

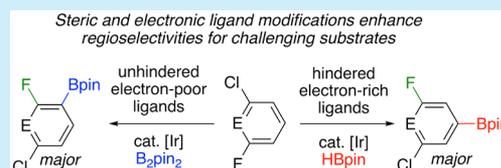
C–H Borylation Catalysts that Distinguish Between Similarly Sized Substituents Like Fluorine and Hydrogen

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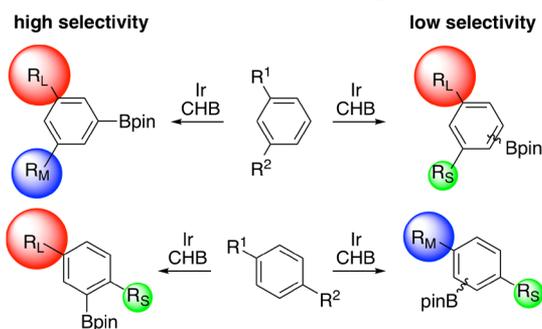
S Supporting Information

ABSTRACT: By modifying ligand steric and electronic profiles it is possible to C–H borylate ortho or meta to substituents in aromatic and heteroaromatic compounds, where steric differences between accessible C–H sites are small. Dramatic effects on selectivities between reactions using B_2pin_2 or 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBpin) are described for the first time. Judicious ligand and borane combinations give highly regioselective C–H borylations on substrates where typical borylation protocols afford poor selectivities.



C–H borylation (CHB) has gained popularity,¹ in part, because the sterically directed regioselectivity observed for arenes often complements that of electrophilic aromatic substitution (EAS) and directed ortho metalations (DoM).² As shown in **Scheme 1**, CHBs of 1,3-substituted benzenes are

Scheme 1. Sterically Directed CHB Regioselectivities



highly meta selective when the substituents are sufficiently large to block functionalization of the ortho positions. For 1,4-substituted benzenes, regioselectivity can be achieved when substituent sterics differ significantly.³ When these requirements are not met, selectivities erode.

Recent work demonstrated good to excellent selectivities for CHB ortho to F.⁴ This underscores the challenge of selectively borylating C–H bonds meta to F, where the intervening sp^2 C is H-substituted. Driess and co-workers reported a cobalt(II) pincer complex that catalyzes CHB of fluoroarenes with the best meta to F selectivities to date. CHBs of 2,3- and 3-substituted fluorobenzenes were particularly good ranging from more than 99:1 to 7:1.⁵

This is a significant advance. However, Driess reported no CHBs of fluorinated heterocycles, and aromatic substituents besides F were limited to Me and CF_3 . Chirik's Co CHB catalysts do not tolerate heavier halogens,^{4d} and we reported

CHBs with a Co^{II} precatalyst, where even C–F bonds are cleaved.⁶

Given that $C(sp^2)$ –B bonds can be converted to a broad range of functional groups, the ability to functionalize meta or ortho to F in substrates bearing heavier C–halogen bonds opens the cross-coupling “toolbox” for elaborating fluorinated structures. Here we show that, through ligand design, good regioselectivities are achieved for combinations of substrates, substituents, and substitution patterns that are daunting for standard CHBs and other C–H/X transformations.

3-Fluorochlorobenzene is illustrative of remaining challenges in aromatic functionalization (**Figure 1**). While the 2-position

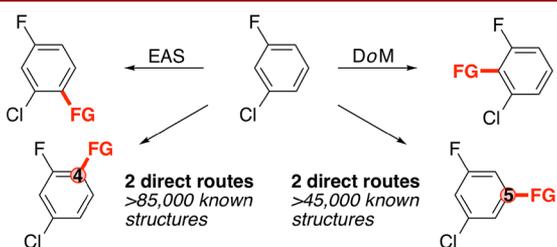


Figure 1. C–H functionalization of 3-fluorochlorobenzene.

can be selectively transformed via DoM,⁷ and EAS can be used to functionalize the 6-position,⁸ selective derivatizations at the 4-position are limited to enzymatic⁹ and electrophilic¹⁰ processes. Moreover, only three reports, all C–H activations, describe functionalization at the 5-position.^{10b,11} Given that tens of thousands of 4- and 5-substituted analogues have been reported, the dearth of direct routes¹² from **1** is remarkable.

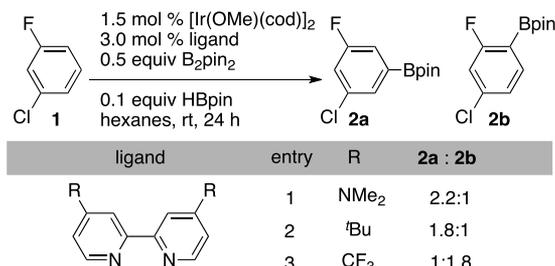
Ir-catalyzed CHB using the common ligand/precatalyst combination of 4,4'-di-tert-butyl-2,2'-dipyridyl/bis(1,5-cyclo-

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octadiene)-di- μ -methoxy-diiridium(I) (dtbpy/[Ir(OMe)(cod)]₂, cod = 1,5-cyclooctadiene) gives a 1:1.8 mixture of 4- and 5-borylated products, respectively. Despite this low regioselectivity, CHBs clearly provide opportunities to functionalize these challenging positions. As electronic effects influence CHB regioselectivities,¹³ borylations of **1** were performed using 4,4'-disubstituted-2,2'-dipyridyl ligands (Scheme 2). The

Scheme 2. Electronic Effects on Regioselectivity^a



^a0.5 equiv of B₂pin₂ equals 1 equiv of transferable Bpin groups.

remote substitution site on the bipyridine ligand ensures electronically determined regioselectivities. Although selectivity changes are modest, Scheme 2 shows that **2a** is favored with the most electron-rich ligand, while **2b** is major for the most electron-poor ligand. On the basis of estimated pK_a values of halogenated benzenes, the C–H bond at the 4-position should be more acidic than the C–H at the 5-position.¹⁴

With the results in Scheme 2 and estimations of ligand steric effects,³ the ligand design approach in Figure 2 was devised for

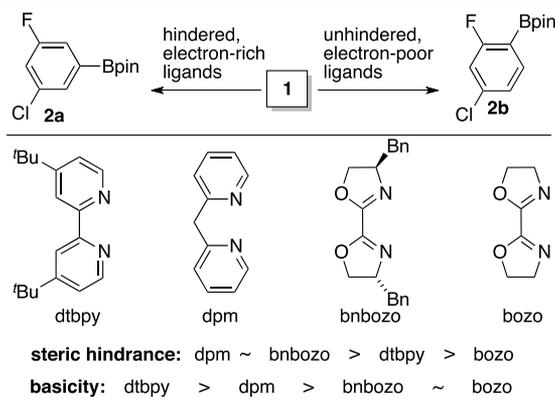


Figure 2. Bidentate nitrogen ligand properties.

selective functionalization at the 4- or 5-positions of **1**. Hindered, electron-rich ligands should favor isomer **2a**, while less encumbered, electron-poor ligands should select for isomer **2b**.

When 4,4'-di-tert-butyl-2,2'-dipyridyl (dtbpy), 2,2'-bis[(4S)-4-benzyl-2-oxazoline] (bnbozo), and 2,2'-bis-2-oxazoline (bozo) are κ^2 -bound to Ir, the resulting five-membered metallacyclic structures are effectively coplanar. Both bozo and bnbozo will be weaker donors relative to dtbpy, since (i)

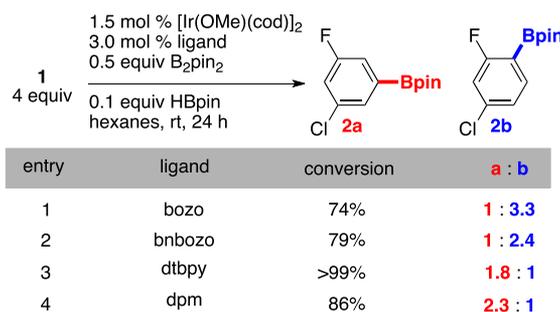
their N(sp²) lone pairs have poorer overlap with Ir orbitals and (ii) bozo and bnbozo are weaker σ -donors than dtbpy, since Brønsted basicities of oxazoles are lower than pyridines.¹⁵ Bozo is less sterically hindered than dtbpy, because its five-membered oxazoline rings are smaller than the pyridine rings in dtbpy. In contrast, the Ir center in five-coordinate trisboryl bnbozo intermediates will be less accessible than for dtbpy and bozo analogues, because the bnbozo benzyl groups will project into the substrates' path to the C–H cleaving transition state.

Dipyridylmethane (dpm) intermediates differ from the others, because the six-membered metallacyclic rings resulting from κ^2 coordination to Ir are puckered. Thus, the Ir center in dpm intermediates will be less accessible than in dtbpy and bozo analogues.

The hypotheses in Figure 2 predict that ortho to F selectivity for CHBs of **1** will increase in the order dpm < dtbpy < bozo, and the meta to F CHB selectivity will follow the reverse order. The positioning of bnbozo is difficult to predict a priori.

Gratifyingly, the experimental selectivities in Scheme 3 follow the predicted order for dpm, dtbpy, and bozo for substrate **1**. CHBs of **1** with bnbozo favor ortho to F product **2b**.

Scheme 3. Ligand Selectivities for Borylation of **1**



It is known that B₂pin₂ is more reactive than 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBpin) in Ir CHB.¹⁶ Thus, reactions with 0.5 equiv of B₂pin₂ proceed first via borylation of the substrate, generating HBpin. Then, the second stage of the reaction produces more borylated product and H₂. For the CHB of **1** with 0.5 equiv of B₂pin₂ catalyzed by dpm/[Ir(OMe)(cod)]₂, the selectivity for isomer **2a** increased as the reaction progressed. This suggested that the regioselectivities with B₂pin₂ and HBpin differ.

This was confirmed by examining dpm/[Ir(OMe)(cod)]₂ catalytic CHBs of **1** with 2 equiv of HBpin or B₂pin₂ under conditions otherwise identical to those in Scheme 3. In Scheme 4, CHB with B₂pin₂ lowered the **2a/2b** ratio from 2.3:1 (Scheme 3) to 1:1. When CHB was performed with HBpin the **2a/2b** ratio rose to 5:1! This is the first time a significant difference in selectivity between B₂pin₂ and HBpin has been observed. For the other ligands in Scheme 3, the boron reagent had little influence on **2a/2b** ratios.

Scheme 4. Boron Reagent Effects on Regioselectivity of **1**

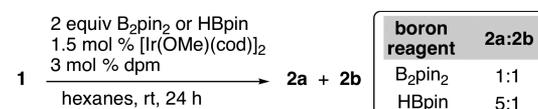
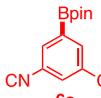
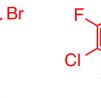
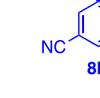
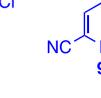
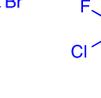
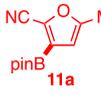
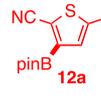
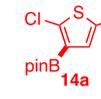
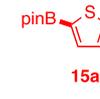
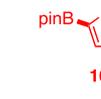
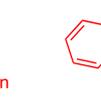
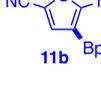
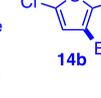
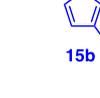
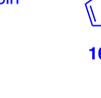
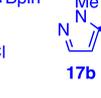
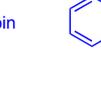


Table 1. Five- and Six-Membered Arene and Heteroarene Selectivities

entry	1	2	3	4	5	6	7	8	9
									
									
	2a:2b dtbpy 1.8:1 dpm 5:1 (51% 5:1) bnbozo 1:2.4 bozo 1:3.3 (16% 2b)	3a:3b dtbpy 3:1 dpm 7:1 (60% 7:1) bnbozo 1:1.6 bozo 1:1.8	4a:4b dtbpy 2.8:1 dpm 8:1 (60% 8:1) bnbozo 1:1.3 bozo 1:2.6	5a:5b dtbpy 6.5:1 dpm 23:1 (91% 5a) bnbozo 4.5:1 bozo 1.8:1	6a:6b dtbpy 4.5:1 ^a dpm 12:1 (74% 6a) bnbozo 3:1 ^a bozo 1.5:1 ^a	7a:7b dtbpy 32:1 ^a dpm 38:1 ^a bnbozo 99:1^a (89% 7a) bozo 27:1 ^a	8a:8b dtbpy 4:1 ^a dpm 5.6:1 ^a bnbozo 13:1^a (89% 13:1) bozo 4.5:1 ^a	9a:9b dtbpy 2:1 dpm 3:1 bnbozo 13:1 (74% 16:1) bozo 2.8:1	10a:10b dtbpy 1:1.6 dpm 1.5:1 (30% 3:1) bnbozo 1:4.5 bozo 1:8.5 (66% 1:9)
entry	10	11	12	13	14	15	16	17	
									
									
	11a:11b dtbpy 5.7:1 dpm 4.8:1 bnbozo >99:1 (96% 11a) bozo 17:1	12a:12b dtbpy 4.6:1 ^a dpm 4.9:1 ^a bnbozo 40:1^a (81% 12a) bozo 6.1:1 ^a	13a:13b dtbpy 5.7:1 ^a dpm 2.7:1 ^a bnbozo 32:1^a (66% 13a) bozo 13:1 ^a	14a:14b dtbpy 5.7:1 ^a dpm 3.2:1 ^a bnbozo 12:1^a (89% 14a) bozo 6:1 ^a	15a:15b dtbpy 1:1.1 ^a dpm (74% 5.5:1)^a bnbozo 1:1.4 ^a bozo 1:8^a (75% 1:8)	16a:16b dtbpy 4:1 ^a dpm 11:1^a (82% 11:1) bnbozo 6.1:1 ^a bozo 1:1 ^a	17a:17b dtbpy 1:9 dpm 1:6.3 bnbozo 1:9 bozo 1:32^a (63% 17b)	18a:18b dtbpy 1:32 dpm 1:18 bnbozo 1:>99 (93% 18b) bozo 1:14	

^aSee Supporting Information for variations to the standard conditions, which are as follows: 1 mmol of substrate, 1.5 mol % [Ir(OMe)(cod)]₂, 3 mol % ligand, 1–3 equiv of HBpin, 3 mL of solvent. Reaction times vary from 1 to 72 h, isomer ratios were determined by gas chromatography–flame ionization detector or ¹H NMR, and isolated yields are in parentheses.

To test the design principles built from CHBs of **1**, several five- and six-membered ring aromatic and heteroaromatic compounds where CHBs with dtbpy/[Ir(OMe)cod]₂ give isomer mixtures were screened for CHB regioselectivities using dpm, bnbozo, and bozo ligands and [Ir(OMe)cod]₂. Each parent substrate gives two primary regioisomers denoted as **a** (sterically favored) and **b** (electronically favored). Results are shown in Table 1, and ligands that gave the highest selectivities for the respective major isomers are highlighted. Many substrate/ligand combinations yielded more than 10:1 selectivity for isomer **a**. Significantly, dtbpy, the most common Ir CHB ligand, never gave superior regioselectivity.

In keeping with trends illustrated in Figure 2, we sought to further improve steric selectivity by design of a more basic derivative of the dpm ligand. This was accomplished with (4,4'-bis(dimethylamino)2,2'-dipyridyl)methane (dmadpm) (Figure 3). Estimated pK_a values^{15c,d} for the parent 4-dimethylamino monomer are significantly more basic than the corresponding monomer estimates for dtbpy and dpm. Thus, dmadpm tops the steric and basicity ranking.

With these results in hand, we set out to compare dpm selectivity against the more electron-rich dmadpm (Scheme 5).

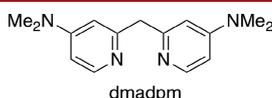


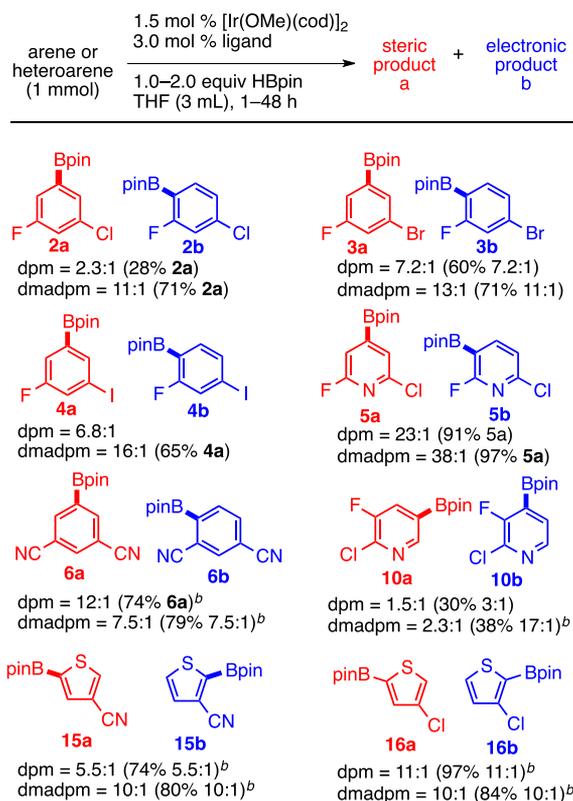
Figure 3. An electron-rich, hindered ligand for CHB.

Where dpm favored the sterically preferred product in Table 1, dmadpm was tested under identical conditions. Improved selectivity was seen for products **2a**, **3a**, **4a**, **5a**, **10a**, and **15a**. For **5a**, selectivity was sufficiently high that pure **5a** was obtained in a 95% yield with 0.25 mol % catalyst. Selectivity worsened for **6a** and **16a**.

The utility of ligand-modulated selectivity that we developed is showcased in Figure 4. C–H borylations are compared to putative Miyaura C–X borylations (X = Br or I). Factors to be considered in choosing between these routes are desired regiochemistry and reactant price.¹⁷

For the synthesis of **2a**, the low cost of the corresponding aryl bromide substrate makes Miyaura borylation the route of choice. In contrast, aryl and heteroaryl halides required for Miyaura routes to **5a**, **6a**, or **12a** range from being costly to nonexistent. It is noteworthy that directed ortho metalations of substrates where Y = H followed by trapping with boron electrophiles will not give **5a** or **6a** as major isomers, and bromothiophenes are known for halogen dance rearrangements. Therefore, Ir CHB is the best option for making isomers **5a**, **6a**, and **12a**.

In summary, ligand modifications can dramatically improve regioselectivity in Ir CHB of substrates, where the most commonly used ligand, dtbpy, gives isomer mixtures that can limit synthetic utility. We also showed that hindered, electron-rich ligands can shift selectivity to steric products, whereas unhindered electron-poor ligands shift selectivity toward electronic products. Electron-poor oxazoline ligands such as bnbozo facilitate high selectivity for activated, five-membered

Scheme 5. Regioselectivities with dmadpm Versus dpm^a

^aIsomer ratios determined by gas chromatography–flame ionization detector or ¹H NMR. Isolated yields in parentheses. ^bSee Supporting Information for variations to the standard conditions.

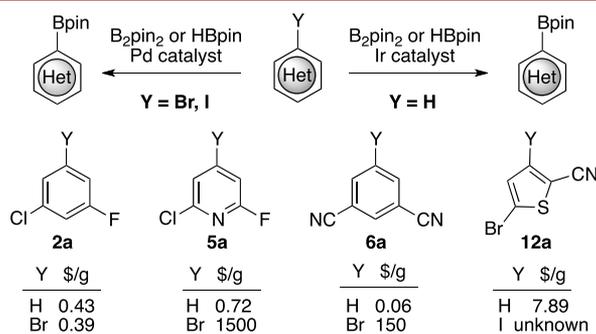


Figure 4. Comparison of C–H and C–X borylation routes.

heterocycles and substrates that are difficult to borylate using conventional pyridyl ligands. In addition, we showed for the first time that the nature of the boron reagent can significantly affect Ir CHB regioselectivity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02299.

Experimental procedures and compound characterization data (PDF)

Accession Codes

CCDC 1434792–1434794, 1436384, 1437270, and 1937214 contain 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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S.L.M., M.R.S., and R.E.M. wrote the manuscript. S.L.M., G.A.C., J.A.F., and B.C. performed research.

Notes

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

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(17) Prices listed were the lowest per gram on quantities up to 1 kg for products in stock or available within one week from United States suppliers as identified through a Scifinder search on June 14, 2019.