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C–H Activation

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Hydrogen Bond Directed *ortho*-Selective C–H Borylation of Secondary Aromatic Amides

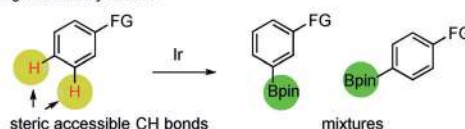
Shao-Tao Bai, Charles B. Bheeter, and Joost N. H. Reek*

Abstract: Reported is an iridium catalyst for *ortho*-selective C–H borylation of challenging secondary aromatic amide substrates, and the regioselectivity is controlled by hydrogen-bond interactions. The **BAIPy**-Ir catalyst forms three hydrogen bonds with the substrate during the crucial activation step, and allows *ortho*-C–H borylation with high selectivity. The catalyst displays unprecedented *ortho* selectivities for a wide variety of substrates that differ in electronic and steric properties, and the catalyst tolerates various functional groups. The regioselective C–H borylation catalyst is readily accessible and converts substrates on gram scale with high selectivity and conversion.

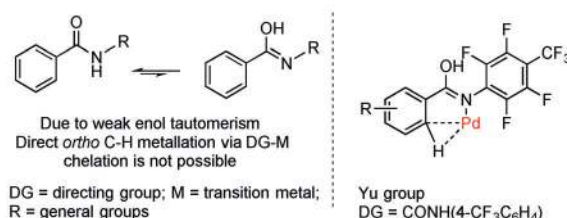
Transition metal catalyzed C–H bond activation enables the functionalization of complex molecules without the need of preactivation, allowing the introduction of functional groups at a late stage of a synthesis sequence.^[1] The direct C–H borylation is of particular interest as the boron functional group allows further modification by a wide variety of transformations, including Suzuki coupling reactions, amination, hydroxylation, and halogenation, providing structural and functional molecular complexity.^[2] Crucial for the application is that the selectivity of the reaction can be controlled, and this is particularly challenging for C–H bonds that are sterically and electronically deactivated. Recently, the use of supramolecular interactions between the substrate and the ligand of a metal complex have been explored to control the selectivity,^[3] and this resulted in catalysts for selective *meta*- or *para*-C–H borylation for electronically (un)activated substrates.^[4] However, *ortho*-selective C–H borylation has only been reported for electronically activated arenes, such as an amine-,^[5] alcohol-,^[6] or thioether-substituted^[7] arenes. Secondary aromatic amides are very common structural motifs in pharmaceuticals, agrochemicals, and fine chemicals,^[8] and the *ortho*-selective C–H borylation of this class of compounds would therefore be highly interesting. However, the direct *ortho*-C–H borylation of this class of compounds is highly challenging. For common iridium-

catalyzed C–H borylation the regioselectivity is largely dictated by steric factors leading to *meta*- and *para*-C–H borylation of aromatic compounds (Figure 1 a).^[1a,2d,9] The use

a) Iridium-catalyzed C–H borylation: start-of-art transformations limited by regioselectivity issues



b) Previous work for *ortho*-C–H borylation of secondary aromatic amides



c) This work: Direct *ortho*-selective C–H borylation of secondary aromatic amides by hydrogen bonds for supramolecular substrate preorganization

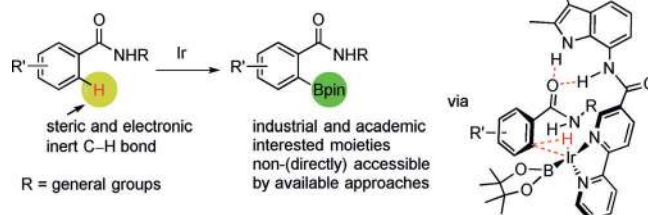


Figure 1. a) General regioselectivity in iridium-catalyzed C–H borylation of aromatic compounds. b) Previous work on *ortho*-selective C–H borylation of secondary aromatic amides by a chelation approach. c) Direct *ortho*-selective C–H borylation of unactivated secondary aromatic amides through hydrogen bonding to the catalyst.

of the amide functionality as a directing group does not work as its coordination to a metal center is generally weak because of unfavorable tautomerization.^[10] Strategies that involve (temporary) directing groups such as silyl, iminyl, and pyridyl, operating by chelation to the metal center, have not been reported for secondary aromatic amides.^[11] To the best of our knowledge, the group of Yu^[11d,e] reported the only protocol for *ortho*-C–H borylation catalyzed by palladium through a metal-substrate chelation approach for substrates with a special electron-withdrawing directing group to promote the enol tautomerization (Figure 1b). Herein, we report the design of a supramolecular iridium-based catalyst for highly *ortho*-selective C–H borylation of these secondary aromatic amides and it is based on substrate orientation using hydrogen bonding.

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We designed the iridium-based borylation catalyst reported here assuming one indole amide hydrogen-bond motif, to preorganize the aromatic amide substrates for *ortho*-C–H borylation, should be sufficient. For *ortho* selectivity, the motif should be close to the catalyst, and as such direct coupling of an indole amide to the ligand 2,2'-bipyridine (**BPy**) was considered. DFT calculations show that the Ir complex of this ligand preorganizes *N*-methylbenzamide (**1s**) with the *ortho*-C–H bond oriented for selective activation (Figure 2). The **BAIPy** ligand was prepared on multigram scale from commercially available compounds in three straightforward synthetic steps (for details see the Supporting Information).

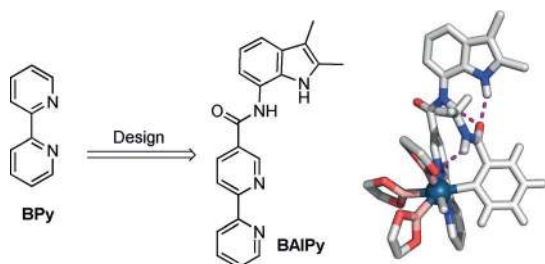


Figure 2. Design of the **BAIPy** ligand containing an indole amide functional group for substrate orientation in *ortho*-selective C–H borylation of secondary aromatic amides. Support for the substrate-catalyst complex formation is provided by DFT modeling of the substrate-**BAIPy**-trisboryl-Ir catalyst complex (the methyl groups on the boryl ligand were omitted for clarity).

Binding studies in [D_8]toluene and [D_8]THF using 1H NMR spectroscopy show that **1s** is indeed bound to the free **BAIPy** ligand with a binding energy around 6.3 and 4.0 kJ mol^{-1} , respectively (see Figures S1–S6, and Tables S1 and S2 in the Supporting Information).

To investigate the performance of the supramolecular catalyst we initially performed catalytic experiments in THF using **1s** as the model substrate. As expected, the catalytic reaction using the parent **BPy**-Ir catalyst leads to the formation of a mixture of *meta*- and *para*-borylated products, and the *ortho*-borylated compound was not detected (**1so** 0.0%, Figure 3). In contrast, the **BAIPy**-Ir catalyst that directs the substrate, by hydrogen bonding to the indole amide motif, shows unprecedented selective *ortho*-C–H borylation (**1so**, 94%). Importantly, the supramolecular interactions direct the C–H activation to a position that is sterically and electronically unfavorable.

DFT calculations to gain more insight into the operational mode of the supramolecular **BAIPy**-Ir complex show that three hydrogen bonds form (the N–O distances of 2.323–2.953 Å) when the substrate binds to the catalyst, leading to preorganization of the *ortho*-C–H bond of the substrate (Figure 4; see Figures S4–S7 and Table S2). In the transition state of the oxidative activation to the iridium center, and in the iridium complex after oxidative addition, these hydrogen bonds stay in place. Importantly, the energy of the transition-state structure **TS-AB** is only around 100.8 kJ mol^{-1} higher than the pre-complex **A**, suggesting that this sterically

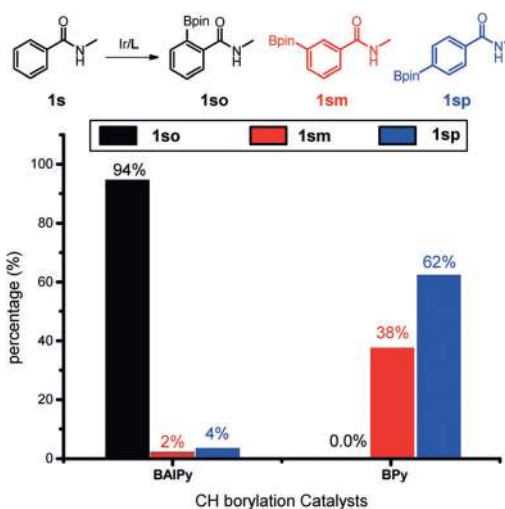


Figure 3. C–H borylation of *N*-methylbenzamide catalyzed by **BAIPy**-Ir (left) versus **BPy**-Ir (right). Reaction conditions: substrate (0.6 mmol), B_2Pin_2 (0.9 mmol), $[Ir(COD)OMe]_2$ (1.5 mol%), ligand (3.3 mol%), THF (0.2 M), 50°C, 24 h. Regioselectivity was determined by GC analysis. COD = 1,5-dicyclooctadiene, Pin = pinacol, THF = tetrahydrofuran.

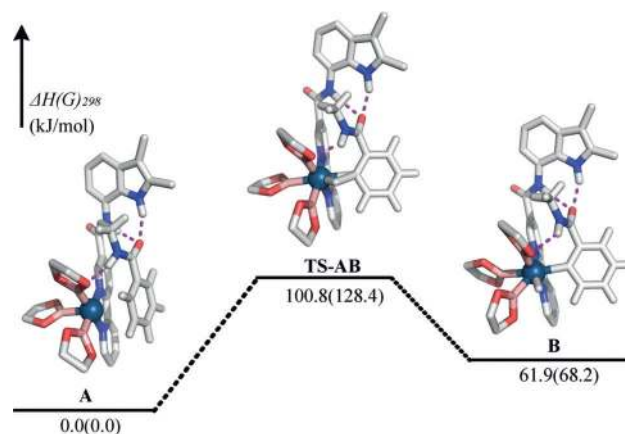


Figure 4. DFT calculated pathway for the C–H bond activation step in the **BAIPy**-trisboryl-Ir catalyzed *ortho*-selective C–H borylation of **1s** (BP86-D3/def2-TZVP, enthalpy and Gibbs free energy are referenced to **A**, and hydrogen bonds shown in purple dotted lines; the methyl groups on the boryl ligand were deleted to reduce computation costs).

hindered and electronically less active *ortho*-C–H bond can be activated at slightly elevated temperature, in line with the experiment. On the contrary, the *meta*- and *para*-C–H borylated compounds can only form when **1s** is not bound to the **BAIPy**-Ir complex through hydrogen bonds. DFT calculations show that the transition-state structures **TS-CD** and **TS-EF** are higher in energy than the counterpart formed in the *ortho*-borylation pathway (159.8 and 166.9 kJ mol^{-1} vs. 100.8 kJ mol^{-1} ; see Figures S7–S10). These calculations provide support that hydrogen-bonding interactions orient the substrate for *ortho*-selective C–H borylation.

Besides the expected two hydrogen bonds formed between the indole amide motif and the carbonyl of the substrate, calculations show that an extra hydrogen bond is formed between the amide-NH of the substrate and the

oxygen atom of the boryl group. Control experiments with *N,N*-dimethylbenzamide (**2s**) and methyl benzoate (**3s**; see Scheme S2), substrates that cannot form this extra hydrogen bond with the catalyst, show that these two substrates are converted with poor *ortho*-C–H borylation selectivity (*ortho* 25% and 0% for **2s** and **3s**, respectively), suggesting that the third hydrogen bond between the substrate and the catalyst is important. The selectivity difference between **2s** and **3s** also reveals that the amide forms a stronger hydrogen-bond interaction than the ester to preorganize the substrate, and is in line with literature.^[12] These control experiments also confirm that control of the regioselectivity is not a result of the classical substrate-chelation effect.

The substrate scope was explored by evaluation of various *N*-methylbenzamides to study the functional-group tolerance and the effect of variation in the sterics and electronics (Table 1a). For the *meta*- and *para*-methyl-substituted *N*-methylbenzamides **4s** and **5s**, respectively, the **BAIPy**-Ir catalyst shows high *ortho* selectivity. The control experiment using the **BPy**-Ir catalyst that does not preorganize the substrate shows no *ortho*-C–H borylation for **5s** (*ortho* 0%) and only moderate *ortho* selectivity for **4s** (*ortho* 84%). Importantly, besides the enhanced selectivity, much higher conversion was obtained for **4s** when **BAIPy**-Ir was used as the catalyst compared to **BPy**-Ir (conversion 82 vs. 4%), showing that substrate preorganization also affects the activity of the catalyst. We next explored a series of substrates that have different substituents at the *para*-position with respect to the methyl amide (**6s**–**11s**) to further evaluate the substrate scope. For **6s**, having an electron-donating methoxy group, the **BAIPy**-Ir catalyst displays enhanced *ortho* selectivity compared to the **BPy**-Ir catalyst (*ortho* 92 vs. 84%). The substrate **7s** contains a widely used trifluoromethyl group and the **BAIPy**-Ir catalyst also shows very high selectivity (*ortho* 99% vs. 77%) for *ortho*-borylation and much higher conversion than the **BPy**-Ir catalyst (conversion 84% vs. 3%). Also for **8s**, containing an additional aromatic ring, the **BAIPy**-Ir catalyst shows unprecedented high *ortho* selectivity, while **BPy**-Ir converts this substrate mainly into the *meta*-C–H borylation product (*ortho* 90% vs. 5%). In addition to the *ortho*-borylated product, some other products are formed in very small amounts, suggesting minor borylation of the appended aromatic ring (<5% total). For **9s**, with the bulky *tert*-butyl group, **BAIPy**-Ir also displays higher selectivity and conversion than **BPy**-Ir catalyst (*ortho* 76% vs. 62%; conversion 54% vs. 6%). The **BAIPy**-Ir catalyst tolerates halides, as **10s** and **11s** are converted with high selectivity by **BAIPy**-Ir (*ortho* 91% and >83%; conversion 86% and 88%), and is again much better than **BPy**-Ir (*ortho* 9% and <17%; conversion 38% and 100%). Unfortunately, the **BAIPy**-Ir catalyst is not active for *ortho*-substituted substrates (for details see the Supporting Information).

To further demonstrate the general applicability of the **BAIPy**-Ir catalyst, we extended the substrate scope to general aromatic amides (Table 1b). Firstly, *N*-benzylbenzamide (**12s**) was studied in detail as a representative substrate of this subset. Interestingly, this substrate has two aromatic rings, both of which contain C–H bonds that can in principle be borylated, however the C–H bonds of the benzyl group are

Table 1: Substrate scope of *ortho*-selective borylation using the **BAIPy**-Ir catalyst.^[a]

a) <i>N</i> -methylbenzamide and its derivatives		
1so BAIPy conv. 75%, <i>ortho</i> 94% BPy conv. 100%, <i>ortho</i> 0%	4so BAIPy conv. 82%, <i>ortho</i> 97% BPy conv. 4%, <i>ortho</i> 84%	5so BAIPy conv. 60%, <i>ortho</i> 94% BPy conv. 66%, <i>ortho</i> 0%
6so BAIPy conv. 79%, <i>ortho</i> 92% BPy conv. 100%, <i>ortho</i> 84%	7so BAIPy conv. 84%, <i>ortho</i> 99% BPy conv. 3%, <i>ortho</i> 77%	8so BAIPy conv. 65%, <i>ortho</i> 90% BPy conv. 78%, <i>ortho</i> 5%
9so BAIPy conv. 54%, <i>ortho</i> 76% BPy conv. 6%, <i>ortho</i> 62%	10so BAIPy conv. 86%, <i>ortho</i> 91% BPy conv. 38%, <i>ortho</i> 9%	11so BAIPy conv. 88%, <i>ortho</i> >83% ^b BPy conv. 100%, <i>ortho</i> <17% ^b
b) General aromatic amides		
12so BAIPy conv. 75%, <i>ortho</i> 91% BPy conv. 99%, <i>ortho</i> 0%	13so BAIPy conv. 91%, <i>ortho</i> 95%	14so BAIPy conv. 100%, <i>ortho</i> 97%
15so BAIPy conv. 85%, <i>ortho</i> 92%	16so BAIPy conv. 91%, <i>ortho</i> >91% ^b	17so BAIPy conv. 61%, <i>ortho</i> 98%
18so BAIPy conv. 99%, <i>ortho</i> >91% ^b	19so BAIPy conv. 72%, <i>ortho</i> >91% ^b	20so BAIPy conv. 82%, <i>ortho</i> 95%
21so BAIPy conv. 56%, <i>ortho</i> 89%	22so BAIPy conv. 55%, <i>ortho</i> >91% ^b	23so BAIPy conv. 94%, <i>ortho</i> 98%
24so BAIPy conv. 83%, <i>ortho</i> 94%	25so BAIPy conv. 46%, <i>ortho</i> >99% ^b	
26so BAIPy conv. 94%, <i>ortho</i> 98%	27so BAIPy conv. 85%, <i>ortho</i> >94%	Agrochemicals or pharmaceuticals
28so BAIPy conv. 99%, <i>ortho</i> 33% and <i>meta</i> 67% ^b	28sm	28s

[a] Typical reaction conditions: substrate (0.6 mmol), B₂Pin₂ (0.9 mmol), [Ir(COD)OMe]₂ (1.5 mol%), ligand (3.3 mol%), THF (0.2 M), 50–60 °C, 24–96 h. Conversion and *ortho* selectivity (percentage among all the C–H borylated products) were determined by either GC analysis or ¹H NMR analysis (see the Supporting Information for yields of isolated products and other details). [b] Estimated by ¹H NMR analysis after chromatography.

almost untouched (<5%), even by **BP**y-Ir, suggesting that there is sufficient difference in reactivity between the rings. As a result, **12s** can be converted by **BAIP**y-Ir with high selectivity into the *ortho*-C–H borylation product (*ortho* 91%). In contrast, **BP**y-Ir delivers only *meta*- and *para*-C–H borylation products (*ortho* 0%), and also quantitative conversion is obtained under these reaction conditions. We further evaluated the steric effects on the selectivity and reactivity by using either *para*- or *meta*-substituted substrates (**13s–25s**), including methyl, methoxy, benzyloxy, *tert*-butyl, trifluoromethoxy, ester groups, and halogens (Table 1b). As expected, the **BAIP**y-Ir catalyst shows unprecedented high selectivity for *ortho*-C–H borylation and decent to good conversion (46–100%). Importantly, extremely high selectivity was also achieved (*ortho* >99%) for the substrate **25s**, which contains an ester group at the *para*-position with respect to the amide. In line with the control experiments displayed in Scheme S2, the catalyst tolerates an ester group as its interaction with the indole amide unit is weaker than that with the amide. Also, a naphthalene amide (**26s**) was converted in high selectivity to the *ortho*-borylated product when using the **BAIP**y-Ir catalyst. Next the peptide-based aromatic amide **27s** was converted with high selectivity (conversion 85%, *ortho* product >94%). Importantly, these results demonstrate the potential of this protocol for late-state functionalization of valuable peptide-based aromatic compounds.

Finally, the *N*-benzylthiophenecarboxamide **28s** was explored as a particular challenging substrate (Table 1b). Generally C–H borylation is directed to C5–H because of steric and electronic effects, and the inert C3–H bond is not borylated.^[13] Using the **BAIP**y-Ir as catalyst we surprisingly formed 67% of the C4-borylated product, which is usually not formed, along with some diborylated product in which both the C4- and C3-positions are functionalized. Importantly, the most activated C5–H bond remains untouched. The wide substrate scope demonstrates the generality of the supramolecular approach for *ortho*-selective C–H borylation of secondary aromatic amides.

We performed a gram-scale C–H borylation reaction using 0.4–3 mol% iridium at 60°C (see Scheme S3), forming the *ortho*-C–H borylated compound **1so** and **12so** with up to 85% yield upon isolation and a turnover number (TON) of 123. The boron functionality allows easy follow-up chemistry to introduce various groups,^[2] and as one typical example, **1so** was transformed into a hydroxy group by an oxidation-hydrolysis sequence with quantitative yield using H₂O₂. Thus, this readily available supramolecular iridium catalyst is feasible for large-scale application to directly install the versatile boron moiety on the aromatic amides.

In summary, we report a readily accessible supramolecular iridium catalyst for *ortho*-selective C–H borylation of valuable secondary aromatic amides, and the catalyst operates by substrate preorganization through hydrogen bonding. Catalytic experiments with *N*-methylbenzamides and aromatic amides (>26 examples), including peptide-based analogues, demonstrate that this supramolecular catalyst converts a variety of secondary aromatic amides, having a variety of functional groups at different positions on the

aromatic ring, making the strategy very general. The supramolecular iridium catalyst has been applied on gram scale with high conversion and selectivity at elevated temperature. These experiments show that substrate orientation using a supramolecular catalyst is a powerful approach for controlling the regioselectivity in C–H borylation reactions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: borylation · C–H activation · hydrogen bonds · iridium · supramolecular chemistry

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