Supramolecular transition metal catalysis

Effector controlled catalysis and supramolecular substrate preorganization

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Chapter 6

Hydrogen bond Directed ortho-selective CH borylation of secondary aromatic amides

Abstract

In this chapter, we report an iridium catalyst for ortho-selective CH borylation of challenging secondary aromatic amides in which the regioselectivity is controlled by hydrogen bond interactions. For this, the BAIPy-Ir catalyst was designed by connecting the indole amide hydrogen bond motif to the bipyridyl ligand of the parent BPy-Ir catalyst. It is demonstrated that three hydrogen bonds are formed between the substrate and the catalyst during the crucial activation step, which allows ortho-CH borylation with high selectivity. The catalyst displays unprecedented ortho-selectivities for a wide variety of secondary amide substrates that differ in electronic and steric properties and the catalyst tolerates various functional groups. The regioselective CH borylation catalyst is readily accessible and demonstrated to convert substrates at gram scale with high selectivity and conversion.

Introduction

Transition metal catalyzed CH 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. The direct CH 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. Crucial for the application is that the selectivity of the reaction can be controlled, which is particularly challenging for CH bonds that are sterically and electronically deactivated in a molecule. Recently, the use of supramolecular interactions between the substrate and the ligand of metal complex have been explored to control the selectivity, which resulted in catalysts for selective meta- or para-CH borylation for electronically (un)activated substrates. However, ortho-selective CH borylation has only been reported for electronically activated arenes, such as an amine, alcohol, or a thio-ether substituted arenes. Secondary aromatic amides are very common structural motifs in pharmaceuticals, agrochemicals and fine chemicals, and the ortho-selective CH borylation of these classes of compounds would therefore be highly interesting. However, the direct ortho-CH borylation of this class of compounds is highly challenging. For common iridium catalyzed CH borylation the regioselectivity is largely dictated by steric factors leading to meta- and para-CH borylation.
of aromatic compounds (Figure 1, a). [1a,2d,8] The use of the amide functionality as a directing group doesn’t work for the amide, as this is generally weak because of unfavorable tautomerism.[9] Strategies that involve (temporary) directing groups such as silyl, iminyl and pyridyl operating via chelation to the metal center have not been reported for secondary aromatic amides.[10] To the best our knowledge, the Yu [10] group reported the only protocol for ortho-CH borylation catalyzed by palladium via metal-substrate chelation approach for substrates with special electron withdraw directing group ([(4-CF\textsubscript{3})C\textsubscript{6}H\textsubscript{4}) to promote the enol tautomeration. However, this directing group has to be installed and removed after the reaction, limiting its application (Figure 1, b). In this paper, we report the design of a supramolecular iridium based catalyst for highly ortho-selective CH borylation of these secondary aromatic amides, based on substrate orientation using hydrogen bonding.

Results and Discussions

We previously reported regioselective hydroformylation by substrate orientation using a supramolecular rhodium catalyst with an integrated binding pocket based on two indole-amide functionalities (DIM-receptor) that allows strong binding of the carboxylate via four hydrogen bonds.[11] Along these lines we designed the iridium based borylation catalyst reported here, assuming that for the current transformation one indole amide hydrogen bond motif to pre-organize aromatic amide substrates for ortho-CH borylation should be sufficient. For ortho selectivity, the motif should be close to the catalyst, and as such direct coupling of the indole amide to the BPy ligand was considered. DFT calculations show that the Ir complex containing of this ligand pre-organizes the N-methylbenzamide 1s with the ortho-CH bond oriented for selective activation.

The ligand BAIPy is prepared in five steps in multi-gram scale with 32% over all yield using simple chemistry (Scheme 1 and details see supporting information). As compound 3 is commercially available, one can obtain the ligand BAIPy via simple condensation reaction. Furthermore, the nitro precursor 4 for the synthesis of the ‘half’-DIM-receptor is readily available without tedious synthetic efforts in contrast to the DIM-receptor. The new ligand was fully characterized by \textsuperscript{1}H, \textsuperscript{13}C, and COSY NMR spectroscopy and HR-MS.

Initial binding studies in toluene-d8 monitored by \textsuperscript{1}H NMR show that N-methylbenzamide 1s is bound to the free BAIPy ligand as the NH-protons of the ligand shift down field upon increasing the concentration of the

Fig. 2. Design of the BAIPy ligand containing an indole amide functional group for substrate orientation for ortho-selective CH borylation of secondary aromatic amide supported by DFT modeling of the substrate-BAIPy-trisboryl-Ir catalyst complex (the methyl groups on the boryl ligand were omitted for clarity).
guest, in line with hydrogen bond formation (Δδ -0.41 and -0.62 ppm) Fig. S1-3, Table S1). Titration show that the binding energy is around 6.3 and 4.0 kJ/mol in toluene-d8 and THF-d8, respectively, in line with the formation of two hydrogen bonds.

To investigate the performances of the supramolecular catalyst we initially performed catalytic experiments in THF using N-methylbenzamide 1s as the model substrate. The ortho-, meta- and para-CH borylated compounds 1so, 1sm, 1sp were prepared in separate experiments to be used as reference for identification of the products (see experimental section). The regioselectivity and the conversion were determined by GC analysis (detail see experimental section). 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 formed at all (1so 0.0%, Fig. 3). In contrast, the BAIPy-Ir catalyst that directs the substrate via hydrogen bonding to the indole amide motif, shows unprecedented selective ortho-CH borylation (1so 94%, Fig. 3). Importantly, the supramolecular interactions direct the CH activation to a position that is sterically and electronically unfavorable.

DFT calculations on the regioselectivity determining CH activation step were performed to gain more insight in the operational mode of the supramolecular catalyst.

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**Scheme 1. Preparation of ligand BAIPy.** Conditions: a. I2, pyridine, 90 °C, 6 h; b. NH4OAc, methacrolein, formamide, 80 °C, 6 h; c. KMnO4, H2O, 70 °C, 5 h; d. Pd/C, 1 bar H2, THF; e. SOCl2, reflux for 2 h; f. trimethylamine, 5, THF/DCM, overnight.

**Fig. 3.** BAIPy-Ir (left) vs. BPy-Ir (right) catalyzed C-H borylation of N-methylbenzamide. Conditions: substrate (0.6 mmol), BPin2 (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.
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molecular BAIPy-Ir complex (Fig. 4, S4-7 and Table S2). These calculations show that three hydrogen bonds form (the N-O distances of 2.323-2.953 Å), rather than the predicted two, when the substrate binds to the catalyst, leading to preorganization of the ortho-CH bond of the substrate. 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 higher than pre-complex A, suggesting that this sterically hindered and electronically less active ortho-CH can be activated at slightly elevated temperatures, in line with the experiment. On the contrary, the meta- and para-CH borylated compounds are only formed when 1s is not binding to the BAIPy-Ir complex via H-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 vs. 100.8 kJ/mol, Fig. S4-7). These calculations support that hydrogen bonding interactions orientate the substrate for ortho-selectivity CH borylation.

Note that besides the expected two hydrogen bonds formed between the indole amide motif and the carbonyl of the substrate, an extra hydrogen bond is formed between the amide-NH of the substrate and the oxygen of the boryl group. To further study the relevance of this additional interaction, we performed some control experiments with N,N-dimethylbenzamide 2s and methyl benzoate 3s (Scheme 2), substrates that cannot form this extra hydrogen bond with the catalyst. These two substrates, 2s and 3s, are converted but with poor ortho-CH borylation selectivity (ortho 25% and 0% for 2 and 3 respectively). As this is in contrast to the ortho-selective conversion of 1s under identical conditions (ortho 94%), these results suggest that the third hydrogen bond between the substrate and the catalyst is important. The selectivity difference between 2s and 3s (ortho 25% and 0%) also reveals that the amide forms a stronger hydrogen bond interaction to preorganize the substrate than the ester, in line with literature.\(^{[13]}\) Importantly, these control experiments confirm the crucial role of the three hydrogen bonds in controlling the selectivity for the ortho-CH borylation of aromatic amides. Besides that, these control experiments also confirm that substrate-Ir chelation via the Ir-amide moiety is not involved in regioselectivity control. The substrate scope was extended to various N-methylbenzamides to evaluate functional group tolerance and the effect of steric and electronic variation (Table 1, a). For meta- and para-methyl substituted N-methylbenzamides 4s and 5s, BAIPy-Ir catalyst shows high selectivity (ortho 97% and 94%). The control experiment using the BPy-Ir catalyst that doesn’t pre-organize the substrate shows no ortho-CH 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 substrate 4s when BAIPy-Ir was used as 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 para-position with respect to the methyl amide 6s-11s to further evaluate the substrate scope. For 6s that has an electron donating methoxy group, the BAIPy-Ir catalyst displays enhanced ortho-selectivity compared to the BPy-Ir catalyst (ortho 92% vs. 84%). Substrate 7s contains a widely used trifluoromethyl and the BAIPy-Ir catalyst also shows very high selectivity (ortho 99% vs. 77% for BPy-Ir) for ortho-borylation and much higher conversion than the BPy-Ir catalyst (conversion 84% vs. 3%).

Also for 8s, the substrate that contains an additional aromatic ring, the BAIPy-Ir catalyst shows unprecedented high ortho-selectivity, while the BPy-Ir catalyst converts this substrate mainly to the meta-CH borylation product (ortho 90% vs. 5%). Next to the ortho-borylated product, some other products are formed in very small amounts, suggesting minor borylation at the introduced aromatic ring (<5% total). For 9s with the bulky tert-butyl group, the BAIPy-Ir catalyst also displays higher selectivity and conversion than the BPy-Ir catalyst (ortho 76% vs. 62%; conversion 54% vs. 6%). The BAIPy-Ir catalyst tolerates halides as also 10s and 11s are converted with high selectivity by the BAIPy-Ir catalyst (ortho 91% and >83%; conversion 86% and 88%), which is again much better than BPy-Ir catalyst (ortho 9% and <17%; conversion 38% and 100%). Unfortunately, BAIPy-Ir catalyst is not active for ortho-substituted substrates (details see experimental section).

To further demonstrate the general applicability of the BAIPy-Ir catalyst, we extended the substrate scope to general secondary aromatic amides (Table 1, b). Firstly, N-benzylbenzamide 12s was studied in detail as representative substrate of this subset. Interestingly, this substrate has two aromatic rings of which the CH bonds can in principle be borylated, however the CH bonds of the benzyl group are almost untouched (<5%), even by the BPy-Ir, suggesting that there is sufficient difference in reactivity between the rings. As a result, 12s can be converted by the BAIPy-Ir catalyst with high selectivity for ortho-CH borylation (ortho 91%). In contrast, the BPy-Ir catalyst shows only meta- and para-CH borylation products (ortho 0%), and also quantitative conversion is obtained under these conditions. We further evaluated the steric effects on the selectivity and reactivity by using para- or meta-substituted sub-
Hydrogen bond directed ortho-selective CH borylation of secondary aromatic amides

Table 1. Substrate scope of ortho-selective borylation using the BAIPy-Ir catalyst.\textsuperscript{a}

<table>
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<tr>
<td>conv. 79%, ortho 94%</td>
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<td>BPy</td>
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<table>
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<th>b) General aromatics amides</th>
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<td><img src="image" alt="Chemical structure" /></td>
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<tr>
<td>conv. 75%, ortho 91%</td>
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<tr>
<td>BPy</td>
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</table>

| BAIPy | 16so | BAIPy | 17so | BAIPy | 18so | BAIPy | 19so |
| conv. 91%, ortho >91% | conv. 81%, ortho 96% | conv. 99%, ortho >91% | conv. 72%, ortho >91% |

| BAIPy | 20so | BAIPy | 21so | BAIPy | 22so | BAIPy | 23so |
| conv. 82%, ortho 95% | conv. 56%, ortho 89% | conv. 55%, ortho >91% | conv. 94%, ortho 98% |

| BAIPy | 24so | BAIPy | 25so | BAIPy | 26so | BAIPy | 27so |
| conv. 83%, ortho 94% | conv. 46%, ortho >99% | conv. 94%, ortho 98% | conv. 85%, ortho >94% |

\textsuperscript{a} Typical conditions: substrate (0.6 mmol), B\textsubscript{2}Pin\textsubscript{2} (0.9 mmol), [Ir(COD)OMe\textsubscript{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 GC analysis or \textsuperscript{1}H NMR analysis (see SI for isolated yields and other details).\textsuperscript{b} Estimated by \textsuperscript{1}H NMR analysis after chromatography.
strates 13s-25s, including benzyloxy, methyl, methoxyl, tert-butyl, trifluoromethoxyl, ester groups and halogens (Table 1, b). As expected, the BAIPy-Ir catalyst shows unprecedented high selectivity for ortho-CH borylation and decent to good conversion (46-100%). Importantly, extremely high selectivity was also achieved (ortho >99%) for substrate 19s that contains an ester group at the para-position with respect to the amide. In line with the control experiments displayed in scheme 1, the catalyst also tolerates an ester group as the interaction with the indole amide unit is weaker compared to the amide. Also a naphthalene amide (26s) was converted in high selectivity to the ortho borylated product when using the BAIPy-Ir catalyst. Next a 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. We also applied our catalytic protocol to N-benzylthiophenecarboxamide 28s as a particular challenging substrate. Generally CH borylation is directed to the position C5-H because of steric and electronic effects, and the inert C3-H bond is not borylated.[14] Using the BAIPy-Ir as catalyst we surprisingly formed 67% of the C4 borylated product, which is usually not formed at all, along with some diborylated product in which both the C4 and C3 positions are functionalized. Importantly, the most activated C5-H bond remains untouched (Table 1b). The wide substrate scope demonstrates the generality of the supramolecular approach for ortho-selective CH borylation of aromatic amides.

To further demonstrate the application potential of this supramolecular catalyst, we performed a gram scale CH borylation reaction using 0.4-3 mol% iridium at 60 °C (Scheme 3). Pleasingly, 1.45 and 3.0 grams of ortho-CH borylated compound 1so and 12so were isolated with 85% and 49% yield, respectively. The boron functionality allows easy follow-up chemistry to introduce various groups[2], and as one typical example 1so was transformed into a hydroxyl group via 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.

**Scheme 3.** Application of the supramolecular catalyst in gram scale ortho-CH borylation.

**Conclusions**

In summary, we report a readily accessible supramolecular iridium catalyst for ortho-selective CH borylation of valuable secondary aromatic amides which operate via substrate pre-organization via hydrogen bonding. Experiments show that three hydrogen bonds between the substrate and the catalyst are needed to obtain high selectivities. Catalytic experiments with N-methylbenzamides and general aromatic amides (>26 examples) demonstrate that this supramolecular catalyst converts a variety of secondary aromatic amides with different func-
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...tional groups at different positions on the aromatic ring, making the strategy very general. The supramolecular iridium catalyst has been applied at gram scale with high conversion and selectivity at elevated temperature. These experiments show that supramolecular substrate orientation is a powerful approach to control the regioselectivity in challenging CH borylation reactions.

Acknowledgements

We acknowledge Dr. Vivek Sinha and Pim R. Linnebank for fruitful discussions. S.-T. Bai thanks the China Scholarship Council for a PhD fellowship (CSC student number 201506010269) and the University of Amsterdam is acknowledged for financial support.

Experimental Section

General Information

All reactions involving air- or moisture sensitive materials were carried out under nitrogen atmosphere using standard Schlenk techniques or in Glove-Box. THF, pentane, hexane and toluene were distilled from sodium-benzophenone under nitrogen atmosphere; dichloromethane, methanol were distilled from CaH₂ under nitrogen atmosphere; triethylamine was distilled from KOH pellets under nitrogen atmosphere. Toluene-d₈ and CDCl₂ were dried over molecular sieves (3Å) and degassed by three freeze-pump-thaw cycles. ¹H NMR, 1D ¹H NOESY NMR, 2D ¹H NOESY NMR, ¹H-¹H COSY and ¹³C NMR experiments were performed on Bruker AMX 300 MHz, Bruker AMX 400 MHz or Bruker AMX 500 MHz. ¹H NMR chemical shifts are given in ppm, and were calibrated by using the residual solvent as internal reference (CHCl₃ 7.26 ppm, CH₂Cl₂ 5.32 ppm, THF 3.58 ppm, DMSO 2.50 ppm, Acetone 2.05 ppm). ¹³C NMR chemical shifts were reported in ppm with the solvent peaks used as internal reference (CHCl₃ 77.16 ppm, CH₂Cl₂ 53.84 ppm, THF 67.21 ppm, DMSO 39.52 ppm, Acetone 29.84 ppm). Mass spectra were collected on an AccuTOF GC v 4g, JMS-T100GCV Mass spectrometer (JEOL, Japan), GCMS (EI) or FD/FI probe (FD/FI) equipped with FD Emitter, Carbotec (Germany), FD 13 µm, current rate 51.2 mA/min over 1.2 min, or FI Emitter, Carbotec (Germany), FI 10 µm, flashing current 40 mA on every spectra of 30 ms. All reagents were purchased from commercial suppliers and used without further purification, unless otherwise noted.

Synthesis of supramolecular ligand (BAIPy)

5-Methyl-2,2'-bipyridine (2)
2-Acetylpyridine (5.6 mL, 50.0 mmol) and I₂ (14.2 g, 56.0 mmol) were dissolved in pyridine (60 mL) and refluxed for 6 hours. The reaction mixture was then cooled to room temperature and the resulting suspension was filtered, and washed with ethyl ether. The pure 1-(2-pyridylacetyl)pyridinium iodide was obtained after re-crystallization from a saturated EtOH solution and used subsequently. Methacrolein (4.0 mL, 48.3 mmol) and NH₄OAc (18.6 g, 241.3 mmol) were subsequently added to a solution of 1-(2-py-
ridylacetyl)pyridinium iodide in formamide. The resulting reaction mixture was heated at 80 °C under nitrogen atmosphere for 6 hours. Then the crude mixture was cooled, water was added and the mixture was carefully extracted with Et₂O (3x300 mL). The combined organic phases were dried and filtered and the solvent was removed. The residue was purified by column chromatography (eluent of DCM/MeOH 20/1) to give orange product 2. Identical to literature. Yield of 51%.

1H NMR (400 MHz, CDCl₃) δ 8.67 – 8.66 (m, 1H, Ha), 8.51 (brs, 1H, He), 8.35 (dt, J = 7.9, 1.1 Hz, 1H, Hg), 8.28 (d, J = 8.1 Hz, 1H, Hd), 7.80 (td, J = 7.8, 1.7 Hz, 1H, Hb), 7.64 – 7.61 (m, 1H, Hf), 7.28 (ddd, J = 7.2, 4.8, 1.1 Hz, 1H, Hc), 2.40 (s, 3H, Me).

2,2′-Bipyridinyl-5-carboxylic acid (3)
Potassium permanganate (15.0 g, 94.9 mmol) was added in 7 portions with 1 hour intervals to a solution of 5-methyl-2,2′-bipyridine 2 (3.9 g, 22.9 mmol) in water. The mixture was heated at 70 °C for 3 hours and then at 90 °C for 4 hours. The resulting brown mixture was then filtered while hot through celite and washed with hot water (2x25 mL). The filtrate was concentrated to approximately 10 mL under reduced pressure, and then 1M HCl was added slowly until a pH of 4 was obtained. The residue was then filtered and dried to obtain pure 3 as white powder. Identical to literature. Yield of 83%.

1H NMR (400 MHz, DMSO-d₆) δ 9.16 (s, 1H, He), 8.73 (d, J = 4.7 Hz, 1H, Ha), 8.51 (d, J = 8.3 Hz, 1H, Hg), 8.46 – 8.40 (m, 2H, Hd,f), 8.00 (t, J = 7.7 Hz, 1H, Hb), 7.54 – 7.50 (m, 1H, Hc).

2,3-Dimethyl-1H-indol-7-amine (5)
2,3-Dimethyl-7-nitro-1H-indol 4 (1.74 g, 0.2 mmol) was dissolved in a suspension of Pd/C (0.4 g) in THF/Methanol. The suspension was stirred vigorously under 1 bar of H₂ atmosphere for 2 hours. After completion (monitored by TLC, ethyl acetate/petroleum ether 1/1), the suspension was filtered over celite and the filtrate was concentrated to dry for subsequent condensation reaction without further purification.

N-(2,3-dimethyl-1H-indol-7-yl)-[2,2′-bipyridine]-5-carboxamide (BAIPy)
2,2′-Bipyridinyl-5-carboxylic acid 3 (2.0 g, 10.0 mmol) was suspended in SOCl₂ (10 mL). The suspension was heated to reflux for 2 hours until the suspension became homogeneous solution. The volatiles were then removed under vacuum and the resulting acyl chloride was dried for following condensation re-
action without further purification.
The acyl chloride was re-dissolved in dry THF and DCM mixtures. Then the acyl chloride solution was added slowly into a solution of the crude amine 5 in THF, followed by adding TEA (4.5 mL, 30.0 mmol) into the reaction mixtures under ice-water bath. The resulting mixture was stirred overnight under room temperature. Then the volatiles were removed and supramolecular ligand BAIPy was obtained after column chromatography as dark brownish powder (ethyl acetate/petroleum ether 2/1 to 1/1).

Yield of 75%.

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.48 (s, 1H, indole-NH), 10.27 (s, 1H, amide-NH), 9.30 (s, 1H, He), 8.76 (d, $J = 4.4$ Hz, 1H, Hd), 8.57 – 8.49 (m, 3H, Ha,f,g), 8.01 (td, $J = 7.7$, 1.8 Hz, 1H, Hc), 7.53 (dd, $J = 7.5$, 5.0 Hz, 1H, Hb), 7.27 – 7.25 (m, 2H, Hh,j), 6.96 (t, $J = 7.6$ Hz, 1H, Hi), 2.34 (s, 3H, Me), 2.18 (s, 3H, Me).

$^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 163.65, 157.25, 154.43, 149.54, 148.88, 137.55, 136.90, 131.40, 130.47, 130.40, 129.11, 124.82, 121.51, 121.08, 119.85, 117.89, 115.47, 115.05, 105.54, 11.22, 8.44.

HRMS (PD+(eiFi)) calcd. for C$_{21}$H$_{18}$N$_4$O [M]+ 342.1481, found 342.1455.

Hydrogen bonding interaction studies between ligand BAIPy and substrate 1s

Table S1. $^1$H NMR titration experiments of aromatic amide 1s and BAIPy in toluene-d8

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Conditions: titration experiments were performed at room temperature.

Computational methods and results

Turbomole program$^{[16]}$ coupled to the PQS Baker optimizer$^{[17]}$ via the BOpt package$^{[18]}$ was used for all
DFT geometry optimizations. Geometries were fully optimized as minima using the BP86 functional\(^{[19,20]}\) and the resolution-of-identity (ri) method\(^{[21]}\) using the Turbomole def2-TZVP basis\(^{[22]}\) for all atoms. Grimme’s dispersion corrections (D3 version, implemented with the keyword disp3 in Turbomole\(^{[23]}\)) were applied in all calculations. All minima (no imaginary frequencies) were characterized by calculating the Hessian matrix. ZPE and gas-phase thermal corrections (entropy and enthalpy, 298 K, 1 bar) from these analyses were calculated. The relative enthalpy (free) energies obtained from these calculations are reported in the main text of this paper.

**Figure S1.** \(^1\)H NMR experiments of aromatic amide 1s and BAIPy in Toluene-d8 (indole-NH and amide-NH of the ligand indicated by arrows)

**Figure S2.** Fitting curve of the titration experiments (http://app.supramolecular.org/bindif), using the assumption of 1:1 binding, and using a Nelder-Mead algorithm (the binding energy calculated according to equation of \(\Delta G = RT\ln(K_{\text{bind}})\)).
Hydrogen bond directed *ortho*-selective CH borylation of secondary aromatic amides

Figure S3. DFT calculated pathway for the C-H bond activation step in BAIPy-Ir catalyzed *meta*-selective C-H borylation of 1s without substrate pre-binding to the catalyst via hydrogen bonds (BP86-D3/def2-TZVP and hydrogen bonds shown in purple dots; Enthalpy and Gibbs Free energies were reported).

Figure S4. DFT calculated pathway for the C-H bond activation step in BAIPy-Ir catalyzed *para*-selective C-H borylation of 1s without substrate pre-binding to the catalyst via hydrogen bonds (BP86-D3/def2-TZVP and hydrogen bonds shown in purple dots; Enthalpy and Gibbs Free energies were reported).
Figure S5. DFT calculated energies of the starting complexes for BAIPy-Ir catalyzed ortho-, meta-, and para-selective C-H borylation of 1s (BP86-D3/def2-TZVP; hydrogen bonds shown in purple dots; Enthalpy and Gibbs Free energies were reported).

Figure S6. DFT calculated energies of the C-H activation step for BAIPy-Ir catalyzed ortho-, meta-, and para-selective C-H borylation of 1s (BP86-D3/def2-TZVP and hydrogen bonds shown in purple dots; Enthalpy and Gibbs Free energies were reported).
Hydrogen bond directed ortho-selective CH borylation of secondary aromatic amides

Table S2. Gas phase thermochemical data (BP86-D3/def2-TZVP)\textsuperscript{a}

<table>
<thead>
<tr>
<th>species</th>
<th>SCF</th>
<th>ZPE</th>
<th>Enthalpy correction</th>
<th>Free energy correction</th>
<th>SCF+ZPE</th>
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<td>-2412.0348</td>
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</table>

\textsuperscript{a} SCF = self-consistent field energy of the stationary point geometry (atomic units)
ZPE = Zero-point energy (atomic units)
\(H\) corr and \(G\) corr = correction to enthalpy and Gibb’s free energy respectively at 298 K (atomic units)
\(H\) and \(G\) = enthalpy and Gibb’s free energy (atomic units)

Aromatic compounds 1s-28s

General procedures A for the synthesis of substrates: To a dichloromethane solution of benzoic acid derivative (1 eq.), 1 drop of DMF and oxalyl chloride (1.5 eq.) were added slowly. The reaction mixture was stirred vigorously for 1-2 hours. After the suspension becoming homogeneous solution, the volatiles were removed under vacuum. The resulting crude acyl chloride was re-dissolved in dichloromethane. \(\text{MeNH}_2\) (1.5 eq.) in water and TEA (3 eq.) was added sequentially dropwise into the reaction mixture under ice-water bath and then stirred at room temperature overnight. Water was added into the suspension and the resulting mixture was extracted with ethyl acetate (3x100 mL). The combined organic phase was dried over MgSO\(_4\), filtrated and evaporated. The pure product was obtained after crystallization using ethyl acetate and hexane or pentane mixture.

General procedures B for the synthesis of substrates: Benzoic acid derivative (1 eq.), benzylamine (1.0 eq.) and EDC (1.5 eq.) were dissolved in DMF followed by vigorously stirring overnight. Then 1M HCl solution was added into the suspension and the resulting mixture was extracted with ethyl acetate (3x100 mL). The combined organic phase was dried over MgSO\(_4\), filtered and evaporated. The pure product was obtained after crystallization using ethyl acetate and hexane or pentane mixture.

\[ \text{O} \]
\[ \text{N} \]
\[ 1s \]

\(N\)-Methylbenzamide (1s)\textsuperscript{[23]}

Obtained from commercial source.
\[^1\text{H}\text{ NMR (400 MHz, CDCl}_3\text{)} \delta 7.78 – 7.74 (m, 2H), 7.51 – 7.47 (m, 1H), 7.47 – 7.40 (m, 2H), 6.18 (brs, 1H), 3.02 (d, \(J = 4.8\text{ Hz}\), 3H).\]
N-Dimethylbenzamide (2s)\textsuperscript{[24]}
Obtained from commercial source.

Methyl benzoate (3s)\textsuperscript{[25]}

\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{) } & \delta 7.42 - 7.38 \text{ (m, 5H)}, 3.11 \text{ (s, 3H)}, 2.98 \text{ (s, 3H)}. \\
\text{1H NMR (400 MHz, CDCl}_3\text{) } & \delta 8.06 - 8.03 \text{ (m, 2H)}, 7.58 - 7.54 \text{ (m, 1H)}, 7.46 - 7.42 \text{ (m, 2H)}, 3.92 \text{ (s, 3H)}. \\
\end{align*}

N,4-dimethylbenzamide (4s)
General procedures A; Yield of 85%.
\begin{align*}
\text{1H NMR (500 MHz, CDCl}_3\text{) } & \delta 7.65 \text{ (d, } J = 7.5 \text{ Hz, 2H)}, 7.16 \text{ (d, } J = 7.7 \text{ Hz, 2H)}, 6.55 \text{ (brs, 1H)}, 2.94 \text{ (d, } J = 4.6 \text{ Hz, 3H)}, 2.35 \text{ (s, 3H)}. \\
\text{13C NMR (126 MHz, CDCl}_3\text{) } & \delta 168.36, 141.65, 131.94, 129.19, 126.98, 26.79, 21.43. \\
\text{HRMS (EI+(eiFi)) calcd. for C}_9\text{H}_11\text{NO } [\text{M}]+ 149.0841, \text{ found } 149.0851. \\
\end{align*}

N,3-dimethylbenzamide (5s)
General procedures A; Yield of 98%.
\begin{align*}
\text{1H NMR (500 MHz, CDCl}_3\text{) } & \delta 7.56 \text{ (s, 1H)}, 7.54 - 7.52 \text{ (m, 1H, amide-NH)}, 7.34 - 7.25 \text{ (m, 1H, amide-NH)}, 7.18 - 7.14 \text{ (m, 2H)}, 2.87 \text{ (d, } J = 4.8 \text{ Hz, 3H}), 2.24 \text{ (s, 3H)}. \\
\text{13C NMR (126 MHz, CDCl}_3\text{) } & \delta 168.69, 137.99, 134.47, 131.79, 128.11, 127.64, 123.94, 26.61, 21.10. \\
\text{HRMS (EI+(eiFi)) calcd. for C}_9\text{H}_11\text{NO } [\text{M}]+ 149.0841, \text{ found } 149.0841. \\
\end{align*}

4-Methoxy-N-methylbenzamide (6s)
General procedures A; Yield of 97%.
\begin{align*}
\text{1H NMR (500 MHz, CDCl}_3\text{) } & \delta 7.75 - 7.72 \text{ (m, 2H)}, 6.91 - 6.87 \text{ (m, 2H)}, 6.37 \text{ (brs, 1H)}, 3.82 \text{ (d, } J = 4.7 \text{ Hz, 3H)}, 2.96 \text{ (s, 3H)}. \\
\text{13C NMR (126 MHz, CDCl}_3\text{) } & \delta 167.95, 162.14, 128.75, 127.04, 113.79, 55.47, 26.88. \\
\text{HRMS (FD+(eiFi)) calcd. for C}_9\text{H}_11\text{NO}_2\text{ [M]}^+ 165.0790, \text{ found } 165.0843. \\
\end{align*}
Hydrogen bond directed ortho-selective CH borylation of secondary aromatic amides

\[
\text{N-Methyl-4-(trifluoromethyl)benzamide (7s)}
\]
General procedures A; Yield of 87%.
\[^1\text{H}\text{ NMR (500 MHz, CDCl}_3\text{)} \delta 7.86 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H), 6.49 (brs, 1H), 3.01 (d, J = 4.7 Hz, 3H).\]
\[^{13}\text{C}\text{ NMR (126 MHz, CDCl}_3\text{)} \delta 167.14, 138.02, 133.24 (m, two bond F-C coupling), 127.48, 125.70 (m, three bonds F-C coupling), 123.79 (m, one bond C-F coupling), 27.08.\]
HRMS (EI+(eif/i)) calcd. for C\(_9\)H\(_8\)F\(_3\)NO [M]+ 203.0558, found 203.0507.

\[
\text{N-Methyl-[1,1'-biphenyl]-4-carboxamide (8s)}
\]
General procedures A; Yield of 83%.
\[^1\text{H}\text{ NMR (500 MHz, CDCl}_3\text{)} \delta 7.86 – 7.83 (m, 2H), 7.65 – 7.58 (m, 4H), 7.47 – 7.43 (m, 2H), 7.39 – 7.36 (m, 1H), 6.39 (brs, 1H), 3.03 (d, J = 4.9 Hz, 3H).\]
\[^{13}\text{C}\text{ NMR (126 MHz, CDCl}_3\text{)} \delta 168.09, 144.27, 140.19, 133.49, 129.01, 128.06, 127.51, 127.30, 26.97.\]
HRMS (EI+(eif/i)) calcd. for C\(_{14}\)H\(_{13}\)NO [M]+ 211.0997, found 211.0985

\[
\text{4-(Tert-butyl)-N-methylbenzamide (9s)}
\]
General procedures A; Yield of 87%.
\[^1\text{H}\text{ NMR (500 MHz, CDCl}_3\text{)} \delta 7.69 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 6.29 (brs, 1H), 2.99 (d, J = 5.1 Hz, 3H), 1.32 (s, 9H).\]
\[^{13}\text{C}\text{ NMR (126 MHz, CDCl}_3\text{)} \delta 168.36, 154.91, 131.87, 126.79, 125.58, 35.01, 31.29, 26.90.\]
HRMS (EI+(eif/i)) calcd. for C\(_{12}\)H\(_{17}\)NO [M]+ 191.1310, found 191.1306

\[
\text{4-Chloro-N-methylbenzamide (10s)}
\]
General procedures A; Yield of 89%.
\[^1\text{H}\text{ NMR (500 MHz, CDCl}_3\text{)} \delta 7.69 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 6.33 (brs, 1H), 2.98 (d, J = 4.8 Hz, 3H).\]
\[^{13}\text{C}\text{ NMR (126 MHz, CDCl}_3\text{)} \delta 167.34, 137.73, 133.20, 128.92, 128.44, 26.99.\]
HRMS (EI+(eif/i)) calcd. for C\(_8\)H\(_8\)ClNO [M]+ 169.0294, found 169.0293

\[
\text{4-Bromo-N-methylbenzamide (11s)}
\]
General procedures A; Yield of 97%.
\[^1\text{H}\text{ NMR (500 MHz, CDCl}_3\text{)} \delta 7.62 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 6.18 (brs, 1H), 3.00 (d, J = 4.9
Chapter 6

$\text{Hz, 3H).}$

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 167.39, 133.69, 131.95, 128.61, 126.17, 27.02.

HRMS (EI+(eiFi)) calcd. for C$_8$H$_7$BrNO [M-H]$^-$ 211.9711, found 211.9712.

$\text{N-Benzylbenzamide (12s)}^{[26]}$

General procedures B; Yield of 90%.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.81 – 7.78 (m, 2H), 7.53 – 7.48 (m, 1H), 7.45 – 7.41 (m, 2H), 7.37 – 7.27 (m, 5H), 6.40 (brs, 1H), 4.66 (d, $J = 5.6$ Hz, 2H).

$\text{N-Benzyl-4-methylbenzamide (13s)}^{[27]}$

General procedures B; Yield of 90%.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.69 (d, $J = 8.2$ Hz, 2H), 7.38 – 7.27 (m, 5H), 7.23 (d, $J = 8.0$ Hz, 2H), 6.36 (brs, 1H), 4.65 (d, $J = 5.6$ Hz, 2H), 2.39 (s, 3H).

$\text{N-Benzyl-3-methoxybenzamide (14s)}^{[27]}$

General procedures B; Yield of 90%.

$^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.36 – 7.27 (m, 8H), 7.06 – 7.03 (m, 1H), 6.59 (brs, 1H), 4.60 (d, $J = 5.8$ Hz, 2H), 3.83 (s, 3H).

$\text{N-Benzyl-3-methylbenzamide (15s)}^{[28]}$

General procedures B; Yield of 91%.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62 (s, 1H), 7.58 – 7.55 (m, 1H), 7.37 – 7.29 (m, 7H), 6.38 (brs, 1H), 4.65 (d, $J = 5.4$ Hz, 2H), 2.39 (s, 3H).

$\text{N-Benzyl-3-benzyloxybenzamide (16s)}^{[28]}$

General procedures B; Yield of 95%.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 – 7.29 (m, 13H), 7.12 – 7.09 (m, 1H), 6.37 (brs, 1H), 5.10 (s, 2H), 4.64 (d, $J = 5.2$ Hz, 2H).

$\text{N-Benzyl-3-chlorobenzamide (17s)}^{[29]}$

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Hydrogen bond directed ortho-selective CH borylation of secondary aromatic amides

General procedures B; Yield of 95%.
1H NMR (400 MHz, CDCl₃) δ 7.71 – 7.69 (m, 1H), 7.45 – 7.28 (m, 8H), 6.48 (brs, 1H), 4.94 – 4.59 (m, 2H).

N-Benzyl-3-benzyloxybenzamide (18s) [30]
General procedures B; Yield of 89%.
1H NMR (400 MHz, CDCl₃) δ 7.93 (d, J = 1.8 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.40 – 7.27 (m, 6H), 6.46 (brs, 1H), 4.72 – 4.57 (m, 2H).

N-Benzyl-4-(tert-butyl)benzamide (19s) [28]
General procedures B; Yield of 89%.
1H NMR (400 MHz, CDCl₃) δ 7.74 – 7.72 (m, 2H), 7.46 – 7.44 (m, 2H), 7.36 – 7.27 (m, 5H), 6.35 (brs, 1H), 4.66 (d, J = 5.7 Hz, 2H), 1.33 (s, 9H).

N-Benzyl-4-(trifluoromethoxy)benzamide (20s) [31]
General procedures B; Yield of 95%.
1H NMR (300 MHz, CDCl₃) δ 7.86 – 7.81 (m, 2H), 7.38 – 7.27 (m, 5H), 7.27 – 7.24 (m, 2H), 6.39 (brs, 1H), 4.64 (d, J = 5.6 Hz, 2H).

N-Benzyl-4-methoxybenzamide (21s) [29]
General procedures B; Yield of 95%.
1H NMR (400 MHz, CDCl₃) δ 7.77 – 7.74 (m, 2H), 7.36 – 7.27 (m, 5H), 6.93 – 6.90 (m, 2H), 6.32 (brs, 1H), 4.64 (d, J = 5.6 Hz, 2H), 3.84 (s, 3H).

N-Benzyl-4-(trifluoromethyl)benzamide (22s) [29]
General procedures B; Yield of 87%.
1H NMR (400 MHz, CDCl₃) δ 7.89 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H), 7.38 – 7.27 (m, 5H), 6.56 (brs, 1H), 4.64 (d, J = 5.6 Hz, 2H).
N-Benzyl-4-chlorobenzamide (23s)\textsuperscript{[27]}
General procedures \textbf{B}; Yield of 89%.
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.74 – 7.72 (m, 2H), 7.40 – 7.38 (m, 2H), 7.35 – 7.27 (m, 5H), 6.46 (brs, 1H), 4.63 (d, \(J = 5.5\) Hz, 2H).

N-benzyl-4-bromobenzamide (24s)\textsuperscript{[31]}
General procedures \textbf{B}; Yield of 89%.
\(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 7.68 – 7.65 (m, 2H), 7.60 – 7.57 (m, 2H), 7.36 – 7.27 (m, 5H), 6.49 (brs, 1H), 4.60 (d, \(J = 5.9\) Hz, 2H).

Methyl 4-(benzylcarbamoyl)benzoate (25s)\textsuperscript{[29]}
General procedures \textbf{B}; Yield of 87%.
\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.09 (d, \(J = 8.4\) Hz, 2H), 7.86 – 7.83 (m, 2H), 7.38 – 7.27 (m, 5H), 6.42 (brs, 1H), 4.66 (s, 2H), 3.94 (s, 3H).

N-Benzyl-2-naphthamide (26s)\textsuperscript{[28]}
General procedures \textbf{B}; Yield of 89%.
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.31 (d, \(J = 1.6\) Hz, 1H), 7.97 – 7.81 (m, 4H), 7.59 – 7.51 (m, 2H), 7.45 – 7.29 (m, 5H), 6.57 (brs, 1H), 4.72 (d, \(J = 5.6\) Hz, 2H).

Methyl benzoyl-L-valinate (27s)\textsuperscript{[32]}
General procedures \textbf{B}; Yield of 95%.
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.82 – 7.80 (m, 2H), 7.54 7.43 (m, 2H), 6.64 (d, \(J = 8.6\) Hz, 1H, amide-NH), 4.79 (dd, \(J = 8.6, 4.9\) Hz, 1H, Ha), 3.77 (s, 3H, OMe), 2.33 – 2.23 (m, 1H, Hb), 1.21 – 0.94 (m, 6H, isopropyl-Me).

N-Benzylthiophene-2-carboxamide (28s)\textsuperscript{[27]}
General procedures \textbf{B}; Yield of 88%.
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$^1$H NMR (500 MHz, CDCl$_3$) δ 7.50 (d, $J = 3.8$ Hz, 1H), 7.49 (d, $J = 5.0$ Hz, 1H), 7.37 – 7.29 (m, 5H), 7.08 (dd, $J = 5.0$, 3.8 Hz, 1H), 6.21 (brs, 1H), 4.64 – 4.62 (m, 2H).

N-Benzyl-2-methylbenzamide (29s)$^{[29]}$
General procedures B; Yield of 89%.
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.29 (m, 7H), 7.23 – 7.17 (m, 2H), 6.01 (brs, 1H, amide-NH), 4.65 – 4.63 (m, 2H, Bn-CH$_2$), 2.48 (s, 3H, aryl-Me).

N-Benzyl-2-fluorobenzamide (30s)$^{[33]}$
General procedures B; Yield of 85%.
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.15 (td, $J = 7.9$, 1.9 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.38 – 7.27 (m, 6H), 7.16 – 7.08 (m, 1H), 7.04 (brs, 1H, amide-NH), 4.69 (dd, $J = 5.6$, 1.5 Hz, 2H, Bn-CH$_2$).

N-Methyl-2-methylbenzamide (31s)$^{[34]}$
General procedures B; Yield of 89%.
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.36 – 7.13 (m, 2H), 7.13 – 7.00 (m, 2H), 5.85 (s, 1H), 2.84 (d, $J = 4.9$ Hz, 3H), 2.30 (s, 3H).
$^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.94, 136.62, 136.08, 131.03, 129.84, 126.76, 125.75, 77.42, 77.16, 76.91, 26.67, 19.83.
HRMS (EI+(eiFi)) calcd. for C$_9$H$_{11}$NO [M]+ 149.0841, found 149.0905

Preparation of the reference borylated compounds

General procedures: A mixture of halogenate aromatic amides (1 eq.), PdCl$_2$(dpff) (0.03 eq.), KOAc (3 eq.) and bis(pinacolato)diboron (1.5 eq.) in 1,4-dioxane was heated at 80 °C overnight. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na$_2$SO$_4$, filtered off and concentrated under reduced pressure. The product was purified by chromatography using deactivated silica gel and ethyl acetate and petroleum ether or hexane as the eluent.$^{[35-40]}$

N-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (1so)
Gray solid; Isolated Yield of 30%.
$^1$H NMR (500 MHz, CDCl$_3$) δ 9.78 (s, 1H, amide-NH), 7.80 (d, $J = 7.6$ Hz, 1H, Ha), 7.60 (d, $J = 7.1$ Hz, 1H, Hd), 7.40 (t, $J = 7.3$ Hz, 1H, Hc), 7.14 (t, $J = 7.6$ Hz, 1H, Hb), 2.46 (d, $J = 4.5$ Hz, 3H, Me), 1.35 (s, 12H, pin-Me).
$^{13}$C NMR ($126$ MHz, CDCl$_3$) $\delta$ 172.41, 133.29, 132.76, 130.36, 127.52, 123.61, 81.19, 27.26, 25.33.
HRMS (FD+(eiFi)) calcd. for $C_{14}H_{20}$BNO$_3$ [M]$^+$ 261.1539, found 261.1511.

N-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (1sm)
Gray solid; Isolated Yield of 70%.
$^1$H NMR (500 MHz, THF-$d_8$) $\delta$ 8.15 (s, 1H, Ha), 7.95 (dt, $J = 7.7, 1.6$ Hz, 1H, Hd), 7.82 – 7.81 (m, 1H, Hb), 7.65 – 7.62 (m, 1H, amide-NH), 7.37 (t, $J = 7.5$ Hz, 1H, Hc), 2.87 (d, $J = 4.5$ Hz, 3H, Me), 1.33 (s, 12H, pin-Me).
$^{13}$C NMR (126 MHz, THF-$d_8$) $\delta$ 167.19, 137.55, 135.47, 133.40, 131.04, 128.02, 84.42, 26.41, 25.62.
HRMS (FD+(eiFi)) calcd. for $C_{14}H_{20}$BNO$_3$ [M]$^+$ 261.1536, found 261.1511.

N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (1sp)
Gray solid; Isolated Yield of 80%.
$^1$H NMR (500 MHz, THF-$d_8$) $\delta$ 7.80 – 7.76 (m, 4H), 7.58 (brs, 1H, amide-NH), 2.87 (d, $J = 4.7$ Hz, 3H, Me), 1.32 (s, 12H, pin-Me).
$^{13}$C NMR (126 MHz, THF-$d_8$) $\delta$ 167.01, 138.34, 135.07, 126.72, 84.43, 25.62.
HRMS (FD+(eiFi)) calcd. for $C_{14}H_{20}$BNO$_3$ [M]$^+$ 261.1536, found 261.1525.

N-benzyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (12so)
Gray solid; Isolated Yield of 25%.
$^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 9.72 (brs, 1H, amide-NH), 8.05 (d, $J = 7.9$ Hz, 1H, Ha), 7.65 (d, $J = 7.3$ Hz, 1H, Hb), 7.54 (t, $J = 7.3$ Hz, 1H, Hc), 7.39 – 7.26 (m, 6H, Hd and Bn-aryl-H), 4.03 (d, $J = 6.0$ Hz, 2H, Bn-CH$_2$), 1.27 (s, 12H, pin-Me).
$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ 171.93, 137.53, 134.59, 132.93, 131.11, 128.89, 128.42, 128.17, 127.99, 124.77, 81.96, 44.86, 25.13.
HRMS (FD+(eiFi)) calcd. for $C_{20}H_{24}$BNO$_3$ [M]$^+$ 337.1853, found 337.1850.

N-benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (12sm)
Gray solid; Isolated Yield of 65%.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.08 (t, $J = 1.4$ Hz, 1H, Ha), 8.02 (dt, $J = 7.7, 1.6$ Hz, 1H, Hd), 7.93 (dt, $J = 7.3, 1.2$ Hz, 1H, Hb), 7.47 (t, $J = 7.6$ Hz, 1H, Hc), 7.40 – 7.28 (m, 5H, Bn-aryl-H), 6.49 (brs, 1H, amide-NH), 4.66 (d, $J = 5.7$ Hz, 2H, Bn-CH$_2$), 1.34 (s, 12H, pin-Me).
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 167.35, 138.36, 138.07, 133.80, 132.22, 130.83, 128.92, 128.38, 128.19, 127.76, 84.30, 44.30, 25.02.
HRMS (FD+(eiFi)) calcd. for $C_{20}H_{24}$BNO$_3$ [M]$^+$ 337.1853, found 337.1851.
Hydrogen bond directed ortho-selective CH borylation of secondary aromatic amides

*N*-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (**12sp**)
Gray solid; Isolated Yield of 85%.

\[^1\text{H}\] NMR (300 MHz, CDCl\textsubscript{3}) δ 7.88 – 7.85 (m, 2H), 7.77 (d, $J = 8.2$ Hz, 2H), 7.37 – 7.26 (m, 5H, Bn-aryl-H), 6.40 (brs, 1H, amide-NH), 4.66 (d, $J = 5.7$ Hz, 2H, Bn-CH\textsubscript{2}), 1.35 (s, 12H, pin-Me).

\[^{13}\text{C}\] NMR (75 MHz, CDCl\textsubscript{3}) δ 167.39, 138.24, 136.69, 135.11, 128.94, 128.11, 127.79, 126.21, 84.28, 44.32, 25.02.

HRMS (FD+ (EI, F)) calcd. for C\textsubscript{20}H\textsubscript{24}BNO\textsubscript{3} [M]+ 337.1853, found 337.1847.

Iridium catalyzed ortho-selective C-H borylation

General procedures: A mixture of [Ir(OMe)(cod)]\textsubscript{2} (5.967 mg, 9.0 μmol, 1.5 mol%), ligand BAIPy (6.174 mg, 19.8 μmol, 3.3 mol%) or BPy (2.808 mg, 19.8 μmol, 3.3 mol%) in THF (3.0 ml) was added into pre-dried vial with bis(pinacolato) diboron (228.0 mg, 0.898 mmol, 1.50 equiv.) and aromatic amides (0.598 mmol, 1.0 equiv.) in Glove-box. The mixture was then stirred at 50-60 °C for 24-96 hours under nitrogen atmosphere. The conversion and selectivity was analysed by GC (Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min) using 1,3,5-trimethoxybenzene as the internal standard and NMR technique of the purified reaction mixture. The product was isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether or hexane (10:0.5 to 2:1) as the eluent (for details see below). Isolated yield is lower than the calculated yield due to decomposition of the borylated compound during purification using silica (the off up to 25%). The decomposed boronic acid were observed by NMR. Attempt to convert the borylated products to BF\textsubscript{3}K salts without success for easy separation of the product via crystallization.

*N*-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (**1so**)
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 2:1) as the eluent.

BAIPy-Ir catalyst; Isolated yield of 63%.

BPy-Ir catalyst; Isolated yield of 0%.

Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min. Retention time: t (Sub) = 12.683 min, t (ortho) = 19.275 min, t (meta) = 20.535 min and t (para) = 20.272 min.

\[^1\text{H}\] NMR (500 MHz, CDCl\textsubscript{3}) δ 9.78 (s, 1H, amide-NH), 7.80 (d, $J = 7.6$ Hz, 1H, Ha), 7.60 (d, $J = 7.1$ Hz, 1H, Hd), 7.40 (t, $J = 7.3$ Hz, 1H, Hc), 7.14 (t, $J = 7.6$ Hz, 1H, Hb), 2.46 (d, $J = 4.5$ Hz, 3H, Me), 1.35 (s, 12H, pin-Me).

\[^{13}\text{C}\] NMR (126 MHz, CDCl\textsubscript{3}) δ 172.41, 133.29, 132.76, 130.36, 127.52, 123.61, 81.19, 27.26, 25.33.

HRMS (FD+ (EI, F)) calcd. for C\textsubscript{14}H\textsubscript{20}BNO\textsubscript{3} [M]+ 261.1539, found 261.1511.

*N,N*-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (**2so**)
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (5:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; Isolated yield of 25%.
Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min. Retention time: t (Sub) = 12.642 min, t (ortho) = 18.723 min, t (meta) = 24.397 min and t (para) = 24.815 min.

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \] \( \delta \) 7.76 – 7.74 (m, 1H, Hd), 7.46 (td, \( J = 7.5, 1.4 \text{ Hz}, 1H, \text{ Hb} \)), 7.37 (td, \( J = 7.5, 1.2 \text{ Hz}, 1H, \text{ Hc} \)), 7.24 (d, \( J = 7.6 \text{ Hz}, 1H, \text{ Ha} \)), 2.99 – 2.84 (m, 6H, amide-Me), 1.30 (s, 12H, pin-Me).

\[ ^13C \text{ NMR (126 MHz, CDCl}_3 \] \( \delta \) 172.28, 143.68, 135.28, 131.18, 128.18, 125.88, 84.10, 25.09.

HRMS (FD+(eiFi)) calcd. for C\textsubscript{15}H\textsubscript{22}BNO\textsubscript{3} [M]+ 275.1696, found 275.1693.

Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (3sm) and Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (3sp)

\[ ^1H \text{ NMR in line with literature.}^{[28-29]} \]

\[ N,4 \text{-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (4so) } \]

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 2:1) as the eluent.

BAIPy-Ir catalyst; isolated yield of 61%.

BPy-Ir catalyst; isolated yield of -%.

Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min. Retention time: t (Sub) = 14.857 min, t (ortho) = 20.905 min, t (meta) = 20.308 min.

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \] \( \delta \) 8.77 (s, 1H, amide-NH), 7.59 (d, \( J = 7.9 \text{ Hz}, 1H, \text{ Hc} \)), 7.39 (s, 1H, Ha), 7.00 (d, \( J = 7.8 \text{ Hz}, 1H, \text{ Hb} \)), 2.65 – 2.62 (m, 3H, Me), 1.36 (s, 12H, pin-Me).

\[ ^13C \text{ NMR (126 MHz, CDCl}_3 \] \( \delta \) 172.24, 143.06, 131.11, 128.39, 81.23, 27.27, 25.35, 21.90.

HRMS (FD+(eiFi)) calcd. for C\textsubscript{15}H\textsubscript{23}BNO\textsubscript{3} [M]+ 276.1771, found 276.1495.

\[ N,5 \text{-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (5so) } \]

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; isolated yield of 45%.

BPy-Ir catalyst; isolated yield of -%.

Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min. Retention time: t (Sub) = 14.745 min, t (ortho) = 20.965 min, t (meta) = 21.780 min.

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \] \( \delta \) 7.73 (brs, 1H, amide-NH), 7.50 (s, 1H, Ha), 7.46 (d, \( J = 7.4 \text{ Hz}, 1H, \text{ Hb} \)), 7.27 (d, \( J = 7.5 \text{ Hz}, 1H, \text{ Hc} \)), 2.74 (d, \( J = 4.8 \text{ Hz}, 3H, \text{ amide-Me} \)), 2.36 (s, 3H, aryl-Me), 1.33 (s, 12H, pin-Me).

\[ ^13C \text{ NMR (126 MHz, CDCl}_3 \] \( \delta \) 171.21, 138.98, 132.55, 132.12, 125.33, 82.73, 27.11, 25.25, 21.43.

The borylated product was also transformed into hydroxyl group functionalized product for confirmation as shown below.

HRMS (FD+(eIFi)) calcd. for C\textsubscript{15}H\textsubscript{24}BNO\textsubscript{3} [M+H]+ 276.1771, found 276.1495.
Hydrogen bond directed ortho-selective CH borylation of secondary aromatic amides

2-Hydroxy-N,N,5-dimethyl-benzamide (5so′)

1H NMR in line with commercial compound.

1H NMR (500 MHz, CDCl₃) δ 12.09 (s, 1H, OH), 7.20 (d, J = 8.4 Hz, 1H, Hb), 7.12 (s, 1H, Ha), 6.89 (d, J = 8.6 Hz, 1H, Hc), 6.31 (brs, 1H, amide-NH), 3.01 (d, J = 4.8 Hz, 3H, Me), 2.28 (s, 3H, aryl-Me).

4-Methoxy-N-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (6so)

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; Isolated yield of 59%.

BPY-Ir catalyst; Isolated yield of 64%.

Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min. Retention time: t (Sub) = 16.605 min, t (ortho) = 22.218 min, t (meta) = 21.535 min.

1H NMR (500 MHz, CDCl₃) δ 9.80 (brs, 1H, amide-NH), 7.70 (d, J = 8.5 Hz, 1H, Ha), 7.05 (d, J = 2.4 Hz, 1H, Hc), 6.58 (dd, J = 8.5, 2.3 Hz, 1H, Hb), 3.83 (s, 3H, OMe), 2.50 – 2.49 (m, 3H, Me), 1.33 (s, 12H, pin-Me).

13C NMR (126 MHz, CDCl₃) δ 172.20, 163.83, 125.44, 125.31, 114.09, 114.02, 80.97, 55.47, 27.42, 25.36.

HRMS (FD+(eiFi)) calcd. for C₁₅H₂₂BNO₄ [M]+ 291.1645, found 291.1637.

N-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)benzamide (7so)

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; Isolated yield of 77%.

BPY-Ir catalyst; Isolated yield of 7%.

Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min. Retention time: t (Sub) = 13.195 min, t (ortho) = 19.230 min, t (meta) = 17.618 min.

1H NMR (500 MHz, THF-d₈) δ 9.19 – 9.18 (m, 1H, amide-NH), 7.80 (d, J = 8.1 Hz, 1H, Ha), 7.73 (d, J = 1.7 Hz, 1H, Hc), 7.52 (dd, J = 8.1, 1.9 Hz, 1H, Hb), 2.86 (d, J = 4.6 Hz, 3H, Me), 1.32 (s, 12H, pin-Me).

13C NMR (126 MHz, THF-d₈) δ 170.15, 139.22, 133.34 (m, two bonds C-F coupling), 127.92 (m, three bonds C-F coupling), 125.20 (m, three bonds C-F coupling), 125.13 (m, one C-F coupling), 82.18, 27.32, 25.43.

HRMS (FD+(eiFi)) calcd. for C₁₅H₂₀BF₃NO₃ [M-H]⁻ 330.1413, found 330.1460.

N-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-carboxamide (8so)

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to
2:1) as the eluent.

**BAIPy-Ir catalyst; isolated yield of 56%.

**BPpy-Ir catalyst; isolated yield of 0%.

Rtx-1 column, method: Initial temperature = 50 °C for 2 min, then 10°C/min to 300°C for 15 min. Retention time: t (Sub) = 21.670 min, t (ortho) = 26.152 min, t (meta) = 27.382 min.

1H NMR (500 MHz, CDCl3) δ 9.36 (s, 1H, amide-NH), 7.81 (s, 1H, Ha), 7.77 (d, J = 7.9 Hz, 1H, Hb), 7.47 (d, J = 6.5 Hz, 2H), 7.37 (d, J = 6.1 Hz, 3H), 7.26 (d, J = 2.5 Hz, 1H), 2.69 (s, 3H, Me), 1.38 (s, 12H, pin-Me).

13C NMR (126 MHz, CDCl3) δ 171.91, 145.14, 140.66, 132.60, 129.10, 128.80, 127.80, 127.36, 126.77, 123.89, 81.44, 27.33, 25.25.

HRMS (FD+(eIeI)) calcd. for C20H24BNO3 [M]+ 337.1853, found 337.1846.

4-(Tert-butyl)-N-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (9so)

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

**BAIPy-Ir catalyst; isolated yield of 41%.

**BPpy-Ir catalyst; isolated yield of -%.

Rtx-1 column, method: Initial temperature = 50 °C for 2 min, then 10°C/min to 300°C for 15 min. Retention time: t (Sub) = 17.562 min, t (ortho) = 22.218 min, t (meta) = 21.535 min.

1H NMR (500 MHz, CDCl3) δ 9.59 (s, 1H, amide-NH), 7.80 – 7.78 (m, 1H, Hb), 7.59 – 7.56 (m, 1H, Ha), 7.20 (dd, J = 8.2, 1.8 Hz, 1H, Hc), 2.43 – 2.42 (m, 3H, Me), 1.36 (s, 12H, pin-Me), 1.28 (s, 9H, tert-butyl).

13C NMR (126 MHz, CDCl3) δ 172.27, 155.94, 130.95, 126.86, 124.95, 123.42, 81.18, 35.25, 27.07, 25.38.

HRMS (FD+(eIeI)) calcd. for C18H28BNO3 [M]+ 317.2166, found 317.2157.

4-Chloro-N-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (10so)

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

**BAIPy-Ir catalyst; isolated yield of 65%.

**BPpy-Ir catalyst; isolated yield of 0%.

Rtx-1 column, method: Initial temperature = 50 °C for 2 min, then 10°C/min to 300°C for 15 min. Retention time: t (Sub) = 15.508 min, t (ortho) = 21.555 min, t (meta) = 24.407 min.

1H NMR (500 MHz, CDCl3) δ 9.66 (s, 1H, amide-NH), 7.69 (d, J = 8.2 Hz, 1H, Ha), 7.54 (d, J = 2.0 Hz, 1H, Hc), 7.15 (dd, J = 8.3, 2.0 Hz, 1H, Hb), 2.62 (d, J = 4.5 Hz, 3H, Me), 1.34 (s, 12H, pin-Me).

13C NMR (126 MHz, CDCl3) δ 171.56, 140.05, 131.38, 130.66, 127.99, 124.76, 81.52, 27.59, 25.31.

HRMS (FD+(eIeI)) calcd. for C14H19BClNO3 [M]+ 295.1147, found 295.1140.

4-Bromo-N-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (11so)

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

**BAIPy-Ir catalyst; isolated yield of 70%.
Hydrogen bond directed ortho-selective CH borylation of secondary aromatic amides

BPy-Ir catalyst; Isolated yield of 0%.
Rtx-1 column, method: Initial temperature = 50 °C for 2 min, then 10°C/min to 300°C for 15 min. Retention time: t (Sub) = 16.623 min.

\(^1\)H NMR (500 MHz, CD\(_2\)Cl\(_2\)) \(\delta 9.96 (s, 1H, amide-NH), 7.70 (d, \(J = 1.9\) Hz, 1H, Hc), 7.65 (d, \(J = 8.2\) Hz, 1H, Ha), 7.34 (dd, \(J = 8.2, 1.9\) Hz, 1H, Hb), 2.59 (d, \(J = 4.7\) Hz, 3H, Me), 1.32 (s, 12H, pin-Me).

\(^{13}\)C NMR (126 MHz, CD\(_2\)Cl\(_2\)) \(\delta 171.82, 133.61, 132.14, 131.11, 129.21, 125.52, 81.66, 27.66, 25.35.

HRMS (FD+(eiFi)) calcd. for C\(_{14}\)H\(_{19}\)BBrNO\(_3\) [M]\(^+\) 339.0644, found 339.1269.

\(-\hspace{2cm}\)

\(N\)-Benzyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (12so)
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; Isolated yield of 65%.
BPy-Ir catalyst; Isolated yield of 0%.
Rtx-1 column, method: Initial temperature = 50 °C for 2 min, then 10°C/min to 300°C for 15 min. Retention time: t (Sub) = 19.867 min, t (ortho) = 25.213 min, t (meta) = 26.078 min and t (para) = 26.815 min.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.72 (brs, 1H, amide-NH), 8.05 (d, \(J = 7.9\) Hz, 1H, Ha), 7.65 (d, \(J = 7.3\) Hz, 1H, Hb), 7.54 (t, \(J = 7.3\) Hz, 1H, Hc), 7.39 – 7.26 (m, 6H, Hd and Bn-aryl-H), 4.03 (d, \(J = 6.0\) Hz, 2H, Bn-CH\(_2\)), 1.27 (s, 12H, pin-Me).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 171.93, 137.53, 134.59, 132.93, 131.11, 128.89, 128.42, 128.17, 127.99, 124.77, 81.96, 44.86, 25.13.

HRMS (FD+(eiFi)) calcd. for C\(_{20}\)H\(_{24}\)BNO\(_3\) [M]\(^+\) 337.1853, found 337.1850.

\(-\hspace{2cm}\)

\(N\)-Benzyl-4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (13so)
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (6:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; Isolated yield of 71%.
Rtx-1 column, method: Initial temperature = 50 °C for 2 min, then 10°C/min to 300°C for 15 min. Retention time: t (Sub) = 21.605 min, t (ortho) = 26.025 min, t (meta) = 31.597 min.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.85 – 7.72 (m, 1H, amide-NH), 7.61 – 7.57 (m, 1H, Ha), 7.42 (s, 1H, Hc), 7.36 – 7.27 (m, 5H, Bn-aryl-H), 7.11 (d, \(J = 7.9\) Hz, 1H, Hb), 4.43 – 4.39 (m, 2H, Bn-CH\(_2\)), 2.37 (s, 3H, aryl-Me), 1.31 (s, 12H, pin-Me).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 170.37, 142.27, 137.51, 133.23, 133.23, 129.24, 128.92, 128.42, 128.17, 127.99, 124.19, 82.54, 44.80, 25.09.

HRMS (FD+(eiFi)) calcd. for C\(_{21}\)H\(_{26}\)BNO\(_3\) [M]\(^+\) 351.2010, found 351.2004.

\(-\hspace{2cm}\)

\(N\)-Benzyl-5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (14so)
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; Isolated yield of 81%.
Rtx-1 column, method: Initial temperature = 50 °C for 2 min, then 10°C/min to 300°C for 15 min. Retention time: t (Sub) = 22.013 min, t (ortho) = 26.440 min, t (meta) = 26.890 min.

\(^1\)H NMR (500 MHz, THF-d\(_8\)) \(\delta\) 8.07 (s, 1H, amide-NH), 7.42 (d, \(J = 8.1\) Hz, 1H, Hc), 7.40 – 7.38 (m, 2H), 7.29 – 7.26 (m, 2H), 7.21 – 7.18 (m, 2H), 6.95 (dd, \(J = 8.2, 2.4\) Hz, 1H, Hb), 4.56 (d, \(J = 5.9\) Hz, 2H, Bn-CH\(_2\)), 3.78 (s, 3H, OMe), 1.29 (s, 12H, pin-Me).

\(^13\)C NMR (126 MHz, THF-d\(_8\)) \(\delta\) 169.13, 161.12, 142.22, 140.45, 134.63, 128.82, 128.51, 127.45, 115.71, 111.58, 83.20, 44.34, 24.82.

HRMS (FD+(e)iFi) calcd. for C\(_{21}\)H\(_{26}\)BNO\(_4\) [M]+ 367.1959, found 367.1963.

\(N\)-Benzyl-5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (15so)

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:0.5 to 10:3.5) as the eluent.

**BAIPy-Ir catalyst; Isolated yield of 62%.

Rtx-1 column, method: Initial temperature = 50 °C for 2 min, then 10°C/min to 300°C for 15 min. Retention time: t (Sub) = 20.753 min, t (ortho) = 25.383 min, t (meta) = 23.213 min.

\(^1\)H NMR (500 MHz CD\(_2\)Cl\(_2\)) \(\delta\) 8.66 – 8.59 (m, 1H, amide-NH), 7.71 – 7.67 (m, 1H, Ha), 7.55 – 7.51 (m, 1H, Hc), 7.35 – 7.26 (m, 6H, Hb & Bn-aryl-H), 4.25 (d, \(J = 5.7\) Hz, 2H, Bn-CH\(_2\)), 2.37 (s, 2H, aryl-Me), 1.27 (s, 12H, pin-Me).

\(^13\)C NMR (126 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 171.05, 138.14, 136.80, 132.94, 132.15, 128.91, 128.37, 128.34, 127.88, 125.53, 82.71, 44.67, 25.12, 21.47.

HRMS (FD+(e)iFi) calcd. for C\(_{21}\)H\(_{26}\)BNO\(_3\) [M]+ 351.2010, found 351.2011.

\(N\)-Benzyl-5-(benzyloxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (16so)

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:0.5 to 10:4.0) as the eluent.

**BAIPy-Ir catalyst; Isolated yield of 69%.

\(^1\)H NMR (500 MHz CD\(_2\)Cl\(_2\)) \(\delta\) 7.61 (d, \(J = 8.1\) Hz, 1H, Hc), 7.50 – 7.25 (m, 11H, 2xBn-aryl & Ha), 7.05 (dd, \(J = 8.2, 2.6\) Hz, 1H, Hb), 6.95 (s, 1H, amide-NH), 5.11 (s, 2H, OBn-CH\(_2\)), 4.59 (d, \(J = 5.7\) Hz, 2H, NHBn-CH\(_2\)), 1.29 (s, 12H, pin-Me).

\(^13\)C NMR (126 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 169.13, 160.52, 142.35, 140.52, 138.86, 137.09, 136.30, 128.98, 128.94, 128.44, 128.33, 127.96, 127.78, 116.69, 113.71, 84.20, 70.44, 44.61, 25.05.

HRMS (FD+(e)iFi) calcd. for C\(_{27}\)H\(_{30}\)BNO\(_4\) [M]+ 443.2273, found 443.2272.

\(N\)-Benzyl-5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (17so)

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:0.5 to 10:4.0) as the eluent.
Hydrogen bond directed ortho-selective CH borylation of secondary aromatic amides

BAIPy-Ir catalyst; isolated yield of 39%.

Rtx-1 column, method: Initial temperature = 50 °C for 2 min, then 10°C/min to 300°C for 15 min. Retention time: t (Sub) = 20.888 min, t (ortho) = 25.492 min, t (meta) = 26.518 min.

1H NMR (500 MHz, CD2Cl2) δ 7.56 (d, J = 7.3 Hz, 2H, Hb & c), 7.45 – 7.33 (m, 7H, Ha & Bn-aryl-H & amide-NH), 4.74 (d, J = 5.7 Hz, 2H, Bn-CH2), 1.31 (s, 12H, pin-Me).

13C NMR (126 MHz, CD2Cl2) δ 169.46, 137.19, 133.27, 131.10, 130.57, 130.19, 129.23, 128.37, 128.32, 82.49, 45.74, 25.74.

HRMS (FD+(eiFi)) calcd. for C20H23BClNO3 [M]+ 371.1463, found 371.1478.

N-Benzy-5-bromo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (18so)

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:0.5 to 10:3.0) as the eluent.

BAIPy-Ir catalyst; isolated yield of 64%.

1H NMR (500 MHz, CD2Cl2) δ 9.54 (s, 1H, amide-NH), 8.19 (s, 1H, Ha), 7.67 (dd, J = 7.7, 1.8 Hz, 1H, Hb), 7.57 (d, J = 7.9 Hz, 1H, Hc), 7.43 – 7.23 (m, 5H, Bn-aryl-H), 4.11 (d, J = 5.9 Hz, 2H, Bn-CH2), 1.27 (s, 12H, pin-Me).

13C NMR (126 MHz, CD2Cl2) δ 170.28, 137.30, 137.23, 135.68, 133.24, 128.97, 128.45, 128.15, 127.58, 122.79, 82.61, 44.98, 25.23.

HRMS (FD+(eiFi)) calcd. for C20H23BBrNO3 [M]+ 415.0954, found 415.0950.

N-Benzyl-4-(tert-butyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (19so)

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; isolated yield of 55%.

Rtx-1 column, method: Initial temperature = 50 °C for 2 min, then 10°C/min to 300°C for 15 min. Retention time: t (Sub) = 23.132 min.

1H NMR (500 MHz, THF-d8) δ 8.43 (s, 1H, amide-NH), 7.63 (d, J = 8.2 Hz, 1H, Ha), 7.52 (d, J = 2.3 Hz, 1H, Hc), 7.37 – 7.34 (m, 3H), 7.28 – 7.25 (m, 2H), 7.21 – 7.18 (m, 1H, Hb), 4.52 (d, J = 5.8 Hz, 2H, Bn-CH2), 1.32 (s, 9H, tert-butyl), 1.31 (s, 12H, pin-Me).

13C NMR (126 MHz, THF-d8) δ 169.65, 153.94, 140.08, 135.79, 135.76, 128.88, 128.85, 128.42, 127.54, 124.51, 82.67, 44.42, 35.28, 31.42, 24.97.

HRMS (FD+(eiFi)) calcd. for C24H32BF3NO3 [M]+ 393.2480, found 393.2494.

N-Benzyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethoxy)benzamide (20so)

Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (8:1 to 1:1) as the eluent.
BAIPy-Ir catalyst; isolated yield of 63%.
Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min. Retention time: t (Sub) = 20.075 min, t (ortho) = 24.377 min, t (meta) = 25.197 min.

\[ ^{1}H \text{ NMR (500 MHz, CDCl}_3 \delta 9.37 (s, 1H, amide-NH), 8.00 (d, J = 8.2 Hz, 1H, Ha), 7.41 (s, 1H, Hc), 7.32 – 7.27 (m, 3H), 7.20 – 7.19 (m, 2H), 7.11 (d, J = 8.1 Hz, 1H, Hb), 4.16 (m, 2H, Bn-CH}_2, 1.23 (s, 12H, pin-Me). \]

\[ ^{13}C \text{ NMR (126 MHz, CDCl}_3 \delta 170.37, 152.94, 136.33, 132.38, 128.91, 128.14, 127.93, 126.08, 122.86, 120.27, 82.17, 44.99, 24.99. \]

HRMS (FD+(eiFi)) calcd. for C\(_{21}\)H\(_{23}\)BF\(_3\)NO\(_4\)[M]+ 421.1676, found 421.1672.

**N-Benzyl-4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (21so)**
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; isolated yield of 43%.
Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min. Retention time: t (Sub) = 22.408 min, t (ortho) = 26.468 min, t (meta) = 27.472 min.

\[ ^{1}H \text{ NMR (500 MHz, CDCl}_3 \delta 8.35 (brs, 1H, amide-NH), 7.75 – 7.72 (m, 1H, Ha), 7.36 – 7.26 (m, 5H), 7.11 (s, 1H, Hc), 6.81 – 6.77 (m, 1H, Hb), 4.36 – 4.34 (m, 2H, Bn-CH}_2, 3.87 (s, 3H, OMe), 1.33 (s, 12H, pin-Me). \]

\[ ^{13}C \text{ NMR (126 MHz, CDCl}_3 \delta 170.86, 163.51, 137.07, 128.83, 128.27, 127.92, 126.75, 125.49, 115.33, 114.70, 82.03, 55.54, 45.06, 25.12. \]

HRMS (FD+(eiFi)) calcd. for C\(_{21}\)H\(_{26}\)BNO\(_4\)[M]+ 367.1959, found 367.1956.

**N-Benzyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)benzamide (22so)**
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; isolated yield of 40%.
Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min. Retention time: t (Sub) = 21.518 min, t (ortho) = 25.950 min, t (meta) = 26.437 min.

\[ ^{1}H \text{ NMR (500 MHz, CDCl}_3 \delta 8.67 (s, 1H, amide-NH), 7.94 (d, J = 8.3 Hz, 1H, Ha), 7.87 (s, 1H, Hc), 7.57 – 7.56 (m, 2H), 7.36 – 7.22 (m, 4H), 4.29 (d, J = 5.5 Hz, 2H, Bn-CH}_2, 1.28 (s, 12H, pin-Me). \]

\[ ^{13}C \text{ NMR (126 MHz, CDCl}_3 \delta 169.66, 138.63, 136.50, 133.83 (m, two bonds C-F coupling), 128.95 (m, three bond C-F coupling), 128.77, 128.15, 128.01, 126.19 (m, one bond C-F coupling), 125.59 (m, three bond C-F coupling), 124.79, 82.89, 45.01, 24.99. \]

HRMS (FD+(eiFi)) calcd. for C\(_{21}\)H\(_{23}\)BF\(_3\)NO\(_3\)[M]+ 405.1727, found 405.1743.

**N-Benzyl-4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (23so)**
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; isolated yield of 75%.
Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min. Retention time: t (Sub) = 21.518 min, t (ortho) = 25.950 min, t (meta) = 26.437 min.

\[ ^{1}H \text{ NMR (500 MHz, THF-d}_8 \delta 8.52 (s, 1H, amide-NH), 7.65 (d, J = 8.3 Hz, 1H, Ha), 7.43 – 7.42 (m, 1H, Hc), \]

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7.38 – 7.34 (m, 2H), 7.38 – 7.36 (m, 2H), 7.34 – 7.28 (m, 1H, Hb), 7.24 – 7.21 (m, 1H), 4.61 (d, J = 5.8 Hz, 2H, Bn-CH₂), 1.31 (s, 12H, pin-Me).

13C NMR (126 MHz, THF-d₈) δ 168.90, 139.49, 137.86, 136.29, 135.24, 132.01, 129.00, 128.60, 128.36, 127.82, 125.89, 82.79, 44.84, 24.82.

HRMS (FD+(eqI/Fi)) calcd. for C₂₀H₂₃BClNO₃ [M]+ 371.1463, found 371.1456.

N-Benzyl-4-bromo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (24so)
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; Isolated yield of 67%.
Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min. Retention time: t (Sub) = 22.460 min, t (ortho) = 26.720 min, t (meta) = 39.940 min.

1H NMR (500 MHz, THF-d₈) δ 8.49 (s, 1H, amide-NH), 7.59 – 7.57 (m, 2H), 7.50 – 7.47 (m, 1H), 7.38 – 7.36 (m, 2H), 7.31 – 7.27 (m, 2H), 7.24 – 7.20 (m, 1H), 4.60 (d, J = 5.8 Hz, 2H, Bn-CH₂), 1.31 (s, 12H, pin-Me).

13C NMR (126 MHz, THF-d₈) δ 169.96, 139.51, 135.07, 131.37, 128.99, 128.60, 127.81, 126.13, 82.86, 44.83, 24.82.

HRMS (FD+(eqI/Fi)) calcd. for C₂₀H₂₂BrNO₃ [M]+ 415.0940, found 415.0959.

Methyl 4-(benzylcarbamoyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (25so)
BAIPy-Ir catalyst; Isolated yield of 32%.
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (5:1 to 2:1) as the eluent.

Rtx-1 column, method: Initial temperature = 50 ºC for 2 min, then 10ºC/min to 300ºC for 15 min. Retention time: t (Sub) = 24.250 min, t (ortho) = 28.308 min, t (meta) = 29.335 min.

1H NMR (500 MHz, CD₂Cl₂) δ 9.08 (s, 1H, amide-NH), 8.22 (s, 1H, Hc), 8.09 – 7.91 (m, 2H, Ha & Hb), 7.34 – 7.25 (m, 5H, Bn-aryl-H), 4.20 (d, J = 5.8 Hz, 2H, Bn-CH₂), 3.94 (s, 3H, COOMe), 1.28 (s, 12H, pin-Me).

13C NMR (126 MHz, CD₂Cl₂) δ 170.39, 166.86, 139.50, 139.50, 133.47, 132.74, 129.92, 128.99, 128.35, 128.35, 128.11, 124.93, 82.82, 52.64, 45.03, 25.11.

HRMS (FD+(eqI/Fi)) calcd. for C₂₂H₂₆BF₃NO₅ [M]+ 395.1904, found 395.1959.

N-Benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-naphthamide (26so)
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:0.5 to 10:3.0) as the eluent.

BAIPy-Ir catalyst; Isolated yield of 64%.

1H NMR (500 MHz CD₂Cl₂) δ 8.30 (s, 1H, amide-H), 8.15 (brs, 1H, Ha), 8.06 (s, 1H, Hb), 7.90 (d, J = 7.6 Hz, 1H, Hd), 7.87 – 7.82 (m, 1H, Hc), 7.56 – 7.55 (m, 2H, Bn-aryl-H), 7.33 – 7.25 (m, 5H, Bn-aryl-H), 4.33 (d, J = 5.8 Hz, 2H, Bn-CH₂), 1.37 (s, 12H, pin-Me).

13C NMR (126 MHz, CD₂Cl₂) δ 170.44, 138.35, 135.09, 134.66, 133.21, 132.95, 129.08, 128.92, 128.49, 128.23, 128.09, 127.84, 127.19, 125.47, 83.34, 44.67, 25.19.
HRMS (FD+(eiFi)) calcd. for C_{24}H_{26}BNO_{3} [M]^+ 387.2010, found 387.1994.

Methyl (2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl)valinate (27so)
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (5:1 to 2:1) as the eluent.

BAIPy-Ir catalyst; Isolated yield of 63%.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.62 (d, \(J = 7.7\) Hz, 1H, Ha), 7.58 (d, \(J = 7.4\) Hz, 1H, Hd), 7.49 (t, \(J = 7.3\) Hz, 1H, Hb), 7.44 (t, \(J = 7.5\) Hz, 1H, Hc), 6.85 (d, \(J = 8.6\) Hz, 1H, amide-NH), 4.71 (dd, \(J = 8.6, 5.2\) Hz, 1H, He), 3.76 (s, 3H, OMe), 2.26 (h, \(J = 6.7\) Hz, 1H, Hf), 1.35 (d, \(J = 5.9\) Hz, 12H, pin-Me), 1.03 – 0.98 (m, 6H, isopro-pyl-Me).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 172.61, 168.99, 138.57, 133.24, 130.97, 129.36, 125.24, 83.85, 58.33, 52.48, 32.01, 25.02, 24.95, 19.23, 18.25.

HRMS (FD+(eiFi)) calcd. for C_{19}H_{28}BNO_{5} [M]^+ 361.2064, found 361.2059.

N-benzyl-3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (28so) and N-Benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (28sm)
Isolated by chromatography using deactivated silica gel and ethyl acetate and petroleum ether (10:1 to 1:1) as the eluent.

BAIPy-Ir catalyst; Isolated yield of 85%.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) 28so \(\delta\) 9.11 (t, \(J = 4.9\) Hz, 1H, amide-NH), 7.92 (s, 1H, Ha), 7.31 – 7.27 (m, 5H, Bn-aryl-H), 4.51 (d, \(J = 4.8\) Hz, 2H, Bn-CH\(_2\)), 1.29 (s, 12H, pin-Me), 1.18 (s, 12H, pin-Me).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) 28sm \(\delta\) 7.57 (d, \(J = 3.7\) Hz, 1H, Hb), 7.48 (d, \(J = 3.6\) Hz, 1H, Hc), 7.27 – 7.18 (m, 5H, Bn-aryl-H), 6.68 (t, \(J = 5.8\) Hz, 1H, amide-NH), 4.53 (d, \(J = 5.8\) Hz, 2H, Bn-CH\(_2\)), 1.29 (s, 12H, pin-Me).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) 28so and 28sm 1:2 mixtures \(\delta\) 161.80, 161.77, 156.14, 146.13, 144.50, 138.04, 137.76, 137.18, 129.63, 128.76, 128.70, 128.68, 127.88, 127.63, 127.60, 84.89, 84.55, 84.42, 44.73, 44.04, 24.88, 24.80, 24.51.

28sm HRMS (FD+(eiFi)) calcd. for C_{18}H_{22}BNO_{5}S [M]^+ 343.1413, found 343.1378.

28so HRMS (FD+(eiFi)) calcd. for C_{24}H_{33}B_{2}NO_{5}S [M]^+ 469.2274, found 469.2272.

BAIPy-Ir catalyst showed no reactivity for ortho-functionalized benzamides under optimized reaction conditions.

References

[1] For reviews on transition metal-catalyzed CH functionalization and the reference cited therein, see: (a) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig. Chem. Rev. 2010,
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