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C(sp^2)−H Borylation of Fluorinated Arenes Using an Air-Stable Cobalt Precatalyst: Electronically Enhanced Site Selectivity Enables Synthetic Opportunities

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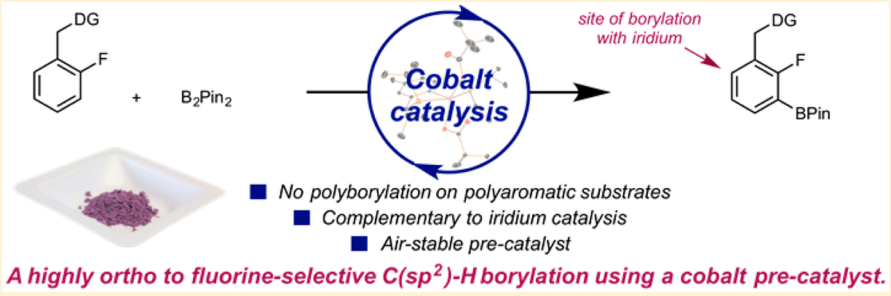
Supporting Information



ABSTRACT: Cobalt catalysts with electronically enhanced site selectivity have been developed, as evidenced by the high *ortho*-to-fluorine selectivity observed in the C(sp^2)−H borylation of fluorinated arenes. Both the air-sensitive cobalt(III) dihydride boryl 4-Me-(^{iPr}PNP)Co(H)$_2$BPin (**1**) and the air-stable cobalt(II) bis(pivalate) 4-Me-(^{iPr}PNP)Co(O$_2$C^{t}Bu)$_2$ (**2**) compounds were effective and exhibited broad functional group tolerance across a wide range of fluoroarenes containing electronically diverse functional groups, regardless of the substitution pattern on the arene. The electronically enhanced *ortho*-to-fluorine selectivity observed with the cobalt catalysts was maintained in the presence of a benzylic dimethylamine and hydrosilanes, overriding the established directing-group effects observed with precious-metal catalysts. The synthetically useful selectivity observed with cobalt was applied to an efficient synthesis of the anti-inflammatory drug flurbiprofen.

INTRODUCTION

The direct, selective C−H functionalization of organic molecules in the absence of directing groups is a grand challenge in modern catalysis. Fluorinated arenes are prominent targets given the prevalence of this subunit in pharmaceuticals,[1] agrochemicals,[2] and organic materials (Figure 1).[3] Efficient methods for the synthesis of *o*-fluorinated aryl boronate esters are attractive, given the versatility of the boron substituent for elaboration by Suzuki−Miyuara cross-coupling, Chan−Lam−Evans coupling, and a host of other methods.[4]

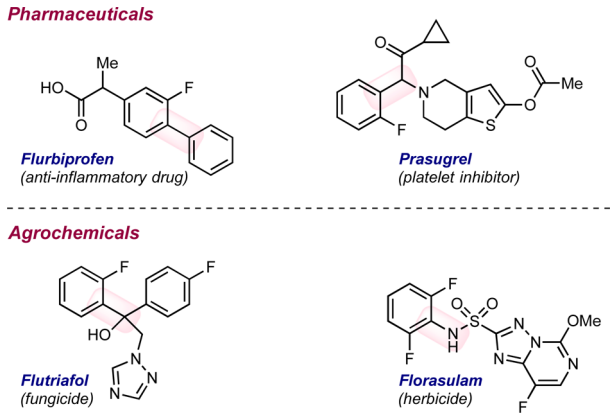


Figure 1. Examples of *o*-fluoroaryl motifs in pharmaceuticals and agrochemicals.

Iridium-catalyzed C−H borylation has emerged as one of the most widely used C−H functionalization methods due to its high efficiency and complementary selectivity to traditional electrophilic aromatic substitution.[5,6] Iridium complexes containing bipyridine or phenanthroline ligands are the most widely used and mechanistically well understood[7−9] and exhibit predictable site selectivity that is typically controlled by the steric accessibility of the C−H bond.

Distortion interaction analysis established that the regioselectivity in these reactions is largely controlled by the interaction of the arene carbon with the iridium catalyst, although fluorinated arenes were not thoroughly addressed in this study.[9] It is well-established that the C−H bond *ortho* to fluorine in fluoroarenes is more acidic relative to the *meta* and *para* C−H bonds;[10] however, selective, catalytic C−H borylation of this position in the presence of other sterically accessible C−H bonds still remains a challenge.[11] Alternative strategies for the preparation of single regioisomers of fluorinated aryl boronate esters have been developed, including

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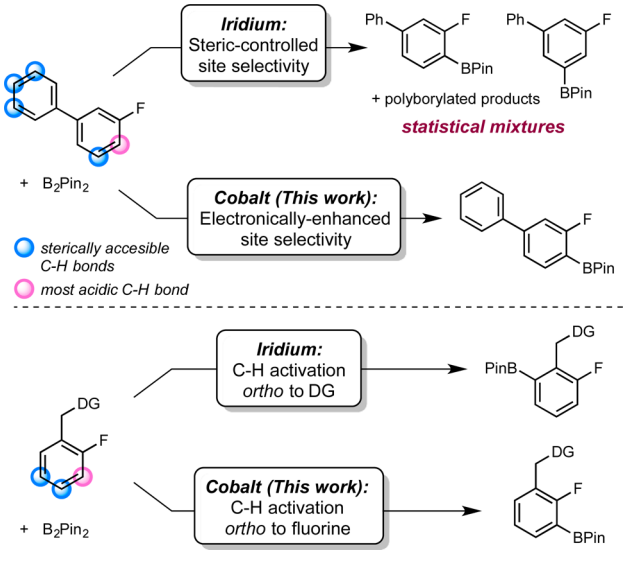
installation and removal of blocking groups to increase the selectivity of the iridium-catalyzed reaction.[12] Use of NHC-[13a] and PSiN-ligated platinum catalysts,[13b] as well as phosphine-[14a] and POP-supported rhodium catalysts,[14b] have all been explored to increase the *ortho*-to-fluorine selectivity in fluoroarene borylation. While these were important advances, the requirement of excess arene, elevated temperatures, and multiple fluorines in the arene substrate detract from the general utility of these methods.[13,14]

In a recent patent application, specific electron-poor bidentate ligands, such as 4,4′-bis(trifluoromethyl)-2,2′-bipyridine (btfbpy) and 4,4′,5,5′-tetrakis(trifluoromethyl)-2,2′-bipyridine (ttfbpy), have been claimed to enable selective iridium-catalyzed C−H borylation of 1-chloro-3-fluoro-2-substituted benzenes.[15] Up to 82:18 *ortho*:*meta* selectivity was reported for the iridium-catalyzed C−H borylation of 1-chloro-2,3-difluorobenzene using ttfbpy as the ligand. Monodentate pyridine ligands were also claimed to be effective ligands to achieve high *ortho*-to-fluorine selectivity in the iridium-catalyzed C−H borylation of 3-fluorotoluene. Specifically, an 82:18 (4.7:1) *ortho*:*meta* selectivity was reported with 2-methoxy pyridine (2-OMe-Py) as the ligand.

First-row transition-metal catalysts for C−H borylation are attractive not only for their potential cost and environmental advantages but also for the opportunity for new reactivity and selectivity over known precious-metal catalysts.[16] Among the base-metal examples reported, [(^{iPr}PNP)Co]-based catalysts are the most active for the C(sp^2)−H borylation of arenes and heteroarenes.[17] Mechanistic studies support a Co(I)−Co(III) pathway, in which a cobalt(I)−boryl is responsible for C−H activation. Substitution of the 4-position of the pincer prevented catalyst deactivation by C−H borylation of the ligand and inspired the preparation of improved, second-generation 4-methyl- and 4-pyrrolidinyl-substituted catalysts.[18] With the first-generation cobalt alkyl, (^{iPr}PNP)CoCH_2SiMe_3, unprecedented 89:11 *ortho*:*meta* selectivity for the borylation of fluorobenzene with B_2Pin_2 (Pin = pinacolate) was observed.[17] Here, we describe a more general cobalt-catalyzed method for the *ortho*-to-fluorine-selective borylation of a wide range of fluorinated arenes (Scheme 1). The cobalt precatalysts, including an air-stable variant, offer distinct selectivity enhancements over known precious-metal catalysts, enabling an efficient synthesis of the anti-inflammatory drug flurbiprofen.

Scheme 1. Cobalt-catalyzed C(sp^2)−H Borylation with Enhanced *ortho* Site Selectivity with Fluoroarenes



RESULTS AND DISCUSSION

Synthesis of 4-Me-(^{iPr}PNP)Co(O_2C^tBu)$_2$ (2). The 4-methyl-substituted pincer 4-Me-^{iPr}PNP was selected for these studies due to its relative ease of synthesis, electron-donating properties, and resistance to deactivation by borylation during turnover.[18] The cobalt(III) dihydride boryl (**1**) and cobalt(II) bis(pivalate) (**2**) complexes were used as precatalysts (Figure 2). Complex **1** was selected due to the precedent for cobalt(III)

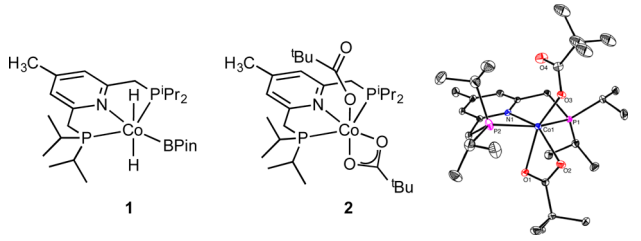


Figure 2. Cobalt precatalysts **1** and **2** and the solid-state molecular structure of **2** at 30% probability ellipsoids. Hydrogen atoms omitted for clarity.

precursors as effective precatalysts for C−H borylation,[18] while complex **2** was prepared due to its relative ease of synthesis and its air stability. Recent studies from our laboratory[19] and others[20] have demonstrated both the air stability and utility of cobalt[19a−e,20] and nickel[19f] carboxylates as catalyst precursors.

Cobalt complex **2** was synthesized by the straightforward addition of the free ligand to anhydrous cobalt pivalate[21] and was isolated in 49% yield as a purple powder with an $S = {}^3/_2$ ground state [μ_{eff} = 4.1(1) μ_B at 23 °C, solid state]. Structural characterization (Figure 2) established a six-coordinate cobalt complex with κ^1 and κ^2 carboxylate ligands. A single paramagnetically shifted *tert*-butyl resonance was observed by ^{1}H NMR spectroscopy, suggesting rapid interconversion of κ^1 and κ^2 carboxylate ligands on the NMR time scale, similar to related pyridine diimine[19c] and terpyridine cobalt complexes.[19d,e] It is also possible that the κ^1 and κ^2 forms are indistinguishable by NMR spectroscopy. Compound **2** exhibited excellent bench stability, as no change in the ^{1}H NMR spectrum of the compound was observed after exposure of the solid to air for 5 days [Figure S1, Supporting Information (SI)].

Substrate Scope Using 1 as a Precatalyst. The site selectivity of cobalt-catalyzed C(sp^2)−H borylation was explored in a variety of arenes with various substitution patterns (Table 1). Precatalyst **1** was evaluated initially with a series of 3-substituted fluoroarenes. Efficient borylation was observed over the course of 24 h at 50 °C with B_2Pin_2. The arylboronate products were obtained in high yields and *ortho*-to-fluorine selectivity with arenes containing ester (**4a**), trifluoromethyl (**4b**), sulfonamide (**4c**), and amide (**4d**) functional groups. Recrystallization of the regioisomeric mixture of **4d** yielded regiochemically pure **4d** in 69% isolated yield. With polyaromatic substrates (**4e**, **4f**, **4g**, **4h**), exclusive borylation of the ring containing the fluorine atom was observed despite the presence of multiple sterically accessible C(sp^2)−H bonds. Fluoroarenes containing electron-donating groups (**4i**, **4j**, **4k**, **4l**) were borylated with reduced *ortho*-to-

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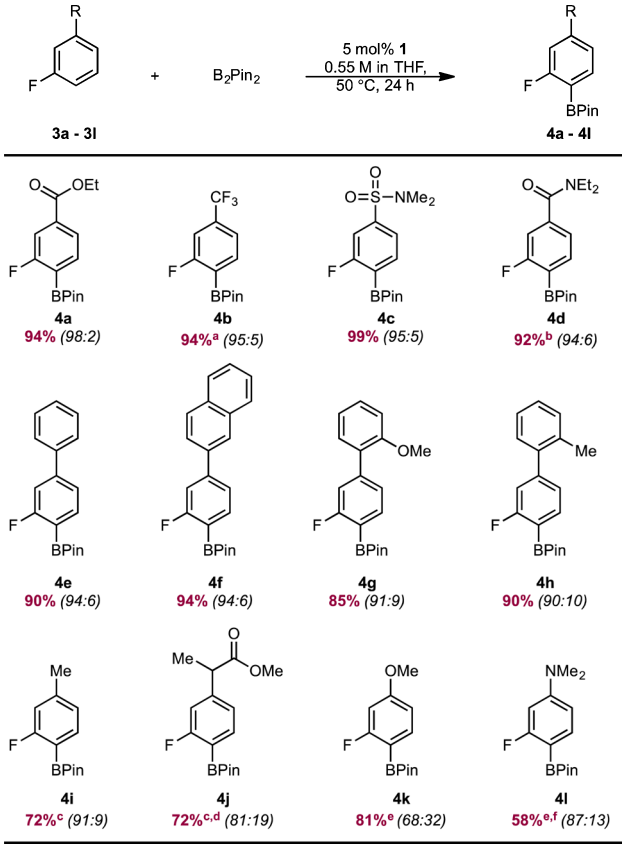
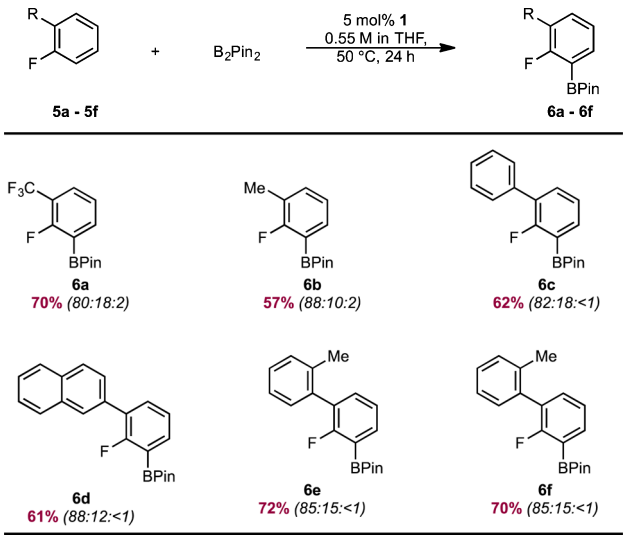
Table 1. Substrate Scope of the *ortho*-to-Fluorine C(sp^2)−H Borylation[g] of 3-Substituted Fluoroarenes Catalyzed by 1



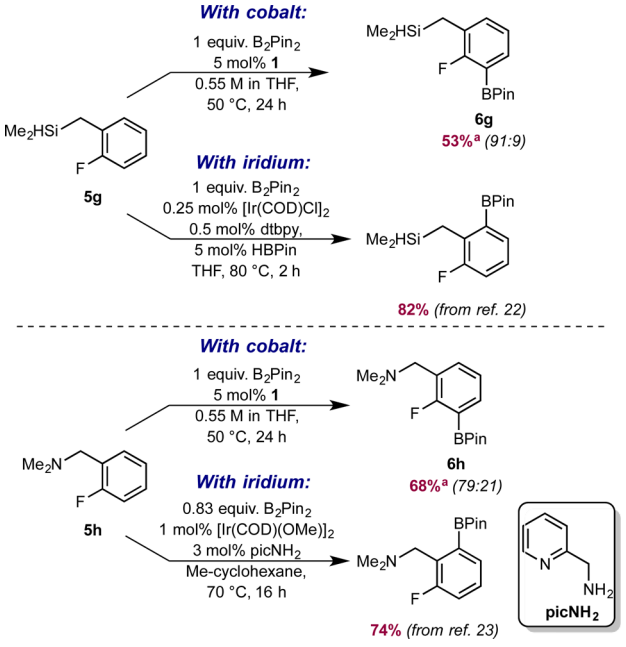
[a]With 1 mol % of **1**. [b]Yield of 69% (>99:1 *ortho*:*meta*) after recrystallization. [c]Reacted for 48 h. [d]On 2.74 mmol scale. [e]Reacted for 72 h. [f]Conditions: 25 mol % of **1**, 80 °C, 1.1 M in THF, 5 equiv of **3l**. [g]Typical reaction conditions: arene (0.55 mmol), B_2Pin_2 (0.55 mmol), **1** (0.0275 mmol, 5 mol %), THF (1 mL), 50 °C. Reported numbers are isolated yields after column chromatography. Numbers in parentheses correspond to the regioselectivities (*ortho*:*meta* ratio) determined by ^{19}F NMR spectroscopy.

Table 2. Substrate Scope of the *ortho*-to-Fluorine C(sp^2)−H Borylation of 2-Substituted Fluoroarenes Catalyzed by 1[a]



[a]Reaction conditions: arene (0.55 mmol), B_2Pin_2 (0.55 mmol), **1** (0.0275 mmol, 5 mol %), THF (1 mL), 50 °C. Reported numbers are isolated yields after column chromatography. Numbers in parentheses correspond to the regioselectivities (*ortho*:*meta*:*para* ratio) determined by ^{19}F NMR spectroscopy.

Scheme 2. Complementary Selectivity in Cobalt- and Iridium-Catalyzed C(sp^2)−H Borylation of 5g and 5h[a]



[a]Reported numbers are combined NMR yield of *ortho* and *meta* monoborylated products (crude mixture) determined by ^{19}F NMR spectroscopy using 4-F-toluene as the internal standard, and numbers in parentheses are the *ortho*:*meta* ratios.

fluorine selectivity. These observations support the hypothesis that the site selectivity of the catalytic borylation reaction of fluoroarenes is determined by the relative acidity of the C−H bond in addition to the steric factors that typically dictate selectivity with precious-metal catalysts.[5,6]

Fluoroarenes containing substituents at the 2-position were also suitable substrates for cobalt-catalyzed borylation (Table 2). With this class of substrates, where three sterically accessible C−H bonds are present, selective borylation of the C−H bond ortho to fluorine was observed with negligible borylation of the C−H bond *para* to fluorine. As in the case of 3-substituted fluoroarenes, no polyborylation of the polyaromatic substrates (**6c**, **6d**, **6e**, **6f**) was detected.

Fluoroarenes containing a benzylic hydrosilane group and a benzylic dimethylamine, well-known *ortho*-directing groups in iridium-catalyzed C−H borylation,[22,23b] were selectively borylated *ortho* to fluorine rather than *ortho* to these functional groups to yield fluoroarenes **6g** and **6h** (Scheme 2). In iridium catalysis, benzylic hydrosilanes are proposed to direct *ortho*-borylation from formation of a putative iridium bis(boryl) silyl intermediate arising from reaction of the silane Si−H bond with the iridium tris(boryl) followed by selective C−H activation (Scheme 3). If a similar sequence was operative with cobalt, the intermediate cobalt silyl complex obtained from reaction of **5g** with the cobalt(I) boryl[18] lacks an additional boryl ligand to promote C−H activation and C−B bond formation and likely accounts for the lack of the directing effect with the first-row transition metal. Instead, borylation of the most acidic C(sp^2)−H bond is observed, consistent with the enhanced electronic selectivity imparted by cobalt.

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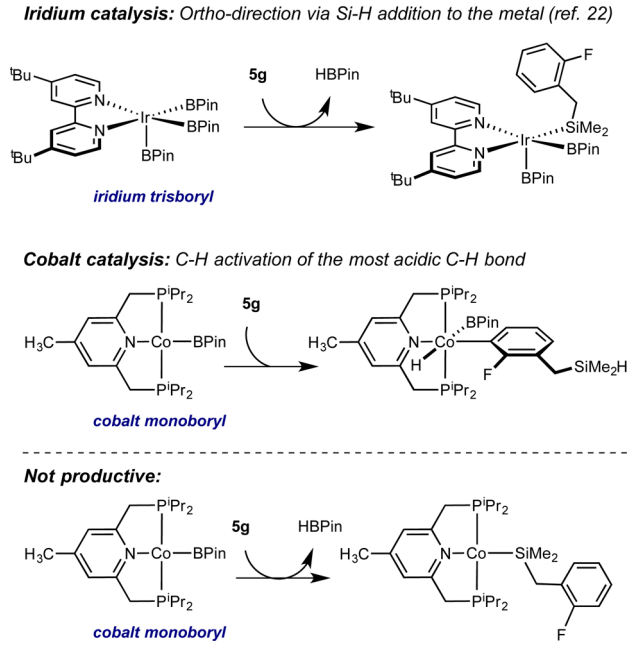
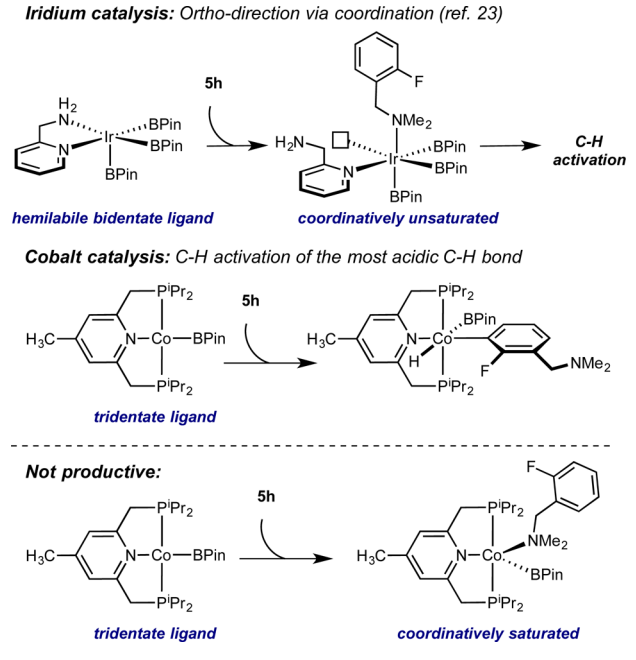
Scheme 3. Proposed Origin of the Complementary Selectivity in Cobalt- and Iridium-Catalyzed C(sp^2)−H Borylation of 5g



Iridium catalysts containing hemilabile *N,N* ligands[23a] promote *ortho*-borylation using a benzylic dimethylamine as a directing group.[23b] The *ortho* selectivity is proposed to arise from coordination of the [NMe_2] group to the metal followed by dissociation of an amine nitrogen from the supporting *N,N* chelate, opening a site for C−H activation (Scheme 4).[23b] With cobalt, the benzylic dimethylamino group has proven ineffective for directing *ortho* selectivity, likely due to the tridentate pincer. While dissociation of one of the phosphine arms is possible,

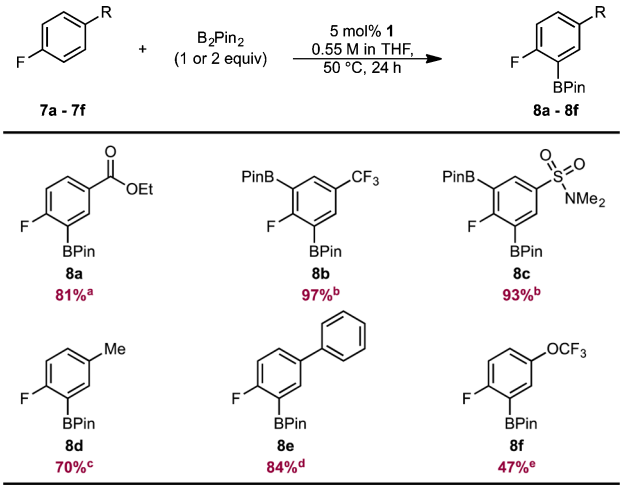
Scheme 4. Proposed Origin of the Complementary Selectivity in Cobalt- and Iridium-Catalyzed C(sp^2)−H Borylation of 5h



coordination of the amine does not influence the outcome of the C(sp^2)−H borylation, and the first-row metal maintains its preference for the most acidic C−H bond. This outcome arises from reversible coordination of the amine without concurrent C−H activation, perhaps due to the formation of a coordinatively saturated intermediate, or lack of coordination of the [NMe_2] group.

Exclusive *ortho*-to-fluorine selectivity was observed in the C(sp^2)−H borylation of 4-substituted fluoroarenes containing a variety of functional groups (Table 3). These findings are

Table 3. Substrate Scope of the *ortho*-to-Fluorine C(sp^2)−H Borylation of 4-Substituted Fluoroarenes Catalyzed by 1[f]



[a]Isolated as a 91:9 mixture of mono- and diborylated products. Reported numbers correspond to % yield of monoborylated product. [b]Used 2 equiv of B_2Pin_2. [c]Isolated as a 93:7 mixture of mono- and diborylated products. Reported numbers correspond to % yield of monoborylated product. [d]Isolated as a 94:6 mixture of mono- and diborylated products. Reported numbers correspond to % yield of monoborylated product. [e]NMR yield of **8f** determined by ^{19}F NMR spectroscopy using 4-F-toluene as the internal standard. [f]Typical reaction conditions: arene (0.55 mmol), B_2Pin_2 (0.55 mmol), **1** (0.0275 mmol, 5 mol %), THF (1 mL), 50 °C. Numbers in parentheses are isolated yields after column chromatography.

similar to what was observed in the iridium-catalyzed C−H borylation to furnish **8d**[24] and **8f**,[25] with slightly higher *ortho*-to-fluorine selectivity for **8f**. As with 3- and 2-substituted polyaromatic fluoroarenes, exclusive borylation of the fluorine-containing ring was observed in *p*-fluorobiphenyl (**7e**) to yield a 94:6 ratio of mono:diborylated products, where the BPin groups are located *ortho* to fluorine.

Unfortunately, fluoroarenes containing bromo and chloro substituents (**3m**, **3n**, and **3o**) were incompatible with cobalt-catalyzed C(sp^2)−H borlyation (Figure 3). Performing a stoichiometric reaction between **1** and **3n** resulted in immediate formation of (4-Me-^{iPr}PNP)CoCl (**9**).[18] Reaction of 3-fluorotoluene (**3i**) with B_2Pin_2 at 50 °C (0.55 M in THF)

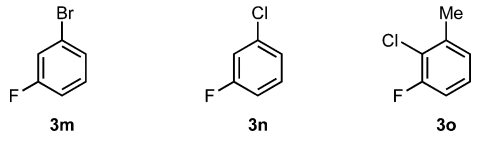


Figure 3. Fluoroarenes incompatible with cobalt-catalyzed C(sp^2)−H borylation.

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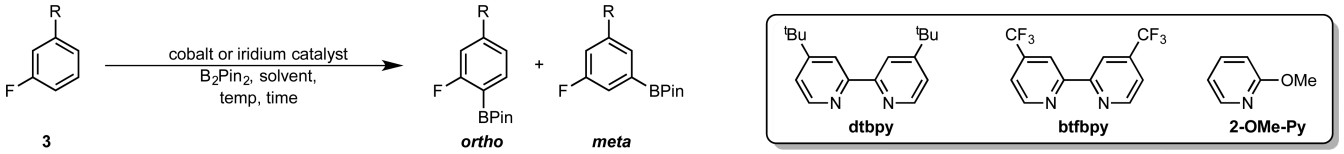
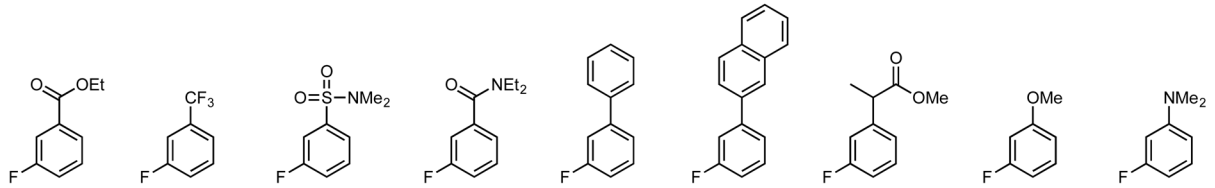
Table 4. Comparison of Cobalt- and Iridium-Catalyzed C−H Borylation of 3-Substituted Fluoroarenes[d]





	3a	3b	3c	3d	3e	3f	3j	3k	3l
Cobalt[a]:	94% (98:2)	94% (95:5)	99% (95:5)	92% (94:6)	90% (94:6)	94% (94:6)	72% (81:19)	81% (68:32)	24% (86:14)
Iridium (A)[b]:	27% (46:54)	98% (41:59)	92% (38:62)	94% (41:59)	11% (40:60)	12% (47:53)	80% (36:64)	58% (43:57)	99% (45:55)
Iridium (B)[b]:	64% (56:44)	>99% (40:60)	99% (36:64)	91% (39:61)	32% (37:63)	35% (35:65)	87% (37:63)	93% (38:62)	n.d.
Iridium (C)[b]:	54% (68:32)	59% (55:41)	78% (48:52)	45% (59:41)	37% (66:34)	26% (67:33)	25% (53:47)	14% (61:39)	3% (70:30)
Iridium (D)[b]:	8% (53:47)	37% (61:39)	37% (49:51)	n.d.	3% (47:53)	8% (50:50)	5% (44:56)	4% (37:63)	4% (50:50)

[a]Using conditions reported in Table 1. Isolated yield after column chromatography. [b]Reported numbers are combined NMR yield of *ortho* and *meta* monoborylated products (crude mixture) determined by ^{19}F NMR spectroscopy using 4-F-toluene as the internal standard. Conditions varied as follows. Iridium (A): arene (0.28 mmol), B_2Pin_2 (0.28 mmol), $[Ir(COD)OMe]_2$ (2.5 mol %), dtbpy (5 mol %), THF (0.5 mL), 50 °C, 24 h. Iridium (B):[26] arene (0.50 mmol), B_2Pin_2 (0.37 mmol), $[Ir(COD)OMe]_2$ (0.1 mol %), dtbpy (0.2 mol %), THF (1 mL), 50 °C, 24 h. Iridium (C):[15] arene (0.34 mmol), B_2Pin_2 (0.17 mmol), $[Ir(COD)OMe]_2$ (1 mol %), btfbpy (2 mol %), Hünig's base (1 mL), 60 °C, 12 h. Iridium (D):[15] arene (0.17 mmol), B_2Pin_2 (0.17 mmol), $[Ir(COD)OMe]_2$ (1 mol %), 2-OMe-Py (2 mol %), THF (1 mL), 80 °C, 16 h. [c]Iridium (E):[27] Same as conditions B but using 0.25 mmol of B_2Pin_2. Combined NMR yield of *ortho* and *meta* monoborylated products (crude mixture) determined by ^{19}F NMR spectroscopy using 4-F-toluene as the internal standard. [d]Regioselectivities were determined by ^{19}F NMR spectroscopy. n.d. = not determined.

in the presence of 5 mol % of **9** resulted in no product formation after 24 h of heating, establishing formation of **9** as a catalyst deactivation pathway.

Comparisons with Iridium Catalysts. The unique selectivity of the cobalt catalyst was confirmed by direct comparison of the activity and selectivity of **1** to iridium catalysts. A variety of 3-substituted fluoroarenes were selected as substrates given the availability of two sterically accessible but electronically differentiated C(sp^2)−H bonds (Table 4). Four different reaction conditions were selected for the iridium cases to ensure fair and representative comparisons between the precious and earth-abundant transition-metal catalysts. Conditions A and B draw on the state-of-the-art and widely used $[Ir(COD)OMe]_2$/dtbpy (dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine)[6c] employing the optimized conditions for cobalt (conditions A) and also using conditions reported in the literature (conditions B).[26] The other two conditions employed $[Ir(COD)OMe]_2$ in combination with 4,4′-bis(trifluoromethyl)-2,2′-bipyridine (conditions C) and 2-methoxypyridine (conditions D), ligands claimed to enhance *ortho*-to-fluorine selectivity in the iridium-catalyzed C−H borylation of 1-chloro-3-fluoro-2-substituted benzenes and 3-fluorotoluene.[15] In all cases, iridium catalysis proved significantly less selective for the borylation of 3-substituted fluoroarenes with B_2Pin_2, as nearly statistical distributions of *ortho* and *meta* borylated products were observed. The higher activity of the $[Ir(COD)OMe]_2$/dtbpy catalyst mixture compared to cobalt is highlighted in the borylation of the electron-rich fluoroarene **3l**. For conditions A and B, complete conversion of arene was observed in the borylation of **3a**, **3j**, and **3k** with iridium; however, a lower combined NMR yield of the desired monoborylated products was obtained presumably due to competing reactions of the ester (**3a**, **3j**) and the methoxy (**3k**) groups. The borylation of polyaromatic fluoroarenes (**3e**[27] and **3f**) highlights the advantages of the cobalt catalyst. With iridium, complex mixtures of products were observed, a result of competing borylation of the other sterically accessible C−H bonds in the adjacent aryl ring (see Figures S6 and S7, SI). With cobalt, however, the selectivity is high and only borylation of the fluorinated ring was observed, furnishing monoborylated products **4e** and **4f** in 90% and 94% combined yields, respectively, with 96:4 *ortho*:*meta* selectivity in both cases. Using the electron-poor ligand 4,4′-bis(trifluoromethyl)-2,2′-bipyridine for iridium (conditions C) resulted in an enhancement of the *ortho*-to-fluorine selectivity for arenes **3a**, **3e**, **3f**, **3k**, and **3l** relative to the $[Ir(COD)OMe]_2$/dtbpy mixture; however, the selectivities were still inferior to that observed with cobalt. Finally, the use of 2-methoxypyridine as the ligand for the iridium-catalyzed reaction (conditions D) resulted in poor conversion and nearly statistical distributions of *ortho* and *meta* borylated products (Table 4).

Evaluation of the Air-Stable Cobalt Complex 2 for *ortho*-to-Fluorine C−H Borylation of Fluoroarenes. The improved regioselectivity observed with **1** prompted evaluation of the C−H borylation of arene **3b** with the air-stable cobalt complex **2** (see Table 5).

Catalytic C−H borylation was accomplished using **2** and B_2Pin_2 at 50 °C (entry 5), although an approximate 12-h induction period was observed. Addition of HBPin as an activator[19a] produced comparable activity to **1** (entry 2). Precatalyst **2** was exposed to air for 1 h without any measurable erosion of activity or selectivity (entry 3). At 80 °C, however, comparable activity as well as selectivity with **1** was achieved

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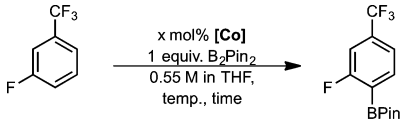
J. Am. Chem. Soc. 2017, 139, 2825−2832

Table 5. C(sp²)–H Borylation of 3b with 2[a]



3b 4b

entry	precatalyst	mol %	time (h)	temp (°C)	% yield[b]	*o*:*m*[c]
1	**1**	1	24	50	94	95:5
2[d,e]	**2**	5	1.5	50	>98[f]	93:7
3[d,g]	**2**	5	1.5	50	>98[f]	93:7
4[d]	$Co(OPiv)_2$	5	1.5	50	<5	N/A
5	**2**	1	24	50	46	94:6
6	**2**	1	24	80	68	92:8
7[h]	**2**	1	24	80	94	93:7
8[i]	**2**	1	24	80	<5[j]	N/A
9[i,k]	**2**	1	24	80	>98[j]	92:8

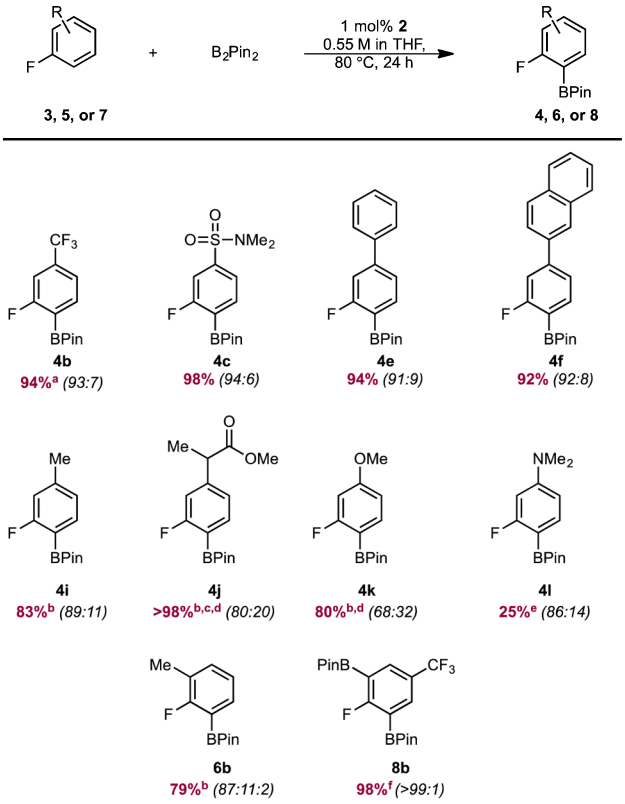
[a]Reactions were run with equimolar amounts of **3b** and B_2Pin_2 on a 0.55 mmol scale. [b]Isolated yield after column chromatography. N/A = Not applicable [c]Ratio of *ortho*:*meta* determined by ^{19}F NMR. [d]Added 20 mol % of HBPin. [e]Run in THF-d_8. [f]Percent conversion determined by ^{19}F NMR. [g]Precatalyst exposed to air for 1 h. [h]Run on a 5.5 mmol scale. [i]Precatalyst exposed to air for 14 days. [j]Percent conversion determined by GC. [k]Added 4 mol % of HBPin.

with **2** (entries 6 and 7) without the need for an external activator. The reaction was successfully scaled to 5.5 mmol using only 1 mol % of **2** to generate the desired *o*-fluoroboronate ester **4b** in 94% isolated yield with 93% regiochemical purity (entry 7). Complete conversion of the arene was observed (92:8 *ortho*:*meta* selectivity) when the reaction was carried out at 80 °C using 1 mol % of precatalyst **2** that was exposed to air for 14 days, albeit with the requirement of 4 mol % of HBPin as an activator (entries 8 and 9). Using anhydrous cobalt(II) pivalate as the precatalyst resulted in no reaction, highlighting the necessity of the bis(phosphine)-pyridine ligand for the C–H borylation reaction (entry 4).

The borylation of a variety of fluoroarenes with different functional groups and substitution patterns was explored using the optimized conditions for arene **3b** with complex **2** as the precatalyst. The activity and selectivity with **2** proved general among a range of fluorinated arenes, as high isolated yields and *ortho*-to-fluorine selectivity were observed regardless of the substituent on the arene and its substitution pattern (Table 6). As with **1**, exclusive *ortho*-to-fluorine borylation was observed with polyaromatic substrates **4e** and **4f**.

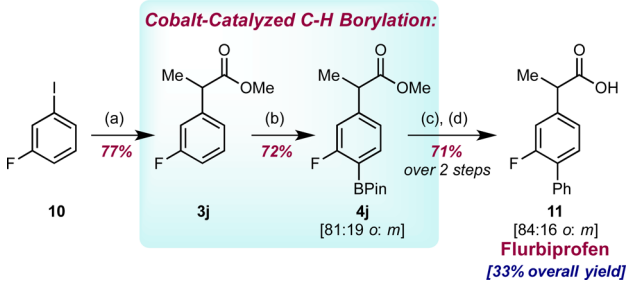
Application of Cobalt-Catalyzed C(sp²)–H Borylation to the Synthesis of Flurbiprofen. The utility enabled by the increased site selectivity of the cobalt-catalyzed C(sp²)–H functionalization was applied to the total synthesis of the anti-inflammatory drug flurbiprofen (Scheme 5). Fluoroarene **3j** was prepared by slightly modifying the procedure reported by Durandetti et al.[28] Cobalt-catalyzed *ortho*-to-fluorine-selective C–H borylation of **3j**, followed by Suzuki–Miyaura cross-coupling with phenyl bromide and then ester hydrolysis, afforded flurbiprofen (**11**) in 33% overall yield from commercially available **10** with 84% regiochemical purity. Thus, our cobalt-catalyzed method enables a four-step synthesis, streamlined from the eight-step route reported previously[29] and highlights the utility of regioselective C–H functionalization in synthetic applications.

Table 6. Substrate Scope of the *ortho*-to-Fluorine C(sp²)–H Borylation of Fluoroarenes Catalyzed by the Air-Stable Precatalyst 2[g]



[a]On 5.5 mmol scale. [b]With 5 mol % of **2**. [c]Percent conversion determined by GC. [d]Reaction time of 48 h. [e]With 10 mol % of **2**, 72 h. [f]With 2 equiv of B_2Pin_2. [g]Typical reaction conditions: arene (0.55 mmol), B_2Pin_2 (0.55 mmol), **2** (0.0055 mmol, 1 mol %), THF (1 mL), 80 °C. Reported numbers are isolated yields after column chromatography. Numbers in parentheses correspond to the regioselectivities (*ortho*:*meta*:*para* ratio) determined by ^{19}F NMR spectroscopy.

Scheme 5. Application of *ortho*-to-Fluorine-Selective C–H Borylation to the Synthesis of Flurbiprofen (11)[a]



[a]Reagents and conditions: (a) Methyl-2-chloropropionate (5.2 equiv), Mn powder (6 equiv), TFA (30 μL), (bpy)$NiBr_2$ (7 mol %), DMF, 50 °C, 16 h; (b) B_2Pin_2 (1 equiv), **1** (5 mol %), THF, 50 °C, 48 h; (c) PhBr (1.1 equiv), Pd(dppf)Cl_2 (5 mol %), K_2CO_3 (4 equiv), THF/H_2O (20:1), 50 °C, 16 h; (d) NaOH (5 equiv), THF/H_2O (1:1), 90 °C, 24 h, then 12 M HCl. Reported numbers are isolated yields after column chromatography. Regioselectivities were determined by ^{19}F NMR spectroscopy. The overall yield of flurbiprofen (**11**) is corrected for the *meta*-phenylated regioisomer.

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CONCLUSIONS

An efficient, highly *ortho*-to-fluorine-selective cobalt-catalyzed method for the C(sp^2)−H borylation of fluorinated arenes has been developed. An air-stable, pincer-ligated cobalt(II) bis(pivalate) was synthesized in a single step from the free ligand and appropriate cobalt precursor and was effective for catalytic C(sp^2)−H functionalization of electronically diverse substrates, regardless of the substitution pattern on the arene. Common directing groups in iridium-catalyzed C−H functionalization, such as a benzylic dimethylamino substituent or a hydridosilane, did not alter the electronically enhanced site selectivity of the cobalt catalyst, highlighting the complementarity of earth-abundant and precious-metal catalysts. The improved regioselectivity of the cobalt-catalyzed C(sp^2)−H borylation was applied to a streamlined synthesis of the anti-inflammatory drug flurbiprofen. These studies represent one of the rare examples of selective C−H functionalization that, in the absence of directing groups, offers new opportunities for reaction development and applications in synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b13346.

Crystallographic data of **2** in CIF format (CIF)

Complete experimental details, characterization data, NMR spectroscopic data (PDF)

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Notes

The authors declare the following competing financial interest(s): J.V.O. and P.J.C. are inventors on U.S. Patent Application 61/913,522 (Filed: December 9, 2014, Published: June 18, 2015).

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