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Achieving High Ortho Selectivity in Aniline C–H Borylations by Modifying Boron Substituents

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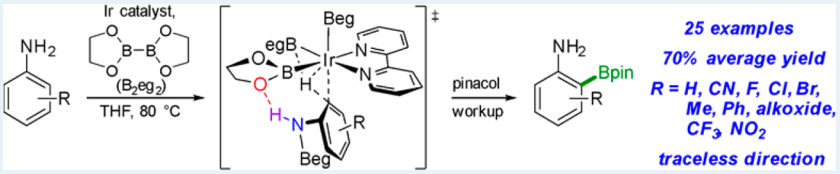
Supporting Information



ABSTRACT: High ortho selectivity for Ir-catalyzed C–H borylations (CHBs) of anilines results when B_2eg_2 (eg = ethylene glycolate) is used as the borylating reagent in lieu of B_2pin_2, which is known to give isomeric mixtures with anilines lacking a blocking group at the 4-position. With this modification, high selectivities and good yields are now possible for various anilines, including those with groups at the 2- and 3-positions. Experiments indicate that ArylN(H)Beg species are generated prior to CHB and support the improved ortho selectivity relative to B_2pin_2 reactions arising from smaller Beg ligands on the Ir catalyst. The lowest-energy transition states (TSs) from density functional theory computational analyses have N–H···O hydrogen-bonding interactions between PhN(H)Beg and O atoms in Beg ligands. Ir-catalyzed CHB of PhN(H)Me with B_2eg_2 is also highly ortho-selective. ^{1}H NMR experiments show that N-borylation fully generates PhN(Me)Beg prior to CHB. The TS with the lowest Gibbs energy was the ortho TS, in which the Beg unit is oriented anti to the bipyridine ligand.

KEYWORDS: *C–H activation, hydrogen bonding, computational chemistry, aniline, ortho functionalization*

INTRODUCTION

Anilines are chemicals with important dye, pharmaceutical, agrochemical, and polymer applications.[1] Aniline is commercially prepared by benzene nitration followed by hydrogenation of the nitrobenzene intermediate. Most commercially available substituted anilines are prepared by derivatization of aniline, often through electrophilic aromatic substitution (EAS).[2] The NH_2 group is classified as a strong ortho/para director,[3] even though traditional nitration conditions give 32–49% *m*-nitroaniline along with the major para isomer.[4] The best selectivities for EASs are typically C4 functionalizations, and most ortho-selective examples are for anilines substituted at C4. For anilines that are unsubstituted at C4, EASs generate significant quantities of para isomers even in some of the most ortho-selective methods.[5] The best traditional synthetic method for aniline ortho functionalization is directed ortho metalation (DoM) of carbamate derivatives followed by addition of an electrophile to the ortho carbanion.[6] This approach requires conversion of the aniline to the carbamate, which is removed after the reaction if aniline products are desired.

Even though DoM reactions are remarkably powerful,[7] catalytic methods can exhibit complementary selectivities and functional group tolerance.[8] There are several examples of catalytic ortho functionalizations of aniline. Most require the installation of a directing group prior to C–H functionalization. Removal of the directing group is required to restore the nitrogen functionality to that in the aniline starting material.[9−11] While the NH_2 group would be untouched in ideal catalytic ortho functionalization of primary anilines, the next most desirable process is one where there is no trace in the product of any in situ modification of the amino group during catalysis.

Traceless Ir-catalyzed C–H borylation (CHB) of primary anilines has been described in the literature.[12] C–H borylation is a synthetic method where sp^2, sp^3, and sp C–H bonds are converted to C–B bonds.[13−15] With few exceptions,[16,17] most examples require a catalyst, and metal-catalyzed CHBs have been reported for a number of transition metals.[13,18−20] Some of the earliest reports of metal-catalyzed CHBs of arene C(sp^2)–H bonds indicated that the least hindered C–H bonds were generally more reactive.[21−23] This feature became a hallmark of Ir-catalyzed CHBs because the regioselectivities generally complement those found in EAS and DoM as well as the regioselectivities in early examples of catalytic intra- and

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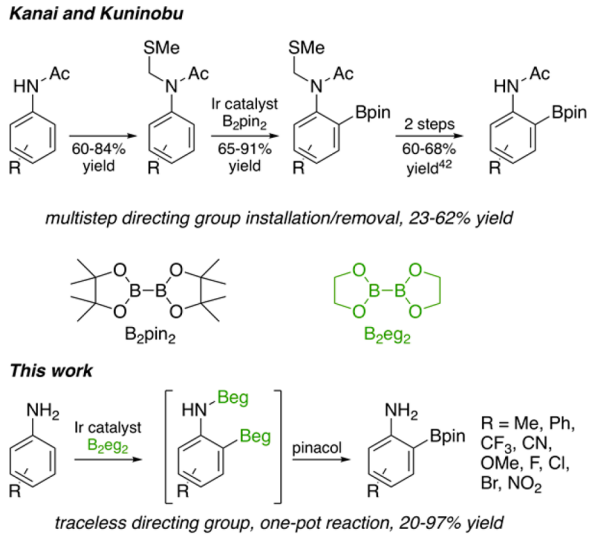
intermolecular C−H functionalizations that are ortho-selective.[24,25]

The first report of catalytic ortho CHBs relied on classic chelate-directed mechanisms where a substrate functional group binds to a vacant metal site.[26−28] Directing effects of this type have been branded as "inner-sphere".[29] Other inner-sphere approaches, like relay-directed ortho CHBs of silylated phenols and anilines, where reversible Si−H oxidative addition to Ir was proposed to direct borylation, were also developed.[30]

Mechanisms for ortho-directed CHBs where the metal center is *not* a directing element have been proposed.[31,32] In line with Taube's definition, these are defined as "outer-sphere" mechanisms.[29,33] Examples of outer-sphere direction in ortho CHBs include Lewis acid−base,[34−36] hydrogen bonding,[12,33,37] electrostatic interactions,[38] and an example where both inner- and outer-sphere mechanisms are plausible.[39] The electrostatic mechanism is a more subtle variant of the ion-pairing mechanisms proposed by Phipps and co-workers in recently designed meta-selective CHBs,[40] which complements other meta-selective CHBs where outer-sphere mechanisms are proposed to account for selectivity.[34,37,41]

Kanai and Kuninobu recently disclosed ortho CHBs of aniline and phenol derivatives (Scheme 1).[36] The bipyridine

Scheme 1. Comparison of the Kanai−Kuninobu CHB of N-Acylated Anilines with This Work[36,43,44]



with the best selectivity is not commercially available. It has an electron-withdrawing aryl group at the bipyridine 5-position and was synthesized from commercially available precursors.[42] To achieve ortho CHB of primary anilines, thiomethyl methylene (CH_2SMe) and acyl groups must be attached to N. While this approach provides excellent ortho selectivities, ligand synthesis and the additional synthetic steps to add and subsequently remove functional groups at N are unappealing if ortho-borylated primary anilines are the desired product.

The previously reported traceless CHBs of primary anilines built on an initial report of ortho CHBs of *N*-Boc-anilines.[12,33] For these aryl carbamates, experiment and theory were consistent with an outer-sphere mechanism involving N−H···O hydrogen bonding between the aniline substrate and an Ir−Bpin ligand giving rise to the ortho selectivity.[33] As shown in Figure 1, previous CHBs required C4 substituents larger than H to achieve high ortho selectivity.[12,33] Additionally, sub-

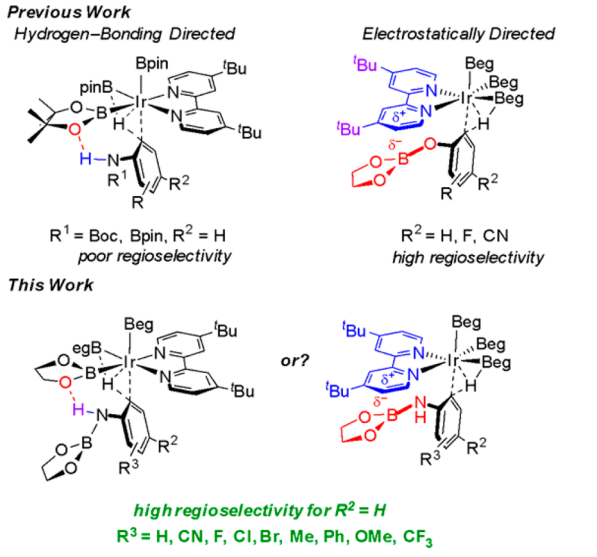


Figure 1. Proposed transition states for ortho borylations of anilines and phenols.

stitution at C2 was deleterious to ortho selectivity. Given the fact that C−B bonds can be readily converted to a host of functional groups and the aforementioned limited scope of previous ortho-directed CHBs of anilines, a method overcoming these shortcomings would be highly desirable.

Traceless ortho-directed CHB of phenols was also recently described.[38] The initial CHB substrates were phenol *O*-boronate esters (ArOBpin, pin = pinacolate). Experimental and computational studies pointed to transition state (TS) stabilization arising from electrostatic interactions between the bipyridine bound to Ir and OBpin of the phenol boronate ester. Like previous aniline borylations, 4-substituents larger than H were necessary to achieve synthetically useful ortho selectivity.

An in silico redesign of the catalyst predicted that the ortho CHB transition state could be significantly stabilized if the Bpin groups on Ir and the phenol boronate ester were replaced with Beg (eg = ethylene glycolate). Indeed, this led to exquisite ortho selectivities for Ir-catalyzed CHBs of phenols when the diboron reagent B_2eg_2 was used in lieu of HBpin. This raised the question of whether ortho selectivities for aniline CHBs could be similarly improved using B_2eg_2. If the ortho selectivities indeed improve, is the transition state stabilization due to electrostatic interactions or enhanced hydrogen bonding? This paper addresses these questions using experiment and theory synergistically.

RESULTS AND DISCUSSION

Ir-catalyzed CHB of aniline with B_2eg_2 was used to optimize the reaction conditions. First, a tetrahydrofuran (THF) solution of aniline, 0.5 equiv of B_2eg_2, and 0.5 mol % $[Ir(OMe)(cod)]_2$ was briefly heated to generate PhN(H)Beg, which was verified by $^{11}B/^{1}H$ NMR spectroscopy. Then NEt_3, 4,4′-di-^{t}Bu-2,2′-bipyridine (dtbpy), and additional B_2eg_2 and $[Ir(OMe)(cod)]_2$ were added, and the resulting solution was heated at 80 °C until borylation ceased. The best results were obtained with a 2.5 mol % loading of $[Ir(OMe)(cod)]_2$, 5 mol % dtbpy, 2.0 equiv of B_2eg_2, and 2.0 equiv of NEt_3. When CHB was complete, the eg group was transesterified by treating the reaction mixture with 3.0 equiv of pinacol, and the more stable Bpin product was purified and isolated in 67% yield.

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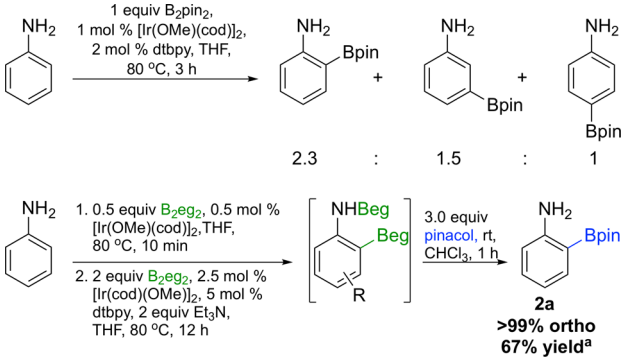
Conversion to products suffered at lower catalyst loadings; however, high regioselectivity was achieved. The regioselectivities for aniline CHBs with B_2pin_2 and B_2eg_2 are compared in Scheme 2. To avoid significant diborylation, the control

Scheme 2. Aniline CHBs with B_2pin_2 and B_2eg_2



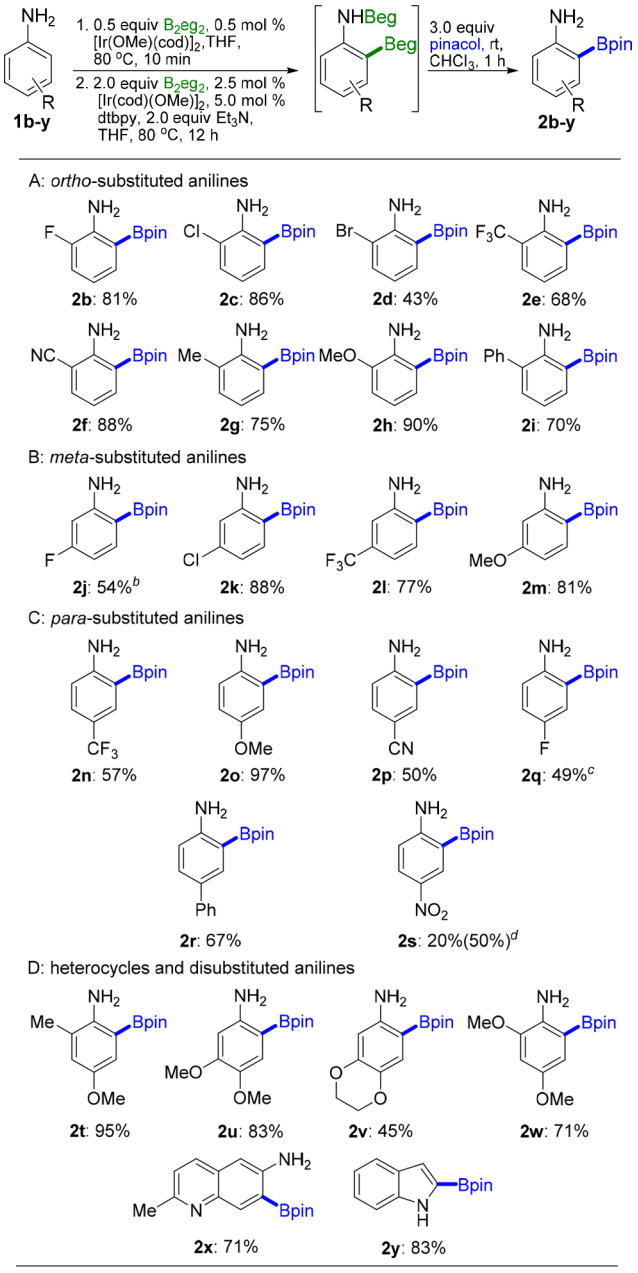
[a]At a 0.5 mmol scale, 67% yield was obtained. At a 5 mmol scale with a 1 mol % loading of $[Ir(OMe)(cod)]_2$ (0.25 mol % in step 1 and 0.75 mol % in step 2), the yield increased to 75%.

reaction used less B_2pin_2 and a shorter reaction time. Notably, the 2.7:1.8:1 ortho:meta:para isomer ratio for CHB with B_2pin_2 is similar to the ratio previously reported for Ir-catalyzed aniline CHB with HBpin (ortho:meta:para = 2.3:1.5:1).[12] While the major regioisomer is the ortho product, which suggests some favorable interactions for ortho CHB with B_2pin_2, substantial quantities of meta and para CHB products dampen the synthetic utility. In contrast, B_2eg_2, which is easily prepared from commercially available $(OH)_2B-B(OH)_2$ and ethylene glycol, provides exquisite ortho selectivity.

We next assessed the substrate scope for ortho selectivity. Table 1 lists the results for 24 substrates. The catalyst loadings in Table 1 are (6 mol % Ir) higher than we usually use for borylations because the reactions were run with 0.5 mmol of aniline substrates using weighed amounts of the $[Ir(OMe)(cod)]_2$. When CHB of aniline was performed on a 5 mmol scale with 0.25 and 0.75 mol % loadings of the precatalyst (2 mol % Ir) in steps 1 and 2, respectively, in Scheme 2, ortho-borylated product **2a** was isolated in 75% yield. The average isolated yield is 71 ± 4% for substrates in Table 1. For substrate **1q**, 20% diborylation contributed to the low yield of monoborylated product. The only diborylated isomers detected were 2,6-regioisomers. The reaction with substrate **1s** had the lowest yield, but it is the first metal-catalyzed CHB of a nitro-containing substrate that gives more than trace quantities. In crude reaction mixtures, CHB was detected only at sites ortho to NH_2.

Gratifyingly, CHBs of meta-substituted anilines **1j–m** did not generate 5-borylated products, as had been found for Ir-catalyzed CHBs of anilines **1k–m** with HBpin.[12] The yields of ortho-borylated products from CHB of anilines **1k**, **1l**, and **1m** increased over those previously reported from CHBs with HBpin by 46%, 24%, and 55%, respectively. Furthermore, this methodology outperforms previously reported CHB of *N*-Boc-anilines. No CHBs of 2-substituted *N*-Boc-anilines have been reported, and the ortho selectivity eroded for substrates that lacked blocking groups at the 4-position. For example, CHB of 3-chloro-*N*-Boc-aniline provided 92% yield but exhibited an ortho:meta selectivity of only 2:1.[33] In addition, this yield does not include removal of the Boc group; however, substrate **1k**

Table 1. Ortho Borylation of Substituted Anilines with B_2eg_2[a]



[a]All reactions were carried out on a 0.5 mmol scale, and yields are reported for isolated materials after column chromatographic separation. [b]The other ortho-borylated isomer was observed but underwent rapid protodeboronation. [c]20% ortho,ortho diborylation was observed. [d]Isolated yield: 20%. GC conversion: 50%.

provided only the ortho-borylated product **2k**, which was isolated in 88% yield. Substrates **1b–i** underwent CHB with B_2eg_2 at C6 exclusively, yielding ortho-borylated products **2b–i**. This stands in sharp contrast to previously reported CHBs of 2-substituted anilines with HBpin, where ortho borylation was not observed.[12] Borylation of quinoline **1x** proceeded smoothly, providing the 7-borylated product **2x** in 71% isolated yield. Indole CHB with either B_2eg_2 or B_2pin_2 gives the 2-borylated products in comparable yields.[45] Compounds **2c–i** and **2t–x** are new. Of these, **2g** is the only structure whose boronic acid has been reported in the primary literature.[46] Significantly, the

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transformations in Table 1 do not require installation and removal of a directing group and use dtbpy, the most commonly used ligand in Ir-catalyzed CHBs.

The improved selectivity raises the interesting question of whether its molecular origin arises from ligand−substrate electrostatic interactions or hydrogen bonding (Figure 2). To

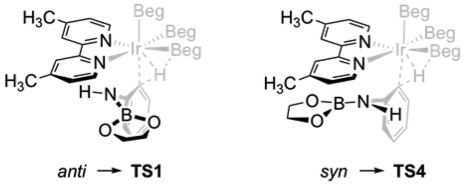

Figure 2. Proposed transition states for ortho borylations of anilines and phenols.

tackle this question, we turned to theory. Density functional theory (DFT) calculations used the M06 functional with the 6-31G* basis set for light atoms and the SDD basis set and core potential for Ir. The polarizable continuum model was the self-consistent reaction field method applied for the THF solvent. Compared with other systems that we have studied, transition state location was challenging. Low-energy imaginary frequencies associated with Me group rotations in the dtbpy ligands plagued calculations on the full system. Replacing the bipyridine ^{t}Bu groups with Me groups made the problem more manageable, but Me rotations still generated multiple imaginary rotational frequencies when software default values for step sizes and integration grids were used. Ultimately, TSs with a single imaginary frequency corresponding to C−H scission were located. The maximum atom displacement in all of the calculated TSs exceeded software convergence thresholds. In addition, the root-mean-square (RMS) displacement exceeded the software convergence defaults in approximately half of the calculated TSs. For two of these TSs, the maximum displacement was 10 times greater than the convergence default. We mention them only in passing (vide infra). Atomic Cartesian coordinates and energies for these TSs are included in the Supporting Information (SI).

Four transition states (**TS1−4**) were located for ortho borylation. Starting points for TS location included syn and anti orientations of the PhN(H)Beg moiety with respect to the bipyridine ligand (Figure 2) and two additional geometries with close contacts between the aniline N−H and O atoms of a Beg ligated to Ir. Figure 3 depicts the TSs and their relative Gibbs energies. **TS1** is analogous to the lowest-energy transition state for phenol ortho borylation. In the other three TSs, the PhN(H)Beg H is hydrogen-bonded to a Beg O. The H···O distances in **TS2**, **TS3**, and **TS4** are 2.07, 2.28, and 2.49 Å, respectively.

The $\Delta\Delta G^{\ddagger}$ values for **TS2−4** relative to **TS1** are given as G_{rel} in Figure 3. The hydrogen-bonded TSs **TS2**, **TS3**, and **TS4** are stabilized by 1.9, 2.6, and 1.7 kcal·mol^{-1}, respectively, relative to **TS1**. Notably, the starting geometry for **TS4** was similar to that for **TS1** except that the Beg moiety was syn to the 4,4′-dimethylpyridine ligand (Figure 2). The syn PhOBeg TS has short (∼3.0 Å) contacts between the Beg group and the bipyridine ligand that are reminiscent of π stacking.[38] The analogous TS was not found for PhN(H)Beg. Instead, the N(H)Beg group rotated about the N−C_{ipso} bond to engage in hydrogen bonding between the aniline proton and an Ir−Beg oxygen. A TS analogous to the syn geometry for PhOBeg was located for CHB of PhN(Me)Beg (**TS8**, vide infra).

The highest-energy hydrogen-bonded TS (**TS4**) has the longest H···O distance, but it is only 0.2 kcal·mol^{-1} less stable than **TS2**, where the H···O distance is 0.42 Å shorter. The number of heavy atoms in **TS1−4** is too large to apply the level of theory that is typically used to quantify stabilization from hydrogen bonding.[47] The ν_{N-H} values for N−H vibrations of the N(H)Beg group in **TS2** (3533 cm^{-1}), **TS4** (3541 cm^{-1}), and **TS3** (3557 cm^{-1}) do not correlate with distance, which is not surprising since Beg O lone pair interactions with the aniline H differ with the Beg ligand orientation. The ν_{N-H} values in **TS2−4** are 62−38 cm^{-1} lower than that calculated for PhN(H)Beg (ν_{N-H} = 3595 cm^{-1}) at the same level of theory. On the basis of the infrared shift, H···O distance, and N−H lengthening (see the SI), the hydrogen-bonding interaction is classified as a weak hydrogen bond, which is mostly electrostatic in nature.[48]

The TS for para CHB (**TS5**) was also located. Its Gibbs energy was higher than those of all of the hydrogen-bonding TSs, and it was separated from the lowest-energy TS (**TS3**) by 1.0 kcal·mol^{-1}. Attempts to locate the TS for meta CHB yielded a structure with one imaginary frequency (**TS$_{meta}$**; see pp S43−S44 in the SI), but the respective RMS and maximum displacements were 10 and 34 times greater than the software default convergence criteria. The theoretical $\Delta\Delta G^{\ddagger}$ value of 1.0

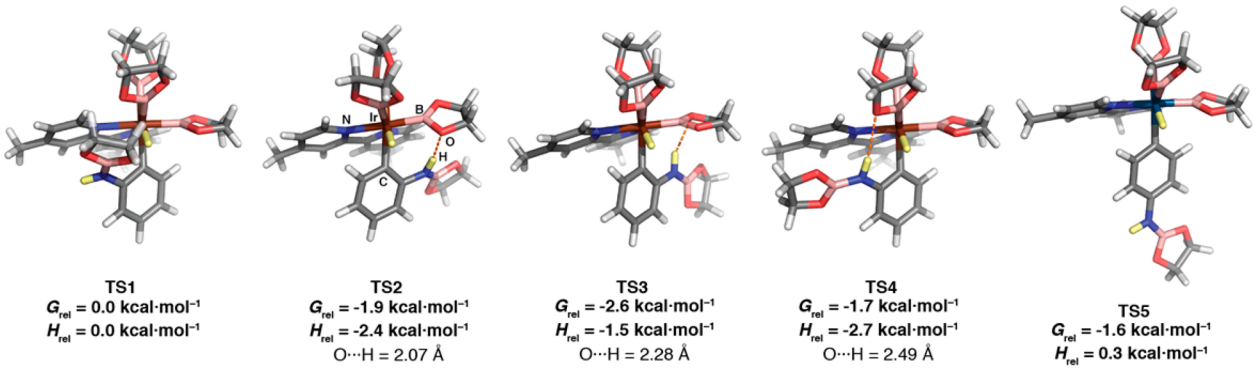

Figure 3. Computed transition states for Ir-catalyzed CHB of PhN(H)Beg with B_2eg_2. The N−H hydrogen and the C−H hydrogen in the bond being cleaved are yellow. Dashed orange lines indicate hydrogen-bonding interactions. G_{rel} and H_{rel} are $\Delta\Delta G^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ values relative to **TS1**, respectively. DFT calculations were performed using the M06 functional with the 6-31G* basis set for light atoms and the SDD basis set and core potential for Ir.

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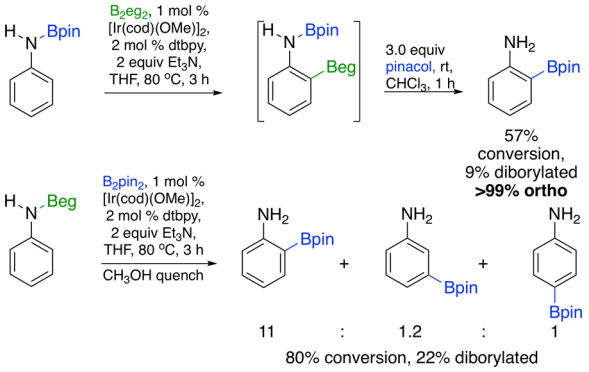
kcal·mol^{-1} between **TS3** and **TS5** predicts an ortho:para ratio of 8.2:1. While the ortho:para ratio of 26:1 predicted from the calculated $\Delta\Delta H^{\ddagger}$ values matches experiment more closely, both the $\Delta\Delta G^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ predictions fall short of the observed experimental selectivity. This is not uncommon in combined experimental/computational studies.

The computational results predict that Beg outperforms Bpin because the N(H)Beg substituent and Beg ligands can adopt optimal hydrogen-bonding configurations with minimal steric interference. CHBs of PhN(H)Bpin with B_2eg_2 and PhN(H)-Beg with B_2pin_2 were performed as an experimental test of this hypothesis (Scheme 3).

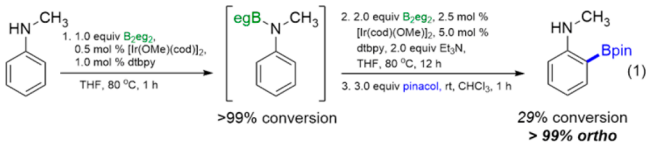
Scheme 3. Aniline CHBs of PhN(H)Bpin with B_2eg_2 and PhN(H)Beg with B_2pin_2



CHB of PhN(H)Bpin exhibits the same high ortho selectivity when B_2eg_2 is the borylating agent as is observed for CHB of aniline with B_2eg_2. When the NBeg in the structure of **TS3** is converted to NBpin and the syn bipyridine Me is converted to ^{t}Bu, the closest C···C contact (4.31 Å) is longer than the closest C···C contact (3.96 Å) in the crystal structure of Ir(Bpin)$_3$(dtbpy)(coe) (coe = cyclooctene).[23] Consequently, retention of high ortho selectivity for the NBpin/B_2eg_2 combination is not surprising.

In contrast, the ortho selectivity erodes when PhN(H)Beg is borylated with B_2pin_2, although the ortho:meta:para ratio of 11:1.2:1 is better than the 2.5:1.5:1 ratio for Ir-catalyzed CHB of aniline with HBpin.[12] The TSs for the PhN(H)Beg/Ir−Bpin structures were not calculated. However, it is not unreasonable to expect that the calculated steric destabilization from changing Beg to Bpin in phenol ortho CHB transition states would translate to aniline CHBs.[38] The experiments in Scheme 3 demonstrate that the B substituents on the boryl ligands, and thus the CHB reagent, have the greater influence on the ortho selectivity.

Meta and para CHB of *N*-methylaniline would further support the hypothesis that hydrogen bonding is responsible for the high ortho selectivity of B_2eg_2 in aniline CHBs since PhN(Me)Beg lacks an NH moiety. Remarkably, CHB of PhN(H)Me yields only the ortho isomer, albeit with only 24% conversion. In operando NMR spectroscopy shows that PhN(H)Me is fully converted to PhN(Me)Beg before CHB ensues (eq 1). Even though the conversion of PhN(Me)Beg to borylated products is low, the ortho product is the only CHB isomer detected.



This surprising result raises an obvious question. Would calculations also favor ortho CHB when hydrogen bonding is not an option? The calculated TS structures for meta CHB (**TS6**) and ortho CHB with anti (**TS7**) and syn (**TS8**) dispositions of the Beg group relative to the bipyridine ligand are shown in Figure 4.

In line with phenol ortho CHBs, the Gibbs energy of the syn TS (**TS8**) is higher than that of the anti TS (**TS7**). Other shared features of **TS8** with the syn phenol TS include short contacts between the NBeg N and O atoms and the bipyridine N and flanking C atoms and a distortion of the pyridine Ir−N bond. This distortion reduces the σ overlap of the pyridine N lone pair with Ir and is best quantified by $\angle_{\sigma}$, which is defined in eq 2:

$$\angle_{\sigma} = 180^{\circ} - \angle C4_{py}{-}N_{py}{-}Ir \qquad (2)$$

When the Ir atom lies in the pyridine plane, the σ overlap is maximized, and $\angle_{\sigma} = 0$. The $N_{py}{-}B_{Beg}$ distances, $C_{py}{-}O$ distances, and $\angle_{\sigma}$ values for the phenol and aniline TSs are summarized in Table 2. The N−B and C−O distances in **TS8** are 0.05−0.13 Å longer than the corresponding values in the phenol ortho borylation TS. The negative charge on the EBeg group (E = NMe, O) is smaller for NMe than for O. Consequently, the electrostatic interaction is weaker, which is consistent with the elongation of the EBeg contacts with the syn pyridine of the bipyridine ligand when E = N(Me)Beg. The

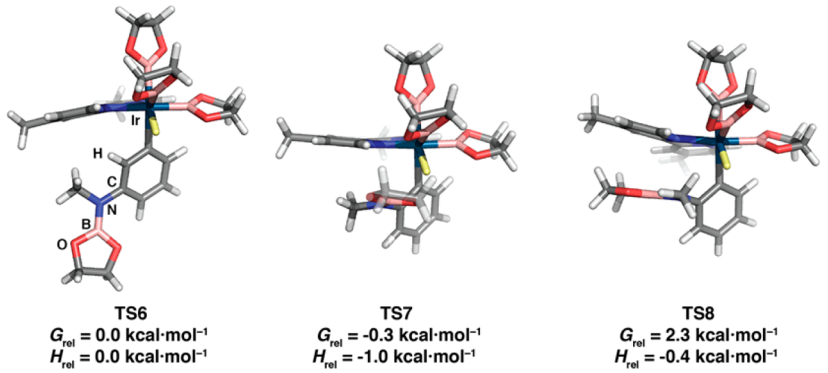


Figure 4. Computed transition states for Ir-catalyzed CHB of PhN(CH$_3$)Beg with B_2eg_2. The hydrogen in the C−H bond being cleaved is shown in pale yellow. G_{rel} and H_{rel} are $\Delta\Delta G^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ values relative to **TS6**.

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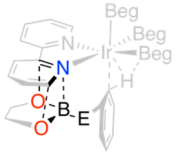
Table 2. Structural Comparisons between Syn TSs in 4-C_6H_4OBeg and $C_6H_5NMe(Beg)$ CHBs



E = NMe (**TS8**), O

E	N–B (Å)	C–O (Å)	$\angle_\sigma$ (°)
NMe	3.10	3.14, 3.33	11.8
O[a]	2.97	3.09, 3.24	18.5

[a]Data for **TS5-OBeg$_{syn\text{-}dtbpy}$** in Figure 3 of ref 36.

6.5° decrease in $\angle_\sigma$ when E is switched from NMe to O also supports weakening of the electrostatic interaction between N(Me)Beg and the syn pyridine.

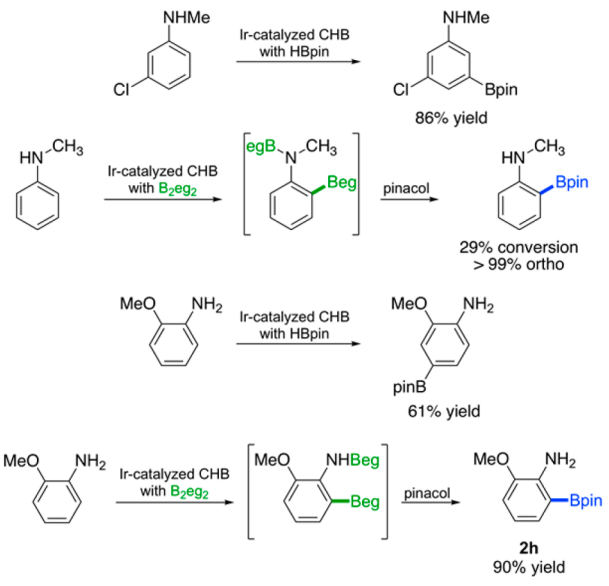
The G_{rel} and H_{rel} values ($\Delta\Delta G^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ values relative to **TS6**) in Figure 4 predict that the ortho CHB **TS7**, where the Beg group is anti to the bipyridine ligand, has the lowest energy. The theoretical $\Delta\Delta G^{\ddagger}$ value of −0.3 kcal·mol^{-1} predicts an ortho:meta ratio of 1.5:1, and the $\Delta\Delta H^{\ddagger}$ value predicts a higher ortho:meta ratio of 4.1:1. Although the ortho isomer is predicted to be the major one, the actual selectivity is much higher. While the trend in the computed ratio correlates with the experimental results, future studies at a higher level of theory are warranted. Overall, the experimental findings show that hydrogen bonding is not required for ortho selectivity for *N*-methylaniline when the CHB reagent is switched from B_2pin_2 to B_2eg_2.

In addition to removing previous limitations for ortho CHBs of anilines with B_2pin_2 and HBpin, CHBs with B_2eg_2 can complement the selectivities for aniline CHBs with commonly used boron reagents. Scheme 4 shows two examples highlighting the most dramatic differences in CHB selectivities.

CONCLUSIONS

The important findings of this study are listed below:

Scheme 4. Regiochemical Consequences of Beg and Bpin Reagents in Aniline CHBs



- By changing the boron reagent from HBpin or B_2pin_2 to bis(ethylene glycolato)diboron (B_2eg_2), ortho CHBs can now be accomplished with a wide variety of anilines. Substrates whose previously poor (or altered) regioselectivity is now overcome include (i) anilines with no substituents at the 4-position, (ii) 2-substituted anilines, (iii) 3-substituted anilines, and (iv) *N*-methylaniline.
- CHB ortho to NH_2 in 2-methylquinolin-6-amine is possible.
- The substituents on the Ir boryl ligands have the greatest impact on the selectivity.
- The ortho-borylated isomer is the only product observed in the Ir-catalyzed CHB of *N*-methylaniline with B_2eg_2. ^{1}H NMR studies show that PhN(H)Me is fully converted to PhN(Beg)Me before CHB ensues. Thus, hydrogen bonding in the TS cannot account for the ortho selectivity.
- For Ir-catalyzed CHB of PhN(H)Beg, computational studies revealed three NH···O hydrogen-bonding transition states where the aniline N(Beg)H interacted with an Ir Beg ligand. The NH···O TSs have lower Gibbs energies than an ortho CHB TS that lacks hydrogen bonding.
- The Gibbs energies of the three NH···O TSs are also lower than that for the para CHB TS of PhN(H)Beg.
- Of three TSs calculated for Ir-catalyzed CHB of PhN(Me)Beg, the ortho TS where the Beg moiety is anti to the bipyridine ligand has the lowest Gibbs energy. This TS closely resembled the favored TS for CHB ortho to the OBeg of 4-FC_6H_4OBeg, where the selectivity is proposed to arise from electrostatic interactions between the OBeg unit and the proximal pyridine ring of the bipyridine ligand.

In summary, the diboron reagent B_2eg_2 lifts the limitations seen in Ir-catalyzed CHBs of anilines with HBpin. Experiment and theory are consistent with stabilization of hydrogen-bonding TSs when Bpin Ir boryl ligands are replaced by less sterically encumbered Beg ligands. Further exploration of other diboron reagents and the synthetic utility of the associated CHB products is underway in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b00641.

Experimental details, product characterizations, computational methods, energies, and Cartesian coordinates (PDF)

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Notes

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

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(43) The yields for deprotection are given in an end note in ref 35. The products are not specified, and experimental details were not reported. We presume that the deprotected compounds are N-acylated since all of the ArN(Ac)(CH_2SMe) reactants were prepared from acylated anilines.
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