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Regiochemical Switching in Ir-Catalyzed C−H Borylation by Altering Ligand Loadings of N,B-Type Diboron Species

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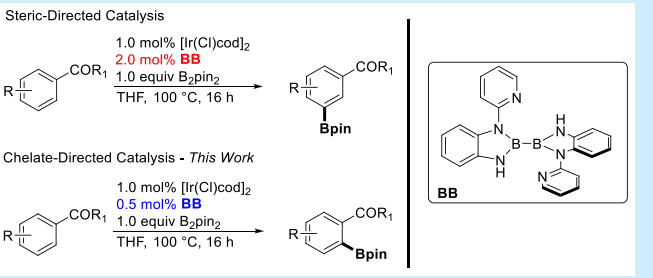
ABSTRACT: Traditional reaction conditions in Ir-catalyzed C−H borylation consist of a 2:1 ligand to Ir metal ratio, affording C(sp^2)−H borylation at the least sterically hindered position. We found that lowering the ligand to metal ratio of a N,B-type diboron (BB) preligand in respect to the Ir^I precatalyst to 0.5:1 affords the chelate controlled ortho product. Switching from steric-directed to chelate-directed products is shown for various substituted arenes and (hetero)arenes containing Lewis-basic functionalities. This work offers the first example of obtaining complementary regioisomers as the major product by altering the ligand loading in CHB.



Organoboron compounds are known for their use as intermediates in the syntheses of simple and complex molecules whose applications encompass pharmaceuticals, agrochemicals, and polymeric materials.[1−3] Of the many routes in creating organoboranes, iridium-catalyzed C−H borylation (CHB) has found its way as an atom economical approach in making this important class of compounds. Generally, the regioselectivity of iridium catalysts ligated with commonly used bipyridine or phenanthroline ligands is complementary to electrophilic aromatic substitution in that the product regioselectivity is determined by steric effects rather than electronics.[4−7]

For iridium-catalyzed CHBs, monodentate boryl actor ligands such as pinacolborane (HBpin) or bis(pinacolato)-diboron (B_2pin_2) serve as the boron source. Catalysis is initiated when either actor ligand oxidatively adds to the metal and later reductively eliminates with the substrate to form the organoboron product. Notably, these boryl ligands are susceptible to being removed from the metal during catalysis.[8]

In 2015, the Li group developed a catalyst system that uses a N,B-type bidentate spectator ligand (BB) that helps facilitate C−H activation.[8] The ligand is designed to stabilize the typically reactive boryl ligand through chelation[9] where the electron donation of the nitrogen atoms can donate into the p-orbital of boron and reduce its predisposition of being removed from the metal.[10−12] In Li's work, Complex 1, which bears two B,N-bidentate ligands about Ir, was shown to be generated by reacting the preligand with $[Ir(Cl)cod]_2$ (Figure 1).[8]

From this stabilization, an electron-rich ligand that has strong sigma donation to the metal center was created. This ligand system showed a competence for steric-directed catalysis. Given the use of a dimeric preligand, it was

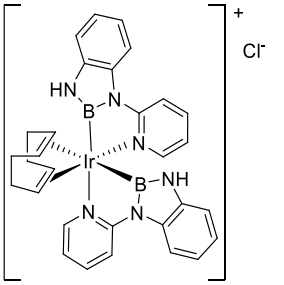


Figure 1. Double B,N-bidentate ligated catalyst by Li and co-workers (Complex 1).

hypothesized that this catalyst could be altered by reducing the number of B,N ligands attached to the metal center, thereby creating an open coordination site to yield chelate-directed ortho products. In this work, the method of changing the regioselectivity of a traditionally steric-directing catalyst for *ortho* C−H borylation is described.

The method for changing the regioselectivity of Complex 1 for *ortho* CHB was initially attempted by using a base additive, KO-*t*-Bu, to observe a Lewis acid−base interaction with one of boron's p orbitals and initiate cleavage of the bidentate ligand. Similar reactions have precedent in our research group.[13] This method was not successful in accomplishing the expected

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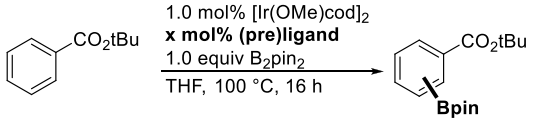
outcome and, in fact, inhibited borylation proportional to the amount of KO-*t*-Bu used based on both conversion and *ortho* selectivity (see SI, p S28).[14]

In Li's catalyst system,[8] the B,N-bidentate ligand (BB) was used in a 2:1 ratio to $[Ir(OMe)cod]_2$, where there are two bidentate ligands per iridium metal. This system yielded products borylated in positions predominantly based on steric factors. However, we found that reducing the preligand loading to a 1:1 ratio was met with dramatic changes in regioselectivity, now favoring the *ortho* product. The preligand loading results are shown in Table 1.

Table 1. Comparison of Preligand Loading and Regioselectivity



entry	ligand	preligand loading (mol %)	conv (%)	o:(m + p) (%)
1	BB	2	99	1:99
2	BB	1	80	60:40
3	BB	0.75	74	90:10
4	BB	0.50	67	95:5
5[a]	BB	0.50	90	96:4
6	dtbpy	2	99	1:99
7	dtbpy	0.50	74	1:99
8[a]	dtbpy	0.50	76	1:99

[a]Reactions run with 0.5 mmol substrate, 0.5 mmol B_2pin_2, 1 mol % $[Ir(OMe)cod]_2$, and x mol % BB or dtbpy in 1 mL of THF. Conversions and selectivity were determined by ^1H NMR analysis of crude material. Entries 5 and 8 were run using 1 mol % $[Ir(Cl)cod]_2$ as precatalyst.

The results of Table 1 demonstrated that using the BB preligand in lower loadings resulted in higher *ortho* selectivity. In fact, as the loading decreased, more chelate product was formed. These results did not follow those of typical CHBs using iridium catalysts. Stoichiometrically, traditional catalyst systems like Hartwig, Ishiyama, and Miyaura's use of 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) and $[Ir(OMe)cod]_2$ require a 2:1 ratio of ligand to precatalyst.[4] Previous work done by our group on ligand to precatalyst ratio had shown that optimal catalytic activity resulted when the preligand is in slight excess of the precatalyst. Attempts using a 1:1 preligand to precatalyst ratio have been performed before using dtbpy or 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen) and $[Ir(OMe)cod]_2$, but resulted in lower catalytic activity.[15] Similarities are found in this work where we observe that decreasing the amount of dtbpy to precatalyst lessens the reactivity of the system but has no effect on regioselectivity (entries 6−8). Table 1 demonstrates that this concept is not suited for the standard L_2 type bidentate ligand dtbpy.

To determine the cause of contrast between the steric and chelate conditions, crystals were grown in the catalyst system used for chelate-directed CHB (Figure 2). This was accomplished by heating a 1:1 ratio of $[Ir(Cl)cod]_2$ and BB in THF at 30 °C for 3 h. From the yellow solid that formed, crystals were grown via solvent displacement by using DCM/hexanes. This iridium complex (IrBB) possessed the double N,B-bidentate ligands and was cationic, similarly to the original Complex 1. However, instead of having a chloride counter-anion, this new complex had a dichloro cyclooctadiene iridium I species functioning as the counteranion.

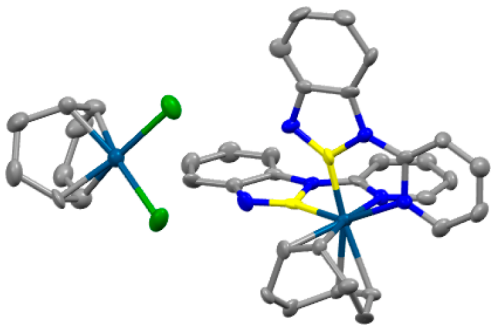


Figure 2. Crystal structure of IrBB with 50% probability ellipsoids and hydrogen atoms omitted for clarity. Ir (dark blue); N (blue); boron (yellow); Cl (green); C (gray). CCDC number 2236745.

IrBB was used as a catalyst for chelate-directed CHBs under the standard reaction conditions. Though this complex was not catalytically competent at room temperature, we observed *ortho*-borylated arene products (o:(m + p) = 95:5) with 77% conversion at 100 °C. At temperatures of 80 °C and lower, reactivity dropped significantly though *ortho*-borylation was still preferred (see SI, p S25). This data suggests the possibility of the preassembled catalyst playing a key role in the catalytic cycle and regioselective outcome.

Based on the promising results in Table 1, a substrate scope was carried out using the reaction conditions from entry 4 for achieving *ortho* regioselectivity. To fully assess how the preligand loading differs in this catalytic system, reactions were run in parallel to Li's original system (entry 1) alongside our optimized reaction conditions with 0.5 mol % BB and $[Ir(Cl)cod]_2$ (Scheme 1). (Scheme 1: Reactions run with 0.5 mmol substrate, 0.5 mmol B_2pin_2, 1 mol % iridium precatalyst, and 0.50 mol % BB preligand for chelate conditions or 2 mol % BB for steric conditions, in 1.0 mL THF for 8−16 h. Selectivity was determined by 1H NMR analysis of crude material. Isolated yields are shown. Note: N,N-dimethylbenzamide was used in the generation of **2c** and **3c**).

For the esters and amide tested, it was found that changing the ligand loading flips the regioselectivity, with ortho-selectivity ranging from 60 to 96% being observed with 0.5 mol % BB. Steric controlled conditions (2 mol % BB) gave almost exclusively the meta and para steric products (**3a**−**3h**). CHB reactions for both conditions were effective for a variety of functional groups with both electron withdrawing or donating substituents.

To see the efficacy of the chelate-directed conditions, ortho borylation was attempted for substrate **1d**, which has only one ortho site to the ester directing group and a bulky substituent in *meta* to the ester. Borylation of this substrate was in a steric position for both ligand loading conditions. This result illustrates the limits for switching regioselectivity by adjusting preligand loading.

Mono and disubstituted thiophene (**1i** and **1j**) and furan (**1k** and **1l**) heterocycles were tested for their competency under both borylation conditions(Scheme 2). (Scheme 2: Reactions run with 0.5 mmol of substrate, 0.5 mmol of B_2pin_2, 1 mol % iridium precatalyst, and 0.50 mol % BB for chelate conditions or 2 mol % BB for steric conditions, in 1.0 mL of THF for 4 h. Selectivity determined by 1H NMR analysis of crude material. Isolated yields are shown.) Monosubstituted

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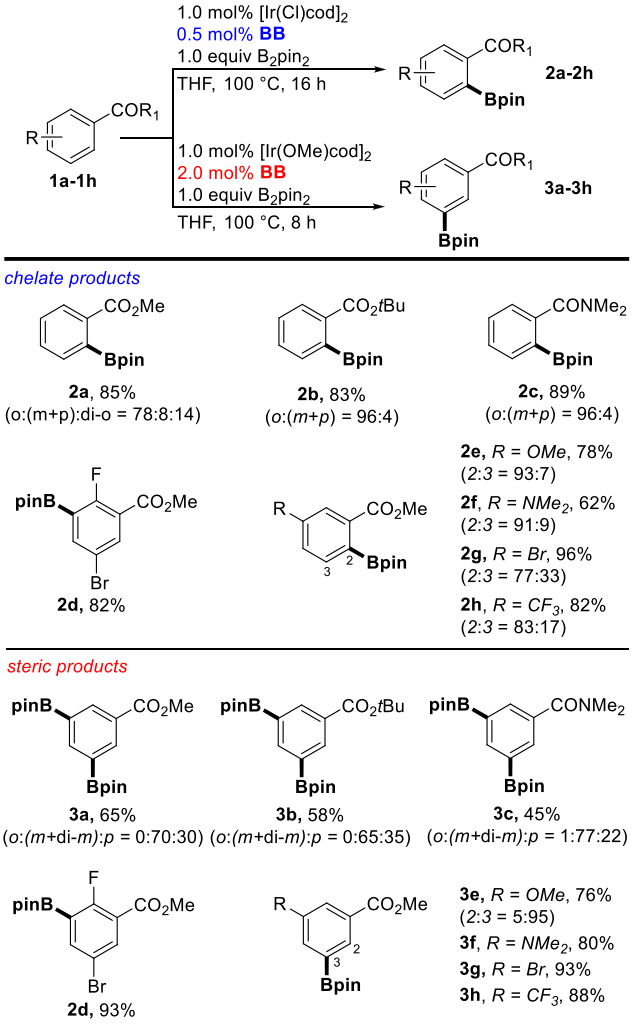
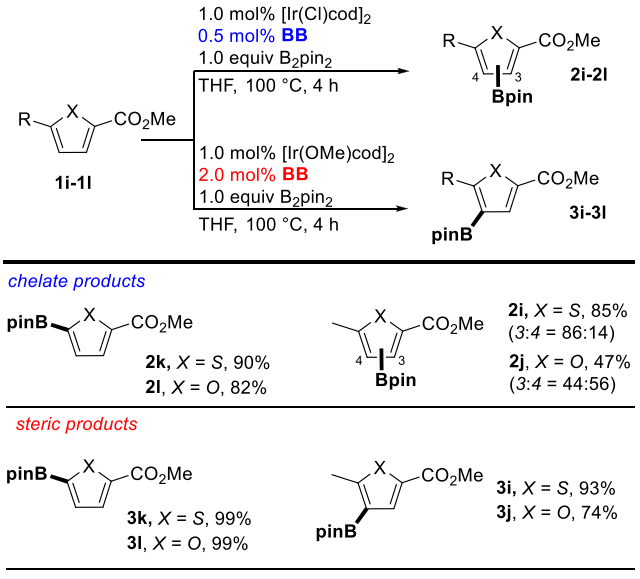
Scheme 1. CHBs of Arenes Using Conditions for Steric- and Chelate-Directed Catalysis



Scheme 2. CHBs of (Hetero)arenes Using Conditions for Steric- and Chelate-Directed Catalysis



heteroarenes **1k** and **1l** showed that the ester was incapable of directing *ortho* as it could not overcome the borylation of the more reactive 5-position of each substrate.[16] By blocking the 5-position with a methyl group (**1j** and **1l**), the heterocycle could be *ortho* borylated to the ester under chelate conditions. Interestingly, we found major differences in disubstituted heterocyclic products **2i** and **2j**, the latter showing steric preference regardless of the decreased preligand loading. Steric conditions gave products borylated at position 4 for both heterocycles.

Borylating substrates **1a**−**1l** using 0.5 mol % BB and $[Ir(OMe)cod]_2$ resulted in modest if any changes in reactivity or regioselectivity relative to using $[Ir(Cl)cod]_2$ (see SI for details). In contrast, with 2 mol % BB, using $[Ir(OMe)cod]_2$ gave higher yields and almost solely the steric product for all substrates in Schemes 1 and 2.

Shortly after Li's initial findings using BB,[5] an asymmetric analog of this ligand was designed for chelate-directed CHB, consisting of a boron covalently bonded to a silyl moiety (SiB, Figure 3).[17] The reaction of SiB and $[Ir(Cl)cod]_2$ formed a

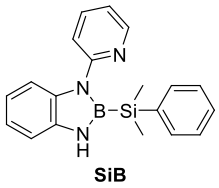


Figure 3. Boron−silicon ligand (SiB) used for chelate-directed CHB.

complex where the ligand oxidatively adds to the metal center with a single B,N-bidentate ligand and a silyl group. To test this ligand in our system, we compared the reduced ligand loading conditions with BB to the standard conditions with SiB. Similar conversions and levels of *ortho* selectivity were observed (see SI, S29).

Although both catalyst systems can produce chelate-directed products, the BB ligand at lower loadings is more appealing to use for catalyzed CHBs. Its synthesis can be done within two steps starting from commercially available materials and implements a simpler workup/purification that does not produce as large a waste stream as opposed to the SiB ligand synthesis.

Given that spectator boryl ligands have found their way as a powerful and versatile ligand class in CHBs for both $C(sp^2)$−H and $C(sp^3)$−H, as evidenced by the prominent work done by the Li and Xu groups,[18−25] the insights on potential modifications using dimer boron preligands like BB can be valuable in future iterations of this ligand type. From the beginnings of iridium catalyzed CHBs,[26] boron has typically been an actor ligand, but through new developments has shown to be a promising support ligand that can be used for regiochemical switching.

In conclusion, a catalyst system was modified from steric- to chelate-directed by changing the preligand loading by using a 0.5:1 ratio of BB to iridium dimer precatalyst.[14] This system works well for *ortho* CHB to esters, amides, and (hetero)arenes and is the first case reported in Ir-catalyzed CHB where catalyst regioselectivity can be altered via loading of preligand. Reaction mechanisms and other boron dimer derivatives are currently being investigated.

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■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c02760.

Experimental procedures, spectral data, and crystallographic data of IrBB (PDF)

Accession Codes

CCDC 2236745 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors. Laboratory work was performed by ACO and PAM. All authors have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): MRS and REM own a percentage of BoroPharm, Inc.

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