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Ligand-Enabled, Iridium-Catalyzed *ortho*-Borylation of Fluoroarenes

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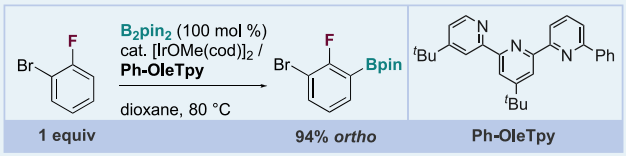
ABSTRACT: A terpyridine derivative and an iridium complex catalyze the C−H borylation of a stoichiometric amount of a fluoroarene with high *ortho*-selectivity and tolerance of functional groups such as bromide, chloride, ester, ketone, amine, and *in situ*-borylated hydroxyl. Complex drug molecules such as haloperidol can be selectively borylated *ortho* to the F atom. The terpyridine ligand undergoes rollover cyclometalation to produce an *N,N,C*-coordinated iridium complex, which may either selectively borylate the fluoroarene by itself or undergo reductive elimination to produce a borylated ligand.



KEYWORDS: *iridium catalysis, terpyridine ligand, fluoroarene, borylation, rollover cyclometalation*

Fluoroarenes are ubiquitous molecular motifs for drug discovery,[1] and they have recently also received attention as optoelectronic molecules for materials science.[2] Late-stage diversification[3] of these compounds[4] is of paramount importance for both fine-tuning of properties and introducing drastic changes to compounds, for example, to create more potent and less cytotoxic drug molecules. Synthetic methods that are tailored toward this end must functionalize fluoroarenes in a regioselective manner,[5] must tolerate sensitive functional groups so that they can be used at a late stage, and must allow incorporation of broad functionality. Transition-metal-catalyzed C−H borylation of arenes[6] is an attractive approach because the resulting boron compounds can be further elaborated easily,[7] and iridium-,[8] cobalt-,[9] or platinum-catalyzed[10] *ortho*-selective borylation of fluoroarenes have been reported, with various degrees of success in controlling regioselectivity and chemoselectivity (see Scheme 1a). Here, we report that a terpyridine derivative, in combination with an iridium complex, catalyzes the stoichiometric borylation of a range of fluoroarenes with high *ortho*-selectivity to fluorine (Scheme 1b). The catalytic system tolerates functional groups such as bromide, chloride, ester, ketone, amine, and *in situ*-borylated hydroxyl, and the C−H bond *ortho* to fluorine is selectively borylated in the presence of other potential directing groups. The synthetic potential of the method is illustrated by the selective borylation of the complex drug molecule haloperidol. Preliminary mechanistic studies suggest that the terpyridine ligand undergoes rollover cyclometalation to generate an *N,N,C*-coordinated iridium complex (**A**), which enables *ortho*-selective reaction either by itself or after undergoing reductive elimination to produce a borylated ligand (**B**) that can also selectively borylate a fluoroarene.

Iridium-catalyzed borylation of arenes has become a benchmark reaction in C−H activation chemistry.[6] The bipyridine derivative 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) is the most commonly used ligand,[11] but regioselectivity is largely controlled by steric factors, and for substrates such as fluorobenzene, a mixture of isomers is produced. A tridentate ligand has the potential to modify the coordination sphere of the metal catalyst and impart selectivity, but this feature has rarely been investigated for iridium-catalyzed borylation,[12] probably because of the perceived crowded environment of the Ir(III) active species.[13] Terpyridine derivatives have often been used as tridentate ligands for catalysis,[14] including for C−H borylation.[15] These compounds act mostly through the *N,N,N*-coordination mode, and, despite numerous studies on rollover cyclometalation[16] and suggestions of potentially enhanced reactivity of the resulting metal complexes,[17] the *N,N,C*-coordination mode[18] has remained underexplored for catalysis,[19] including C−H activation.[20] Introduction of appropriate substituents on a terpyridine compound (such as **R-OleTpy**) may promote rollover cyclometalation[21,22] to produce an *N,N,C*-ligated iridium complex (such as **A** in Scheme 1b), and we were intrigued by the possibility of selective interaction between such catalytic species unsymmetrically biased by strong σ-donation, and a fluoroarene substrate. When we performed the reaction of 0.60 mmol of fluorobenzene (**1a**) with B_2pin_2 (100 mol %) in the presence of $[IrOMe(cod)]_2$ (1.5 mol %) and **Ph-OleTpy** (3 mol %) in dioxane at 80 °C for 44 h, we obtained the borylated product **2a** in 47% yield and 93:7 regioselectivity (*ortho*/*meta* + *para*), together with diborylated compound (16% based on **1a**, and 32% based on B_2Pin_2; a mixture of 2,6-/2,5-/2,4-/3,5-isomers in 36:56:8:<1 ratio). We note that control experiments

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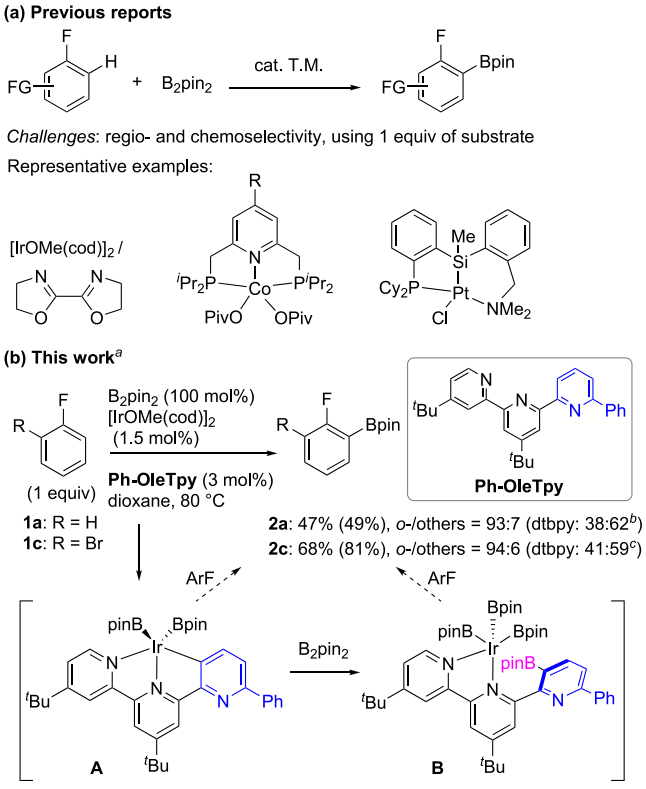
Scheme 1. *ortho*-Selective Borylation of Fluoroarenes[a]

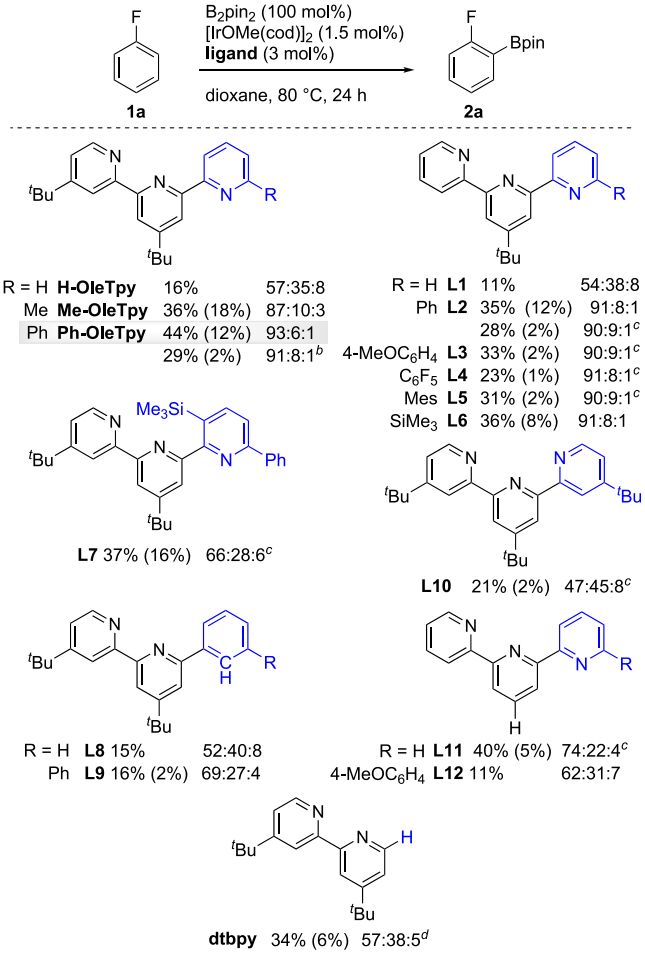


[a]Yields in parentheses and selectivity determined by ^{19}F NMR spectroscopic analysis. The term "*ortho*" refers to the site vicinal to fluorine. Diborylated product was also obtained; for details, see Scheme 3 (presented later in this work) and the Supporting Information (SI). [b]B_2pin_2 (50 mol %), $[IrOMe(cod)]_2$ (0.75 mol %), and dtbpy (1.5 mol %). [c]Conditions are the same as those for footnote (b), 50 °C.

(Supporting Information (SI)) showed that HBin, which forms from the reaction of B_2pin_2 with the fluoroarene, reacts much slower than B_2pin_2 under these conditions. Under the same reaction conditions (shorter reaction time: 24 h), 2-bromofluorobenzene (**1c**) reacted with high yield (81% determined by NMR analysis, 68% after isolation) and selectivity (*ortho*/others = 94:6), together with a small amount (5% based on **1c**) of diborylated compound, and recovery of the starting material was 6%. We note that, in some cases, isolation by column chromatography resulted in a decreased yield, because of the overadsorption of pinacol boronic esters on silica gel,[23] and we report both the yield based on NMR analysis and that obtained after isolation. The bromide group was tolerated under the reaction conditions, and no debrominated product was observed. When the same reaction was conducted using dtbpy as a ligand at 50 °C, a mixture of regioisomers was obtained.

The key structural elements of the **R-OleTpy** ligand that enable high *ortho* selectivity are illustrated in Scheme 2: a terpyridine backbone having a 2-substituent on the peripheral pyridine ring, and a *tert*-butyl group on the central pyridine ring. Under the optimized reaction conditions (1.5 mol % catalyst, 100 mol % B_2pin_2, and 0.8 mol/L substrate concentration), the conversion of the starting material **1a** was high, but a significant amount of diborylation also proceeded. We confirmed that diborylation does not significantly affect the selectivity, as demonstrated by perform-

Scheme 2. Effect of the Ligand on the Borylation of Fluorobenzene (1a)[a]



[a]Reaction conditions: fluorobenzene (**1a**, 0.20 mmol), B_2pin_2 (100 mol %), $[IrOMe(cod)]_2$ (1.5 mol %), and ligand (3 mol %) in dioxane (0.8 mol/L), 80 °C, 24 h. The yield and selectivity (reported as *ortho*/*meta*/*para*) were estimated by GC using tridecane or hexadecane as internal standard. The yield of the diborylated product is shown in parentheses. For details, see the SI. [b]B_2pin_2 (50 mol %) in dioxane (0.2 mol/L). [c]Fluorobenzene (0.40 mmol), B_2pin_2 (50 mol %), $[IrOMe(cod)]_2$ (0.75 mol %), ligand (1.5 mol %), and dioxane (0.4 mol/L), 80 °C, 24 h. [d]Conditions are the same as those for footnote (c), 15 °C, 12 h.

ing the reaction using the **Ph-OleTpy** ligand under standard conditions for 24 h (*ortho*/*meta*/*para* = 93:6:1, 12% diborylation), and at lower concentration with 50 mol % B_2pin_2 to minimize diborylation (*ortho*/*meta*/*para* = 91:8:1, 2% diborylation). Under the latter, low-conversion conditions and at 15 °C, the standard dtbpy ligand was largely unselective (57:38:5). The presence of a 2-substituent on the pyridine ring (R) was crucial; its absence (H-OleTpy and **L1**) led to a decrease in both yield and selectivity. The size and electronic nature of R did not significantly impact either reactivity or selectivity (**L2**−**L6**). We speculate that this ligand accelerates rollover metalation by sterically destabilizing the *N*,*N*,*N*-coordination mode; accordingly, the reaction using a terpyridine ligand (**L10**), in which rollover metalation is sterically blocked, was unselective. Changing the nitrogen group on the peripheral pyridine to carbon (**L8** and **L9**) greatly reduced the selectivity, possibly because of slower

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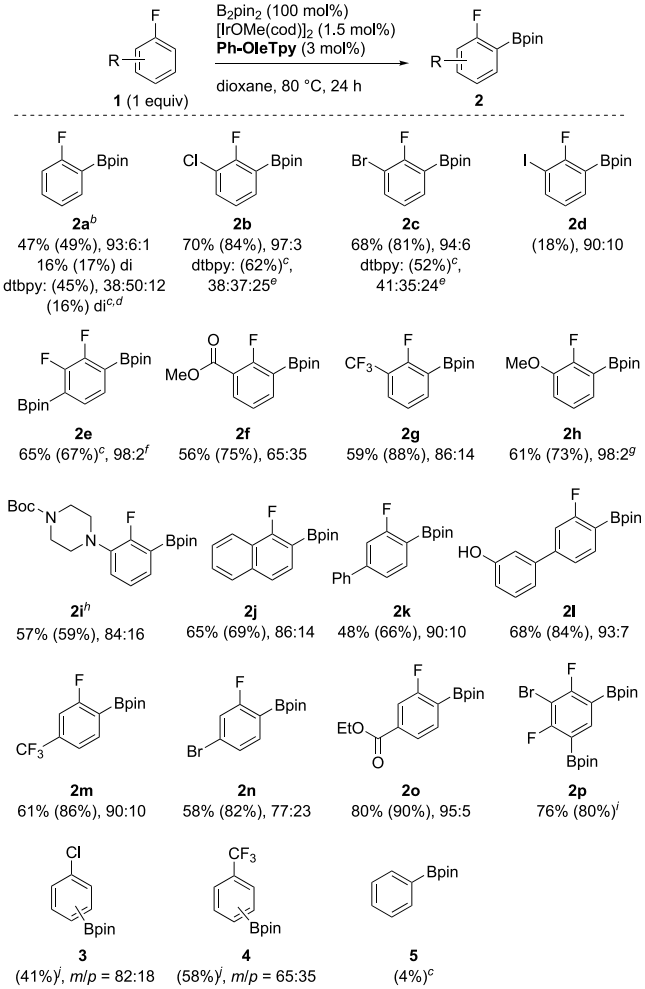
rollover metalation of the phenyl ring as compared with the electron-deficient pyridine. The *tert*-butyl group on the peripheral pyridine ring was not important for selectivity (**Ph-OleTpy** vs **L2**), but substantial influence of the *tert*-butyl group on the central ring was clear (**L12**), possibly by increasing the coordination ability of the sterically hindered pyridine, and kinetically preventing borylation of this ring.[20] By introducing a trimethylsilyl group at the site of rollover metalation (**L7**), borylation proceeded with low selectivity, suggesting the importance of rollover metalation. In the absence of a ligand, the borylated product was obtained in a trace amount (2% (SI)). We chose **Ph-OleTpy** as the optimal ligand with respect to both reactivity and selectivity. Details of the optimization studies, such as the nature of the iridium precursor and the borylating reagent, are described in the SI.

We then investigated the reaction scope and found that a variety of fluoroarenes can be regioselectively borylated *ortho* to fluorine (Scheme 3). As shown in Scheme 1, fluorobenzene (**1a**) reacted with high regioselectivity, but a significant amount of diborylated product was also obtained. 2-Chlorofluorobenzene (1b) and 2-bromofluorobenzene (**1c**) reacted with high yield and regioselectivity, and we did not observe dehalogenation. The reaction of 2-iodofluorobenzene (**1d**) was also regioselective, but this substrate was much less reactive and was mostly recovered (80%), together with a small amount (2%) of deiodinated product (fluorobenzene). We speculate that unproductive oxidative addition of the C−I bond may have inactivated the iridium catalytic species. 1,2-Difluorobenzene (**1e**) was regioselectively diborylated in good yield. An ester group *ortho* to fluorine was tolerated (**1f**), but the regioselectivity decreased (isomer ratio 3-/4- = 65:33), probably because the electron-withdrawing nature of the ester group activated the 4-position toward oxidative addition. Accordingly, when the ester group was placed *meta* to fluorine (**1o**), the regioselectivity was high. An electron-donating methoxy group *ortho* to fluorine (**1h**) did not significantly decrease the yield, and the borylated product was obtained with high regioselectivity. A substrate bearing a protected piperazine group *ortho* to fluorine (**1i**) also reacted well, albeit with slightly decreased selectivity. 1-Fluoronaphthalene (**1j**) reacted in good yield but with lower regioselectivity, presumably because of the activating effect of the fused benzene ring, similar to that of the 2-ester group. The reaction was also regioselective for *meta*-substituted fluorobenzenes (**1k**−**1o**). While a *meta* trifluoromethyl-substituted substrate reacted with high selectivity (**1m**), the presence of a *meta* bromide decreased the selectivity (**1n**), presumably because of increased electron density at the C−H site proximal to fluorine. In the reaction of 3-fluorobiphenyl (**1k**), the phenyl ring bearing the F atom was borylated selectively. A hydroxyl group was protected *in situ* by borylation with HBpin, the phenyl ring bearing the F atom reacted selectively over the electron-rich phenol ring (**1l**), and the regioselectivity was high. 2-Bromo-1,3-difluorobenzene (**1p**) was regioselectively diborylated in high yield. The regioselectivity is unique to fluoroarene substrates; for chlorobenzene (**3**) or trifluorotoluene (**4**), the *ortho*-borylation was sterically retarded, and a mixture of *meta*- and *para*-isomers was obtained. Unsubstituted benzene (**5**) was largely unreactive under these conditions. Other unsuccessful substrates are described in the SI. A nitrile group retarded the reaction, possibly because of unproductive coordination to the iridium species; in agreement with this hypothesis, benzonitrile itself was unreactive, and adding 50 mol % of benzonitrile to the reaction of fluorobenzene under standard conditions completely shut down the reaction. Pyridine compounds reacted with low yield and selectivity; the discussion on the reaction of these compounds is complicated by the decomposition of α-borylated pyridines under iridium catalysis.[24] Fluoroarene derivatives bearing a methyl group (for example, 3-fluorotoluene) reacted regioselectively, but the reaction was complicated by competing benzylic borylation.[25]

The reaction could be applied for the selective functionalization of complex molecules such as haloperidol, one of the most

Scheme 3. Reaction Scope[a]



[a]Reaction conditions: fluoroarene (**1**, 0.40 mmol), B_2pin_2 (100 mol %), $[IrOMe(cod)]_2$ (1.5 mol %), and **Ph-OleTpy** (3 mol %) in dioxane (0.8 mol/L), 80 °C, 24 h. The yield of the isolated monoborylated product (**2**) is reported, unless otherwise noted; the yield in parentheses was determined by ^{19}F NMR analysis using trifluorotoluene as internal standard. The isomer ratio is reported as *ortho*-to-fluorine/others and was based on GC, ^{19}F, or ^{1}H NMR analysis. For details, see the SI. [b]Substrate (0.60 mmol), 44 h; regioisomers of the diborylated product: 2,6-/2,5-/2,4-/3,5- = 36:56:8:<1. [c]Estimated by GC using tridecane as internal standard. [d]B_2pin_2 (50 mol %), $[IrOMe(cod)]_2$ (0.75 mol %), and dtbpy (1.5 mol %) in dioxane (0.4 mol/L); regioisomers of the diborylated product: 2,6-/2,5-/2,4-/3,5- = 7:50:19:24. [e]Substrate (0.20 mmol) and B_2pin_2 (50 mol %) in dioxane (0.2 mol/L), 50 °C, 15 h. [f]B_2pin_2 (150 mol %); 3,6-/3,5-regioisomer ratio. [g]67 h. [h]Substrate (0.20 mmol), 65 h. [i]B_2pin_2 (200 mol %). [j]Determined by ^{1}H NMR analysis using 1,1,2,2-c-tetrachloroethane as internal standard.

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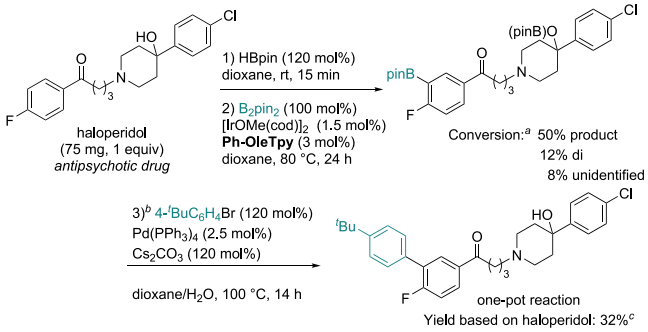
commonly used antipsychotic drugs.[26] Synthesis and evaluation of derivatives of haloperidol is of much interest for medicinal chemistry, but chemical modification of the carbon framework is tedious.[27] Late-stage functionalization of this molecule via C−H bond activation is attractive, but has been less investigated,[28] possibly because of difficulties associated with controlling regioselectivity and the required tolerance of functionality such as carbonyl, amino, hydroxy, and chloro groups. After protection with HBpin *in situ*, we subjected haloperidol to our optimized reaction conditions, and we observed 50% conversion into the desired *ortho*-to-fluorine monoborylated product, together with 12% of diborylated product and 8% of an unidentified product (Scheme 4). After

Scheme 4. Selective Borylation of Haloperidol[a]



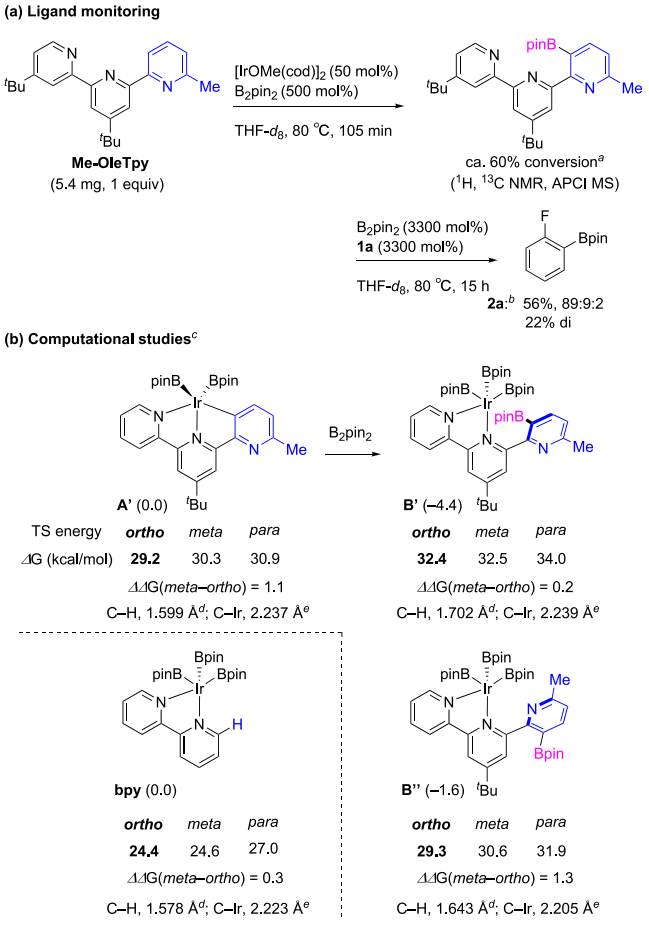
[a]Determined by ^{19}F NMR analysis. [b]Stoichiometry based on the estimated amount of borylated product. [c]Determined after isolation using silica gel column chromatography.

removing the solvent *in vacuo*, the borylated haloperidol was reacted in one pot with an aromatic bromide under palladium catalysis, to obtain the corresponding haloperidol derivative in 32% yield as a single isomer, after isolation by silica gel column chromatography.

Finally, we investigated the origins of the high *ortho* selectivity induced by the **R-OleTpy** ligands. The mechanism of iridium-catalyzed arene borylation has been much investigated, and it is generally accepted that the oxidative addition of an Ir(III) species to the arene C−H bond is the turnover-limiting and regioselectivity-determining step.[29] The regioselectivity in the reaction of mono- or disubstituted benzenes is typically controlled by sterics, and electronic effects are more complex; for example, factors such as the acidity of the C−H bond and the energy of the forming C−Ir bond have been proposed to govern regioselectivity.[30] However, these studies on iridium catalysis have largely ignored the reaction of fluoroarene derivatives; Chirik[31] proposed that the regioselectivity in the cobalt-catalyzed borylation of fluoroarenes is dictated by the "*ortho* fluorine effect",[32] the strengthening of the newly forming C−Co bond by the neighboring F atom.

To gain insight into the reaction mechanism, we investigated by NMR analysis and mass spectroscopy the reaction of a stoichiometric amount of **Me-OleTpy** and iridium precursor with an excess of B_2pin_2, to observe the formation of a borylated ligand as the main product (Scheme 5a). This borylated ligand could not be isolated because of fast protodeborylation,[24] but the addition of fluorobenzene (**1a**) to the reaction mixture resulted in *ortho*-selective borylation, matching the selectivity profile of the catalytic reaction. Computational analysis using a simplified ligand model (Scheme 5b; for structures of the transition states (TS) and

Scheme 5. Mechanistic Considerations



[a]Estimated by ^{1}H NMR analysis using mesitylene as internal standard. [b]Conversion of fluorobenzene and isomer ratio determined by ^{19}F NMR analysis. [c]Relative Gibbs energies calculated at the M06/SDD:6-311+G(d,p)$_{1,4\text{-dioxane(SMD)}}$//B3LYP-D3/SDD:6-31G(d,p) level of theory. [d]The length of the cleaving *ortho* C−H bond of **1a** at the transition state. [e]The length of the forming *ortho* C−Ir bond of **1a** at the transition state.

details of the computational study, see the SI) showed that an iridium complex bearing the borylated ligand (**B′**) oxidatively adds the *ortho* C−H bond of fluorobenzene selectively, although the energy difference of *ortho* and *meta* transition states is low (0.2 kcal/mol) and comparable to that of a bipyridine ligand (0.3 kcal/mol). The presence of the B atom may indicate potential B−F interaction with the substrate[33] (B−F distance in *ortho* TS from **B′** is 3.776 Å); however, a detailed investigation showed that oxidative addition proceeds more readily from isomer **B″** (activation energy 29.3 kcal/mol vs 32.4 kcal/mol for **B′**), where the Bpin on the pyridyl group is turned away from the substrate and B−F interaction is not possible. The transition state is late (C−H bond length at TS from **B″**: 1.643 Å), and we propose that the strengthening of the C−Ir bond by the *ortho* fluorine effect is important for selectivity (energy difference of ortho TS vs meta TS: 1.3 kcal/mol),[31] and this effect may be enhanced by the strong donating *N,N,C*-ligand.[32]

The regioselective formation of the borylated ligand strongly suggests initial rollover cyclometalation to generate the *N,N,C*-iridium complex (**A** in Scheme 1b), which undergoes reductive

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elimination in the presence of B_2pin_2 to give **B**. However, we should note that the borylated ligand, despite being the major product in the NMR spectrum, accounted for only ∼60% of the material balance. This suggests the presence of other undetected species, possibly including **A**. Computations showed that *N*,*N*,*C*-iridium complex **A′** is also *ortho*-selective (energy difference of *ortho* TS vs *meta* TS: 1.1 kcal/mol). Moreover, a surrogate of the borylated ligand, silylated **L7**, was poorly selective, suggesting the importance of a cyclometalated intermediate. Thus, at present, we cannot conclusively establish whether the *N*,*N*,C-iridium complex (**A**) or the borylated ligand complex **B** is the active species responsible for *ortho*-selective C−H activation of fluoroarenes.

In summary, we found that a terpyridine derivative enables iridium-catalyzed selective *ortho*-borylation of fluoroarenes. The reaction conditions tolerate several sensitive functional groups (bromide, chloride, ester, ketone, amine, and *in situ*-borylated hydroxyl) and allow functionalization of complex drug molecules such as haloperidol. Preliminary mechanistic studies suggest that the ligand undergoes rollover cyclometalation to generate an *N*,*N*,C-iridium complex, which may undergo reductive elimination in the presence of B_2pin_2 to produce a borylated ligand; computations showed that both of these intermediates can cleave the *ortho* C−H bond of fluorobenzene selectively. We hope that these findings will stimulate interest in the reactivity of *N*,*N*,C-coordinated metal complexes and their use for catalysis, a topic that is under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01206.

Experimental procedures, compound data, NMR spectra (PDF)

Coordinates of the optimized structures (TXT)

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Author Contributions

The manuscript was written through contributions of all authors. O.K. performed the experiments, and S.A. conducted the mechanistic study. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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