequent  $H_2$  elimination (see Figure 2 for the Gibbs free energy diagram and Figure 3 for the corresponding



**Figure 1.** Structure of **5** in the solid state based on X-ray diffraction studies.



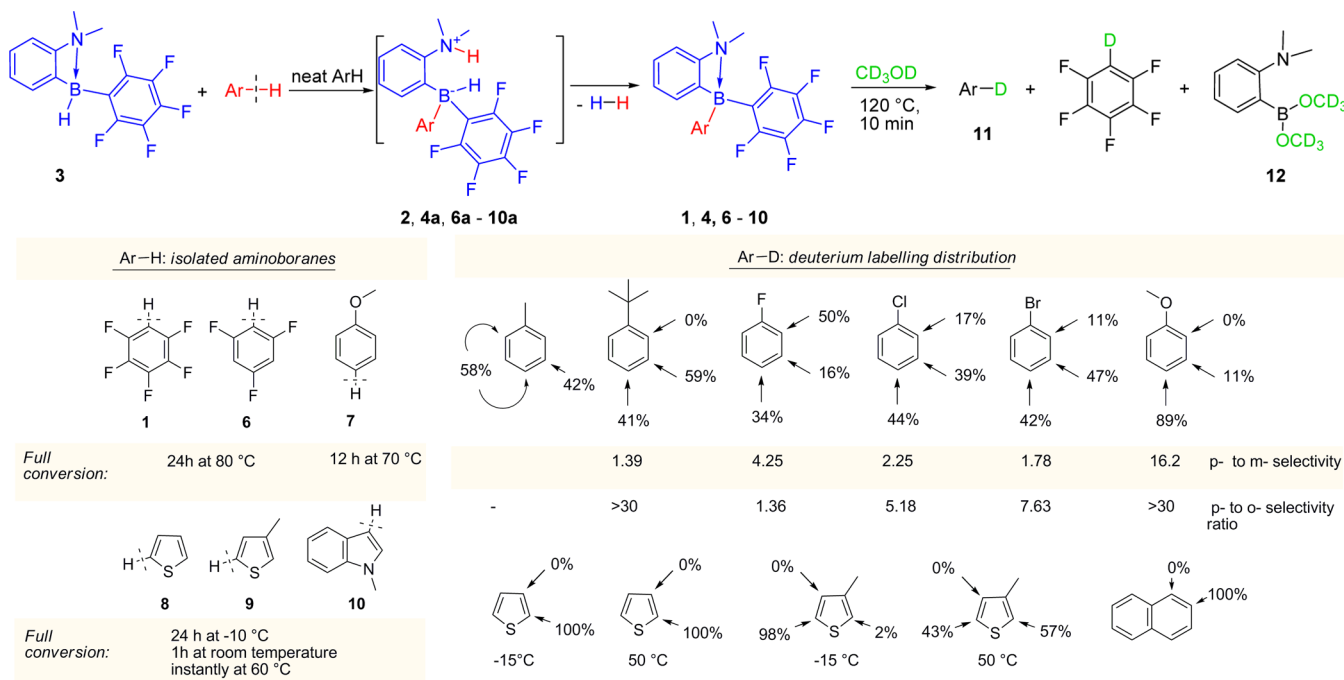
**Figure 2.** Gibbs free energy diagram computed for the C–H borylation of benzene with **3**. Relative stabilities of the involved species (in kcal/mol, with respect to reactants) are given in parentheses. **3'** and **4'** denote the *open* (unquenched) forms of **3** and **4**.



**Figure 3.** Transition states located for the C–H insertion and  $H_2$  elimination steps in the reaction of benzene with **3**.

transition states). Of these two steps, the C–H activation was found to have a higher barrier, and the predicted height is consistent with the elevated temperature required for this reaction. The zwitterionic reaction intermediate (**int**) is notably

**Scheme 3. C–H Borylation of Arenes with 3: Isolated Aryl-Substituted Aminoboranes and Studies of C–H Insertion Regioselectivity by Product Distribution from Site-Selective Deuteriation Are Shown; Para- to Ortho- and Para- to Meta-Borylation Ratios Are Reported As Normalized to the Position Multiplicities**

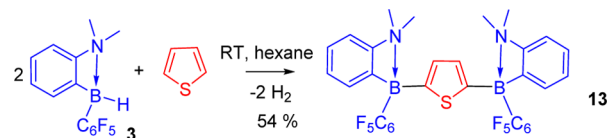


less stable than the reactant state ( $3 + C_6H_6$ ), but the  $H_2$  elimination step is allowed both kinetically and thermodynamically. The overall borylation reaction is predicted to be endergonic, implying that the reaction is unfavored in a closed system, but continuous release of the gaseous  $H_2$  from the solution phase as well as the multiple excess of substrate (i.e., using benzene as the solvent) clearly shifts the equilibrium toward the borylation product.

**Substrate Scope.** With these promising preliminary results in hand, we studied the scope of the C–H borylation with various substrates using several different 2-APBs, though focusing on 3 as the most reactive species studied. This *ansa*-aminoborane reacts with arenes and hetarenes at temperatures from  $-15\text{ }^\circ\text{C}$  (thiophene) to  $100\text{ }^\circ\text{C}$  (bromobenzene), providing the respective triaryl-substituted aminoboranes and  $H_2$ . Because of the extreme sensitivity of the products to protic compounds, particularly to moisture, we were able to characterize only certain compounds (1, 4, 6–10) that formed selectively under the reaction conditions used (Scheme 3). These aminoboranes exist as intramolecular  $N \rightarrow B$  adducts, as verified by their  $^{11}\text{B}$  NMR chemical shifts, which appear in the range 8–20 ppm, with 1-methylindole derivative 10 as an exception (42.0 ppm). The shift in value demonstrates the correlation between the  $N \rightarrow B$  bond strength and the electron-donating or -accepting properties of the aryl substituents. In addition to the monosubstituted compound 8, the product of double borylation of thiophene, 13, could be isolated when an excess of 3 was used (Scheme 4). The structure of 13 was established by the single-crystal X-ray diffraction method (see the Supporting Information for details).

**Regioselectivity of Borylation.** Reactions between 3 and monosubstituted benzenes produced regioisomeric mixtures of aminoboranes. The regioselectivity of the C–H insertion was studied by treating the product mixture with  $CD_3OD$  (Scheme 3, right part). The  $sp^2\text{-C-B}$  bond deuterolysis selectively labels

**Scheme 4. Formation of 13, the Product of Bisborylation of Thiophene by 3**



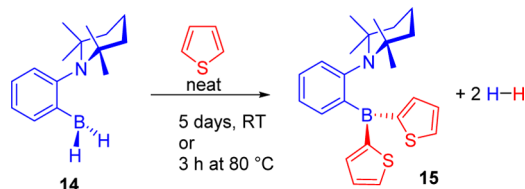
the arene carbon atom with deuterium,<sup>9</sup> as it is the opposite process to C–H insertion. The volatile deuterium-labeled arenes 11 were recondensed under vacuum into a separate vessel and analyzed by  $^2\text{H}$ ,  $^1\text{H}$ , and in some cases  $^{19}\text{F}$  and  $^{13}\text{C}$  NMR spectroscopy. This allowed reliable determination of the regioselectivity of the C–H borylation with high precision (see the Supporting Information for details). The increasing preference for para- over ortho-borylation for fluoro-, chloro-, and bromobenzene and the complete suppression of ortho borylation of *tert*-butylbenzene and anisole demonstrated the pronounced influence of steric effects.

When the electronic effects are taken into account, the observed regioselectivity positions the arene borylation between the classical aromatic electrophilic substitution ( $S_E\text{Ar}$ ) and a random product distribution that to some extent reflects the electrophilic character of the attacking boron species and concerted removal of the proton by the amino group during the  $sp^2\text{-C-H}$  insertion step. High regioselectivities and C–H borylation rates were observed for substrates in which a strong positive mesomeric effect was involved. For example, anisole is borylated more rapidly than benzene with pronounced para selectivity. Electron-rich five-membered hetarenes reacted with 3 even at  $-15\text{ }^\circ\text{C}$ , with exclusive borylation of thiophenes at the  $\alpha$ -positions and *N*-methylindole at the  $\beta$ -position, similar to classical  $S_E\text{Ar}$ . Furthermore, the rates for the C–H borylations of fluoro-, 1,3,5-trifluoro-, and

pentafluorobenzene are comparable to that of benzene. The decrease in the preference for para- over meta-borylation from 4.25 to 1.78 for monohalobenzenes (F > Cl > Br) is consistent with increasing prevalence of inductive over mesomeric effects.<sup>15</sup> Eventually, both *tert*-butylbenzene and toluene produced almost statistic distributions of regioisomeric products of borylation, demonstrating a sharp contrast with classical S<sub>E</sub>Ar substitution, where such substrates usually result in a pronounced ortho/para selectivity. We attributed the exclusive  $\beta$ -borylation of naphthalene to the combination of electronic and steric effects. Deuteration experiments also revealed self-borylation of **3** at the phenylene bridge connecting the reactive N and B centers (see the Supporting Information for details).

**Borylation with 2-TMP-C<sub>6</sub>H<sub>4</sub>BH<sub>2</sub> (14).** Motivated by the goal of establishing general requirements for the powerful sp<sup>2</sup>-C–H borylation reactivity featuring **3** among other FLPs, we explored similar frustrated aminoboranes. First, we reasoned that the Lewis acid–base strength of the active B and N sites has to provide sufficient reactivity for the heterolysis of sp<sup>2</sup>-C–H bonds. Additionally, we suggested that the mutual ortho arrangement of the active sites in **3** facilitates the C–H insertion. The *ansa*-aminoborane **14** reported by us recently is analogous to **3** since this 2-APB is powerful enough to split H<sub>2</sub>,<sup>16</sup> whereas the BH<sub>2</sub> boryl group enables dehydrogenative borylation. On the other hand, the steric surroundings of the reactive centers in **14**, with the bulky tetramethylpiperidino (TMP) group as a Lewis basic center and the smallest possible Lewis acidic BH<sub>2</sub> group, sharply contrast with those in **3**. We found that **14** C–H-borylates thiophene smoothly at room temperature to produce bis(thienyl)aminoborane **15** (Scheme 5). This reaction is stepwise, and the intermediates could be

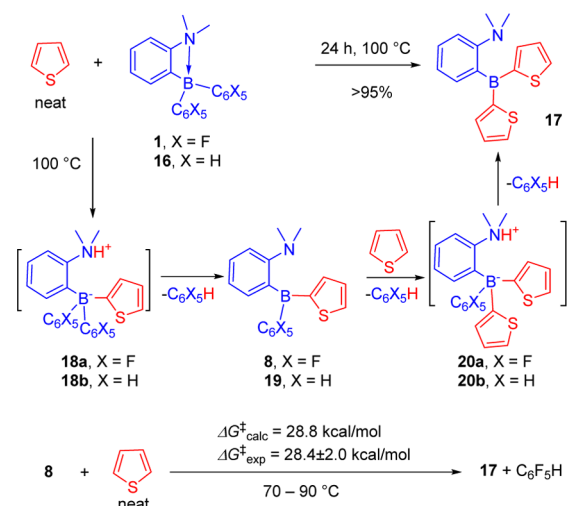
**Scheme 5. C–H Borylation of Thiophene by 14 To Produce Bisborylation Product 15**



detected by NMR spectroscopy (see below for mechanistic studies). These results demonstrate the generality of the 2-APBs' sp<sup>2</sup>-C–H borylation reactivity provided that such 2-APBs are powerful FLPs.

**Interchange of Aryl Groups.** Further exploration of the 2-APBs' C–H borylation reactivities revealed alternatives to the dehydrogenative pathway. The –C<sub>6</sub>F<sub>5</sub> and –C<sub>6</sub>H<sub>5</sub> groups are sp<sup>2</sup> substituents that can easily undergo the protonative B–C bond cleavage, making the interchange of aryl groups feasible. The non-fluorinated compound **16** was prepared analogously to **1** from 2-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>Li and Ph<sub>2</sub>BCl. Upon heating of aminoborane **1** or **16** with thiophene at 100 °C, sequential replacement of both pentafluorophenyl or phenyl groups with thienyls was observed (Scheme 6). Similarly to **3**, aminoboranes **1** and **16** demonstrated high selectivity for  $\alpha$ -borylation of the thiophene core. In the course these two reactions, mixed intermediate aminoborane **8** or **19** was observed by <sup>1</sup>H, <sup>11</sup>B, and <sup>19</sup>F (for **16**) NMR spectroscopy, but no zwitterionic intermediate **18** or **20** could be detected.

**Scheme 6. C–H Borylation of Thiophene with 1 and 16 with Interchange of Aryl Groups**



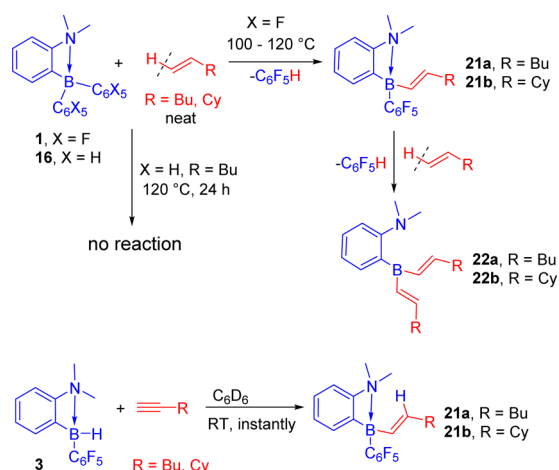
<sup>19</sup>F NMR detection of the characteristic pentafluorophenyl pattern provided a convenient tool for monitoring the conversion of **1** to **17** mediated by **8**. Particularly, we studied the kinetics of the thiophene borylation by **8** (Scheme 6 bottom). A sample of pure **8** in thiophene, prepared through borylation with **3**, was further heated at 70–90 °C, and the consumption of **8** was followed online by <sup>19</sup>F NMR spectroscopy. The extracted kinetic parameters ( $E_a = 19.9 \pm 1.1$  kcal/mol;  $\Delta H^\ddagger = 19.9 \pm 1.1$  kcal/mol;  $\Delta S^\ddagger = -30.9 \pm 3.1$  cal mol<sup>-1</sup> K<sup>-1</sup>;  $\Delta G_{298}^\ddagger = 28.4 \pm 2.0$  kcal/mol) agree well with the results of density functional theory (DFT) calculations for this reaction ( $\Delta G_{298}^\ddagger = 28.8$  kcal/mol). As revealed from the computational analysis, the observed sluggish reaction of thiophene with **1** or **8** compared with **3** can be attributed to the higher steric hindrance of the B center in **1** and **8** (for details, see the Supporting Information).

In addition to aryl interchange in **1**, we found that the borylation by **3** can be diverted along this pathway when the reaction is run in a sealed small-volume vessel. At certain partial pressures of H<sub>2</sub>, the aryl interchange pathway becomes thermodynamically more favored. For example, when **3** was heated with C<sub>6</sub>D<sub>6</sub> or toluene-*d*<sub>8</sub> in a gas-tight NMR tube, a significant amount of C<sub>6</sub>F<sub>5</sub>H was detected by <sup>19</sup>F NMR spectroscopy along with novel B–H species observed in the <sup>1</sup>H NMR spectrum (see the Supporting Information for details).<sup>17</sup>

**Borylation of Olefins.** Olefins represent another major target for sp<sup>2</sup>-C–H functionalization. Previously we reported that facile intramolecular protonation of the B–alkenyl bonds within the 2-(dimethylammonio)phenylborohydride system plays a crucial role in the catalytic hydrogenation of internal alkynes to give *cis*-alkenes.<sup>9</sup> The C–H insertion into the sp<sup>2</sup>-C–H bond of an alkene is the opposite reaction to the protonolysis and should be feasible with 2-APBs, at least kinetically. At the same time, we demonstrated that alkenes are hydroborated by **3** to produce the corresponding alkylboryl derivatives. Therefore, we attempted the interchange of aryl groups with alkenyls (Scheme 7).

Heating **1** with hex-1-ene or vinylcyclohexane at elevated temperatures (100–120 °C) led to the expected C–H borylation via sequential replacement of –C<sub>6</sub>F<sub>5</sub> groups with alkenyls. Interestingly, the fluorine-free aminoborane **16** did not react with hex-1-ene under similar conditions. Borylation did



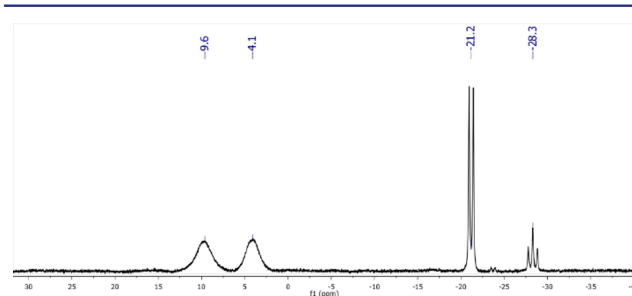
Scheme 7. C–H Borylation of Hex-1-ene and Vinylcyclohexane with **1** with Interchange of Aryl Groups

not stop with monosubstitution, much like the reaction with thiophene, and competitive formation of the bis-substituted products **22** was observed. Therefore, isolation of aminoboranes **21** in pure form was challenging, but at a low conversion level (33% after 24 h at 100 °C) it was possible to isolate **21a** as a 92% pure compound contaminated with 8% **1**. However, the borylation of alkenes, in contrast to thiophene, does not result in solely aminoboranes **22** as the ultimate products. After prolonged heating and complete consumption of **1**, an equilibrium is established between monoinsertion product **21**, alkene, bis-substituted product **22**, and  $C_6F_5H$ . For instance, heating of a 0.46 M solution of **1** in vinylcyclohexane for 36 h at 120 °C resulted in an equilibrium mixture of **21b** and **22b** in the ratio ~60:40.

The C–H borylation of alkenes is exclusively trans-selective, as established by  $^1H$  NMR analysis of the products, deuteration experiments, and independent preparation of aminoboranes **21a** and **21b** via the respective hydroborations of hex-1-yne and cyclohexylacetylene with **3**. Corresponding DFT calculations carried out for the **1** + propene model reaction revealed that trans-borylation is clearly favored both kinetically and

thermodynamically. The observed regioselectivity can be related to the destabilizing steric effects in the species identified along the cis reaction pathway (for details, see the Supporting Information).

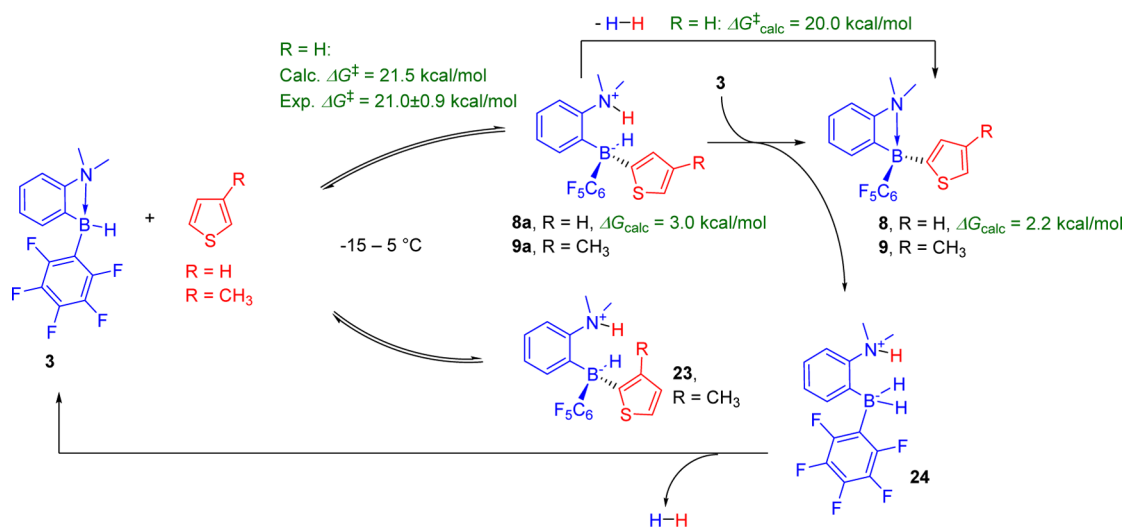
**Mechanistic Studies.** Aminoborane **3** inserts smoothly into the  $\alpha$ -C–H bond of the electron-rich arene thiophene even at  $-15$  °C. The detailed mechanism and kinetics of this reaction were investigated by following the reaction with multinuclear ( $^1H$ ,  $^2H$ ,  $^{11}B$ ,  $^{19}F$ , and  $^{13}C$ ) one- and two-dimensional NMR spectroscopy.<sup>18</sup> In the  $^{11}B$  NMR spectrum, we observed a new doublet resonance at  $-21.2$  ppm that was attributed to the zwitterionic  $\alpha$ -C–H insertion FLP adduct **8a** (Figure 4 and Scheme 8). In addition to **8a**, a new triplet

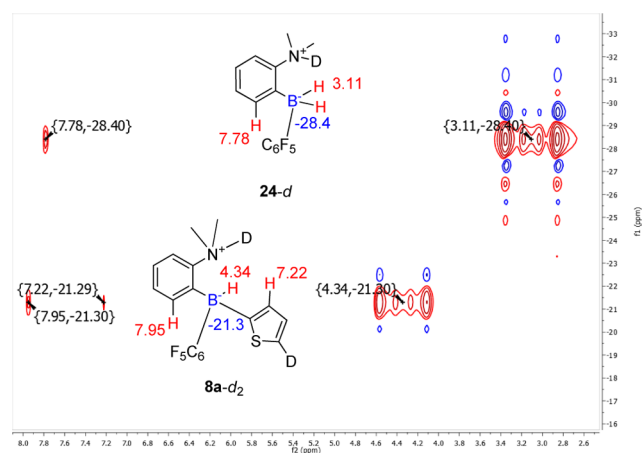


**Figure 4.**  $^{11}B$  NMR spectra for insertion of **3** into thiophene ( $-10$  °C).  $\alpha$ -C–H insertion intermediate **8a** is visible as a doublet at  $-21.2$  ppm; a triplet at  $-28.3$  ppm is attributed to **24**.

resonance observed at  $-28.3$  ppm in the  $^{11}B$  NMR spectrum was attributed to **24**, a dihydrogen adduct of **3**. Also, new signals attributed to intermediates **8a** and **24** were visible in the  $^1H$  and  $^{19}F$  NMR spectra.

To gain deeper insight into the nature of the new resonances in the  $^{11}B$  and  $^1H$  spectra and to provide additional proofs for the structures of **8a** and **24**, we measured a  $^{11}B$ – $^1H$  heteronuclear multiple-quantum coherence (HMQC) spectrum of the reaction between **3** and 2,5-dideuteriothiophene. We observed a long-range correlation (through three bonds) between  $^{11}B$  nuclei and aromatic H atoms located at positions ortho to the B atoms along with intense cross-peaks observed for directly bonded B and H atoms in the partially deuterated

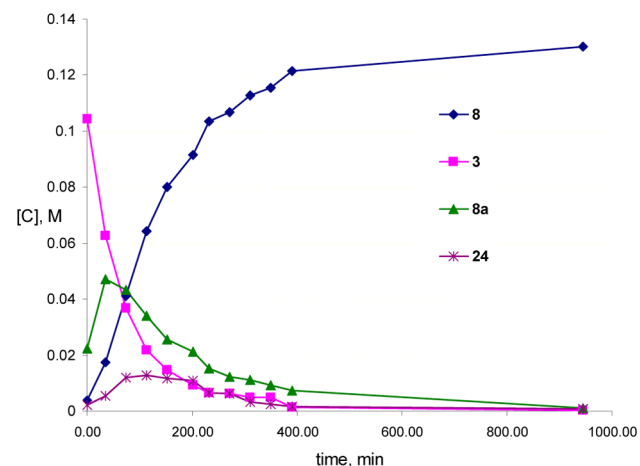
Scheme 8. General Scheme of the C–H Borylation Mechanism of Thiophene and 3-Methylthiophene by **3** at  $-15$  to  $5$  °C; Relative Stabilities and Barriers Are Given with Respect to the Reactant State



**Figure 5.**  $^{11}\text{B}$ – $^1\text{H}$  HMQC spectrum of the reaction between **3** and 2,5-dideuteriothiophene at  $-15\text{ }^\circ\text{C}$  (with suppression of the  $\beta$ -signals of 2,5-dideuteriothiophene in F2). The spectrum demonstrates short-range (through one bond) as well as long-range (through three bonds)  $^{11}\text{B}$ – $^1\text{H}$  couplings in partially deuterated **8a-d<sub>2</sub>** and **24-d**.

intermediates **8a-d<sub>2</sub>** and **24-d** (Figure 5). For the tentative intermediate **8a-d<sub>2</sub>** we observed two long-range cross-peaks revealing the correlation between the B atom and the aromatic signals of the 2-(dimethylamino)phenyl and 5-deuteriothien-2-yl rings.

The reaction between **3** and thiophene was followed using real-time  $^{11}\text{B}$  NMR spectroscopy. Kinetic curves were built for consumption of the starting material **3**, intermediates, and accumulation of **8** (Figure 6). The concentration of **8a** reached

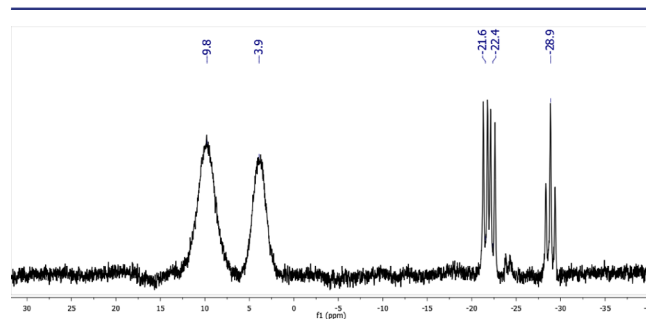


**Figure 6.** Kinetic curves of the starting material, the product and the intermediates for the C–H borylation of thiophene with **3** at  $-10\text{ }^\circ\text{C}$  based on  $^{11}\text{B}$  NMR spectroscopy.

a maximum within 1–2 h and then slowly declined. Interestingly, our observations established that **3** abstracted dihydrogen from **8a**, facilitating its conversion into **8** (Scheme 8). When **3** was reacted with 2,5-dideuteriothiophene, we observed the  $^{11}\text{B}$  NMR signal of **24-d** (Figure 5) as a clear triplet, corresponding to a  $\text{BH}_2$  species. The latter can form as a result of selective and direct B to B hydride and N to N proton (deuteron) transfer from **8a-d<sub>2</sub>** to **3**. The site-selective exchange between **3** and **24** or between **14** and its dihydrogen adduct was evidenced by the presence of the corresponding cross-peaks in the  $^1\text{H}$  NMR exchange spectroscopy (EXSY) spectra.

The rates of  $\alpha$ -C–H insertion of **3** into thiophene were extracted from the kinetic curves for consumption of **3** recorded at temperatures ranging from  $-15$  to  $5\text{ }^\circ\text{C}$ , and the following activation parameters were determined:  $E_a = 11.2 \pm 0.4\text{ kcal/mol}$ ;  $\Delta H^\ddagger = 10.7 \pm 0.4\text{ kcal/mol}$ ;  $\Delta S^\ddagger = -34.8 \pm 1.6\text{ cal mol}^{-1}\text{ K}^{-1}$ ;  $\Delta G_{298}^\ddagger = 21.0 \pm 0.9\text{ kcal/mol}$ . These values are in good agreement with the computed barrier of  $\Delta G_{298}^\ddagger = 21.5\text{ kcal/mol}$  for C–H insertion in the thiophene core. Computations could also account for the observed regioselectivity, since the barrier corresponding to borylation of the  $\beta$ -C–H bond of thiophene was found to be 2.7 kcal/mol higher than that of the  $\alpha$ -C–H borylation (for details, see the Supporting Information).

The borylation of 3-methylthiophene with **3** provided the single product of  $\alpha$ -insertion, **9**, at  $-15\text{ }^\circ\text{C}$ , whereas an  $\sim 1:1$  mixture of two  $\alpha$ -insertion products formed at  $50\text{ }^\circ\text{C}$  (Scheme 3). To shed light on these selectivity issues, we carried out similar mechanistic studies for the reaction between 3-methylthiophene and **3**. Two doublet resonances at  $-21.6$  and  $-22.4$  ppm with very similar intensities were observed by  $^{11}\text{B}$  NMR spectroscopy at  $-5\text{ }^\circ\text{C}$ , and they were attributed to isomeric  $\alpha$ -C–H insertion intermediates **9a** and **23** (Scheme 8 and Figure 7). We suggest that the low-temperature  $\text{H}_2$



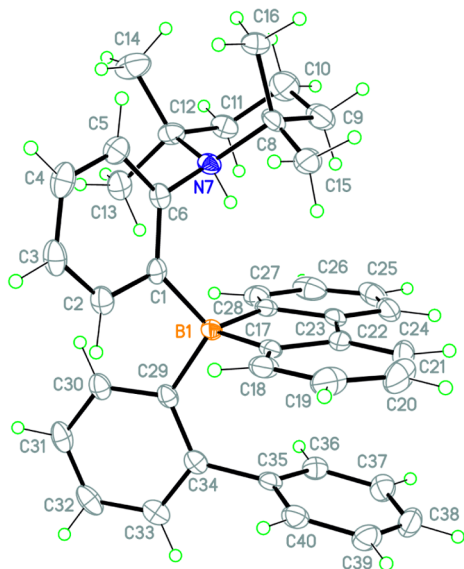
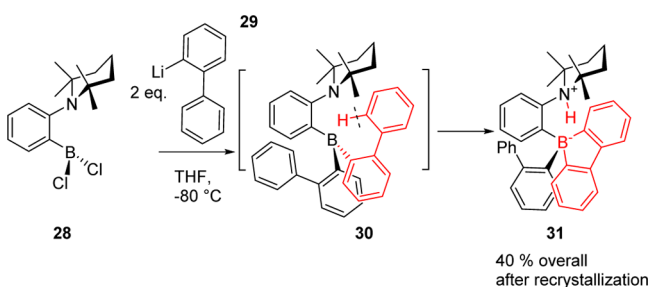
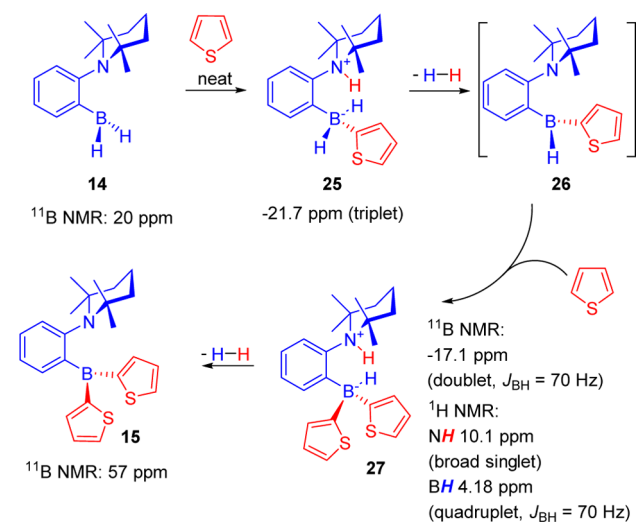
**Figure 7.**  $^{11}\text{B}$  NMR spectra for the insertion of **3** into 3-methylthiophene at  $-5\text{ }^\circ\text{C}$ .  $\alpha$ -C–H insertion intermediates **9a** and **23** are visible as doublets at  $-21$  to  $-23$  ppm; the triplet at  $-28.9$  ppm is attributed to **24**.

elimination process from **9a** is assisted by **3** (see above), whereas  $\text{H}_2$  transfer from **23** to **3** is hindered for steric reasons. The unassisted dehydrogenation of both **9a** and **23** becomes rapid at  $50\text{ }^\circ\text{C}$ , and the C–H insertion becomes the rate-determining step.

The reaction between aminoborane **14** and thiophene (Scheme 9) is interesting because of its relevance to the recently reported catalytic borylation of heteroarenes catalyzed by **14**.<sup>10</sup> Similar reactivity and regioselectivity compared to **3** were observed. We found that in an excess of thiophene, bisthieryl derivative **15** is the ultimate product of the reaction. Besides, by following the reaction with  $^1\text{H}$  and  $^{11}\text{B}$  NMR spectroscopies we detected the intermediates **25** and **27** but found no evidence of monothienylborane **26** (see the Supporting Information for details).<sup>19</sup> These findings provide a valuable addition to the previously proposed mechanism of the catalytic borylation, where only diarylboranes like **26** but not **15**-like ones were considered as possible intermediates.<sup>10</sup>

Further experimental proof that the mechanism of arene borylation goes through an arylborate intermediate was acquired by isolation of compound **31** and determination of its structure by single-crystal X-ray diffraction analysis (Figure 8). Treatment of aminodichloroborane **28** with 2 equiv of 2-

**Scheme 9. Stepwise C–H Borylation of Thiophene with 14; The Formation of Zwitterionic Intermediates 25 and 27 Was Observed by  $^1\text{H}$  and  $^{11}\text{B}$  NMR Spectroscopies**



**Figure 8.** (top) Intramolecular C–H insertion into a 2-biphenyl group of 30 results in the formation of the zwitterionic FLP adduct 31 containing a borafluorene group. (bottom) X-ray structure of 31.

lithiobiphenyl (29) gave compound 31 as the sole product in high yield rather than expected bis(2-biphenyl)borylamine 30. Compound 31 containing a borafluorene unit formed as result of a spontaneous intramolecular C–H insertion of one of the *o*-biphenyl substituents attached to the B atom.

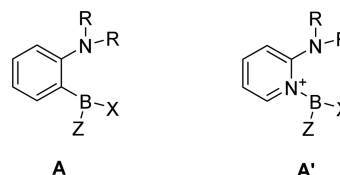
**Catalysis.** With a detailed understanding of the scope and reactivity of 2-APBs, we pursued catalytic implementations.

First, we carried out selective  $\alpha$ -deuteration of the aromatic core in 3-methylthiophene by heating it with a catalytic amount of 3 (6.5 mol %) under 2.2 bar  $\text{D}_2$  at 55  $^\circ\text{C}$  (see the [Supporting Information](#) for details).

Three-coordinate boranes possessing positively charged substituents, known as “borenium cations”, have attracted much interest recently because of their high reactivity. Strong electron-withdrawing properties of the cationic substituents bring high Lewis acidity to such species, and therefore, they show reactivities similar to those of highly Lewis acidic neutrally charged boranes, as exemplified by  $\text{H}_2$  splitting by the borenium cation/*t*-Bu<sub>3</sub>P FLP,<sup>20</sup> by a recent report on trans-hydroboration of alkynes,<sup>21</sup> etc.

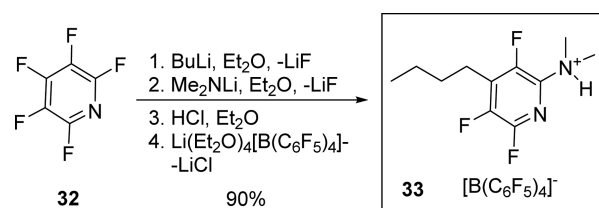
As we concluded above,  $\text{sp}^2\text{-C-H}$  borylation and  $\text{sp}^2\text{-C-B}^-$  protonation is a common reactivity pattern immanent to the frustrated 2-APB core. Isoelectronic or isolobal analogies are commonly used in developing new catalysts, particularly transition-metal-based catalysts. We hypothesized that borenium species A', which is isoelectronic and isostructural to 2-APBs A (Scheme 10), may possess similar C–H-borylating capabilities, significantly extending the concept reported herein, particularly paving the way for catalytic borylation.<sup>22</sup>

**Scheme 10. 2-APBs A and Their Isoelectronic and Isostructural Borenium Cationic Analogues A'**



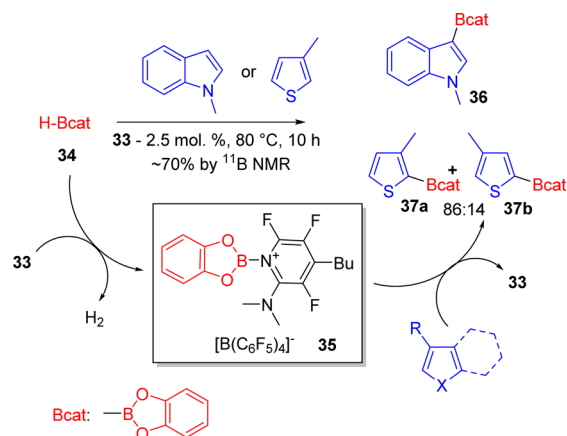
To evaluate this idea, 2-dimethylaminopyridinium salt 33 containing a weakly coordinating  $[\text{B}(\text{C}_6\text{F}_5)_4]^-$  anion was prepared in high yield starting from pentafluoropyridine (32) (Scheme 11). Using this robust air- and moisture-stable

**Scheme 11. Preparation of the Borylation Catalyst 33**



organocatalyst, we carried out the borylation of 3-methylthiophene and *N*-methylindole with catecholborane (34) in  $\sim 70\%$  yield based on NMR analysis of the crude reaction mixtures (Scheme 12). We suggest that the process is mediated by the borenium cation species 35 formed upon reaction between 34 and 33 accompanied by the release of  $\text{H}_2$ . No evidence of decomposition of the catalyst was observed in the course of the reaction. The 2-aminopyridinium system can be potentially promising for catalytic  $\text{sp}^2\text{-C-H}$  borylation of alkenes since the active electrophilic borenium species does not contain B–H moieties and is not able to hydroborate the substrate. Although 34 is a reactive hydroborating reagent, other boranes such as pinacolborane tolerate alkenes. Catalytic studies are underway.

**Scheme 12. C–H Borylation of Hetarenes with Catecholborane (HBcat) Catalyzed by 2-Dimethylaminopyridinium Salt 33 and the Proposed Mechanism**



## CONCLUSIONS

2-Aminophenylboranes (2-APBs, **A** in Scheme 1) easily insert into  $sp^2$ -C–H bonds of arenes, hetarenes, and alkenes, resulting in bond heterolysis and the formation of zwitterionic intermediates (**B** in Scheme 1) detected experimentally and supported by DFT calculations. These C–H insertion intermediates can further decompose with formation of  $sp^2$ -C–H borylation products (**C** in Scheme 1) and  $H_2$ ,  $C_6F_5H$ , or  $C_6H_6$  as byproducts. The C–H borylation reaction is thermodynamically nearly neutral, and in many cases the equilibrium can be shifted by using an excess of the substrate or discharge of  $H_2$  from the reaction. Our previous and present studies demonstrate that the facile  $sp^2$ -C–H insertion of 2-APBs and the easy intramolecular protonation of the  $sp^2$ -C–B bond in the zwitterionic adducts **B** is a common reactivity pattern inherent to 2-APBs. We suggest that the primary factor securing such reactivity is the optimal geometrical arrangement of the amino and boryl groups connected by the rigid phenyl bridge in the ansa system. Importantly, the reactivity is not sensitive to any particular substituents attached to the N and the B atoms, but the Lewis acidity/basicity and the steric balance is crucial. All of the studied 2-APBs that demonstrated borylating reactivity were shown experimentally or computationally to add  $H_2$  reversibly. The reaction is significantly faster with electron-rich arenes, demonstrating domination of electrophilic character for this reaction, but only substituents with a mesomeric effect have a pronounced influence on the reactivity and regioselectivity. We also introduced a conceptually new organocatalytic C–H borylation method that is presumably mediated by borenium species isoelectronic to 2-APBs. With a robust air-stable and moisture-insensitive substituted 2-dimethylaminopyridinium salt as the catalyst, 3-methylthiophene and *N*-methylindole were borylated with catecholborane.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00819. CCDC 1434696 (5), 1434697 (13), and 1434698 (31) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge

Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

Procedures, experimental details, and spectra (PDF)

Crystallographic data for 5, 13, and 31 (CIF)

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

- (1) *Boronic Acids*; Hall, D. G., Ed.; John Wiley & Sons: Hoboken, NJ, 2012; pp 1–133.
- (2) Mkhaldid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.
- (3) (a) Mazzacano, T. J.; Mankad, N. P. *J. Am. Chem. Soc.* **2013**, *135*, 17258. (b) Bose, S. K.; Deißberger, A.; Eichhorn, A.; Steel, P. G.; Lin, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2015**, *54*, 11843. (c) Yan, G.; Jiang, Y.; Kuang, C.; Wang, S.; Liu, H.; Zhang, Y.; Wang, J. *Chem. Commun.* **2010**, 46, 3170. (d) Dombray, T.; Werncke, C. G.; Jiang, S.; Grellier, M.; Vendier, L.; Bontemps, S.; Sortais, J.-B.; Sabo-Etienne, S.; Darcel, C. *J. Am. Chem. Soc.* **2015**, *137*, 4062. (e) Furukawa, T.; Tobisu, M.; Chatani, N. *Chem. Commun.* **2015**, *51*, 6508. (g) Obligation, J. V.; Semproni, S. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 4133.
- (4) Del Grosso, A.; Pritchard, R. G.; Muryn, C. A.; Ingleson, M. J. *Organometallics* **2010**, *29*, 241.
- (5) (a) *Frustrated Lewis Pairs I: Uncovering and Understanding*; Erker, G., Stephan, D. W., Eds.; Topics in Current Chemistry, Vol. 332; Springer: Berlin, 2013. (b) *Frustrated Lewis Pairs II: Expanding the Scope*; Erker, G., Stephan, D. W., Eds.; Topics in Current Chemistry, Vol. 334; Springer: Berlin, 2013. (c) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 6400. (d) Stephan, D. W. *J. Am. Chem. Soc.* **2015**, *137*, 10018. (e) Stephan, D. W. *Acc. Chem. Res.* **2015**, *48*, 306.
- (6) For reviews of FLP-catalyzed hydrogenation, see: (a) Stephan, D. W.; Greenberg, S.; Graham, T. W.; Chase, P.; Hastie, J. J.; Geier, S. J.; Farrell, J. M.; Brown, C. C.; Heiden, Z. M.; Welch, G. C.; Ullrich, M. *Inorg. Chem.* **2011**, *50*, 12338. (b) Stephan, D. W. *Org. Biomol. Chem.* **2012**, *10*, 5740. (c) Paradies, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3552. (d) Hounjet, L. J.; Stephan, D. W. *Org. Process Res. Dev.* **2014**, *18*, 385. For a selection of most recent achievements, see: (e) Tussing, S.; Greb, L.; Tamke, S.; Schirmer, B.; Muhle-Goll, C.; Luy, B.; Paradies, J. *Chem. - Eur. J.* **2015**, *21*, 8056. (f) Lindqvist, M.; Borre, K.; Axenov, K.; Kótai, B.; Nieger, M.; Leskelä, M.; Pápai, I.; Repo, T. *J. Am. Chem. Soc.* **2015**, *137*, 4038. (g) Eisenberger, P.; Bestvater, B. P.; Keske, E. C.; Crudden, C. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 2467. (h) Chatterjee, I.; Oestreich, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 1965. (i) Zhang, Z.; Du, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 623. (j) Gyömöre, Á.; Bakos, M.; Földes, T.; Pápai, I.; Domján, A.; Soós, T. *ACS Catal.* **2015**, *5*, 5366. (k) Scott, D. J.; Simmons, T. R.; Lawrence, E. J.; Wildgoose, G. G.; Fuchter, M. J.; Ashley, A. E. *ACS Catal.* **2015**, *5*, 5540. (l) Zhang, Z.; Du, H. *Org. Lett.* **2015**, *17*, 6266.



(7) (a) Dureen, M. A.; Stephan, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 8396. (b) Jiang, C.; Blacque, O.; Berke, H. *Organometallics* **2010**, *29*, 125. (c) Voss, T.; Mahdi, T.; Otten, E.; Fröhlich, R.; Kehr, G.; Stephan, D. W.; Erker, G. *Organometallics* **2012**, *31*, 2367.

(8) (a) Menard, G.; Stephan, D. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 4409. (b) Menard, G.; Hatnean, J. A.; Cowley, H. J.; Lough, A. J.; Rawson, J. M.; Stephan, D. W. *J. Am. Chem. Soc.* **2013**, *135*, 6446.

(9) Chernichenko, K.; Madarász, Á.; Pápai, I.; Nieger, M.; Leskelä, M.; Repo, T. *Nat. Chem.* **2013**, *5*, 718.

(10) When this article was in preparation, a metal-free C–H borylation of electron-rich hetarenes with pinacolborane was reported. The key step of the reaction is facile insertion into the hetarene core utilizing our recently reported aminoborane **14**. See: Légaré, M. A.; Courtemanche, M. A.; Rochette, É.; Fontaine, F. G. *Science* **2015**, *349*, 513.

(11) Chernichenko, K.; Nieger, M.; Leskela, M.; Repo, T. *Dalton Trans.* **2012**, *41*, 9029.

(12) Reed, C. A.; Fackler, N. L. P.; Kim, K.-C.; Stasko, D.; Evans, D. R.; Boyd, P. D. W.; Rickard, C. E. F. *J. Am. Chem. Soc.* **1999**, *121*, 6314.

(13) Chen, E. Y.-X.; Lancaster, S. J. In *Comprehensive Inorganic Chemistry II*, 2nd ed.; Reedijk, J., Poepelmeier, K., Eds.; Elsevier: Amsterdam, 2013; Vol. 1, pp 707–754.

(14) DFT calculations were carried out using the dispersion-corrected range-separated hybrid  $\omega$ B97X-D functional along with the 6-311G(d,p) basis set as implemented in Gaussian 09. The electronic energies were refined by single-point energy calculations using a larger basis set (6-311++G(3df,3pd)). The SMD continuum model was employed to describe solvation. The reported energies refer to solvent-phase Gibbs free energies. For further details, see the [Supporting Information](#).

(15) We suggest that the para and meta positions in monosubstituted benzenes are unaffected by the steric factors.

(16) Chernichenko, K.; Kótai, B.; Pápai, I.; Zhivonitko, V.; Nieger, M.; Leskelä, M.; Repo, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 1749.

(17) The elimination of  $C_6F_5H$  from reaction intermediate **4a** (indicated in [Figure 2](#)) is predicted to have a considerably higher kinetic barrier than  $H_2$  elimination, but the former process is thermodynamically more favored (for a detailed analysis, see the [Supporting Information](#)).

(18) A sample of **3** was placed in an NMR tube, and thiophene was added via a septum with simultaneous cooling of the tube by liquid nitrogen. After the frozen thiophene was allowed to melt, the contents were homogenized by vigorous shaking, and the tube was placed in the precooled NMR instrument for measurements.

(19) Detection of **26** can be complicated because of overlap of its  $^1H$  and  $^{11}B$  NMR signals with signals of other reaction components and the solvent.

(20) (a) Farrell, J. M.; Hatnean, J. A.; Stephan, D. W. *J. Am. Chem. Soc.* **2012**, *134*, 15728. (b) Farrell, J. M.; Posaratnanathan, R. T.; Stephan, D. W. *Chem. Sci.* **2015**, *6*, 2010.

(21) McGough, J. S.; Butler, S. M.; Cade, I. A.; Ingleson, M. J. *Chem. Sci.* **2016**, DOI: [10.1039/C5SC04798F](https://doi.org/10.1039/C5SC04798F).

(22) Interestingly, in a recent report, 2-(dimethylamino)pyridinium borenium species were shown to react with internal alkynes to produce triple-bond haloborylation products. In contrast to the present work, the 2-dimethylamino group was proposed to play the role of a pendant ligand stabilizing the borenium species. See: Lawson, J. R.; Clark, E. R.; Cade, I. A.; Solomon, S. A.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7518.