Article

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# Metal-Free Borylation of Heteroarenes using Ambiphilic Aminoboranes: On the Importance of Sterics in Frustrated Lewis Pair C-H Bond Activation

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## Abstract

Two novel frustrated Lewis pair (FLP) aminoboranes, (1-Pip-2-$BH_2$-$C_6H_4$)$_2$ (**2**; Pip = piperidyl) and (1-$NEt_2$-2-$BH_2$-$C_6H_4$)$_2$ (**3**; $NEt_2$ = diethylamino), were synthesized and their structural features were elucidated both in solution and in the solid state. The reactivity of these species for the borylation of heteroarenes was investigated and compared to previously reported (1-TMP-2-$BH_2$-$C_6H_4$)$_2$ (**1**; TMP = tetramethylpiperidyl) and (1-$NMe_2$-2-$BH_2$-$C_6H_4$)$_2$ (**4**; $NMe_2$ = dimethylamino). It was shown that **2** and **3** are more active catalysts for the borylation of heteroarenes than the bulkier analogue **1**. Kinetic studies and DFT calculations were performed with **1** and **2** to ascertain the influence of the amino group of this FLP-catalyzed transformation. The C-H activation step was found to be more facile with smaller amines at the expense of a more difficult dissociation of the dimeric species. The bench-stable fluoroborate salts of all catalysts (**1F-4F**) have been synthesized and tested for the borylation reaction. The new precatalysts **2F** and **3F** are showing higher reaction rates and yields for multi-gram scale syntheses.

## Introduction

Arylboronates are ubiquitous reagents in modern synthetic methodologies,[1] notably for the Suzuki-Miyaura coupling reaction.[2] As such, many researchers have been targeting green and cheap strategies to generate these ubiquitous reagents. Of particular interest is the catalytic C-H borylation reaction allowing the preparation arylboronates from readily available arenes and heteroarenes.[3] To this day, the most efficient C-H borylation catalysts use noble metals,[4] but recent advancements have shown that earth-abundant species can also catalyze this challenging transformation.[5] Other synthetic strategies to generate aryl-boron bonds include the electrophilic borylation using stoichiometric[6] or catalytic[7] borenium derivatives and the metal-catalyzed C-X (X = Cl, Br, I) borylation.[8] We also recently introduced a promising approach for the borylation reaction using metal-free frustrated Lewis pairs (FLPs).[9] Repo and coworkers demonstrated that the C-H activation of arenes, the first step in a FLP catalyzed borylation reaction, is a common transformation for ambiphilic aminoborane molecules,[10] suggesting that catalyst design and optimization of this transformation might make this metal-free borylation process more efficient and viable for the preparation of a large range of products.

Since its introduction in 2006 by Douglas Stephan,[11] FLPs have been shown to activate a large range of unreactive substrates and to act as catalysts in several transformations.[12] According to popular perception, a FLP consists of a Lewis acid and base that do not form a Lewis adduct because of steric or geometric congestion. However, several evidences exist that FLP-type transformations can be achieved using Lewis adducts exhibiting no “frustration” at the resting state;[13] such phenomenon has been referred as thermally induced FLPs.[14] For example, Stephan

and Ashley demonstrated that $B(C_6F_5)_3$ can catalyze the hydrogenation of ketones in etheric solvents,[15] even if it is well known that $B(C_6F_5)_3$ forms stable etherate adducts.[16] Several other Lewis adducts have also been involved in what are considered FLP transformations,[17,18] suggesting that such reactivity is not dictated by the absence of Lewis pair formation at the resting state, but rather by the presence of a reactive intermediate or a transition state (TS) where a Lewis pair cooperate for bond activation.[13]

To support this hypothesis, we are interested in investigating the importance of steric hindrance in the borylation of heteroarenes using aminoborane catalysts. Our first report of a catalytic FLP borylation reaction used as catalyst 1-TMP-2-$BH_2$-$C_6H_4$, bearing the sterically hindered 2,2,6,6-tetramethylpiperidine (TMP), and worked according to the mechanism proposed in Figure 1.[9a] This bulky amine has been a versatile Lewis base in FLP-based transformations,[19] but the synthesis of TMP-derivatives is low yielding and relatively expensive. Using smaller and more readily available amines, such as piperidine or diethylamine, could lead to more economical and practical metal-free C-H activation processes. We wish to report here that contrarily to expectations, FLPs with smaller amines generate extremely active catalysts for the metal-free borylation of heteroarenes, surpassing in activity **1** with the bulkier TMP derivative, even if these species exist as stable Lewis adducts. Kinetic and computational studies were carried out to better understand the reasons for such difference in activity.

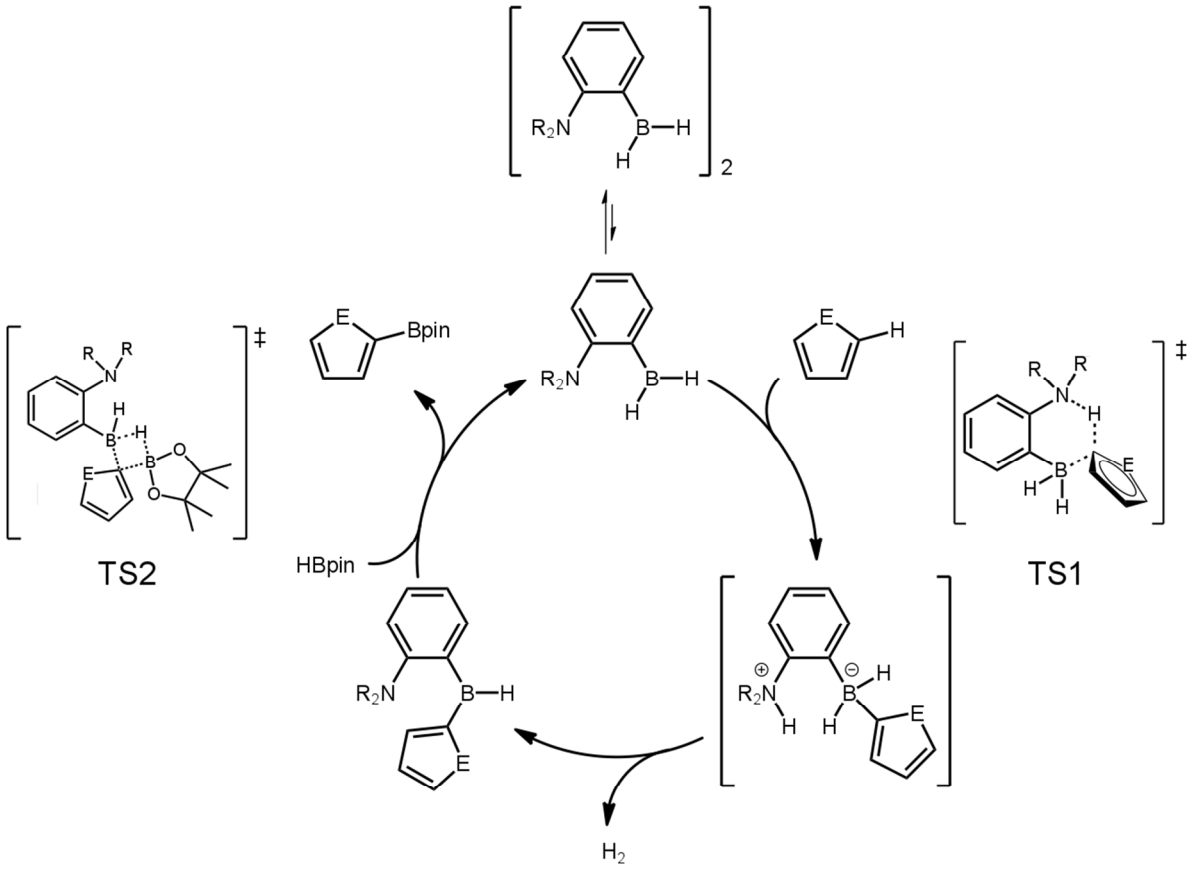
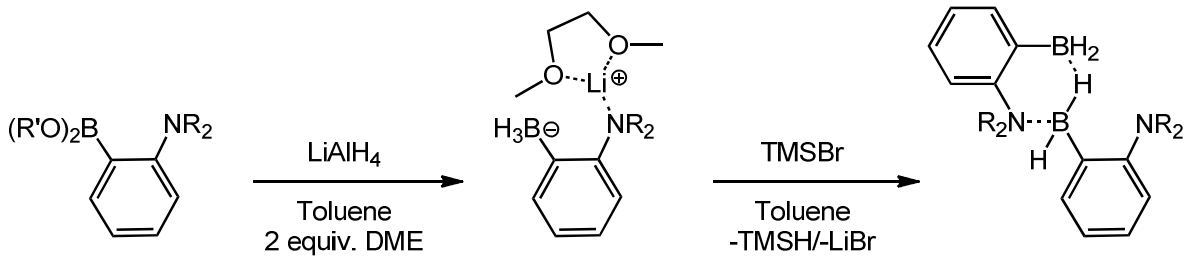



**Figure 1.** Proposed mechanism for the borylation of heteroarenes using aminoborane catalysts. Pin = pinacol, E = S, O, NR.

**Synthesis and characterization of ambiphilic aminoboranes**

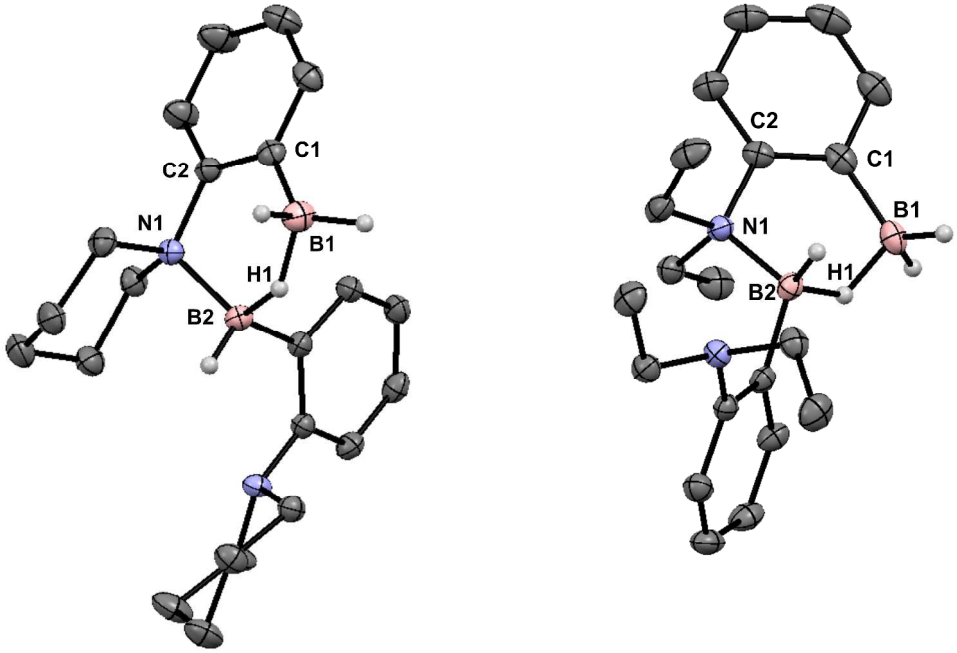
While the synthesis of (1-TMP-2-$BH_2$-$C_6H_4$)$_2$ (**1**)[19d] and (1-$NMe_2$-2-$BH_2$-$C_6H_4$)$_2$ (**4**)[18,20] was previously reported, (1-Pip-2-$BH_2$-$C_6H_4$)$_2$ (**2**) and (1-$NEt_2$-2-$BH_2$-$C_6H_4$)$_2$ (**3**) were prepared following a protocol illustrated in Scheme 1.[21] In a typical synthesis, 1.3 equiv of $LiAlH_4$ were added to the corresponding boronic acid or boronate ester to generate the lithium borohydride salt. The electrophilic abstraction of the hydride was possible by adding 1.1 equiv of TMSBr in toluene, affording the desired products **2** and **3** in 79 and 50 % yield, respectively. It was possible

to isolate quality crystals of **2** and **3**, allowing their X-ray structural characterization. The ORTEP representations are illustrated in Figure 2. As previously observed and reported for **4**,[18] these species adopt a dimer where one B-H bond is activated by the B-N FLP of another molecule, forming a six-membered ring. No significant deviation in the bond lengths was observed between species **2**-**4**, although the B2-H1-B1 angle and the B1-B2 distance for **2** (136(1)° and 2.358(2) Å) are slightly different than for **3** (123.8(9)° and 2.275(3) Å) and **4** (123(1)° and 2.255(3) Å).




**Scheme 1**. Synthesis of aminoborane species **2** ($NR_2$ = piperidyl; R' = Me) and **3** ($NR_2$ = $NEt_2$; R' = H).

Supporting the solid state structures, the $^{11}B\{^1H\}$ NMR spectra of species **2**-**4** at ambient temperature show the presence of two distinct boron resonances in solution (0.5 and -7.7 ppm for **2**; 1.0 and -10.7 ppm for **3**; 3.3 and -10.4 ppm for **4**). In the $^1H$ NMR spectra, broad signals for the hydrides are observed at 4.0 and -0.95 ppm for **2** and at -0.69 for **3**.

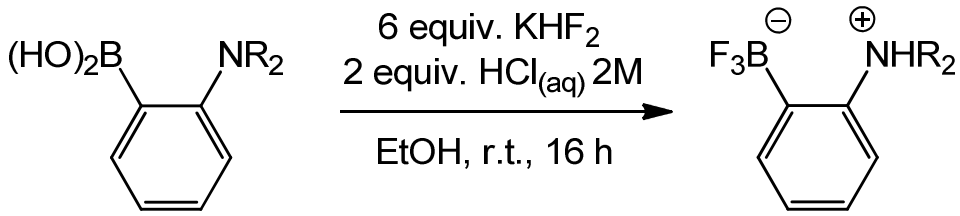



**2** **3**

**Figure 2.** ORTEP representation of compounds **2** and **3**. Ellipsoids are drawn at 50% probability. Hydrogen atoms linked to the carbon atoms are omitted for clarity. Hydrogen (white), carbon (black), nitrogen (blue) and boron (pink). Selected bond lengths [Å] and angles [°] for **2** : N1-B2 1.633(1), B2-H1 1.26(1), B1-H1 1.29(2), B1-C1 1.585(2), C1-C2 1.391(1), C2-N1 1.496(1), N1-B2-H1 109.0(7), B2-H1-B1 136(1), H1-B1-C1 109.3(7), B1-C1-C2 121.0(1), C1-C2-N1 115.1(1), C2-N1-B2 110.31(8); for **3**: N1-B2 1.628(1), B2-H1 1.29(1), B1-H1 1.29(1), B1-C1 1.586(2), C1-C2 1.388(2), C2-N1 1.490(2), N1-B2-H1 105.0(5), B2-H1-B1 123.8(9), H1-B1-C1 107.5(5), B1-C1-C2 122.7(1), C1-C2-N1 116.8(1), C2-N1-B2 109.82(9).

The synthesis of the fluoroborate salts of catalysts **1-4** (**1F-4F**), which are bench-stable borylation precatalysts, was achieved by following the synthetic protocol reported for 1-TMP(H)-2-$BF_3$-$C_6H_4$ (**1F**).[9b,22] The addition of $KHF_2$ to the aminoboronic acid derivatives yielded species **2F** and **3F** in 81% and 85% yield, respectively (Scheme 2). All the $BF_3$ salts were

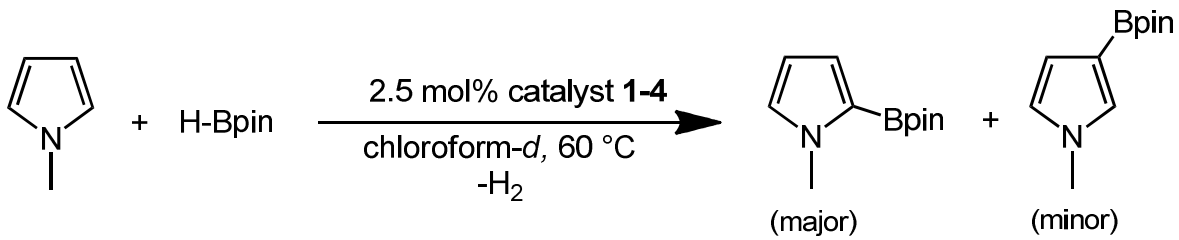
fully characterized by NMR spectroscopy ($^{1}H$, $^{13}C\{^{1}H\}$, $^{11}B$ and $^{19}F$), elemental analysis, and X-ray crystallography, and are typical of such compounds (see ESI).




**Scheme 2.** Synthesis of trifluoroborate precatalysts **2F** ($NR_2$ = piperidyl), **3F** ($NR_2$ = $NEt_2$), and **4F** ($NR_2$ = $NMe_2$).

**Borylation catalysis**

The catalytic activity for the borylation of 1-methylpyrrole using species **2-4** was monitored and compared to that of already reported catalyst **1**.[9a] The experiments were carried out at 60 °C in a J-Young NMR tube using chloroform-*d* as solvent, hexamethylbenzene as internal standard and a catalyst loading of 2.5 mol% (Scheme 3). As seen in Figure 3, a significant difference in the consumption rate of 1-methylpyrrole and production of 1-Me-2-Bpin-pyrrole was observed between all catalysts. Whereas **1** did show about 25% conversion after one hour, as previously reported,[9a] over 50% conversion in 25 minutes was observed with **3**. The piperidine analogue was the most active of all catalysts examined, with over 75% conversion in just 20 minutes, which is about 15 times more active than bulkier FLP **1**. The dimethyl analogue **4** presented the lowest catalytic activity of the four species investigated.



**Scheme 3.** Borylation of 1-methylpyrrole with FLP catalysts **1-4**

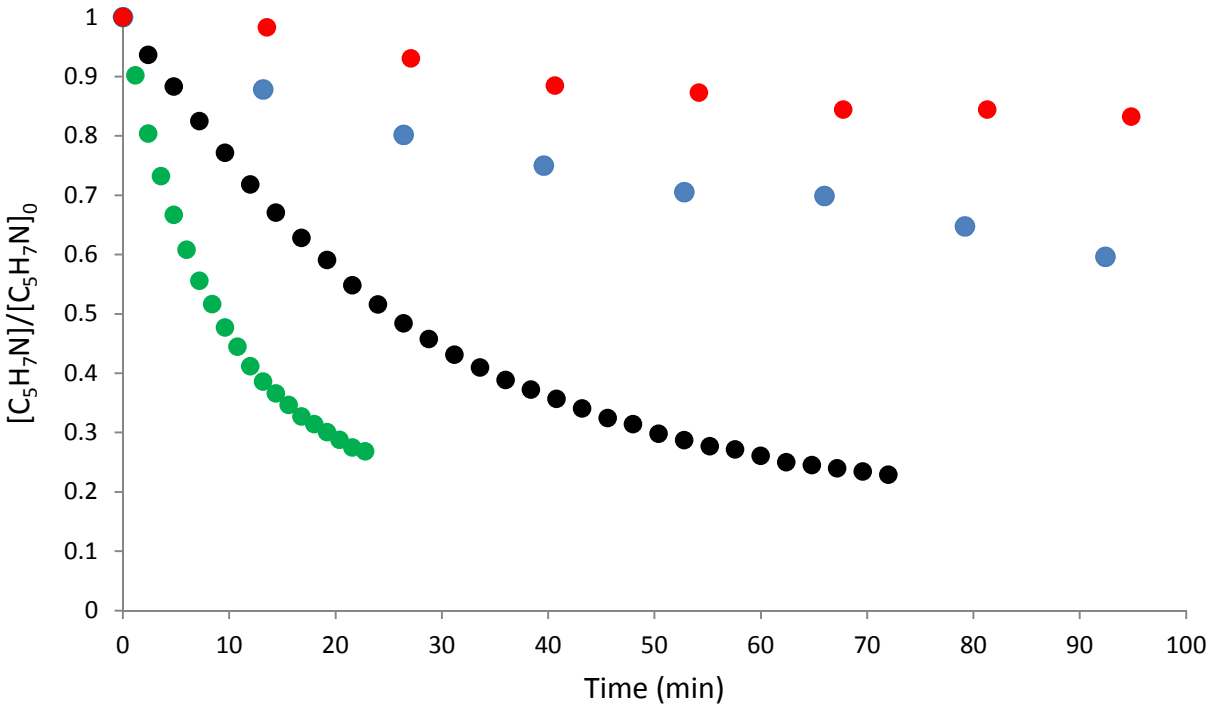
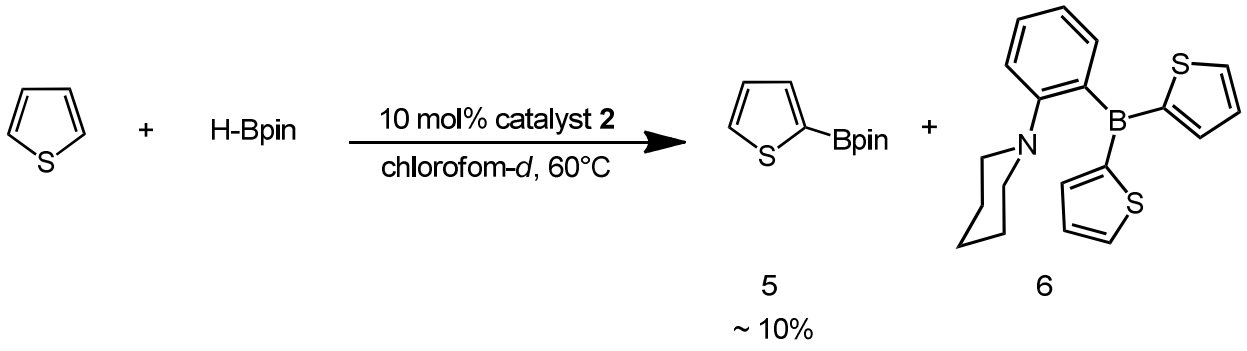



**Figure 3.** Consumption of 1-methylpyrrole ($[C_5H_7N]/[C_5H_7N]_0$) upon the borylation reaction catalyzed by **1** (blue), **2** (green), **3** (black), and **4** (red).

The catalytic borylation of thiophene was also tested and no significant formation of the expected 2-Bpin-thiophene (**5**) was observed for all catalysts, as previously observed for **1**, although approximately 10% conversion was noticed by using catalyst **2**. The analysis of the reaction mixture allowed us to observe the formation of the bis-arylation product 1-Pip-2-B(thiophenyl)$_2$-$C_6H_4$ (**6**) (Scheme 4) as previously reported by Repo when studying the reaction of **1** in neat thiophene.[10] No reactivity was observed when compound **6** was generated

independently and HBpin was added (TS2, Figure 1), suggesting that the absence of metathesis once analogues of **6** are generated is causing the inhibition of catalytic activity in the borylation of pristine thiophene by aminoborane catalysts.

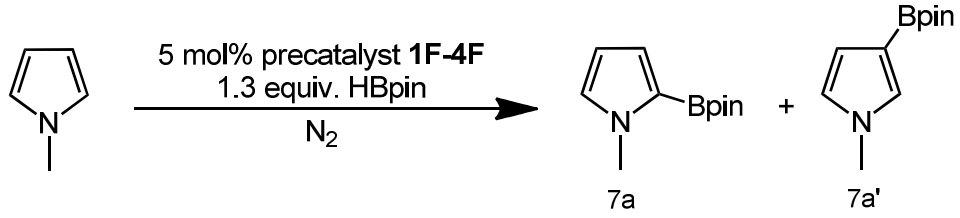



**Scheme 4.** Borylation of thiophene using catalyst **2.**

We recently reported that the fluoride-protected FLP 1-TMP(H)-2-$BF_3$-$C_6H_4$ (**1F**) was an active precatalyst under typical catalytic conditions, *i.e.* in presence of excess HBpin, since little change in yield and activity, other than an induction period for the deprotection step, was observed between **1** and **1F**.[9b] Based on the concomitant generation of FBpin, it was proposed that **1F** generates borohydride **1** under catalytic conditions. Since these bench-stable precatalysts allow for a simplified and practical protocol, a catalytic screening was done using all fluorinated analogues (**1F-4F**). First, 1-methylpyrrole was borylated using 1.3 equiv of HBpin in the presence of 5 mol% of precatalysts **1F-4F** in chloroform-*d* at 80 °C, yielding after 16 hours 2-Bpin-1-methylpyrrole (**7a**) as main species with conversions of 97, 94, 91 and 31%, respectively (Table 1). Although **1F-3F** all gave similar conversion after 16 hours, the activity of **1F** after 4 hours (7%) is significantly lower when compared with **2F** and **3F** (64 and 63%, respectively), suggesting that the induction period is shorter with the smaller FLPs. In an effort to circumvent the use of chlorinated solvents, toluene, THF, and 2-Me-THF were also tested, all giving similar

activities. However, a significant increase in activity and conversion was observed under solvent-free conditions. For example, 57% conversion of the 1-methylpyrrole to generate **7a** was observed with the TMP precatalyst **1F** in two hours while no conversion was monitored in chloroform in the same period. Another significant feature is the increase in selectivity under these new catalytic conditions. Whereas the borylation of 1-methylpyrrole in chloroform gave a 88:12 selectivity for the 2- to 3-position, respectively, under neat conditions the selectivity was found to be 95:5. The increase in selectivity is even more pronounced using the piperidine anologue **2F** where a 98:2 ratio of **7a** to **7a'** was found under neat conditions.

**Table 1**. Catalytic borylation of 1-methylpyrrole in different conditions using precatalysts **1F-4F**.



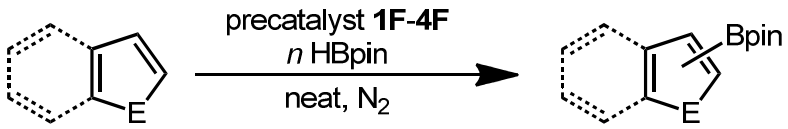

| Solvent | Time (h) | 1F | 2F | 3F | 4F |
|---|---|---|---|---|---|
| $CDCl_3$ | 4 | 7 (86:14) | 64 (98:2) | 63 (98:2) | 3 (100:0) |
| | 16 | 97 (88:12) | 94 (98:2) | 91 (98:2) | 31 (100:0) |
| Toluene | 16 | 91 (89:11) | 93 (98:2) | 90 (98:2) | 34 (100:0) |
| 2-Me-THF | 16 | 95 (90:10) | 95 (98:2) | 90 (98:2) | 33 (100:0) |
| THF | 16 | 93 (88:12) | 93 (98:2) | 92 (99:1) | 39 (100:0) |
| Neat | 1 | 41 (95:5) | 80 (99:1) | 75 (99:1) | 9 (100:0) |
| | 2 | 57 (95:5) | 97 (98:2) | 96 (98:2) | 23 (100:0) |

In parenthesis C2:C3 regioselectivity

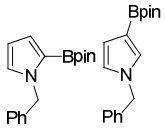
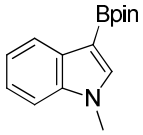
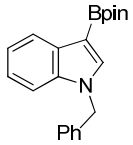
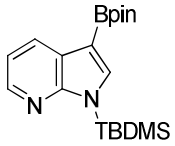
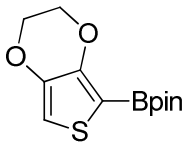
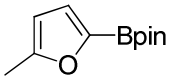
Precatalysts **1F-4F** were also tested with additional substrates under neat conditions, as shown in Table 2. Similarly to the results observed with 1-methylpyrrole, the borylation of 1-Bn-

pyrrole was facilitated using piperidine analogue **2F**, obtaining over 90% conversion to 1-Bn-2-Bpin-pyrrole in 6 hours. 65% conversion was observed for **3F** and only traces of the desired product (2 %) was observed with **1F**. A similar trend was also observed with 1-Me- and 1-Bn-indole, where **2F** gave the highest efficiency of all precatalysts tested, reaching up to 96 and 89 % conversions, respectively. Unfortunately, our attempts to borylate 1-Me-7-aza-indole were not successful, likely due to the coordinative N-B interaction between the active catalyst **1** and the pyridine functionality of 1-Me-7-aza-indole. As expected, bulkier protecting groups on the indole, such as in 1-TBDMS-7-aza-indole, allows the borylation at the 3-position with 82 % conversion (62 % isolated yield) with precatalyst **2F** (100 ºC for 48 hours). The synthesis of 2-Me-5-Bpin-furan was also possible using catalysts **1F**-**3F** with conversions over 90 %. Precatalyst **4F** once again proved to be the worst catalyst, with only 34 % conversion. Interestingly, only for the borylation of EDOT did **1F** prove to be a better catalyst than **2F** and **3F** (96, 31, and 18 % conversion, respectively). It is logical to assume that the second C-H activation of EDOT, which is expected to shut down catalytic activity with all catalysts (*vide supra*), might be more difficult with the bulkier TMP analogue **1F**. To demonstrate the synthetic viability and reproducibility of these protocols, all the borylated products were synthesized on a 2 g scale in good to excellent yields using the best catalyst for each system, although some of the borylation products are sensitive to silica gel complicating the purification procedure.

**Table 2**. Results of screening the precatalysts with some representative heteroarenes




E = N-R[1] (Me, Bn), O, S

| Entry | Product | Precatalyst (mol%) | *n* | Temp. (°C) | Time (h) | Conversion (%)[a] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | **1F** | **2F** | **3F** | **4F** |
| 1 |  **7b 7b'** | (15) | 2 | 80 | 6 | 2 (0)[b] | 91(0)[b] {76}[c] | 65 (0)[b] | 0 |
| 2 |  **7c** | (10) | 2 | 80 | 6 | 63 | 96 {80}[c] | 87 | 10 |
| 3 |  **7d** | (20) | 2.6 | 100 | 8 | 82 | 89 {67}[c] | 82 | 29 |
| 4 |  **7e** | (20) | 3 | 100 | 48 | 46 | 82 {62}[c] | 76 | 24 |
| 5 |  **7f** | (10)[d] | 0.87 | 80 | 6 | 96 {85}[c] | 31 | 18 | 3 |
| 6 |  **7g** | (10)[d] | 0.8 | 80 | 16 | 92 | 96 {77}[c] | 90 | 34 |

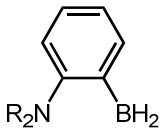
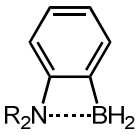
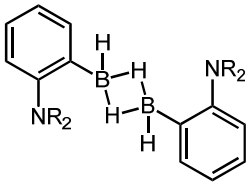
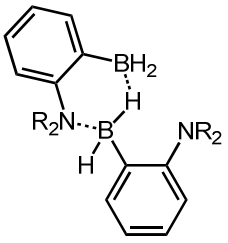
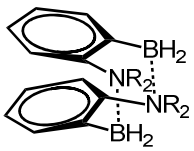
[a] Determined by $^1$H NMR spectroscopy using hexamethylbenzene as an internal standard. [b] Percentage of the minor C3-regioisomer. [c] Isolated yield based on the 2 gram-scale reactions [d]

Catalyst loading corresponds to the amount of HBpin left after subtracting the required amount to generate the $BH_2$ catalyst.

**Mechanistic investigation of the C-H activation**

As observed in the crystallographic studies and in solution, catalysts **1**-**4** are stable dimeric species. Dissociation has to take place in order to generate the FLP intermediate performing the C-H activation step. In addition to the FLP "opened" geometry (Table 3, A), 1-$NR_2$-2$BR'_2$-$C_6H_4$ species can adopt a favourable "closed" geometry (Table 3, B) where an intramolecular B-N interaction is present. The latter isomer was structurally characterized with some examples of aminoboranes bearing a highly Lewis acidic moiety.[17a,23] Three different structures have also been reported for aminoborane dimeric species: a "3-centre-2-electron" interaction such as in **1** (Table 3, C),[19d] a B-H bridged dimer as in **2-4** (Table 3, D),[18] and an eight-membered ring where two B-N interactions are present, which was reported as a minor isomer of **4** (Table 3, E).[9b,18] DFT calculations on all isomers of reported catalysts (Table 3) confirm that the solid-state structures observed are the lowest in energy for species **1**-**4**.

**Table 3.** Stability of the various conformations of aminoborane species **1-4**

| |  Open, **Active FLP** **A** |  Closed B |  Trans dimer C |  B-H bridged dimer D |  Eight-membered ring dimer E |
|---|---|---|---|---|---|
| | $\Delta G^o$ (kcal/mol) | | | | |
| **1** | 7.1 | 5.4 | 0.0 | 15.9 | 47.1 |
| **2** | 9.6 | 1.4 | 4.0 | 0.0 | 3.9 |

| | | | | | |
|---|---|---|---|---|---|
| **3** | 10.7 | 6.2 | 5.7 | 0.0 | 6.6 |
| **4** | 10.6 | 4.1 | 6.1 | 0.0 | 1.2 |

Level of theory : ωB97XD/6-31+G** (SMD, chloroform)

Although the exact value for the dissociation of dimeric **1** has never been measured, it was presumed to be in the higher range of the 11-14 kcal mol$^{-1}$ value.[19d] Dimeric species with smaller amines are expected to generate more stable adducts since both B-H and B-N interactions need to be broken before generating the monomeric species. Using DFT, free energies of 20.7 and 23.3 kcal mol$^{-1}$ were found for breaking the B-H bond of the dimers **2** and **4**, respectively, which is thought to be the limiting step in the dissociation process. Because of the asymmetry in their dimeric structure, NMR spin saturation transfer experiments can be conducted to determine the energy required for scrambling both moieties. The cleavage of both the B-H and the B-N bonds is required for this process to take place and this value should be close to the energy required to generate the FLP intermediate.

When irradiating selectively the doublet of **2** at $\delta_1$ = 7.565, we observed saturation of the signal at $\delta_2$ = 6.866, the corresponding proton on the other aromatic ring of the dimer, suggesting that scrambling is taking place between the two aminoboranes moieties. Using a method developed by Muñoz and co-workers,[24] the difference in the integration of $\delta_2$ with and without saturation divided by the integration of $\delta_1$ without saturation ($\eta_{SSTD} = \frac{\int \delta_2 - \int \delta_2^*}{\int \delta_1}$) was obtained for each saturation time and plotted in an exponential curve to determine the rate constants ($k$) of the scrambling according to the following equation:

$$\eta_{SSTD}(t) = \frac{k}{(1/T_{1A} + k)}(1 - \exp(-(1/T_{1A} + k) \cdot t))$$

The NMR experiments were performed at 60, 57, 54 and 51 °C and the rate constants were plotted according to the Eyring equation (see ESI). Using these results, we obtained a $\Delta G^{\ddagger}$ of 20.5 ± 3.1 kcal.mol$^{-1}$, which correlates with the energy barrier found computationally. Unfortunately, it was not possible to determine the energy required for breaking the dimeric species **4** because of the equilibrium between the B-H bridged dimer and the eight-membered ring dimer (D and E, respectively, Table 3), and the degradation of **4** into diborane species upon heating.[18] Nonetheless, the latter decomposition process and the stability of the dimer can rationalize the lower catalytic activity of catalyst **4**.

Energies of all intermediates and transition states for the proposed C-H bond activation mechanism (Figure 1) were located by DFT and are represented in Figure 6 for 1-Me-pyrrole and Figure 7 for thiophene. To support this mechanism, the consumption of the aminoborane was monitored using $^{11}B\{^{1}H\}$ NMR spectroscopy. In a typical experiment, a large excess of either 1-methylpyrrole or thiophene (775, 1550, or 3100 μM) was added to a known concentration of the aminoborane **1** and **2** (38.8, 77.5, or 155 μM) in chloroform-*d*. A glass capillary containing HBpin was inserted in a quartz NMR tube as external standard. The rate of disappearance of the starting material observed by NMR spectroscopy was compared to kinetic simulations using the energies found computationally (Figures 4-5). It is important to note that this method allows observing the impact of reagent concentration on rate, therefore allowing observing the trends in consumption rather than the exact values. It cannot give a reliable time scale because of the difficulty to find the pre-exponential factor by only knowing the TS of a transformation (see ESI for detailed explanations).

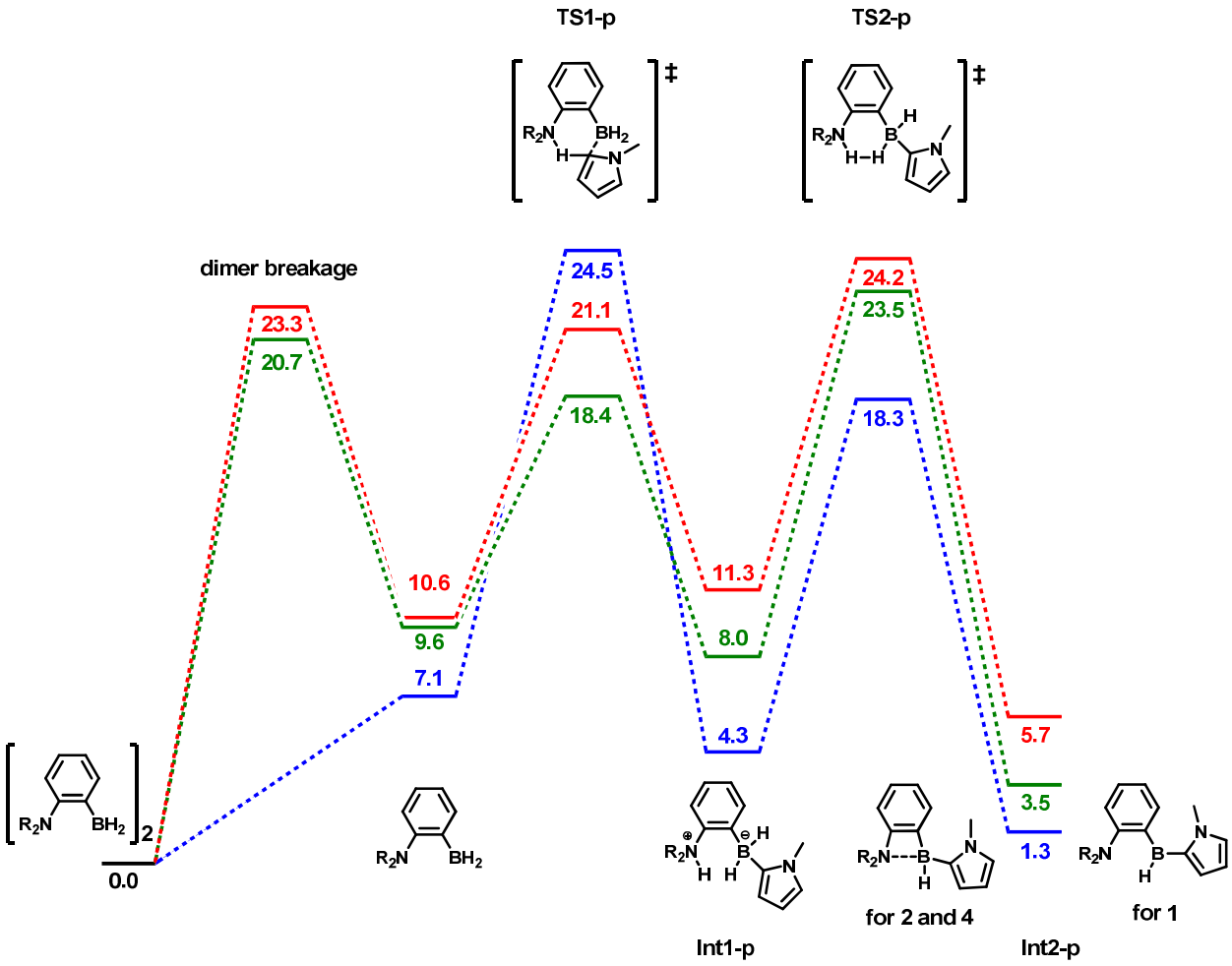



**Figure 4.** Free energies in kcal $mol^{-1}$ for the C-H activation of 1-methylpyrrole with aminoboranes **1** (**Blue**), **2** (**Green**), and **4** (**Red**) calculated at DFT/ωB97XD/6-31+G** (SMD, chloroform) level of theory.

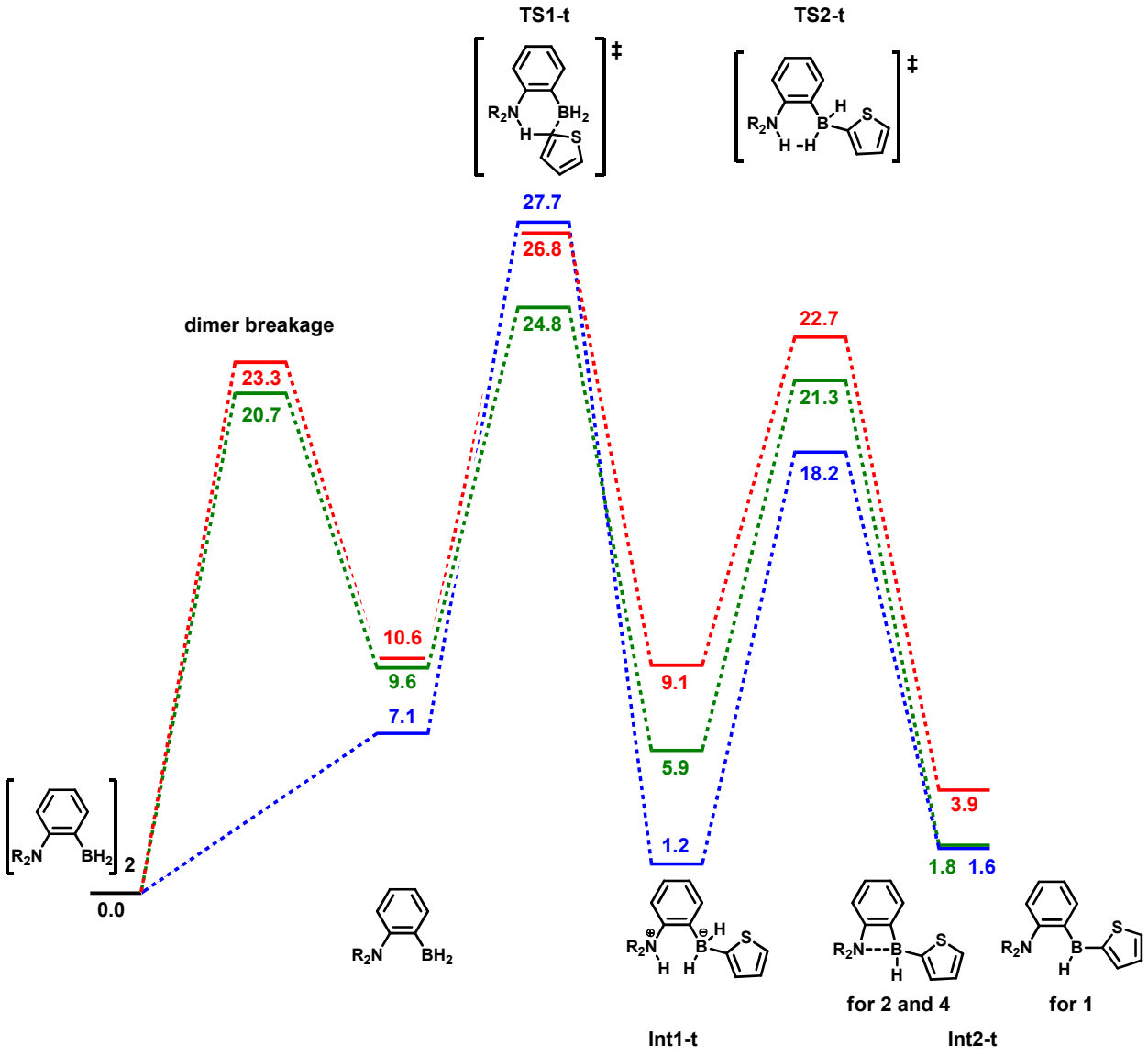



**Figure 5.** Free energies in kcal mol$^{-1}$ for the C-H activation of thiophene with aminoboranes **1** (**Blue**), **2** (**Green**), and **4** (**Red**) calculated at DFT/ωB97XD/6-31+G** (SMD, chloroform) level of theory.

As demonstrated previously by kinetic isotope effect studies, the rate-limiting step in the C-H activation of 1-methylpyrrole using bulky FLP **1** is the concerted C-H activation having an energy barrier of 24.5 kcal mol$^{-1}$.[9a] The energy required to reach this TS can be broken down in the energy required to access the "opened" form (7.1 kcal mol$^{-1}$) and to cleave the C–H bond

(17.4 kcal $mol^{-1}$). The subsequent loss of $H_2$ is easier with a barrier of 18.3 kcal $mol^{-1}$. As expected for such a mechanism, the rate of consumption of **1** is first-order in substrate. With a concentration of 77.5 μM of **1** and of 775 μM of 1-methylpyrrole at 40 °C, half of the starting material is consumed within 35 minutes, whereas increasing the concentration of pyrrole to 3100 μM increased the rate by a factor of 3.5 (Figure 6A). As seen in Figure 6A', these data correlate well with the simulated rates using the energies found by DFT, supporting the proposed mechanism.

As explained above, the absence of catalytic activity in the borylation of thiophene is not related to the absence of C-H activation owing to the fact that the barrier of 27.7 kcal.$mol^{-1}$ for such process is thermally accessible. Accordingly, it takes approximately 300 min for half of **1** to be consumed using 20 equiv of thiophene when heated at 60 °C (Figure 6B). However, a striking feature of this bond activation is the increase in the consumption rate of **1** as reaction goes along rather than the expected logarithmic decay for a pseudo-first order reaction. Although we are not able to propose a precise explanation for this behavior, it suggests that another side reaction is taking place at the later stage of the process that is consuming **1**. Interestingly, it was observed that increasing the concentration of dimer **1** with a fixed concentration of the substrate led to a slower rate of consumption of **1** for 1-methylpyrrole, as illustrated in Figure 7C. Once again, such behavior is supported by kinetic simulations and is related to the presence of an equilibrium favoring the formation of a dimeric species, which reduces the concentration of the "opened" form relative to the dimeric species at higher concentrations. In the case of thiophene, the mismatch between the experimental and simulated values once again presume the presence of an unidentified side reaction (Figure 7D).

Catalyst **2** follows a similar mechanism as **1** for 1-methylpyrrole activation (Figure 5), but the energies differ drastically from those observed for **1**. The most striking feature is the C-H activation step reduced by about 6 kcal $mol^{-1}$, with a TS at 18.4 kcal $mol^{-1}$, even if the active FLP intermediate for the smaller catalyst lies higher in energy (9.6 kcal $mol^{-1}$) when compared with **1** (7.1 kcal $mol^{-1}$). Accounting only for the energy required to cleave the C–H bond from the active FLP intermediate, the smaller analogue **2** requires only 8-9 kcal $mol^{-1}$ compared to the 17 kcal $mol^{-1}$ required by **1**, firmly suggesting that reducing the steric bulk of the FLP leads to a more active catalyst. It is logical to assume that with less steric hindrance, the Lewis pair is more accessible for incoming substrates. However, the energy cost for the extrusion of $H_2$ is more important in **2** requiring 23.5 kcal $mol^{-1}$. It should be noted that such an increase is a consequence of the relatively lower stability of the zwitterionic intermediate **2-Int1p**, which is located at 8.0 kcal $mol^{-1}$ rather than 4.3 kcal $mol^{-1}$ for **1-Int1p.** By normalizing these values for **1**, **2**, and **4**, it was found that all zwitterionic intermediates require approximately 12-15 kcal $mol^{-1}$ to release $H_2$. Notwithstanding, none of these barriers exceed the energy required to dissociate the dimer with 1-methylpyrrole. This behavior is supported experimentally since there is no influence of pyrrole concentration on the C-H activation rate, as illustrated in Figure 8E. Indeed, half of **2** was consumed within 10 minutes when varying the concentration of 1-methylpyrrole from 775 μM to 3100 μM. However, the C-H activation of thiophene is more challenging by about 6 kcal $mol^{-1}$ and is now rate determining; the reaction rates are again affected by thiophene concentration (Figure 8F). All these experimental values are in line with the simulated kinetic data observed when inputting the energies located by DFT (Figures 8-9).

Energies of each step of the mechanism proposed in Figure 1, including the possible additional C-H activation of a substrate, are illustrated in Figures S50-S53 of the supporting information.

The energies found for the metathesis step are all in accordance with our original report and was previously discussed in more detail.[20b]

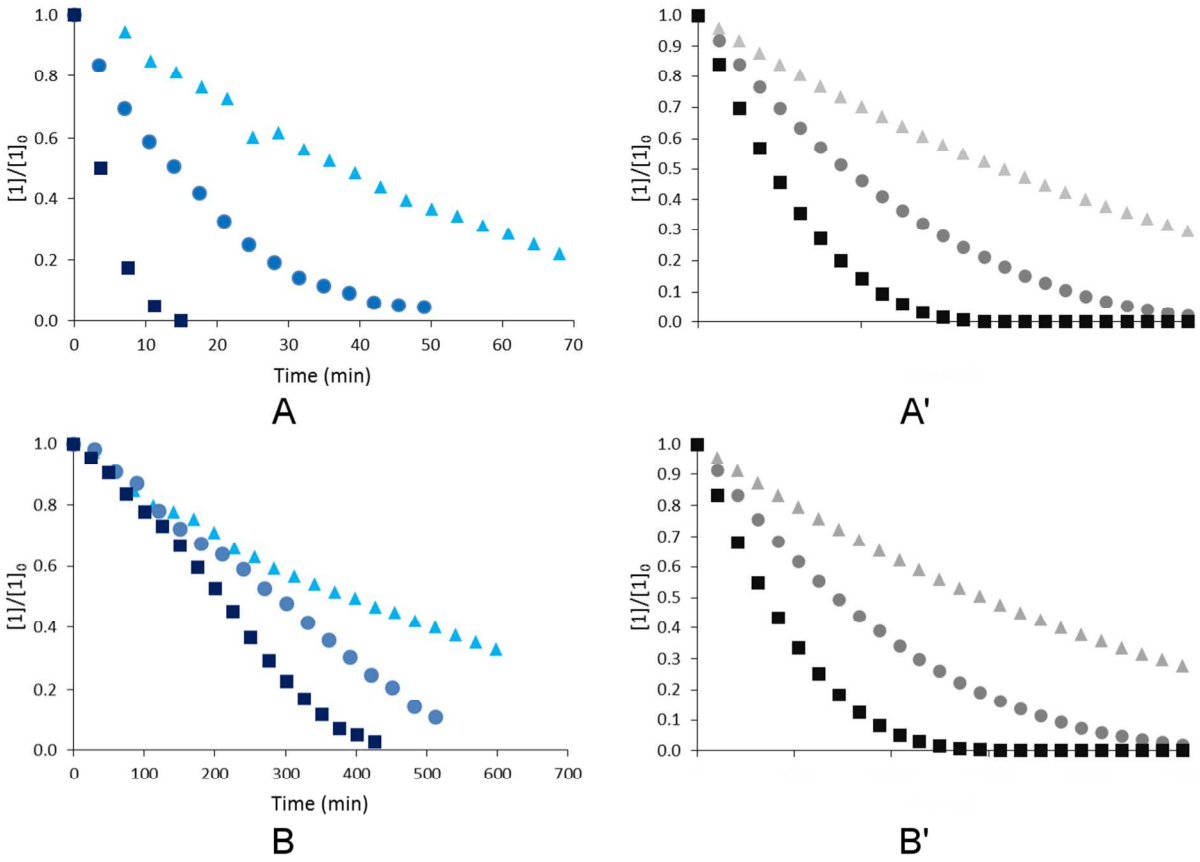



**Figure 6.** Left: Consumption of a 77.5 μM solution of aminoborane **1** in chloroform-*d* at various concentrations (775 ▲, 1550 ● and 3100 ■ μM) of 1-methylpyrrole at 40°C (top row) or thiophene at 60°C (bottom row). Right: Simulated rate of consumption according to DFT data.

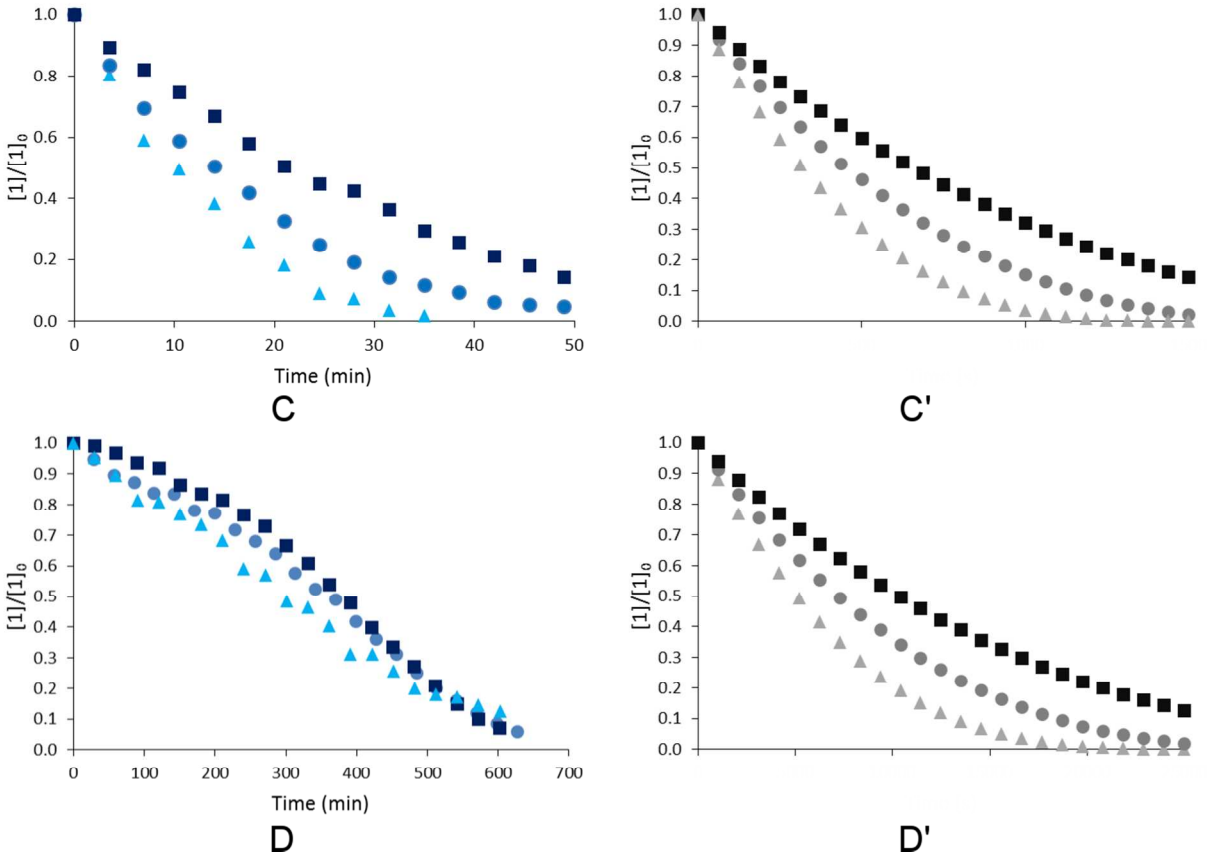



**Figure 7.** Left: Consumption of a solution of aminoborane **1** at various concentrations (38.8 ▲, 77.5 ● and 155 ■ μM) in chloroform-*d* with a 1550 μM concentration of 1-methylpyrrole at 40°C (top row) or thiophene at 60°C (bottom row). Right: Simulated rate of consumption according to DFT data.

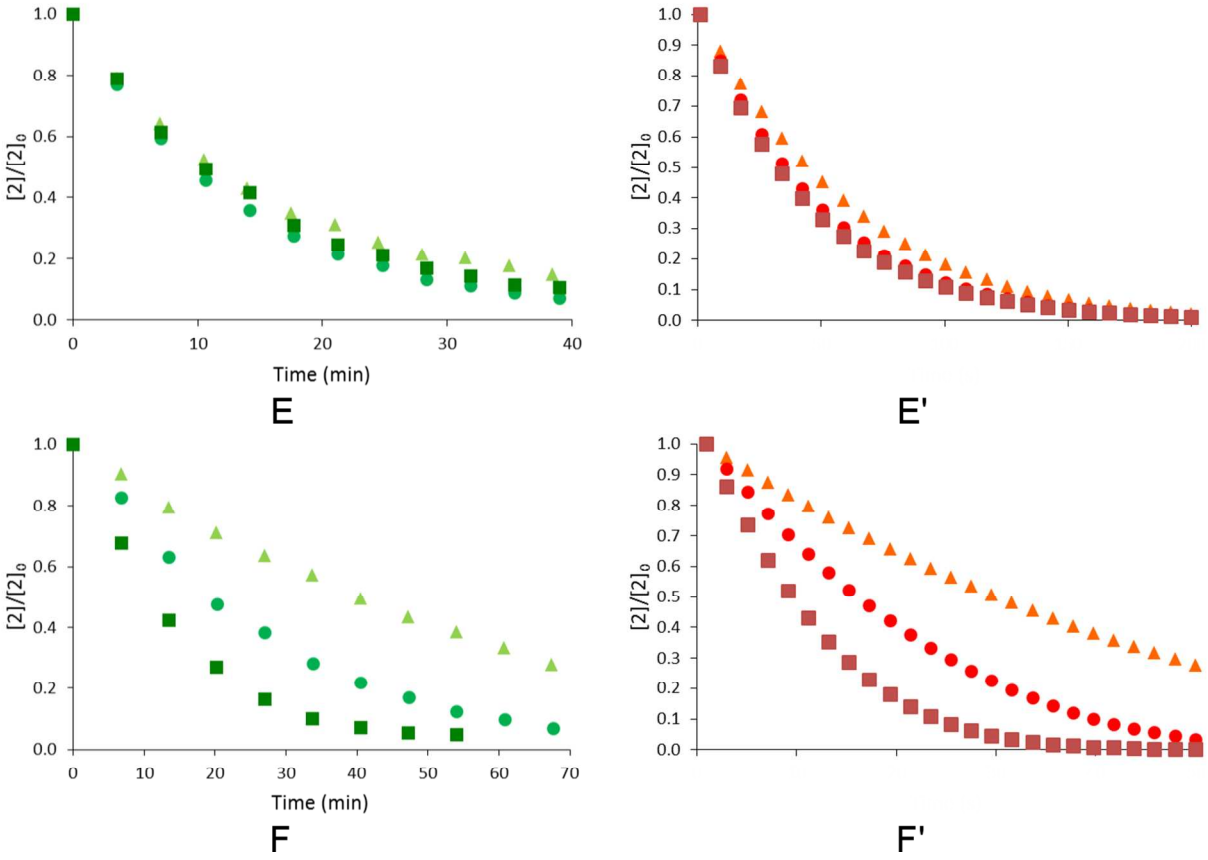



**Figure 8.** Left: Consumption of a 77.5 μM solution of aminoborane **2** in chloroform-*d* at various concentrations (775 ▲, 1550 ● and 3100 ■ μM) of 1-methylpyrrole at 40°C (top row) or thiophene at 60°C (bottom row). Right: Simulated rate of consumption according to DFT data.

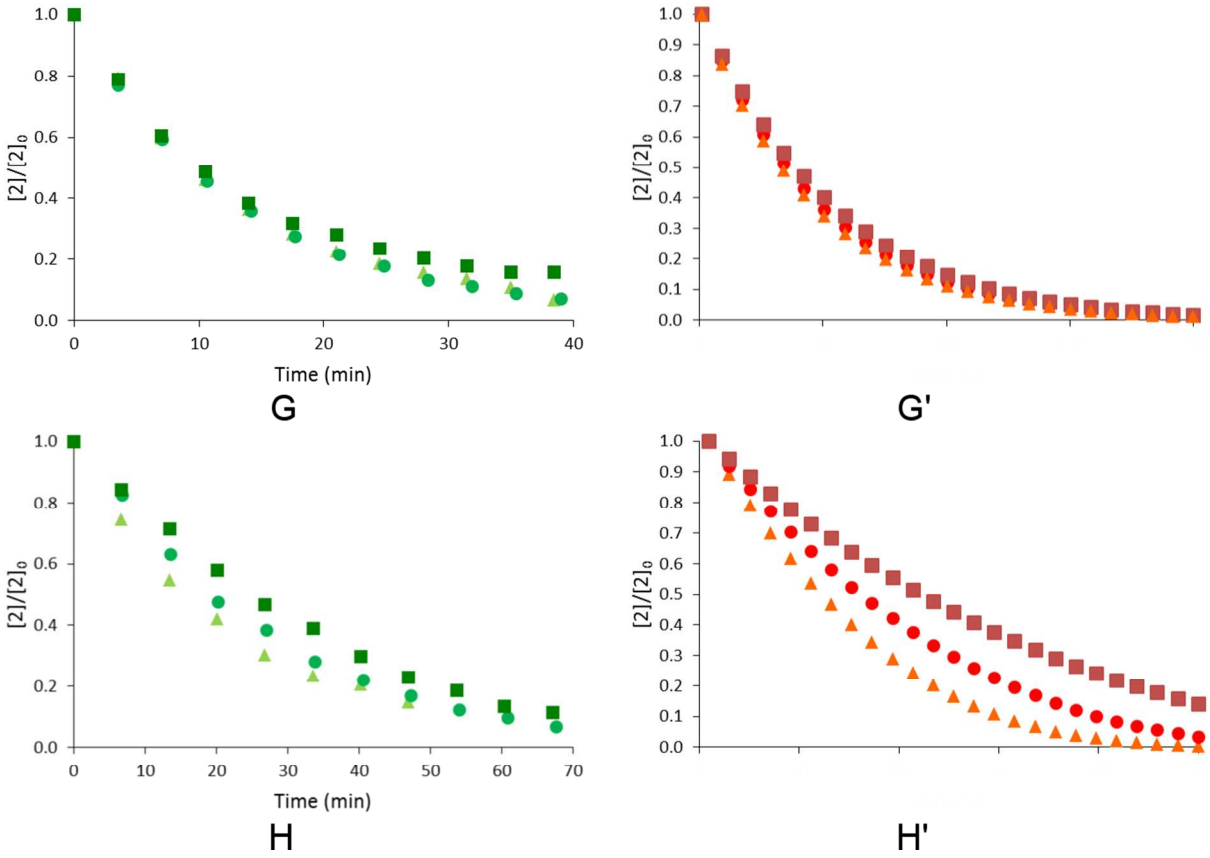



**Figure 9.** Left: Consumption of a solution of aminoborane **2** at various concentrations (38.8 ▲, 77.5 ● and 155 ■ μM) in chloroform-*d* with a 1550 μM concentration of 1-methylpyrrole at 40°C (top row) or thiophene at 60°C (bottom row). Right: Simulated rate of consumption according to DFT data.

## Discussion

Although several observations have surfaced in the past few years supporting that FLP type transformations are possible from stable Lewis pairs,[17] this report is the first to clearly demonstrate that smaller steric congestion can lead to an increase in catalytic activity. Analogously to transition metal catalysis, an unhindered Lewis pair favors the interaction of the

active site with incoming substrates but increases the chance of aggregation and deactivation modes. This is supported by the increased reactivity of (1-Pip-2-$BH_2$-$C_6H_4$)$_2$ (**2**) in the C–H bond activation compared to bulkier (1-TMP-2-$BH_2$-$C_6H_4$)$_2$ (**1**), even if **2** requires approximately 21 kcal mol$^{-1}$ to reach the active and "opened" FLP intermediate where *both* the Lewis base and acid are available. However, it is important to mention that faster reactivity might ensue when only one of the Lewis pair components is required for a reaction to take place, such as in the interaction of a B-H with a protic reagent.[20b] Recently, a computational study was reported proposing that smaller FLPs could yield more active catalysts for the hydrogenation reaction, notably using analogues **2** and **4**.[25] Our experimental results support such hypothesis for the C–H bond activation process, but also illustrate the care that needs to be taken when doing computational design. Indeed, the authors proposed 3-centers-2-electrons resting states (Table 3C) for **2** and **4** rather than the experimentally characterized B-H bridged dimers (Table 3D). As such, the TS are in reality 5 kcal mol$^{-1}$ higher than proposed and dimer dissociation should remain rate limiting under such reaction conditions.

It is quite surprising that the energy required to cleave the C-H bond of 1-methylpyrrole from the "opened" FLP intermediate is only 8.8 kcal mol$^{-1}$ with **2**. For comparison, it was found that the barrier for concerted metalation-deprotonation using [($PR_3$)Pd(Aryl)(C(O)R)] was over 12 kcal mol$^{-1}$ with the most active substrate being $C_6F_5H$.[26] Although significant energy is required in order to access this FLP intermediate, strategies could be introduced to prevent dimerization and access an active FLP state without requiring extra bulk, such as immobilization on solid supports.

FLPs are better known as hydrogenation catalysts. Although it has been stipulated by some that the cleavage of $H_2$ by a FLP is a barrier-free process,[27] the same cannot be said about the release

of $H_2$ from ambiphilic molecules. It was previously demonstrated that this transformation was an important driving force in the formation of diboranes and in the intramolecular $C_{sp3}$-H bond cleavage by aminoboranes.[18,28] With aminoboranes, it can also be stated that loss of $H_2$ can be rate determining in the overall C-H activation process, if we exclude the dissociation of the dimer. As shown by the absence of catalytic activity with thiophene, it now becomes evident that σ-bond metathesis needs to be enhanced in order to increase the reactivity of this system.

Notwithstanding the exceptional activity of the smaller derivatives which are about 15 times more active than the TMP analogues, yielding faster reactions and higher selectivity, this metal-free system has another significant advantage, notably for large-scale applications. Indeed, the diethylamine- and piperidylboranes are significantly cheaper and much easier to synthesize. It is possible to isolate fluoride-protected analogues such as **2F** on 100 gram scale for less than three dollars a gram. Since these precatalysts are air- and moisture-stable, they can be stored for several months without significant loss in activity. Although these catalysts do not provide the same wide and general versatility observed with the best transition metal catalysts, notably in the presence of protic functional groups, they do provide a convenient and cheap alternative with several substrates.

## Conclusion

In this report, we demonstrated that FLPs with small amines, such as (1-Pip-2-$BH_2$-$C_6H_4$)$_2$ (**2**), and their fluoride protected salts are extremely active catalysts for the borylation of heteroarenes, surpassing in activity the TMP analogues. Not only these results suggest that steric hindrance is not required for FLP transformations to take place, but also that small congestion actually leads

to higher reactivity. As demonstrated by DFT and kinetic measurements, the rate limiting step with smaller amines become the dissociation of the dimer and the extrusion of $H_2$. This better understanding of the operating mode of FLP in C-H activation process is critical for the synthesis of more active and robust catalysts for commercial applications. We are currently investigating the wide range of substrates that can be borylated using this procedure, exploiting notably the green and economical advantages that are gained using solvent-free conditions. We hope that additional design might lead to catalysts that can borylate other functional groups, such as C-O and C-N bonds.

## Supporting Information

Experimental procedures, X-ray crystallographic data, and computational details including other calculated reaction pathways, Cartesian coordinates, free energies and enthalpies. This material is available free of charge via the Internet at http://pubs.acs.org.

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## Notes

The authors declare no competing financial interests.

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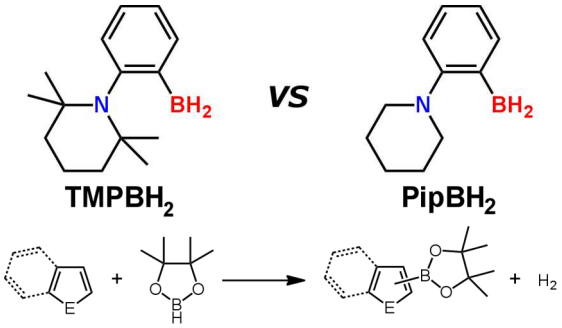
**TOC graphic**

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