

# Steric Shielding Effects Induced by Intramolecular C–H...O Hydrogen Bonding: Remote Borylation Directed by Bpin Groups

Jose R. Montero Bastidas, Arzoo Chhabra, Yilong Feng, Thomas J. Oleskey, Milton R. Smith, III,\* and Robert E. Maleczka, Jr.\*



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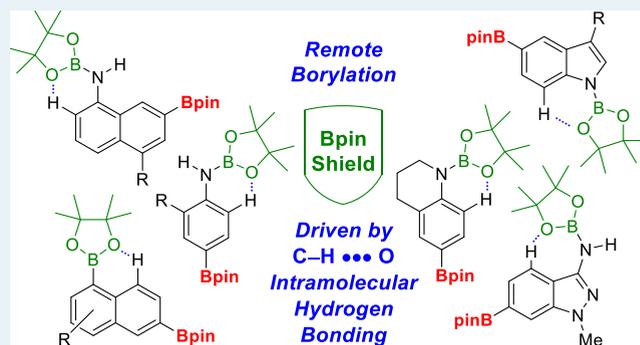
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**ABSTRACT:** Regioselectivities in catalytic C–H borylations (CHBs) have been rationalized using simplistic steric models and correlations with nuclear magnetic resonance (NMR) chemical shifts. However, regioselectivity can be significant for important substrate classes where none would be expected from these arguments. In this study, intramolecular hydrogen bonding (IMHB) can lead to steric shielding effects that can direct Ir-catalyzed CHB regiochemistry. Bpin (Bpin = pinacol boronic ester)/arene IMHB can promote remote borylations of N-borylated anilines, 2-amino-N-alkylpyridine, tetrahydroquinolines, indoles, and 1-borylated naphthalenes. Experimental and computational studies support molecular geometries with the Bpin orientation controlled by a C–H...O IMHB. IMHB-directed remote CHB appeared operative in the C6 borylation of 3-aminoindazole (seven-membered IMHB) and C6 borylation of an osimertinib analogue where a pyrimidine IMHB creates the steric shield. This study informs researchers to evaluate not only inter- but also intramolecular noncovalent interactions as potential drivers of remote CHB regioselectivity.

**KEYWORDS:** C–H borylation, para selectivity, remote functionalization, steric shield, hydrogen bonding, intramolecular interactions, NMR chemical shift displacement, QTAIM



## 1. INTRODUCTION

C–H bonds can be diversified via different C–H functionalization methods. Yet, targeting one C–H reactive site in the presence of similar C–H bonds remains challenging.<sup>1,2</sup> Although considered weak, noncovalent interactions can differentiate the energetics and therefore relative reactivity of otherwise similar reactive sites. For example, an interaction where  $\Delta G^0 \leq -3.5$  kcal/mol will be in force for  $\geq 99\%$  of the molecules at 100 °C. In the area of  $sp^2$  C–H activation, preinstalled directing groups can interact with the catalyst via hydrogen bonding, Lewis acid–base, or electrostatic interactions to selectively functionalize ortho, meta, or para positions of arenes.<sup>3–9</sup> However, selective reactions at distal C–H sites often require the construction of complex directing groups/ligands.<sup>7–11</sup> A different strategy uses steric shields to block nearby C–H bonds, thus leaving the distal position as the only accessible reactive site. For example, Nakao's group used Lewis acidic additives that interact with aryl amides and shield the meta positions, enabling selective para functionalizations.<sup>12–15</sup> In contrast, a complementary approach where intramolecular noncovalent interactions create steric shields leading to remote functionalization is far less common.

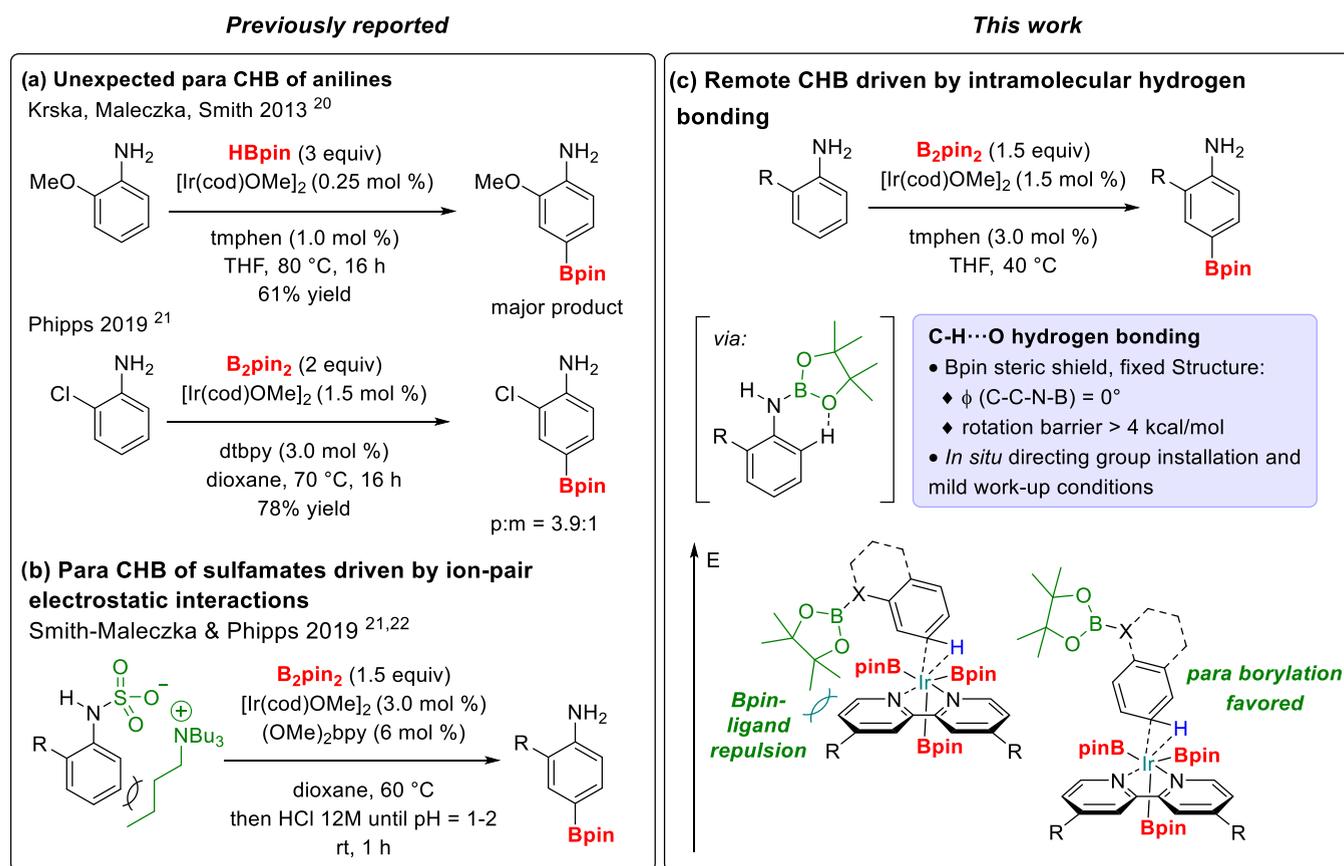
Iridium catalyzed C–H borylation (CHB) is currently a standard protocol to make aryl boronic esters.<sup>16–18</sup> In the last

decade, ortho regioselective  $sp^2$  CHB has been achieved by means of chelating and relay directing groups as well as outer-sphere interactions.<sup>4,7,19</sup> In 2013, our group reported that meta and para-substituted anilines yield the corresponding ortho borylated product courtesy of a N–H hydrogen bonding with the catalyst.<sup>20</sup> Unexpectedly, 2-methoxyaniline was selectively borylated para to nitrogen. A similar result was reported by the Phipps group during their CHB of 2-chloroaniline (Figure 1a).<sup>21</sup> It was proposed that electronic effects might play a role in the change of selectivity for 2-chloro and 2-methoxyaniline, but there was no experimental corroboration of this hypothesis.

More recently, we and the Phipps group independently developed a protocol for para CHB of anilines directed by ion–pair electrostatic interactions of sulfamates with bulky tetraalkylammonium counterions (Figure 1b).<sup>21,22</sup> Steric shieldings of C–H bonds ortho and meta to the sulfamate

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**Figure 1.** (a) Unexpected para CHB of anilines (only reported compounds), (b) previously reported para CHB of anilines driven by ion-pair electrostatic interactions, and (c) this approach: remote CHB driven by intramolecular hydrogen bonding.

by alkyl chains of the tetraalkylammonium cation in the ion pair are proposed to account for the para selectivity. We wondered if a different sort of steric shielding might confer the para selectivity in CHBs of 2-methoxy and 2-chloroaniline mentioned above.

It is well documented that N-borylation of N-unsubstituted anilines occurs rapidly under CHB conditions.<sup>20</sup> We hypothesized that in the presence of an ortho substituent like methoxy or chloro, the N-Bpin group could orientate toward the meta C-H where it would act as a steric shield, leading to para selective CHB (Figure 1c). Bpin would be an attractive steric shield for anilines possessing a N-H bond since *in situ* N-borylation with  $B_2pin_2$  or HBpin is rapid, and the aniline N-H is easily restored during workup by adding methanol, which rapidly cleaves the B-N bond. This contrasts with our previous approach to access para-borylated anilines, which required a step to install the sulfamate group and a step where highly acidic conditions were required to remove it from the product.

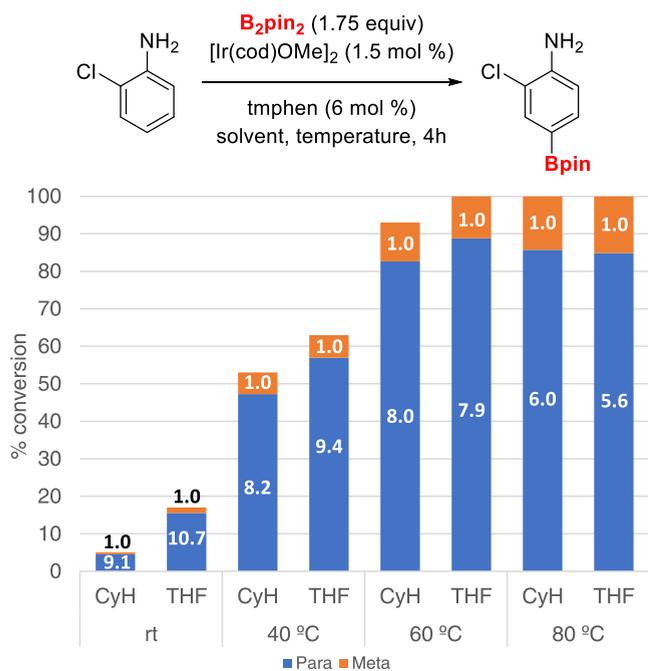
## 2. RESULTS AND DISCUSSION

**2.1. Para C-H Borylation of Anilines, N-Alkylated Anilines, and Indoles.** We set out to examine whether para selectivity after N-borylation of anilines and allied substrates was a general phenomenon. To do so, we first looked to optimize the reaction on 2-chloroaniline. Starting with our previously reported conditions, we compared the regioselectivity when  $B_2pin_2$  was used in place of HBpin and found that the former yielded an improved para to meta ratio: 5.6 to 1 vs 4.5 to 1. With  $B_2pin_2$  as the new boron partner, we then

explored temperature and solvent effects on selectivity (Figure 2). Cyclohexane and THF gave higher para selectivity at lower temperatures but conversion dropped especially with cyclohexane. The best balance between reactivity and selectivity was found with THF at 40 °C. After 4 h, the conversion was 61 and >90% after 24 h.

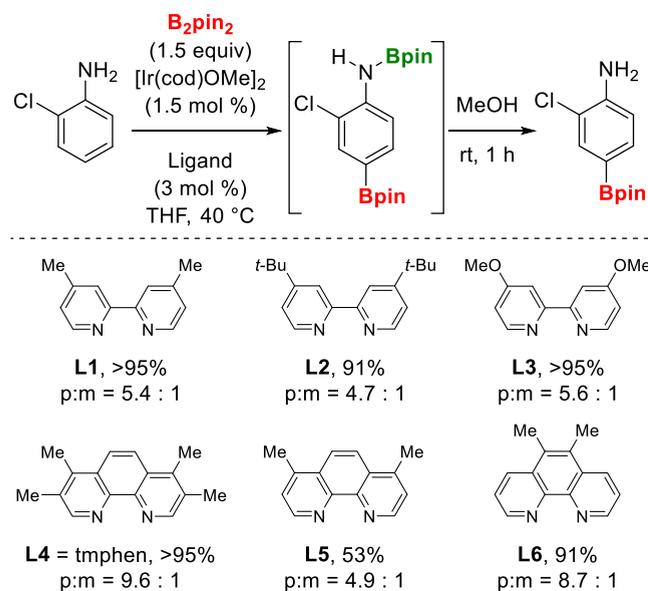
With these conditions in hand, we evaluated the effect of the ligand (Scheme 1). Bipyridine ligands (L1-L3) gave modest para/meta ratios (~5:1). Notably, 4,4'-dimethoxy-2,2'-bipyridine (L3), which was optimal in our previous para-directed CHB of sulfamate salts,<sup>22</sup> did not prove superior in this scenario. Selectivity with ligand L5 was similar but yield suffered. In contrast, the para:meta ratio doubled with phenanthrolines L4 and L6, while yields remained high. We chose tmphen (L4) to continue our studies due to it being slightly better than L6 in terms of regioselectivity and yield.

Next, we evaluated the para borylation of different anilines, all of which are substituted at the 2-position (Scheme 2). The highest para selectivity (C4:C5 > 7:1) was observed in CHBs for substrates, where ortho substituents have electron lone pairs (2a-2d). Given that CHBs are enhanced at the meta positions in monosubstituted benzenes  $C_6H_5X$  when X = Br,<sup>23</sup> I,<sup>17</sup> or OMe,<sup>24</sup> the 2-substituents are enhancing selectivity para to N. In contrast, 2e with a trifluoromethyl ortho substituent saw selectivity drop to 4:1. Benzoate 2f with an electron-withdrawing group by resonance gave an even lower ratio of 2 to 1 para to meta. This result bears some relationship to previous reports of ester groups favoring para CHB. In our case, that position is meta with respect to aniline nitrogen.<sup>25,26</sup>



**Figure 2.** Temperature and solvent effect on the para CHB of 2-chloroaniline. Blue and orange bars represent the conversion to the para and meta isomers, respectively. CyH is cyclohexane and THF is tetrahydrofuran.

### Scheme 1. Ligand Effect on the Selectivity of the *para* CHB of 2-Chloroaniline<sup>a</sup>



<sup>a</sup>The para to meta ratio (p:m) and conversions were calculated by <sup>1</sup>H NMR spectra of crude reaction mixtures.

The size of alkyl ortho substituents (**2g–2i**) showed little effect, as para to meta ratios only ranged from 4:1 to 6:1. It should be noted that the 6:1 observed for 2-methylaniline (**2g**) was achieved by forming the N–Bpin bond prior to the CHB. In contrast, a selectivity of 4:1 is achieved with *in situ* N–Bpin bond formation of **2g**, which suggests a slow formation of the N-borylated intermediate in this case. CHB at C4 was preferred for anilines when C3 was fluorine-substituted (substrate **1k**). This is consistent with an electronic preference

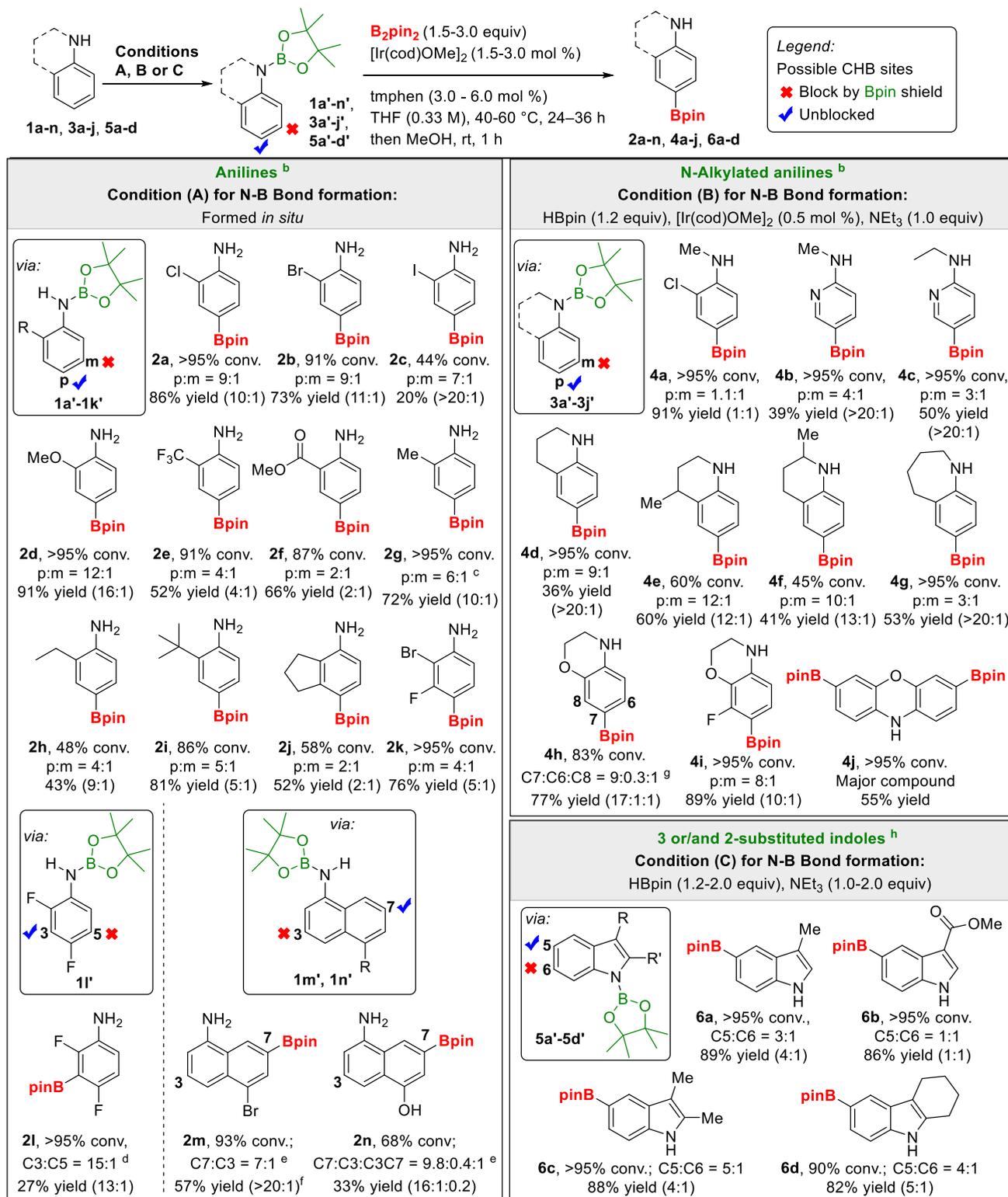
for CHB ortho to F and attenuated steric interference from F since H, and its isotopes are the only substituents that are less sterically demanding.<sup>27,28</sup> Para selectivity for substrate **1j**, albeit modest, is more significant since the only literature report where CHB at C4/C7 of an indane structure is preferred has a *tert*-butyl group at C5, obstructing C4/C6 positions.<sup>29</sup>

Our hypothesis implies that the Bpin steric shield can only block one meta position of arene. This can explain the necessity of an ortho substituent to block the other meta position. CHB of unsubstituted aniline supports this statement as no para to meta selectivity was observed.<sup>30</sup> This feature can allow a meta selective CHB if the para position bears a small substituent. As stated above, fluorine atoms are relatively small and CHB next to them is observed. CHB of 2,4-difluoroaniline (**1l**) presented a more interesting scenario. In this case, where the N–Bpin orientated away from the ortho fluorine, the resultant steric shield would block C5 leaving 3-borylation as the only option. This was the result as C3 borylation occurred with a 15:1 preference over C5 borylation. It can be argued that **1l'** is electronically biased to favor 3-selective CHB. CHB of 2,4-difluorotoluene (see the Supporting Information for details) shows a modest 3 to 1 preference for the 3-borylated product. The C3-selectivity of **1l'** is 5 times more than that of 2,4-difluorotoluene, which shows that both electronics and the Bpin steric shield play a role in the C3-selectivity of **1l'**.

To probe other substrates with substituents at the ortho and meta C–H positions, we examined the CHB of N-borylated 5-substituted 1-naphthylamines **1m** and **1n**. In these substrates, C2, C4, C6, and C8 would be blocked from CHB by substituents, leaving only C3 and C7 sterically unencumbered. However, were our hypothesis correct, the N–Bpin would sterically shield C3, thus favoring C7 in a CHB. Indeed, borylation of **1m** and **1n** yield their 7-borylated product selectively (C7/C3 7:1 and 24:1, respectively). In the case of **1n**, a small amount of diborylation was observed.

We next turned our attention to other *in situ* borylated scaffolds, namely, N-alkylated anilines. Unfortunately, CHB of 2-chloro-N-methylaniline **3a** was not para selective under the optimized conditions. A slow rate of N–Bpin formation could explain the lack of selectivity. However, even after preformation of the N–Bpin bond no selectivity was observed. Thus, we considered other explanations. This led us to propose that a reluctance of N-borylated **3a** to orientate in the same plane as the aromatic ring, which per our hypothesis creates the N–Bpin steric shield, is responsible for the observed regiochemical result. Such a hypothesized planar conformation is supported by modeling the lowest energy conformation of N-borylated intermediates of N-unsubstituted anilines (see Section 2.3 and Figure 5 for further discussion). In contrast, N-borylated 2-chloro-N-methylaniline does not adopt a planar conformation (see Section 2.3 and Supporting Information for details) owing to an A<sub>(1,3)</sub> interaction between the N-methyl with the ortho chlorine. As N-borylated N-alkyl-2-aminopyridines should lack this steric clash, **3b** and **3c** should be para selective. This proved to be the case with **4b** and **4c** both being the major (4:1) CHB products.

1,2,3,4-Tetrahydroquinolines also drew our attention as in these N-alkylated anilines, the covalent chain that links the aromatic ring with nitrogen should allow the N-borylated intermediate to achieve a pseudoplanar conformation (see the Supporting Information for details). Para products **4d–4j** were obtained as the major regioisomer from their corresponding 1,2,3,4-tetrahydroquinolines. The size of the saturated ring

Scheme 2. Remote Regioselective CHB Driven by a N-Bpin Steric Shield<sup>a-h</sup>

<sup>a</sup>Conversions and regioselectivities were measured by <sup>1</sup>H NMR on crude reaction mixtures. Yields refer to isolated material with the ratio of major to minor products in the isolated material given in parentheses. <sup>b</sup>p and m refer to para and meta products, respectively. <sup>c</sup>N-Bpin bond formed prior to CHB with HBpin (1.2 equiv), [Ir(cod)OMe]<sub>2</sub> (0.5 mol %), THF, 80 °C, 2h; under standard condition (A), the results are 61% conv.; p:m = 4:1 with 47% yield (>20:1). <sup>d</sup>C3 and C5 refer to 3- and 5-borylated products, respectively. <sup>e</sup>C3 and C7 refer to 3- and 7-borylated products, respectively, and C3C7 refers to the 3,7-diborylated product. <sup>f</sup>Regioselectivity confirmed by X-ray crystallography. <sup>g</sup>C6, C7, and C8 refer to 6-, 7-, and 8-borylated products, respectively. <sup>h</sup>C5 and C6 refer to 5- and 6-borylated products, respectively. Experimental details are given in the Supporting Information.

does influence the level of selectivity, as illustrated in **4g** where the selectivity was only 3:1. Adding a methyl group about the saturated ring did not significantly change the selectivity, as shown by products **4d–4f**. With **3h**, borylation next to oxygen was also observed, but the para product still predominated (para:others = 7:1). The fluorinated version of **3h**, namely, **3i**, was equally selective. Diborylation of phenoxazine **3j** mainly yielded the bis para compound along with multiple minor products.

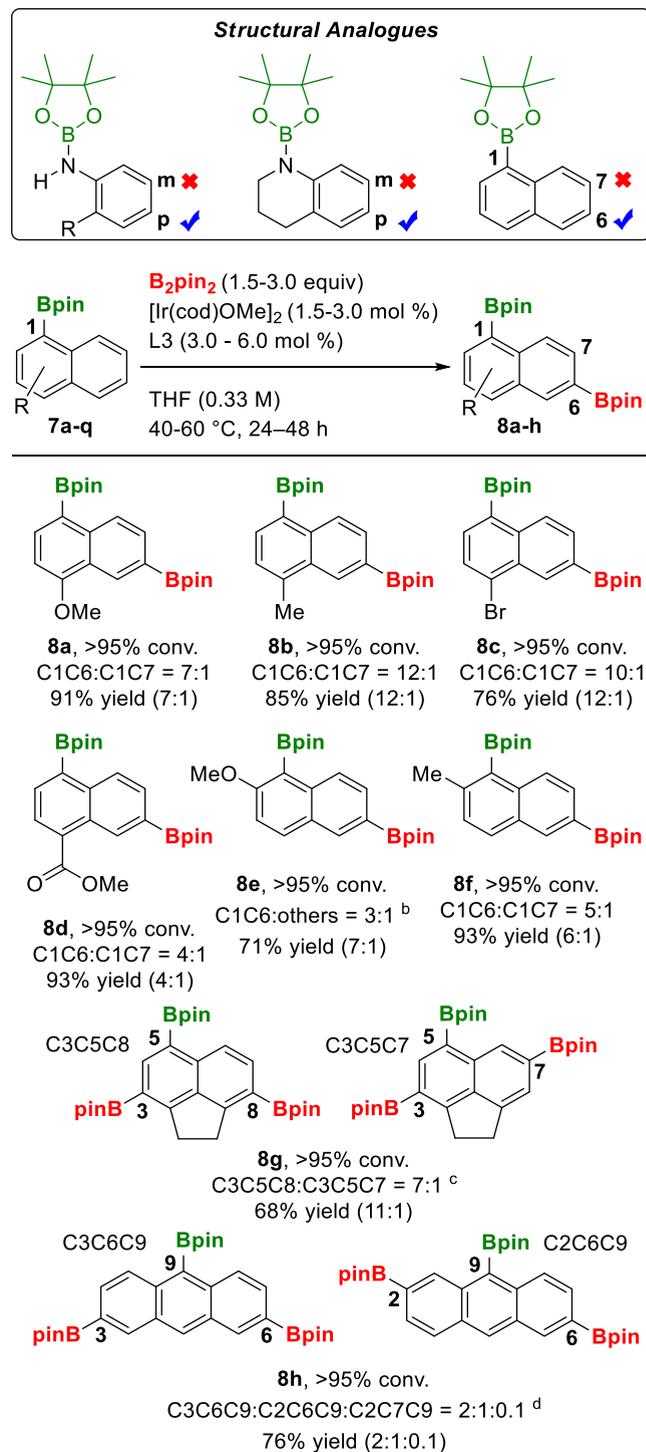
**2.1.1. Indoles.** N-Borylation of indoles is known to block C2 CHB normally seen in the parent compounds, instead yielding the corresponding 3-borylated product.<sup>20</sup> We asked if in a N-borylated 3-substituted indole, the N–Bpin would shield the closer C6-position, leading to the corresponding 5-borylated indoles. C5 and C6 indole functionalization remains rare. Baran's group reported that CHB of 3-substituted N-TIPS-indoles yield the 6-borylated product using phenanthroline as ligand.<sup>31</sup> C5 borylation of indoles has been elusive besides some specific examples employing electrophilic borylation with borenium cations. The examples are limited to N-methyl carbazole or are triggered by the use of an amine pivaloate directing group at the 4 position.<sup>32,33</sup> A protocol to access 3,5-diborylated indoles has been reported, but suffers from low conversions (<30%).<sup>34</sup> Under our optimized conditions and after the formation of the N–Bpin intermediate, 3-methylindole **5a** yielded the 5-borylated product with a modest 3:1 selectivity over the minor 6-borylated isomer. Replacement of the methyl group by a methyl ester as in **5b** resulted in the loss of selectivity. However, the presence of substituents at both C2 and C3 impacted selectivity little, as shown in **6c** and **6d**. It should be stated that for **5c** and **5d**, formation of the N–Bpin intermediate was slow and additional HBpin and triethylamine as well as a 3 h reaction time was needed to afford full N-borylation.

In our efforts to expand the Bpin steric effect to phenols, we found that the CHB of 2-chlorophenol did not show selectivity. Neither QAIM nor  $\Delta\delta$  data (vide infra) show any evidence of IMHB, which explains the experimental result (see the [Supporting Information](#)).

**2.2. C6 Borylation of 1-Borylated Naphthalenes.** We speculated that Bpin groups could create a steric shield even when not part of a N–Bpin moiety. We thus focused on 1-borylated naphthalenes, which could bear geometries similar to those of N-borylated 2-substituted anilines and N-borylated tetrahydroquinolines (Scheme 3). If so, the Bpin-derived steric shield would block the C7-position leaving the C6-position available for CHB. Borylation of 1-borylated naphthalene **7a** supported our proposition and yielded the 1,6-diborylated product selectively. A ligand screening showed that 4,4'-dimethoxy-2,2'-bipyridine (L3) was the best choice for the C6 borylation of 1-borylated naphthalenes (see the [Supporting Information](#) for details). This result is potentially valuable as C6 functionalization of naphthalenes remains rare.<sup>35</sup> A notable exception comes from Nakao's group where a 1-naphthyl amide was made to undergo C6-alkylation using an aluminum Lewis acid as a steric shield.<sup>13,14</sup>

As shown in Scheme 3, a substituent on the C2- or C4-position is needed to avoid borylation at C3 (**7b–7f**). 5-Bpin dihydroacenaphthene **7g** was borylated at both the expected C8 position and at C3. Under conditions that promote diborylation, 3,5,8-triborylated product **8g** was obtained as the major product along with the 3,5,7-triborylated product as a minor isomer. The Bpin shield in 9-borylated anthracene **7h**

Scheme 3. C6 Borylation of 1-Borylated Naphthalenes<sup>a–d</sup>



<sup>a</sup>C1C6 and C1C7 refer to 1,6- and 1,7-diborylated naphthalene products, respectively. Conversions and C1C6/C1C7 ratios were measured by <sup>1</sup>H NMR on crude reaction mixtures. Yields refer to isolated material with the C1C6/C1C7 ratio of the isolated material given in parentheses. <sup>b</sup>For **8e**, there was an unknown minor isomer in the mixture besides 7-borylated. <sup>c</sup>C3C5C8 and C3C5C7 refers to 3,5,8- and 3,5,7-triborylated acenaphthene, respectively. <sup>d</sup>C3C6C9, C2C6C9, and C2C7C9 refer to 3,6,9-, 2,6,9-, and 2,7,9-triborylated anthracene, respectively. Experimental details are given in the [Supporting Information](#).

enabled remote borylation of both sides of the molecule leading to a 2:1 mixture of 3,6,9-triborylated and 2,6,9-triborylated products (**8h**).

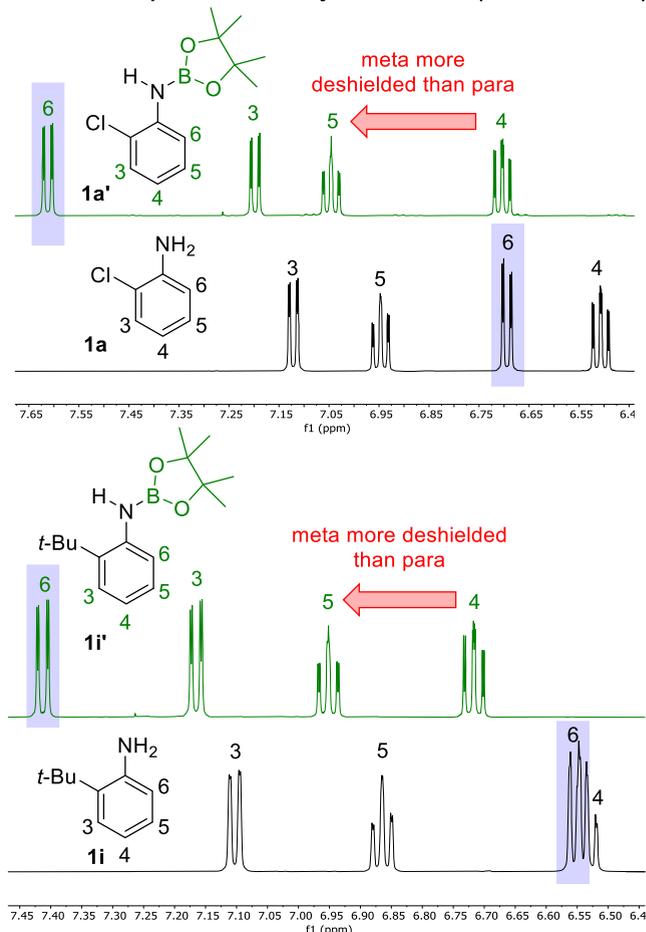
**2.3. Mechanistic Studies.** We began this study by suggesting that the unusual para selective CHB of 2-methoxy and 2-chloroaniline came about by virtue of a N-Bpin steric shielding in contrast to the previously evoked electronic drivers. This steric shielding hypothesis could be understandably challenged as free rotation around the C–N and N–B bonds can avoid any steric perturbation caused by the N–Bpin group. Moreover, even in the orientation that maximizes the putative steric shield, one could question if the N–Bpin group is close enough to the meta C–H so as to block its borylation. To address these questions and better understand the observed selectivities, we performed the experiments described below.

Steel and Marder have shown that  $^1\text{H}$  NMR chemical shifts can be qualitative predictors of CHB selectivity when there is not a steric difference between two reactive sites.<sup>25</sup> More deshielded hydrogens are expected to be more acidic and more reactive toward CHB. Based on 1D-NOE and 2D NMR experiments, we assigned the  $^1\text{H}$  NMR chemical shifts of N-borylated 2-chloro (**1a'**) and 2-tertbutylaniline (**1i'**) (Figure 3). We acquired the spectra in THF- $d_8$  so as to best simulate solution structures present during the CHB. Spectra for both compounds had the meta proton appearing more downfield than the para proton. Per Steel and Marder, this would suggest the meta position should be electronically favored in a CHB. However, a preference for para borylation is the experimentally observed result. This points to factors besides electronic effects being responsible for the para preference.

A closer comparison of the  $^1\text{H}$  NMR of the N-borylated intermediate vs the nonborylated version of 2-chloro and 2-tertbutylaniline revealed a surprising deshielding effect on the chemical shift of the ortho proton after N-borylation (Figure 3). This displacement was also observed in other NMR solvents ( $\text{C}_6\text{D}_6$ , acetone- $d_6$ ,  $\text{CDCl}_3$ , pyridine- $d_5$ ). We attribute the downfield chemical shift movement to an intramolecular C–H...O hydrogen bonding (IMHB) between the oxygen of the N–Bpin group and the ortho hydrogen in the aniline. Deshielding effects on chemical shifts caused by hydrogen bonds are well documented,<sup>36–38</sup> and one of the closest examples to our system is the IMHB present in N1,N'-diBoc-protected pyridine-2-yl guanidine **9a–c**.<sup>39</sup> In this scenario, a C–H...N IMHB is said to change the conformation, vs analogous compound lacking a Boc group, to one where the pertinent protons are deshielded.

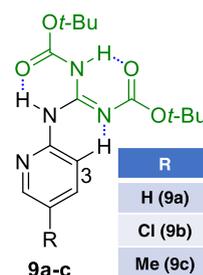
While NMR studies argued against electronic effects being responsible for the para borylation of anilines, those studies did not shed light on the question of whether the N–Bpin group is actually close enough to the meta position to act as a steric shield. To begin addressing this question, we ran CHB reactions with larger diboron partners such as  $\text{B}_2\text{hg}_2$  and  $\text{B}_2\text{pp}_2$  (Figure 4a).  $\text{B}_2\text{hg}_2$  proved less reactive than  $\text{B}_2\text{pin}_2$  in accordance with a previous report;<sup>40</sup> however, the selectivity for the para position improved. We tested a novel diboron partner for CHB,  $\text{B}_2\text{pp}_2$ , and interestingly the conversion to the borylated product was greater than with  $\text{B}_2\text{hg}_2$ . The largest para to meta ratio was also found with  $\text{B}_2\text{pp}_2$ , which is consistent with our steric shield hypothesis. While this improved selectivity could be due to the size of the installed N–Bpp group, a  $\text{B}_2\text{pp}_2$ -derived trisboryl active catalyst could also influence regiochemistry. Thus, we generated N–Bpin and

### $^1\text{H}$ NMR comparison of N-borylated anilines (solvent THF- $d_8$ )

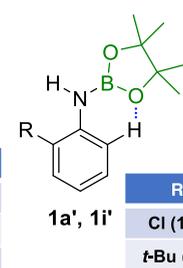


### $\Delta\delta$ displacement by intramolecular hydrogen bonding

Previously reported:<sup>40</sup>



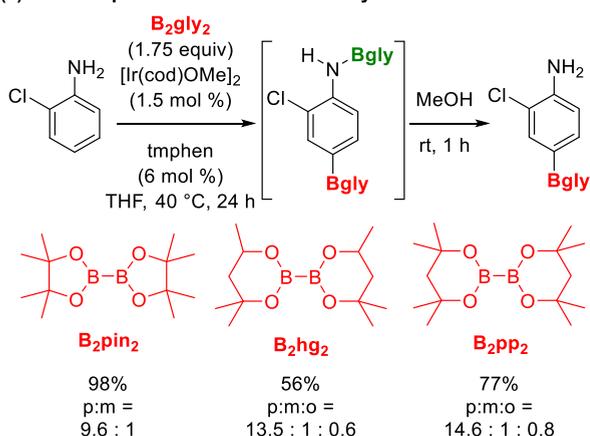
N-borylated anilines:



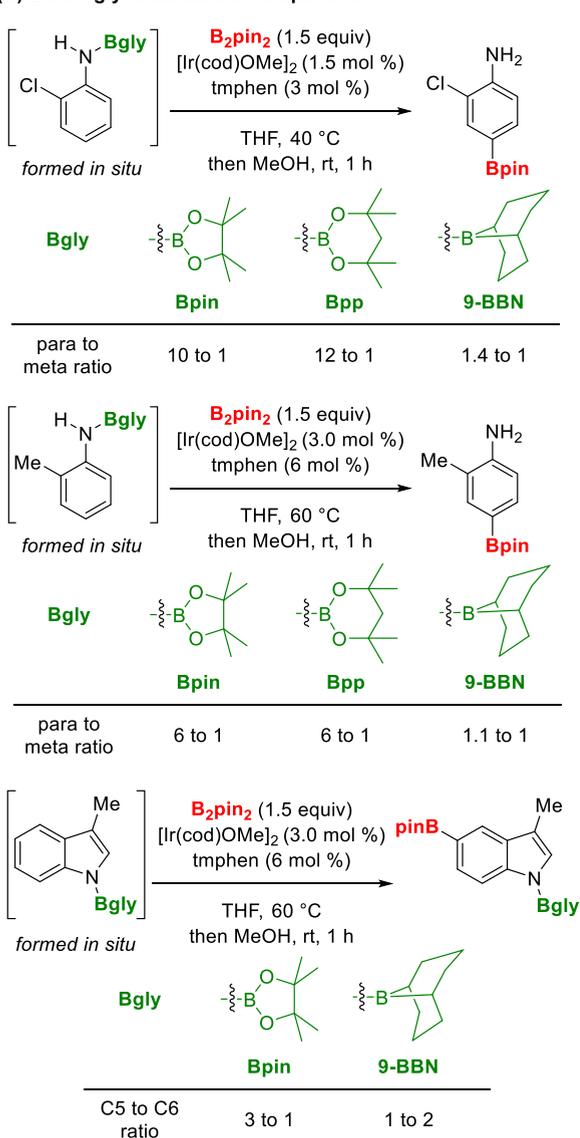
**Figure 3.**  $^1\text{H}$  NMR comparison of N-borylated and unborylated 2-chloro and 2-tertbutylaniline, and  $\Delta\delta$  displacement due to C–H...N and C–H...O IMHB in **9a–c** and **1a'**, **1i'**, respectively.

N–Bpp compounds from 2-chloro and 2-methylaniline. These intermediates were then independently reacted under the same CHB conditions with  $\text{B}_2\text{pin}_2$  as the diboron partner (Figure 4b). For 2-chloroaniline, the N–Bpp borylated derivative yielded a higher para/meta ratio as compared to the N–Bpin substrate. For 2-methylaniline, there was no observable change in selectivity; this may be a reflection of 2-methylaniline being inherently less para selective than 2-chloroaniline. We wondered if a smaller steric shield would reduce the para selectivity. However, CHB of N-Beg borylated 2-chloroaniline with  $\text{B}_2\text{pin}_2$  as the diboron partner yielded mainly the ortho product in accordance with the previously reported ortho CHB of anilines along with only trace amounts of the para and meta

## (a) Diboron partner effect on selectivity



## (b) Boron glycolate shield comparison



**Figure 4.** (a) Diboron partner effect on CHB of 2-chloroaniline and (b) boron glycolate shield effect on the CHB of 2-chloroaniline, 2-methylaniline, and 3-methylindole. For conditions to generate the N-borylated intermediate, see the Supporting Information.

isomers.<sup>30</sup> Switching the steric shield and diboron partner, i.e., CHB of N-Bpin borylated 2-chloroaniline with  $B_2eg_2$  lead to similar results (see the Supporting Information for details).

To probe the significance of the IMHB acceptor ability of N-Bpin toward selectivity, we decided to generate N-BBN, a boron group without oxygen, on aniline. With a N-BBN in place, the para selectivity dramatically drops for both 2-chloro and 2-methylaniline. This further supports IMHB playing a direct role in selectivity. With N-BBN generated from 3-methylindole, the CHB regiochemical preference flips and the C6-borylated isomer is major (2:1) as opposed to the C5 selectivity (3:1) seen with N-Bpin.

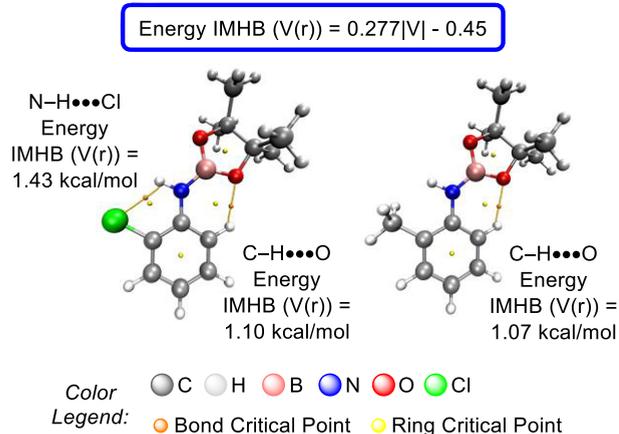
We further evaluated computationally the proximity of the Bpin steric shield to the meta position. We used a B3LYP functional and 6-311++G(d,p) basis set to optimize the geometry of N-borylated 2-chloro (**1a'**) and 2-methylaniline (**1g'**) (Figure 5a). This basis set has been previously reported to work well when IMHB is present.<sup>41</sup> Solid angles around the meta and para positions of **1a'** and **1g'** show that the meta position is more shielded than the para position supporting our hypothesis (see the Supporting Information for details).<sup>42</sup>

Seeking further evidence of IMHB involvement, we examined N-borylated anilines with the Quantum Theory of Atoms in Molecules (QTAIM) developed by Bader using the multiwfn program.<sup>43–45</sup> QTAIM is used to identify IMHB based on a topological analysis of the electronic distribution. Bond critical points (BCP) are defined as the position between two atoms where the electron density reaches a minimum. QTAIM identifies BCP when two atoms are connected by any type of bond including IMHB interactions. The QTAIM analysis of both N-borylated anilines shows a BCP between the oxygen of the N-Bpin group and the nearest ortho hydrogen of the aromatic ring supporting the existence of a C–H...O IMHB. An additional BCP is found in N-borylated 2-chloroaniline between the chloride and the N–H. This additional N–H...Cl IMHB may be one contributor to the greater para CHB selectivity of 2-chloroaniline vs 2-methylaniline.

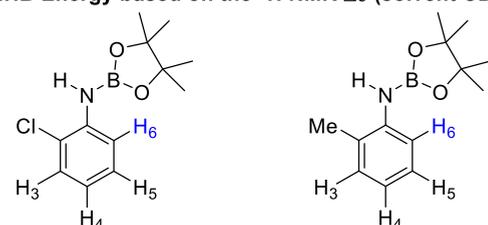
The energy of hydrogen bonds can be estimated by multiplying the potential energy density ( $V(r)$ ) at the BCP found with QTAIM by a scaling factor determined from plotting  $V(r)$  vs experimentally determined hydrogen bonding energies. The linear relationship initially found by Espinosa et al. has been adapted by Afonin et al. for the case of IMHB including cases with C–H...O interactions.<sup>41,46</sup> Afonin's corrected equation to calculate the C–H...O IMHB energy of N-borylated 2-chloro and 2-methylaniline gave comparable energies corresponding to 1.10 and 1.07 kcal/mol, respectively (Figure 5a). IMHB energies can also be estimated using NMR spectroscopy. Typically, there is a linear relationship between the IMHB stabilization energy and the <sup>1</sup>H chemical shift difference,  $\Delta\delta$ , of the hydrogen involved in the IMHB in the target molecule vs a reference in which no IMHB occurs (Figure 5b).<sup>41,47</sup> We used CDCl<sub>3</sub> for these experiments since the relationship was established from <sup>1</sup>H NMR spectra of CDCl<sub>3</sub> solutions. We chose nonborylated anilines as references and found energies of 1.29 and 1.23 kcal/mol for the IMHB of 2-chloro and 2-methylaniline, respectively, in excellent agreement to the energy predictions from QTAIM.

One potential pitfall in attributing para selectivity to IMHB Bpin shielding is the assumption that there is only one energy minimum on the conformational energy surface. For example, the presence of a second local minimum where the plane of the

(a) Quantum Theory of Atoms in Molecules (QTAIM):  
Bond Critical Points (BCP) and IMHB energy



(b) IMHB Energy based on the  $^1\text{H}$  NMR  $\Delta\delta$  (solvent  $\text{CDCl}_3$ )



$^1\text{H}$  Chemical Shift Displacement

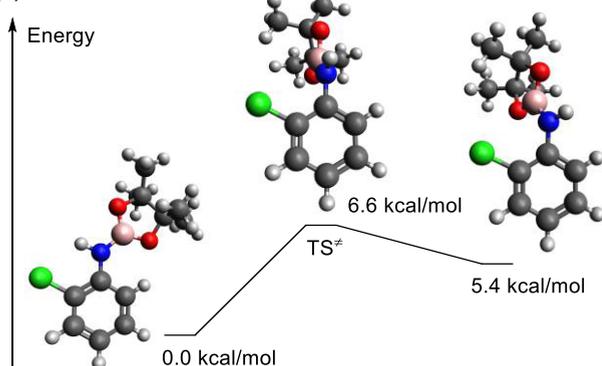
$$\Delta\delta = \delta(\text{N-Borylated Aniline}) - \delta(\text{Unborylated Aniline})$$

|    | $\Delta\delta$ (ppm) |    | $\Delta\delta$ (ppm) |
|----|----------------------|----|----------------------|
| H3 | 0.02                 | H3 | -0.01                |
| H4 | 0.09                 | H4 | 0.04                 |
| H5 | 0.08                 | H5 | 0.04                 |
| H6 | 0.89                 | H6 | 0.83                 |

$$\text{Energy IMHB } (\Delta\delta) = \Delta\delta + (0.4 \pm 0.2)$$



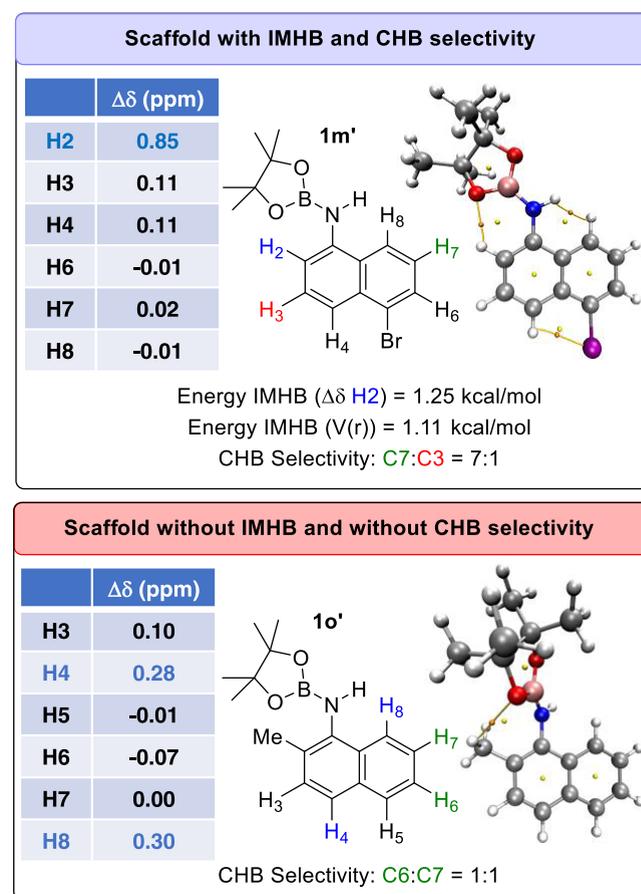
(c) C-N Rotation Barrier



**Figure 5.** (a) QTAIM analysis of N-borylated 2-chloro and 2-methylaniline (left and right, respectively), (b)  $^1\text{H}$  NMR chemical shift deviation of N-borylated 2-chloro and 2-methylaniline respect to unborylated anilines, and (c) C-N rotation barrier for N-borylated 2-chloroaniline.

N-Bpin is orthogonal to the plane containing the aryl ring could erode selectivity if (i) the second local minimum has a comparable or lower Gibbs' energy than the IMHB local minimum and (ii) the barrier connecting the local minima is small. Indeed, theory predicts that there are local minima similar to the aforementioned scenario for N-borylated 2-chloroaniline and 2-methylaniline at 5.4 and 3.1 kcal/mol relative to their respective IMHB local minima (Figure 5c and Supporting Information, respectively), and the corresponding transition states that connect these local minima are 6.6 and 4.6 kcal/mol above the IMHB local minima. Based on the energies of the higher-energy local minima, theory predicts that more than 99% of N-borylated anilines adopt IMHB structures. These findings support the hypothesis that IMHB between the Bpin O and the C6 proton creates a steric shield that accounts for the para selectivity.

We next asked if similar relationships could be found in other scaffolds with and without IMHB (Figure 6 and Supporting Information for details). Accordingly, good CHB selectivities are seen for substrates when protons proximal to



**Figure 6.** Correlation between the presence of IMHB and remote CHB selectivity. The  $^1\text{H}$  NMR chemical shift displacements are shown by the numbers in blue respect to the corresponding nonborylated compound as a reference. The lowest energy conformations are shown, which were calculated by B3LYP functional and 6-311++G(d,p) basis set. QTAIM was performed in each optimized structure and critical points are shown by the dots in orange (BCP) and yellow (RCP). The energy of the C-H...O IMHB was calculated from  $V(r)$  at the corresponding BCP using Afonin's equation and by the displacement of the  $^1\text{H}$  NMR chemical shift of the proton involved in the IMHB.

Bpin substituents have the largest  $^1\text{H}$  NMR chemical shift displacement, as well as a BCP between that proton and the Bpin O from QTAIM analysis. Specific examples are described below.

The H2 of N-borylated 5-bromo-1-aminonaphthalene **1m'** shows a 0.85 ppm difference from the reference 5-bromo-1-aminonaphthalene. By comparison, all of the other protons deviate by <0.2 ppm. QTAIM shows a BCP that supports an IMHB with an energy of 1.11 kcal/mol, which is close to 1.25 kcal/mol calculated based on the spectroscopically observed  $^1\text{H}$  NMR chemical shift displacement. As expected, 5-bromo-1-aminonaphthalene undergoes a C7-selective borylation by blocking the C3 position (Scheme 2).

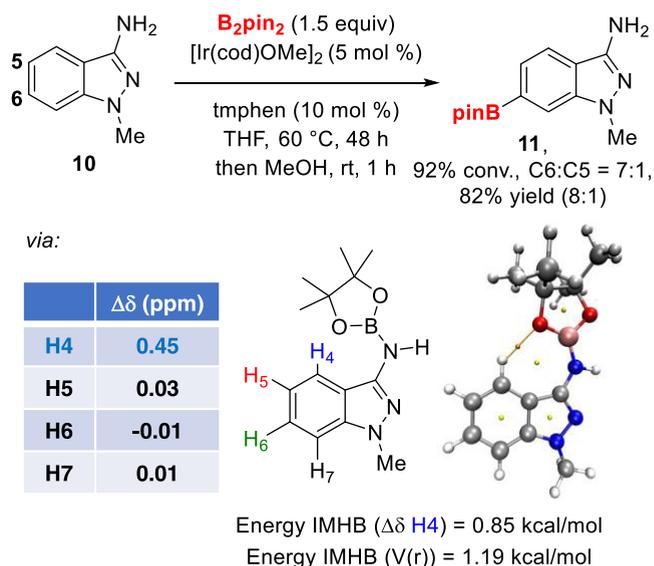
In contrast, N-borylated 2-methylnaphthalene **1o'** show no evidence of C–H...O IMHB with naphthalene as the hydrogen bond donor. H8 might be available for IMHB, but its  $\Delta\delta$  is only 0.30 ppm, which is close to the  $\Delta\delta$  of H4 (0.28 ppm), suggesting that chemical shift displacement results from electronic effects after N-borylation. No BCP is detected with arene as the hydrogen bond donor, but a BCP corresponding to a C–H...O IMHB between the N–Bpin and the methyl group is found. The lack of IMHB with the naphthalene ring might be due to steric effects that disrupts any seven-membered ring IMHB from happening. Accordingly, no selectivity was found under CHB reaction conditions.

Similar  $^1\text{H}$  NMR and QTAIM studies were done in N-borylated N-methyl-2-aminopyridine (**3b'**), 1,2,3,4-tetrahydroquinoline (**3d'**), 3-methylindole (**5a'**), and in 1-borylated naphthalenes **7c** and **7e**, which show the presence of an IMHB and CHB remote selectivity accordingly. N-Borylated 2-chloro-N-methylaniline (**3a'**) did not show CHB as shown in Scheme 2, and there is no presence of an IMHB based on NMR and QTAIM (see the Supporting Information for details).

**2.4. Application of IMHB to Remote Borylation: Seven-Membered Ring IMHB and Pyrimidines as Directing Groups.** Inspired by literature precedent,<sup>37,38,41</sup> we sought to see if a seven-membered ring can be created with IMHB to N–Bpin groups. As explained in the previous section, steric effects can disrupt IMHB. Hence, seven-membered ring IMHB with arenes as hydrogen bond donors are uncommon. However, exceptions appear when a hydrogen bond donor contains a bicyclic moiety with five- and six-membered fused rings.<sup>37,38,41</sup> We expected that 3-aminoindazoles would form a seven-membered IMHB after N-borylation.

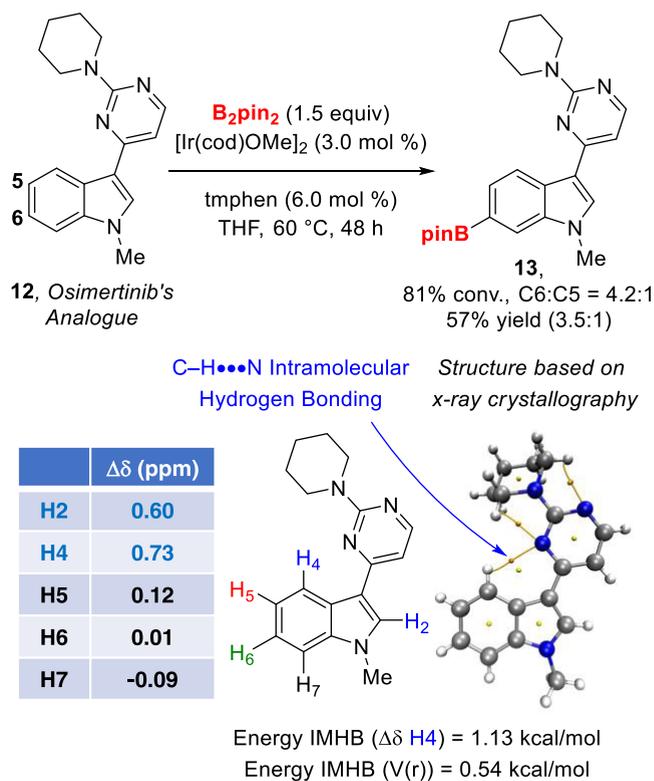
We were pleased to find that N-methyl-3-aminoindazole **10** undergoes a C6-selective CHB (Figure 7).  $^1\text{H}$  NMR comparison of the N-borylated indazol vs the unborylated version shows a significant movement of the chemical shift of the C4 proton, as expected with an IMHB. QTAIM provides more support to this conclusion by recognizing a C–H...O BCP between the C4 proton and the oxygen in the Bpin group. The calculated energies by QTAIM and  $\Delta\delta$  are comparable: 1.19 and 0.85 kcal/mol, respectively.

Certainly, Bpin is not the first IMHB acceptor found in molecules. Nitrogen heterocycles have appeared as part of IMHB networks including C–H...N interactions within heteroarenes.<sup>48–50</sup> Pyridines, pyrimidines, and triazines are key motifs of biologically active pharmaceuticals, and therefore, their potential use as steric shields via IMHB drew our attention.<sup>51–57</sup> In particular, we became interested in osimertinib, an epidermal growth factor receptor tyrosine kinase inhibitor, which presents a pyrimidine group attached to



**Figure 7.** Seven-membered ring IMHB: C6 borylation of 3-aminoindazole.

an indole skeleton.<sup>58</sup> We subjected osimertinib analogue **12** to CHB conditions (Figure 8). The C6-borylated indole **13** was



**Figure 8.** Expanding IMHB to other scaffolds: C6 borylation of an osimertinib analogue with a pyrimidine directing group directed by a C–H...N IMHB.

produced, although with moderate selectivity. We were fortunate to crystallize **12** and the crystal structure showed the C–H...N that we had proposed with the pyrimidine groups as the hydrogen bond acceptor and the C4 hydrogen of the indole being the hydrogen bond donor. We used X-ray coordinates to evaluate the QTAIM topology of **12** and found

a BCP that supports the IMHB C–H...N. Next, changes in  $^1\text{H}$  NMR of **12** taking N-methylindole as the reference were calculated. Surprisingly, we found that both C2 and C4 hydrogens showed a significant chemical shift displacement. We propose that in solution the pyrimidine ring may equilibrate between two conformations involving IMHB with H2 and H4. The IMHB energy for H4 calculated from  $\Delta\delta$  is 1.13 kcal/mol, which is higher than that calculated by QTAIM. This difference might be due to the different conformations found in the solution in contrast to the solid state.

### 3. CONCLUSIONS

A diverse array of regioselective remote CHBs can be driven by intramolecular steric shields created via IMHB. The previously inexplicable para CHB found with 2-chloro and 2-methoxyaniline now is explained by a Bpin steric shield generated after *in situ* N-borylation. Furthermore, N–Bpin steric shields can lead to para CHB of other ortho-substituted anilines, 7-borylation of 1-naphthylamines, para CHB of certain N-alkylated anilines, and to the elusive 5-borylation of indoles. Bpin steric shielding can be extended to motifs without nitrogen, such as 1-borylated naphthalenes, which undergo C6-selective CHB. The wide variety of scaffolds that can be selectively borylated at remote positions due to a Bpin group highlights the versatility of intramolecular steric shields.

We traced back the remote CHB selectivity to the presence of a C–H...O IMHB in N-borylated intermediates with the Bpin as the hydrogen bond acceptor. A BCP found by QTAIM and a characteristic  $^1\text{H}$  NMR chemical shift displacement of the hydrogen bond donor, the ortho aniline hydrogen after N-borylation here, is support for an IMHB. The energetic cost to disrupt the planarity of N-borylated anilines and the necessity of oxygen in the boryl group to achieve a para CHB also support the observed selectivity to involve IMHB. A seven-membered ring IMHB can also produce the steric as shown in the C6-selective borylation of N-methyl-3-aminoindazole. Furthermore, a C5 borylation of the indole ring in an osimertinib analogue where a pyrimidine forms the steric shield via a C–H...N IMHB further expands this means of remote regiocontrol. The most significant outcome of our study is that the IMHB Bpin steric shielding explains regioselectivities in catalytic C–H borylations, where standard steric models and correlations with NMR chemical shifts fail. We anticipate that our efforts presented here will be used to design other methods for remote functionalization driven by intramolecular interactions.

### ■ ASSOCIATED CONTENT

#### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.1c05701>.

Experimental procedures, including preparation of starting materials, compound characterization data, and computational details for the calculations (PDF)

### ■ AUTHOR INFORMATION

#### Corresponding Authors

Milton R. Smith, III – Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States; [orcid.org/0000-0002-8036-4503](https://orcid.org/0000-0002-8036-4503); Email: [smithmil@msu.edu](mailto:smithmil@msu.edu)

Robert E. Maleczka, Jr. – Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States; [orcid.org/0000-0002-1119-5160](https://orcid.org/0000-0002-1119-5160); Email: [maleczka@chemistry.msu.edu](mailto:maleczka@chemistry.msu.edu)

#### Authors

Jose R. Montero Bastidas – Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States; [orcid.org/0000-0002-6325-8565](https://orcid.org/0000-0002-6325-8565)

Arzoo Chhabra – Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States; [orcid.org/0000-0001-8280-8107](https://orcid.org/0000-0001-8280-8107)

Yilong Feng – Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States; [orcid.org/0000-0002-8060-7640](https://orcid.org/0000-0002-8060-7640)

Thomas J. Oleskey – Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States; [orcid.org/0000-0002-0423-9508](https://orcid.org/0000-0002-0423-9508)

Complete contact information is available at: <https://pubs.acs.org/10.1021/acscatal.1c05701>

#### Notes

The authors declare the following competing financial interest(s): M.R.S. and R.E.M. own a percentage of BoroPharm, Inc.

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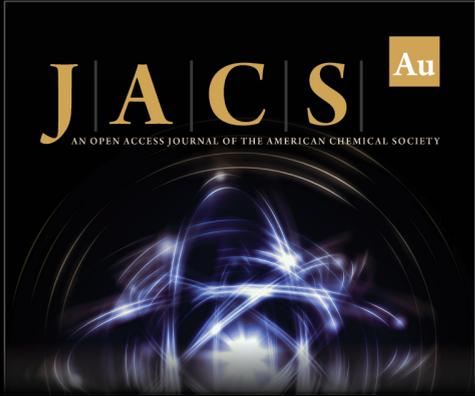
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