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Role of Hemilabile Diamine Ligands in the Amine-Directed C−H Borylation of Arenes

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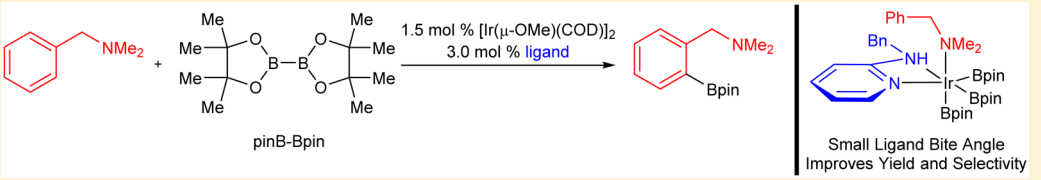
Supporting Information



ABSTRACT: A study of the role played by the bidentate ligand used in amine-directed C−H borylation is described. Both reaction conversion and selectivity were significantly impacted when steric congestion and electronic perturbations of the bidentate diamine ligand were made, but a more significant influence was imparted by reducing the bite angle of the ligand. *N*-Benzylaminopyridine was identified as a general ligand that improves both selectivity and yield for most problematic substrates previously reported with picolylamine as ligand.

INTRODUCTION

C−H functionalization reactions have received significant attention over the past two decades, resulting in a number of key advances that allow the conversion of otherwise unreactive C−H bonds into synthetically valuable functional groups.[1−5] One method shown to be valuable to the synthetic community is the C−H borylation reaction.[6−14] The distinct advantage of this reaction lies both in the versatility of the resulting C−B bonds and the inherent selectivity of the catalysts, which are highly sensitive to steric congestion.[12,15] In the case of arenes, borylation *ortho* to a substituent is kinetically disfavored, resulting in selective functionalization of appropriately substituted arenes (such as 1,3-disubstituted arenes) or substrates with a particularly reactive C−H bond present. Alkanes, on the other hand, are selective for primary C−H bonds,[16−18] with only select examples of the functionalization of secondary alkyl C−H bonds reported.[19,20]

In recent years, substrate-directed C−H borylation has resulted in the selective formation of *ortho*-substituted aryl boronate esters,[15,21−31] reversing the inherent selectivity of the catalyst. Several examples of Lewis base-directed reactions have been reported for halides,[23] ethers,[23] esters,[23,24] phosphines,[31] and nitrogen-containing Lewis bases.[26−30] Our work in this area has largely focused on amine directing groups, which utilize hemilabile diamine ligands to provide an open coordination site on the active iridium catalyst upon dissociation of one arm of the bidentate ligand.[29] In this transformation picolylamine (**3**) was identified as an optimal ligand to promote the catalytic transformation (eq 1). Several substrates, however, provided moderate yields or poor selectivity (for the mono-*ortho*-borylated product over the bis-*ortho*-borylated product). To improve the yields and selectivity of this transformation, and to gain insight into the role of the diamine ligand prior to a full mechanistic interrogation, a ligand study was initiated. The

(1)

nature of the diamine ligand was probed for steric congestion, electronic effects, and the bite angle of the bidentate ligand; the diamine bite angle was found to have a significant effect on both product yield and selectivity. We herein report an improved protocol for amine-directed C−H borylation and insights into the role of the diamine in the catalytic transformation.

The initial report of amine-directed C−H borylation focused on picolylamine (**3**) as the optimal ligand, in conjunction with $[Ir(\mu\text{-OMe})(COD)]_2$ (COD = cyclooctadiene), to mediate *ortho*-selective C−H borylation. The proposed mechanism (Scheme 1)[32] is consistent with that suggested by Fernández and Lassaletta for the directed borylation of hydrazones[27] and involves partial dissociation of one arm of the bidentate diamine ligand to open a coordination site for the required C−H activation step. Notably, picolylamine (**3**, blue in Scheme 1) is less rigid than the traditionally used di-*tert*-butylbipyridine (dtbpy) ligand, which facilitates dissociation of one ligand nitrogen but maintains the second nitrogen (shown in Scheme 1 as the pyridine nitrogen), which is thought to be a critical component of the catalytic reactivity.

The role of the ligand in governing the product yield and the selectivity of the mono-*ortho*-borylation over the bis-*ortho*-borylation products was expected to be governed by two key

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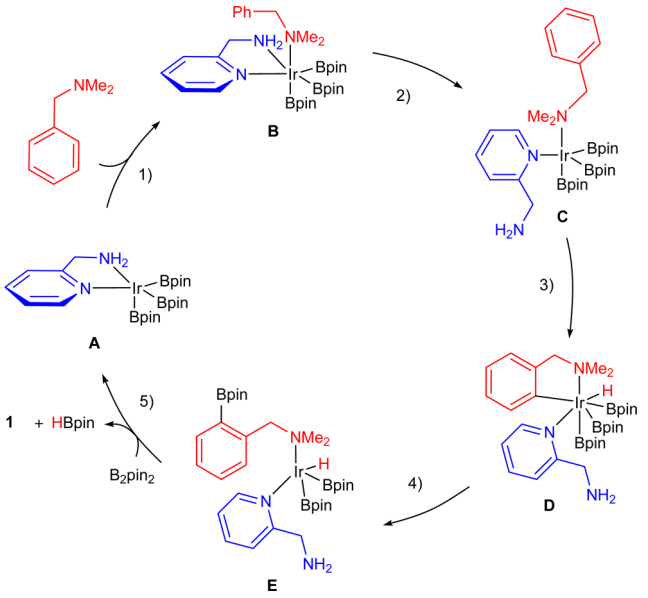
Scheme 1. Proposed Mechanism of Amine-Directed C−H Borylation[29]



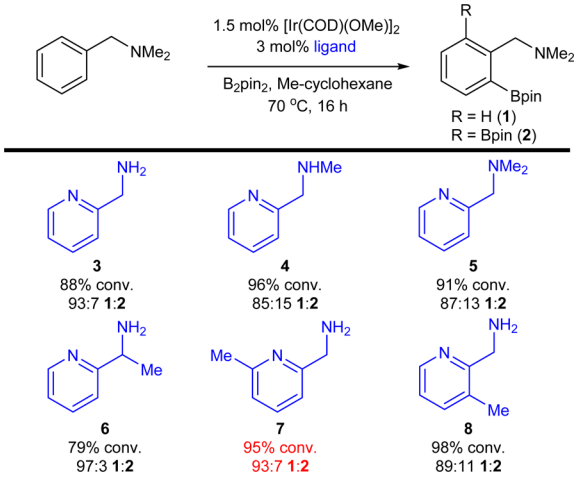
steps: the dissociation of one arm of the diamine ligand (step 2: **B** to **C**) and dissociation of the borylated arene (**1**) to regenerate the active catalyst (step 5: **E** to **A**). In step 2, the nature of the dissociating nitrogen would have a significant effect on the rate of the formation of **C** and likely the overall reactivity of the catalyst. Alternatively, step 5 will be highly influenced by the ability of the dissociated nitrogen to recoordinate to the iridium center and promote dissociation of **1**. Steric congestion around the associated nitrogen will also have a significant influence on the loss of **1** by inducing steric strain between the ligand and the increased steric demands of the borylated arene. A detailed ligand evaluation was expected to provide insights into the proposed catalytic cycle and provide a more focused approach to a full mechanistic study.

RESULTS AND DISCUSSION

The ligand study was initiated by examining the influence that steric congestion around both ligand nitrogens played in reaction conversion and selectivity for the mono-*ortho* borylation product, using the parent *N*,*N*-dimethylbenzylamine (Scheme 2).[33] *N*-Methylpicolylamine (**4**) and *N*,*N*-dimethylpicolylamine (**5**)[29] were examined to determine the effect of the ligand-based amine substituents on the reaction conversion and selectivity, providing significant loss in selectivity in both cases while providing an improved conversion with **4**. Placement of a substituent on the alkyl backbone of the ligand (ligand **6**) provided increased selectivity with a decreased conversion. Substitution on the arene portion of the ligand (ligands **7** and **8**) resulted in the most significant improvements; a methyl adjacent to the pyridine nitrogen (**7**) provided an increase in conversion without the loss of selectivity.

The electronic effects of the ligand were examined by varying the Lewis basicity of both nitrogens (Figure 1). The electron density of the pendant amine was examined initially. Converting the pendant amine to a weaker Lewis base (ligands **9** and **10**) resulted in improved reactivity of the catalyst over picolylamine (**3**), albeit with a significant loss in selectivity. Electron-deficient pyridine **11** resulted in a slight increase in selectivity compared to picolylamine (**3**). Replacement of the

Scheme 2. Effect of Steric Congestion on Conversion and Selectivity of C−H Borylation[a]



[a]Percent conversion and selectivity were determined by ^{1}H NMR spectroscopy; 1.2 equiv of arene to B_2pin_2; all conversions are based on the arene substrate.

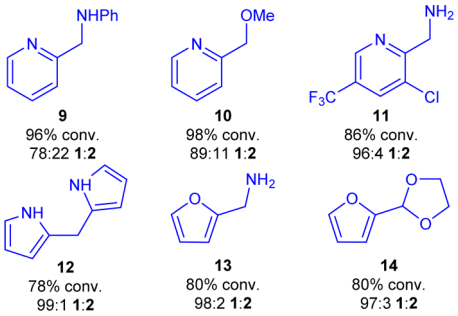


Figure 1. Electronic effects on conversion and selectivity to **1**. Percent conversion and selectivity were determined by ^{1}H NMR spectroscopy; 1.2 equiv of arene to B_2pin_2; all conversions are based on the arene substrate.

pyridine with a pyrrole or furan (ligands **12**−**14**) resulted in low conversion, suggesting an important electronic effect of the pyridine nitrogen in the catalytic cycle. These results are consistent with dissociation of the amine nitrogen (as shown in Scheme 1) and suggest that weakly coordinating pendant Lewis bases increase the catalytic activity.

The final major category that was examined for increased catalytic activity and selectivity was the bite angle[34−36] of the bidentate ligand. Ligands **15** and **16** (Figure 2) were compared to picolylamine (**3**) and found to provide increased conversion in the case of **15** and exceptional selectivity in the case of **16**. Importantly, the high selectivity of **16** was coupled with good conversion. Additional aminopyridine ligands were examined based on the insights gained from the steric and electronic effects discussed above. Substitution of the ligand-based amine nitrogen with a benzyl substituent (ligand **17**) resulted in a slight loss of selectivity but with slightly improved conversion. Addition of a methyl substituent adjacent to the pyridine nitrogen (ligand **18**) did not provide improvement, but an increased conversion was observed with an acylated amine nitrogen (ligand **19**). Finally, an electron-withdrawing $-CF_3$ substituent on the arene (**20**) also improved the conversion but resulted in a significant loss in selectivity.

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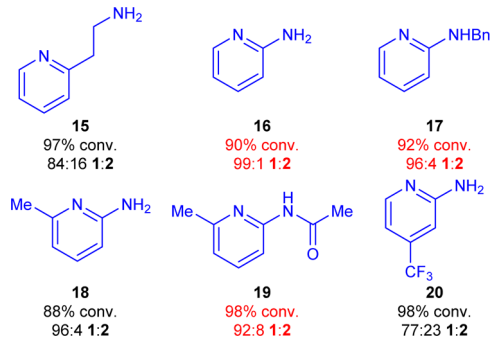
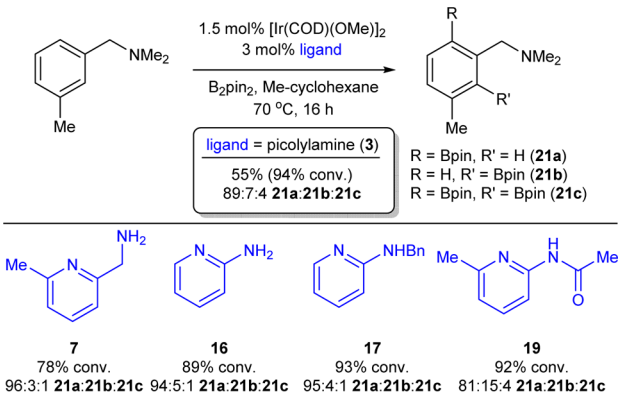


Figure 2. Effect of bite angle on conversion and selectivity to **1**. Percent conversion and selectivity were determined by ^{1}H NMR spectroscopy; 1.2 equiv of arene to B_2pin_2; all conversions are based on the arene substrate.

The small bite angle of 2-aminopyridine ligands likely has two key roles in the catalytic cycle: it provides rapid dissociation of one arm of the bidentate ligand (Scheme 1, **B** to **C**) due to the decreased bite angle and the decreased Lewis basicity of an aniline-type amine; the smaller bite angle could also increase the steric congestion near the catalyst by reducing the ability of the dissociated nitrogen to rotate away from the iridium center.[37] These effects on individual mechanistic steps are subtle and will require a full mechanistic investigation to determine if the proposed catalytic cycle is consistent with this analysis.

The ligand study described above resulted in several improved ligands that could be applied to the substrates that provided poor yield or selectivity using picolylamine (**3**).[29] The most problematic substrates are 3-substituted benzylamines, which provide two monoborylation products (Scheme 3, **a** and

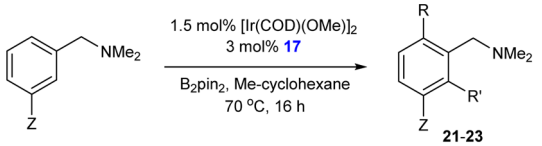
Scheme 3. Products and Ligand Screen from C−H Borylation of *N,N*-Dimethyl-3-methylbenzylamine[a]



[a]Percent conversion and selectivity were determined by ^{1}H NMR spectroscopy; 1.2 equiv of arene to B_2pin_2; all conversions are based on the arene substrate.

b) and bisborylation products (**c**). For these substrates, 85−89% of the borylated material is represented by product **a**. Several ligands identified above were examined with *N,N*-dimethyl-3-methylbenzylamine. Ligand **17** was found to provide the most significant improvement in selectivity for boronate ester **21a**, with a 95:4:1 selectivity of **21a**/**21b**/**21c** while maintaining a 93% conversion.

N-Benzylaminopyridine (ligand **17**) was examined with other 3-substituted benzylamines, providing improved selectivity in each case (eq 2, Table 1). Although 3-methoxy- and 3-chloro-substituted substrates did not improve as much as the 3-methyl-



(2)

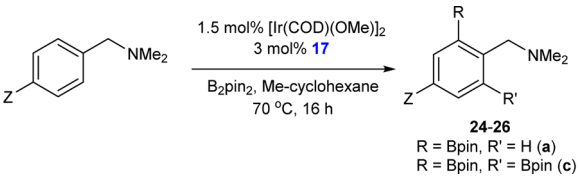
Table 1. C−H Borylation of *N,N*-Dimethyl-3-substituted Benzylamines with Ligand 17[a]

Substrate		3	17
NMe2, Me	**Yield**	55%	85%
	Conv.	94%	93%
	21a:21b:21c	89:7:4	95:4:1
NMe2, Cl	**Yield**	54%	77%
	Conv.	94%	94%
	22a:22b:22c	88:11:1	90:8:2
NMe2, OMe	**Yield**	82%	73%
	Conv.	93%	95%
	23a:23b:23c	88:9:3	90:6:4

[a]Perent conversion and selectivity were determined by ^{1}H NMR spectroscopy; 1.2 equiv of arene to B_2pin_2; conversions are based on the arene substrate. Isolated yields are of a mixture of **a**, **b**, and **c**.

substituted substrate, a consistent increase in selectivity was observed. The increased quantities of **22b** and **23b** are consistent with the known steric and electronic effects observed with electronegative atoms in the nondirected C−H borylation reactions.[38] The chlorine and methoxy substituents provide a slight activation of this sterically congested C−H bond through inductive effects. The general improvement of the isolated yields without an increase in conversion is believed to result from a decrease in unidentified side-products, resulting in clean product formation.

Several 4-substituted benzylic amines were also known to provide low yield or selectivity with picolylamine (**3**) and were examined with ligand **17** (eq 3, Table 2). Improved yield and/



(3)

or selectivity was achieved with 4-bromo-, 4-methyl-, and 4-ethanoate-substituted benzylamines. The 4-methyl-substituted substrate demonstrated a significant improvement in selectivity with ligand **17** without a loss in yield. In the case of **25** and **26**, the conversion and selectivity were similar to those of picolylamine (**3**), but the poor yields were improved. Of particular note is the improved yield of boronate ester **25** (from 37% to 65%), which has resulted in a synthetically viable yield of an intermediate with both a boronate ester and bromine present for additional transformations.

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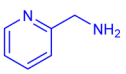
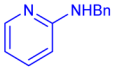
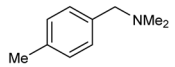
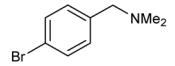
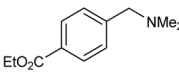
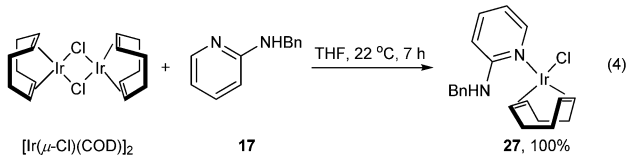
Table 2. C−H Borylation of *N,N*-Dimethyl-4-substituted Benzylamines with Ligand 17

Substrate		 3	 17
	**Yield**	81%	83%[a]
	Conv.	95%	89%
	24a:24c	84:16	94:6
	**Yield**	37%	65%[a]
	Conv.	82%	84%
	25a:25c	97:3	95:5
	**Yield**	49%	57%
	Conv.	90%	88%
	26a:26c	93:7	93:7

[a]Reaction run for 24 h. Percent conversion and selectivity were determined by ^{1}H NMR spectroscopy; 1.2 equiv of arene to B_2pin_2; conversions are based on the arene substrate. Isolated yields are of a mixture of **a** and **c**.

The results described above are a clear indication that the nature of the ligand has subtle influences on the catalytic cycle that can determine the catalyst efficiency and selectivity. In an effort to isolate an active catalyst, several protocols were examined to incorporate ligand **17** into an iridium complex.[8,39] All attempts to form a trisboryl complex from $[Ir(\mu\text{-OMe})(COD)]_2$, **17**, and B_2pin_2 or HBpin by methods analogous to those reported in the literature provided complex mixtures. Direct addition of **17** to $[Ir(\mu\text{-Cl})(COD)]_2$, however, provided iridium complex **27** as a yellow solid in quantitative yield and high purity (eq 4).[40] Recrystallization by slow



evaporation from tetrahydrofuran and pentane provided X-ray quality crystals that were used to assign the structure unambiguously (Figure 3). Complex **27** is a square-planar, Ir(I), d^8 complex in which the diamine ligand is bound in a monodentate fashion through the pyridine nitrogen.

All attempts to convert complex **27** to a boron-containing active catalyst by addition of B_2pin_2 or HBpin were unsuccessful. Subjecting complex **27** to the reaction conditions for C−H borylation, however, demonstrated that the complex is catalytically active.[41] Notably, the catalytic reactivity of **27** is similar to the standard reaction conditions when $[Ir(\mu\text{-Cl})(COD)]_2$ and **17** are added separately and are significantly improved over the conditions with $[Ir(\mu\text{-Cl})(COD)]_2$ in the absence of added ligand.[41]

In summary, a detailed ligand screen has been reported that demonstrates the effects of steric congestion, electronics, and the bite angle of the bidentate ligand. The bite angle of the ligand was found to have the most significant effect on improving both conversion and selectivity of mono-borylation products over bis-borylation products. *N*-Benzylaminopyridine was identified as the optimal ligand for substrate-directed C−H borylation and provided improved yield and selectivity for most 3- and 4-substituted benzylamines.

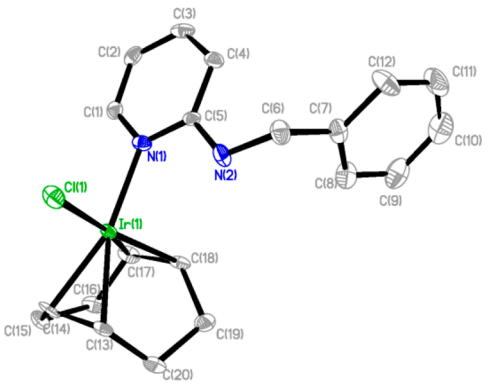


Figure 3. ORTEP drawing for complex **27** with thermal ellipsoids shown at 50% probability. Only one of the two complexes in the asymmetric unit is shown for clarity. The benzylaminopyridine ligand is coordinated to iridium through the pyridine nitrogen (N1) with a bond length of 2.093(6) Å for the complex shown.

EXPERIMENTAL SECTION

General Methods. Oxygen- and moisture-sensitive or hygroscopic materials were handled under purified nitrogen in an inert atmosphere glovebox. All solvents were dried and degassed by standard procedures unless used for purification. TLC analysis used 500 μm, 60 Å silica layer fluorescence UV plates. Flash chromatography was carried out on hand-packed columns of Brockman I basic aluminum oxide, 50−200 μm, 60 Å. NMR spectra were collected on an NMR spectrometer at 400 or 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. ^{1}H NMR spectra are referenced to $CDCl_3$ at 7.26 ppm or to an internal tetramethylsilane (TMS) standard at 0.00 ppm. All benzylic amines were synthesized by known procedures.[29] All deuterated solvents, bis(pinacolato)diboron, $[Ir(\mu\text{-OMe})(COD)]_2$, $[Ir(\mu\text{-Cl})(COD)]_2$, and ligands were purchased and used without further purification. Complex **27** was examined by single-crystal Xray diffraction using a Bruker APEX-II Platform CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.710 73 A) by ω scans at 100 K. The structure was solved and refined using the SHELXTLPLUS package. The structure was solved by direct methods.

Representative Procedure for the C−H Borylation of Benzylic Amines with Various Bidentate Ligands. To a 50 mL PTFE-valved reaction tube, equipped with a stir bar and charged with $[Ir(\mu\text{-OMe})(COD)]_2$ (0.020 g, 0.030 mmol), were added 6-methyl-2-(aminomethyl)pyridine (**7**, 0.0073 g, 0.060 mmol), B_2pin_2 (0.424 g, 1.67 mmol), *N,N*-dimethylbenzylamine (0.270 g, 2.00 mmol), and 4.0 mL of methylcyclohexane. After 16 h at 70 °C, the volatiles were removed *in vacuo*. The unpurified reaction mixture was analyzed by ^{1}H NMR spectroscopy, and characteristic peaks for **1**, **2**,[29] and *N,N*-dimethylbenzylamine (typically the benzylic methylene hydrogens) were used to determine the reaction conversion and selectivity.

Representative Procedure for the C−H Borylation of Substituted Benzylic Amines with *N*-Benzylaminopyridine (17). To a 50 mL PTFE-valved reaction tube, equipped with a stir bar and charged with $[Ir(\mu\text{-OMe})(COD)]_2$ (0.020 g, 0.030 mmol), were added *N*-benzylaminopyridine (**17**) (0.011 g, 0.060 mmol), B_2pin_2 (0.424 g, 1.67 mmol), 3-chloro-*N,N*-dimethylbenzylamine (0.339 g, 2.00 mmol), and 4.0 mL of methylcyclohexane. After 16 h at 70 °C, the volatiles were removed *in vacuo*. The unpurified reaction mixture was analyzed by ^{1}H NMR spectroscopy, and characteristic peaks for **22a**, **22b**, **22c**,[29] and 3-chloro-*N,N*-dimethylbenzylamine (typically the benzylic methylene hydrogens) were used to determine the reaction conversion and selectivity. Purification by chromatography with basic aluminum oxide (98.5:0.5:1 dichloromethane/methanol/triethylamine) followed by bulb-to-bulb distillation (30 min at 60 °C, 0.5 mmHg), to remove unreacted starting material,

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provided **22** (0.453 g, 1.53 mmol, 77%) as a 90:8:2 mixture of **22a**/**22b**/**22c**.

(2-Benzylaminopyridine)chloro(1,5-cyclooctadiene)iridium-(I) (27). To a round-bottom flask containing $[Ir(\mu\text{-}Cl)(COD)]_2$ (0.372 mmol, 0.250 g) and **17** (0.744 mmol, 0.137 g) was added THF (10.0 mL). The reaction was stirred at room temperature for 7 h, then concentrated to give a yellow, amorphous solid (0.3879 g, 0.746 mmol, 100%). Suitable crystals for X-ray analysis were grown from a solution of **27** (20.2 mg) in tetrahydrofuran/pentane (2:1, 0.75 mL) by slow evaporation. Mp: 153.3−158.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 5.9 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.39−7.28 (m, 5H), 6.61 (t, J = 6.9 Hz, 1H), 6.41 (d, J = 8.6 Hz, 1H), 4.53 (d, J = 6.0 Hz, 2H), 4.46 (br s, 2H), 3.25 (br s, 2H), 2.23 (br s, 4H), 1.66−1.63 (m, 2H), 1.53−1.49 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.1, 147.3, 137.7, 137.3, 128.8, 127.6, 126.9, 113.7, 107.9, 71.0 (br), 46.9, 32.2 (br), 31.1 (br). IR (thin film, $CDCl_3$): 3280 (br), 2936 (m), 2911 (m), 2880 (m), 2833 (m), 1616 (s), 1570 (s), 1521 (s), 1448 (s) cm^{-1}. HRMS (EI): calcd for $C_{20}H_{24}ClIrN_2$ $[M + Na]^+$ m/z 541.1132, found $[M + Na]^+$ 541.1128. The structure was confirmed by X-ray crystallography.[41]

■ ASSOCIATED CONTENT

Supporting Information

Representative ^{1}H NMR spectral data of crude and purified arylboronate esters, general experimental information, and crystallographic data and cif files of **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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