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Copper-Mediated Fluorination of Arylboronate Esters. Identification of a Copper(III) Fluoride Complex

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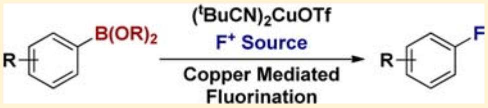
Supporting Information



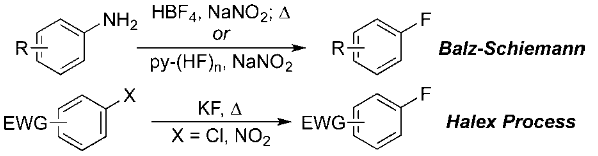
ABSTRACT: A method for the direct conversion of arylboronate esters to aryl fluorides under mild conditions with readily available reagents is reported. Tandem reactions have also been developed for the fluorination of arenes and aryl bromides through arylboronate ester intermediates. Mechanistic studies suggest that this fluorination reaction occurs through facile oxidation of Cu(I) to Cu(III), followed by rate-limiting transmetalation of a bound arylboronate to Cu(III). Fast C−F reductive elimination is proposed to occur from an aryl−copper(III)−fluoride complex. Cu(III) intermediates have been generated independently and identified by NMR spectroscopy and ESI-MS.

INTRODUCTION

A wide range of materials and biologically active molecules contain fluoroarenes. The presence of fluorine atoms in these arenes often affects the reactivity, solubility, and stability of the molecule. In medicinal chemistry, a fluorine atom is used to block metabolic degradation and, thereby, to improve the efficacy of lead compounds. In addition, fluorinated compounds enriched in ^{18}F are used as PET-imaging agents in medicine. However, methods to synthesize aryl fluorides under mild reaction conditions are limited.

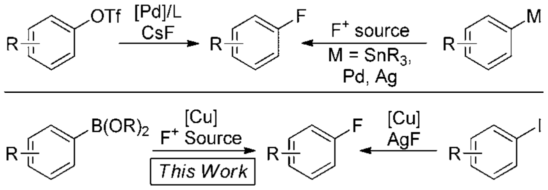
To overcome the limitations of classical methods for the synthesis of aryl fluorides by the Halex[1] or Balz−Schieman reactions (Scheme 1),[2] modern methods based on transition-metal complexes have been sought (Scheme 2). Aryl triflates react with CsF in the presence of a palladium catalyst to form aryl fluorides, but isomeric products are obtained in many cases.[3] Arylstannanes,[4] arylsilver,[5] arylpalladium,[6] and arylnickel[7] complexes have been reported to form aryl fluorides, but the stannanes are toxic, and the silver, palladium, and nickel complexes must be isolated after synthesis from arylboronic acids (Ag, Pd) or aryl bromides (Ni). More recently, Ritter and co-workers reported the direct conversion of phenols to aryl fluorides with a difluoroimidazoline reagent,[8] and we disclosed the conversion of aryl iodides to aryl fluorides with $(^tBuCN)_2CuOTf$ and AgF.[9]

Scheme 1. Conventional Routes to Fluoroarenes



Arylboron reagents are valuable alternative sources of aryl groups for the synthesis of aryl fluorides because they are readily available, are nontoxic, are shelf-stable, and often react under mild conditions with good functional group tolerance. Moreover, they can be prepared by methods, such as C−H bond functionalization, that complement methods used to form aryl iodides and phenols. Finally, reactions of arylboronate esters can occur with reactivity that is orthogonal to that of aryl iodides. However, no direct conversion of arylboron reagents to aryl fluorides has been reported.

Scheme 2. Transition-Metal-Mediated Aryl Fluorination



We report a straightforward copper-mediated fluorination of arylboronate esters under mild conditions with good substrate scope. We show that this reaction can be used in tandem with the borylation of aryl C−H bonds to effect an overall C−H bond fluorination and that it can be used in tandem with the borylation of aryl bromides to convert aryl bromides to aryl fluorides. Mechanistic experiments suggest that the fluorination of arylboronate esters occurs by initial formation of a cationic Cu(III) fluoride complex, which was identified spectroscopically. Stoichiometric reactions of this Cu(III) species show that it is competent to be an intermediate in the fluorination process.

RESULTS AND DISCUSSION

1. Conditions for the Conversion of Arylboronate Esters to Aryl Fluorides. To develop a method for the

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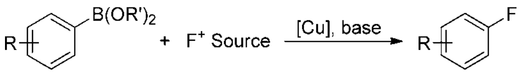
conversion of arylboron nucleophiles to aryl fluorides (Scheme 3), we focused initially on the fluorination of pinacol-derived arylboronate esters (ArBPin). Pinacolate esters can be prepared in quantitative yield by the reaction of boronic acids with equimolar amounts of pinacol and can be prepared by C−H bond functionalization and coupling of aromatic electrophiles with boron reagents.[10] ArBPin reagents are more stable to air and moisture than other arylboronate esters and boronic acids, and they can be purified by silica gel chromatography. They are indefinitely stable on the bench. Finally, ArBPin reagents are inert under many reaction conditions. Thus, the ArBPin can be carried through a synthetic sequence conveniently without cleaving the C−B bond.[10]

Scheme 3. Copper-Mediated Fluorination of ArB(OR)$_2$



A variety of electrophilic fluorine sources (Figure 1) are commercially available. These reagents vary in their reactivity, solubility, and stability. We tested the reactivity of the pinacol ester of 4-butylphenylboronic acid (**1a**) with electrophilic fluorine sources in the presence of a base and copper source. The reactions of this arylboronic ester with the sterically hindered and electron-rich 1-fluoro-2,4,6-trimethylpyridinium (Me_3pyF^+) reagent formed the aryl fluoride in higher yields, when combined with $(^t\text{BuCN})_2\text{CuOTf}$ and AgF,[11] than those conducted with other F$^+$ sources (Table 1). The higher yields with $[\text{Me}_3\text{pyF}]^+$ reagents than with other F$^+$ sources appear to result, in part, from a slower rate of heat- and base-induced decomposition of the F$^+$ source. In addition, ligation of 2,4,6-trimethylpyridine to copper appeared to be important (vide infra). The counterion of $[\text{Me}_3\text{pyF}]^+$ affected the yield; the reactions conducted with $[\text{Me}_3\text{pyF}]\text{PF}_6$ occurred in higher yields than the reactions conducted with $[\text{Me}_3\text{pyF}]\text{BF}_4$ and $[\text{Me}_3\text{pyF}]\text{OTf}$.

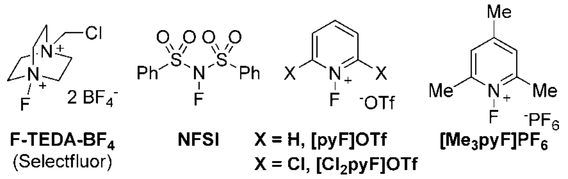
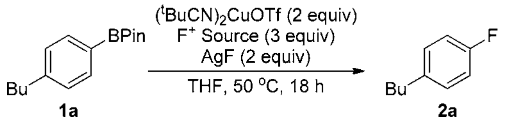


Figure 1. Electrophilic fluorine (F$^+$) reagents.

Electrophilic fluorine sources are susceptible to base-induced decomposition. Thus, a base that promotes transmetalation of the ArBPin without decomposing the F$^+$ source is essential for high conversion of ArBpin reagents to the corresponding aryl fluoride. Reactions conducted with a series of alkoxide bases gave modest yields (10−15%) of the aryl fluoride product in the presence of $(^t\text{BuCN})_2\text{CuOTf}$ and $[\text{Me}_3\text{pyF}]\text{PF}_6$. Reactions conducted with fluoride bases occurred in yields significantly higher than those conducted with alkoxide bases. Reactions conducted with AgF as base occurred in yields significantly higher than those conducted with other fluoride bases we tested (Table 1, entries 8−10). We propose that higher yields are obtained with AgF than with other bases because the low solubility and low nucleophilicity of AgF prevent it from promoting transmetalation of the ArBPin to Cu(I) (vide infra). Also, in contrast to stronger bases, AgF does not lead to the decomposition of the F$^+$ source. Finally, AgF does not react with Cu(I) to form an unstable Cu$^{\text{I}}$F species.[12]

Table 1. Screen of F$^+$ Reagents for the Fluorination of 1a with $(^t\text{BuCN})_2\text{CuOTf}$ and AgF[a]



entry	F$^+$ source	conversion (%)	ArH (%)	ArF (%)
1	F-TEDA-BF$_4$	91	37	27
2	F-TEDA-PF$_6$	100	73	26
3	NFSI	100	90	10
4	$[\text{Cl}_2\text{pyF}]\text{OTf}$	100	100	0
5	[pyF]OTf	100	87	1
6	$[\text{Me}_3\text{pyF}]\text{BF}_4$	84	9	56
7	$[\text{Me}_3\text{pyF}]\text{OTf}$	82	13	64
8	$[\text{Me}_3\text{pyF}]\text{PF}_6$	88	12	75
9[b]	$[\text{Me}_3\text{pyF}]\text{PF}_6$	97	57	24
10[c]	$[\text{Me}_3\text{pyF}]\text{PF}_6$	100	39	38

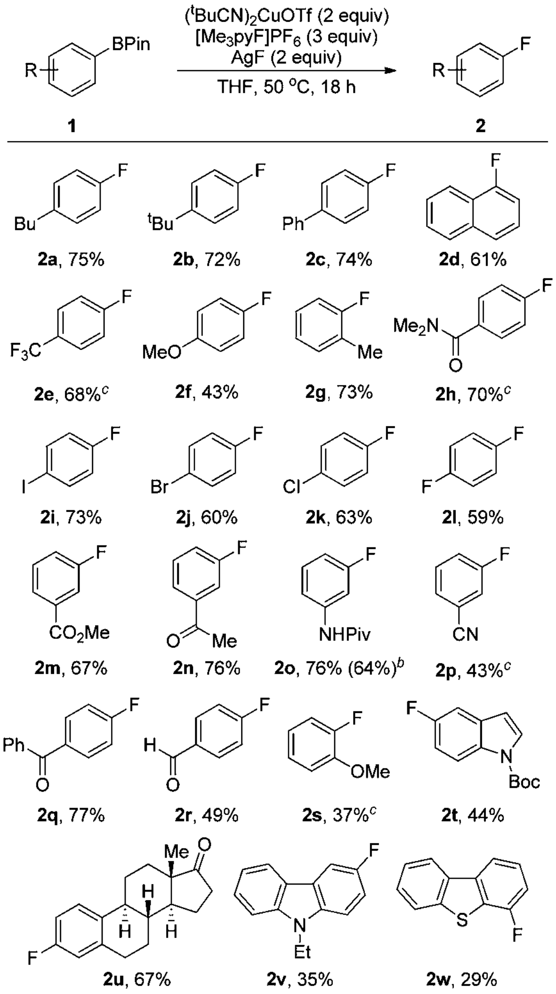
[a] Reactions were performed with 0.1 mmol of **1a** in 2.0 mL of THF for 18 h. Yields were determined by gas chromatography with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. [b] Reactions were performed with KF in place of AgF. [c] Reactions were performed with CsF in place of AgF.

2. Scope of the Fluorination of Pinacolate Arylboronate Esters. The combination of $(^t\text{BuCN})_2\text{CuOTf}$, $[\text{Me}_3\text{pyF}]\text{PF}_6$, and AgF converted a range of arylboronate esters to the corresponding aryl fluorides, and the scope of this process is summarized in Table 2. The same reaction conditions were suitable for the reactions of both electron-rich and electron-deficient arylboronate esters. Substrates containing esters, ketones, aldehydes, amides, nitriles, aryl halides, and some heterocycles underwent fluorination in moderate to good yield. In addition, the ortho-substituted boronate ester **1g** provided 2-fluorotoluene in 73% yield. The corresponding *o*-anisylboronic ester (**1s**) also gave the aryl fluoride product, but in lower yield. The amide-containing aryl fluoride **2o** was isolated in good yield on a 0.5 mmol scale from boronate ester **1o**. The boron byproduct in these fluorination reactions is F-BPin. F-BPin undergoes hydrolysis to HO-BPin during aqueous workup and is easily separated from the aryl fluoride product. The conditions we developed for the fluorination of pinacolate esters also induced the fluorination of boronic acids and other boronic acid derivatives (Table 3).

The major side reaction in the fluorination of arylboronate esters is protodeborylation to form the corresponding arene. This side reaction occurs commonly during reactions of arylboron reagents. The hydrogen atom in this process may originate from multiple sources, including the solvent or adventitious water.

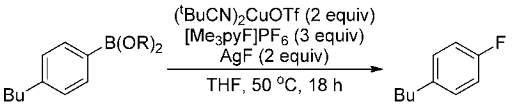
To determine the source of the product of protodeborylation, a deuterium labeling experiment was conducted. The reaction of **1a** under the standard reaction conditions with 2 equiv of added D_2O formed the arene side product in 50% yield with 43% incorporation of deuterium in the arene (eq 1). The arene side product from the reaction of **1a** under the standard reaction conditions in THF-d_8 did not contain deuterium (eq 2). Thus, we suggest that the arene side product in the fluorination of ArBPin results, in part, from a reaction with adventitious water.

Table 2. Fluorination of ArBPin with (^{t}BuCN)$_2$CuOTf and [Me$_3$pyF]PF$_6$[a]



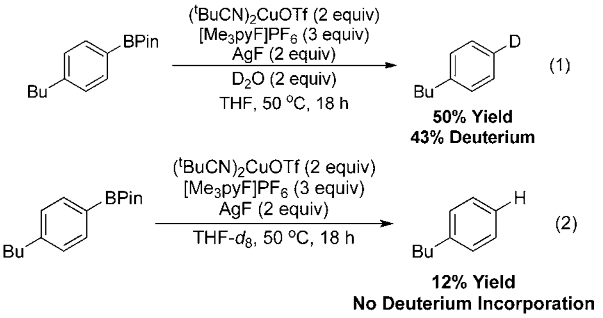
[a] Reactions were performed with 0.1 mmol of **1** to determine yields by ^{19}F NMR spectroscopy with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. ^{19}F NMR chemical shifts were compared with those of the authentic aryl fluorides. [b] Isolated yield from a reaction with 0.5 mmol of ArBPin. [c] Reactions were conducted at 80 °C.

Table 3. Fluorination of Boronic Acid Derivatives with (^{t}BuCN)$_2$CuOTf, [Me$_3$pyF]PF$_6$, and AgF[a]



entry	(OR)$_2$	ArH (%)	ArF (%)
1	(OH)$_2$	5	45
2	BF$_3$K	37	46
3	MIDA	23	18
4	catechol	60	0
5	neopentyl glycol	15	70
6	pinacol	12	75

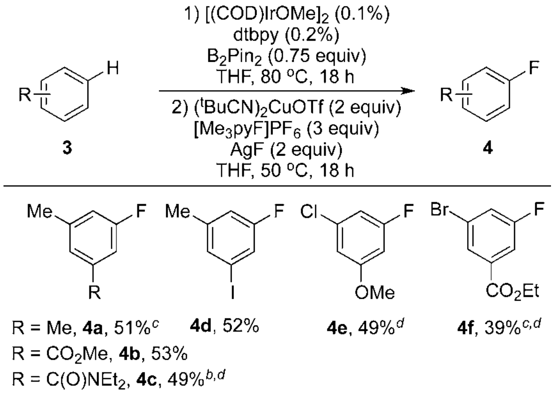
[a] Reactions were performed with 0.1 mmol of arylboron in 2.0 mL of THF for 18 h. Yields were determined by gas chromatography with 1-bromo-4-fluorobenzene as an internal standard added after the reaction.



3. Fluorination of Arenes and Aryl Bromides via Pinacolate Arylboronate Esters.

Arylboronate esters can be prepared by iridium-catalyzed C−H borylation,[13] and this process leads to the borylation at the least hindered C−H bond of arenes. Our group has shown that Ir-catalyzed C−H borylation can be used in tandem with reactions of the resulting ArBPin as a two-step, one-pot route to diversely functionalized arenes.[14] We considered that a similar tandem process could be used to achieve the fluorination of C−H bonds. Indeed, C−H borylation with B$_2$Pin$_2$ catalyzed by the combination of [Ir(COD)OMe]$_2$ and dtbpy provided crude ArBPin intermediates that underwent subsequent copper-mediated fluorination. The ArBPin formed by C−H borylation could be used without purification. Conversion of the crude ArBpin to the corresponding aryl fluoride occurred such that the two-step process gave a good yield of the aryl fluoride (Table 4). Arenes containing electron-donating and electron-withdrawing groups reacted in comparable yield. Ketones, esters, amides, and aryl halides were tolerated over the two-step procedure. This sequence represents a simple strategy for a regioselective C−H fluorination of arenes.

Table 4. Fluorination of Arenes via C−H Borylation[a]

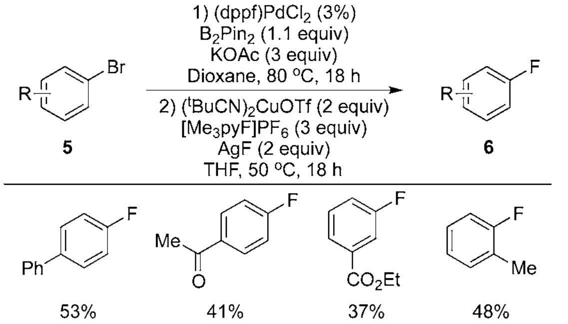


[a] Reactions were performed with 0.1 mmol of arene. Yields were determined by ^{19}F NMR spectroscopy with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. [b] The borylation reaction was performed with 1.5% [Ir] and 3.0% dtbpy. [c] The borylation reaction was performed with 0.5% [Ir] and 1.0% dtbpy. [d] The fluorination reaction was performed at 80 °C for 18 h.

An alternative method to prepare arylboronate esters is the borylation of aryl halides catalyzed by transition metals. Thus, we evaluated whether aryl bromides would react in a one-pot sequence to convert aryl bromides to aryl fluorides through ArBPin intermediates. The combination of a simple palladium precatalyst, B$_2$Pin$_2$, and KOAc[15] led to the high conversion of aryl bromides to ArBPin intermediates under conditions suitable for the conversion of the ArBPin to the corresponding

ArF. The crude mixture from the borylation reaction was filtered, concentrated, and subjected to the fluorination conditions described above. Good yields of the aryl fluorides were obtained over the two-step sequence without purification of the intermediate ArBPin (Table 5). Because methods for the direct fluorination of aryl bromides have not been reported, this two-step strategy provides a unique conversion of aryl bromides to aryl fluorides.

Table 5. Fluorination of Aryl Bromides via Pd-Catalyzed Borylation[a]

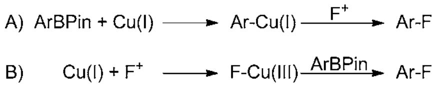


[a]Reactions were performed with 0.1 mmol of aryl bromide. Yields were determined by ^{19}F NMR spectroscopy with 1-bromo-4-fluorobenzene as an internal standard added after the reaction.

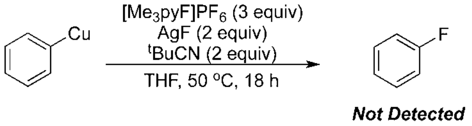
4. Mechanistic Studies on the Fluorination of Arylboronate Esters.

The mechanism of the copper-mediated fluorination of arylboronate esters was studied experimentally. Two simplified reaction pathways are shown in Scheme 4. One pathway (Scheme 4A) begins with transmetalation of the ArBPin to Cu(I), followed by reaction of the arylcopper(I) species with [Me$_3$pyF]PF$_6$. The second pathway (Scheme 4B) begins with formation of a Cu(III) species from reaction of a Cu(I) complex with an F$^+$ source.

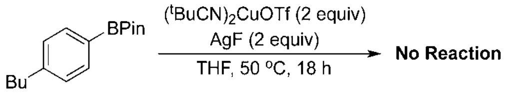
Scheme 4. Potential Reaction Pathways for the Fluorination of ArBPin with (^{t}BuCN)$_2$CuOTf and Me$_3$pyF-PF$_6$



A. Experiments To Distinguish between Pathways A and B by Initial Formation of Copper(I) Aryl or Copper(III) Fluoride Intermediates. To evaluate the potential that mechanism A occurs, we conducted the reaction between the known phenylcopper[16] and [Me$_3$pyF]PF$_6$, AgF, and ^{t}BuCN in THF. After 18 h at 50 °C no fluorobenzene was detected by ^{19}F NMR spectroscopy (eq 3). Furthermore, no reaction occurred between aryl pinacolboronate **1a** and (^{t}BuCN)$_2$CuOTf with added AgF in the absence of [Me$_3$pyF]PF$_6$ over 18 h at 50 °C (eq 4). These results argue against a mechanism involving initial formation of an arylcopper(I) species.



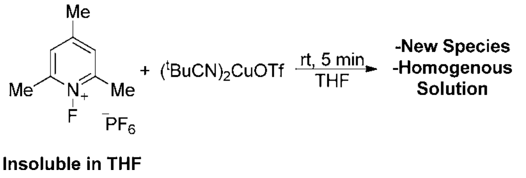
(3)



(4)

We also assessed whether arylsilver species are formed in the reaction. Arylsilver species generated from arylboron reagents have been shown to react with electrophilic fluorine sources to provide aryl fluorides.[5] However, we did not detect any reaction of arylboronate **1a** with AgF in THF at 50 °C over 18 h. Furthermore, many of the reactions we conducted between arylboronates and [Me$_3$pyF]PF$_6$ with other fluoride sources (KF, CsF) formed aryl fluorides. Reactions conducted with AgF occurred in higher yield than those with KF and CsF, but the presence of AgF was not required for the aryl fluoride to form. Thus, the fluorination of arylboronates with [Me$_3$pyF]PF$_6$ is unlikely to occur through arylsilver intermediates. Finally, no aryl fluoride was formed in the absence of copper.

To assess the potential that mechanism B of Scheme 4 occurs, we conducted a series of NMR spectroscopic measurements of the reaction of (^{t}BuCN)$_2$CuOTf with [Me$_3$pyF]PF$_6$. The ^{19}F NMR spectrum of (^{t}BuCN)$_2$CuOTf consists of a sharp singlet at −77.7 ppm in THF. [Me$_3$pyF]PF$_6$ is insoluble in THF, and no ^{19}F NMR signals were observed for a sample of [Me$_3$pyF]PF$_6$ suspended in THF.[17] However, equimolar amounts of (^{t}BuCN)$_2$CuOTf and [Me$_3$pyF]PF$_6$ in THF generated a colorless, homogeneous solution within 5 min at room temperature (eq 5). A new species was formed, as determined by ^{1}H and ^{19}F NMR spectroscopic and ESI-MS measurements. Attempts to isolate this species in pure form have been unsuccessful. Thus, we characterized this copper complex in solution.



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B. Spectroscopic Characterization of a Cu(III) Fluoride Intermediate. The ^{19}F NMR spectrum of the reaction between equimolar amounts of (^{t}BuCN)$_2$CuOTf and [Me$_3$pyF]PF$_6$ in THF at room temperature consisted of a doublet at −72.0 ppm due to the PF$_6$ anion (J = 710 Hz), a broad peak at −71.4 ppm due to the OTf group, and a doublet of doublets at −110.8 ppm (J = 66, 26 Hz) that we propose corresponds to a copper-bound fluoride. The chemical shift of the triflate peak in the new complex was 6.3 ppm downfield of the chemical shift of (^{t}BuCN)$_2$CuOTf, suggesting that the triflate is bound to an electrophilic site, such as the Cu(III) center in the proposed product. Fluoride complexes of d^8 transition-metal centers containing weakly donating ligands have not been reported. The ^{19}F NMR spectra of phosphine-ligated Pd^{II}−F complexes typically contain resonances near −300 ppm. In contrast, the ^{19}F NMR spectra of Pt^{II}−F complexes contain signals as far downfield as −107.6 ppm for *trans*-[Pt(Ph)(F)(PPh$_3$)$_2$].[18] The ^{19}F chemical shifts of alkali-metal fluorides are near −150 ppm. Thus, the ^{19}F chemical shift of the new copper species at −110.8 ppm is consistent with that for a fluoride bound to a cationic Cu(III) site. The sharp, well-resolved peaks in the NMR spectra argue against the formation of a paramagnetic Cu(II) species.

We propose that the doublet of doublets pattern of the fluoride signal (J = 66, 26 Hz) results from scalar coupling between the fluoride ligand and inequivalent α protons of a bound THF. This coupling could result from a hydrogen-bonding interaction or through-space coupling from the electron pairs on the fluoride and the electron density in the C−H bonds.[19] The coupling constants for the fluoride peak are similar in magnitude to ^1J values from H−F hydrogen bonds.[19,20] Because coupling constants are largely dependent on the relative locations and electron density of the coupled atoms, conclusions about the origin of the splitting could not be made on the basis of the magnitude of the coupling constants alone. Thus, further experiments were performed to elucidate the structure of the copper species formed in the reaction between $(^t\mathrm{BuCN})_2\mathrm{CuOTf}$ and $[\mathrm{Me_3pyF}]\mathrm{PF_6}$.

To assess our proposal that the observed splitting is due to coupling between the fluoride and a bound THF, we generated this compound in THF-d_8. The ^{19}F NMR spectrum of the complex generated in THF-d_8 contains a singlet—rather than a doublet of doublets—for the fluoride, and this signal lies upfield (−112.1 ppm) of that for the same peak in the ^{19}F NMR spectrum of the sample in THF (−110.8 ppm). The magnitude of this upfield shift is similar to deuterium isotope effects observed on the chemical shifts of alkyl and vinyl fluorides containing vicinal deuterium atoms.[19,21] These data show that the fluoride is coupled to a bound THF.

To assess further how THF is coordinated to copper, the copper complex was generated in 2,2-dideuteriotetrahydrofuran (see the Supporting Information for the synthesis of 2,2-THF-d_2). If the coupling to fluorine occurred through interactions with one hydrogen atom on each of carbons 2 and 5, a doublet in the ^{19}F NMR spectrum would be expected to be observed, rather than the observed doublet of doublets in fully protiated THF. However, if coupling occurred to two inequivalent hydrogen atoms on the same carbon of the bound THF, then two separate resonances, one a doublet of doublets and one a singlet, would be expected to be observed in THF-d_2 because both isomers would be present in solution in similar amounts (Figure 2).

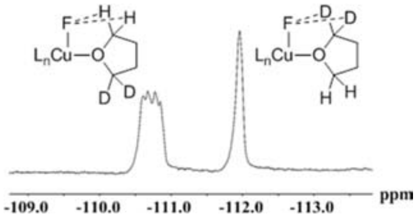


Figure 2. Fluoride peaks in the ^{19}F NMR spectrum of the reaction between $(^t\mathrm{BuCN})_2\mathrm{CuOTf}$ and $[\mathrm{Me_3pyF}]\mathrm{PF_6}$ in THF-d_2.

When the copper complex was generated in THF-d_2, two resonances in the ^{19}F NMR spectrum were observed for the fluorine atom, a doublet of doublets at −110.8 ppm and a singlet at −112.0 ppm. The two isomers were present in solution in a ratio of 1.5:1, favoring the isomer with hydrogen−fluorine coupling by 0.2 kcal/mol.[22] The coupling observed in the ^{19}F NMR spectrum demonstrates that the THF ligand is in a conformation or a coordination sphere in which the geminal α-protons of the bound THF molecule are inequivalent on the NMR time scale.

The ^{1}H NMR spectra of the new species reveals the identity of the dative nitrogen ligands bound to copper. The ^{1}H NMR spectrum of $(^t\mathrm{BuCN})_2\mathrm{CuOTf}$ in THF-d_8 consists of one singlet at 1.41 ppm (free ^{t}BuCN resonates at 1.32 ppm). The ^{1}H NMR spectrum of the new species in THF-d_8 contains a singlet at 1.33 ppm for free ^{t}BuCN and no signals that could be attributed to a bound nitrile. The spectrum also contains resonances at δ 7.49, 2.66, and 2.48 ppm for a 2,4,6-trimethylpyridine unit. These resonances are located downfield of those of free 2,4,6-trimethylpyridine (δ 6.75, 2.36, and 2.20 ppm), and this chemical shift implies that 2,4,6-trimethylpyridine is bound to copper.

A ^{13}C NMR spectrum of the copper species was also obtained. Because the copper species slowly decomposes at room temperature, the ^{13}C NMR spectrum was acquired at −60 °C. The ^{13}C NMR spectrum in THF-d_8 contained resonances for a bound Me$_3$py (δ 158.9, 151.3, 124.4, 20.0, and 17.4 ppm), which were distinct from those for free Me$_3$py (δ 158.1, 147.6, 121.3, 24.4, 20.7 ppm). These spectral data agree with the ^{1}H NMR spectral data indicating that Me$_3$py is ligated to copper.

An assessment of whether the triflate was free or bound and, if bound, what binding mode it adopts was conducted by IR spectroscopy. The IR spectrum of this complex in THF contained characteristic bands for $\nu_{\mathrm{as}}(\mathrm{SO})$ at 1251 and 1292 cm^{-1} (see the Supporting Information). The presence of two vibrations and the 40 cm^{-1} difference between the two vibrations is consistent with a bound, κ^1 triflate ligand.[23]

Finally, the product of the reaction of $(^t\mathrm{BuCN})_2\mathrm{CuOTf}$ with $[\mathrm{Me_3pyF}]\mathrm{PF_6}$ was analyzed by ESI-MS under an inert atmosphere.[24] A 1:1 ratio of $(^t\mathrm{BuCN})_2\mathrm{CuOTf}$ and $[\mathrm{Me_3pyF}]\mathrm{PF_6}$ was allowed to react at room temperature, and the solution was continuously monitored on a Micromass Q-ToF spectrometer in positive-ion mode over 10 min under an inert atmosphere with electrospray ionization. The ions $(^t\mathrm{BuCN})_2\mathrm{Cu}^+$ and $[(\mathrm{Me_3py})(\mathrm{THF})\mathrm{Cu}(\mathrm{F})(\mathrm{OTf})]^+$ were observed as the major peaks in the mass spectrum (see the Supporting Information). The signal attributed to the cation $[(\mathrm{Me_3py})(\mathrm{THF})\mathrm{Cu}(\mathrm{F})(\mathrm{OTf})]^+$ has a mass to charge ratio of 424.10 for the base peak and the characteristic isotope pattern of copper (Figure 3). Together, these data indicate that the species formed from the reaction between $(^t\mathrm{BuCN})_2\mathrm{CuOTf}$ and $[\mathrm{Me_3pyF}]\mathrm{PF_6}$ has the general formula $[(\mathrm{Me_3py})(\mathrm{THF})\mathrm{Cu}(\mathrm{F})(\mathrm{OTf})(\mathrm{PF_6})]$.

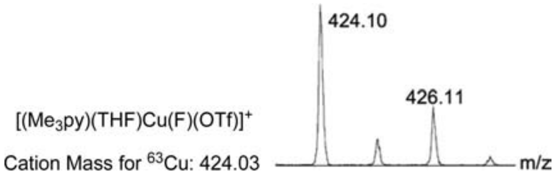


Figure 3. Proposed formula and ESI-MS of the cationic portion of the Cu(III) fluoride intermediate.

We used computational methods with DFT to assess potential structures the Cu(III) fluoride species detected by NMR spectroscopy and mass spectrometry. Energy minimizations of a complex containing one fluoride, one triflate, one bound THF, one trimethylpyridine, and one PF$_6$ unit were conducted with DFT using WB97XD functionals that include empirical dispersion corrections. These calculations indicated that the stereoisomer shown in Figure 4 with the Me$_3$py trans and the triflate cis to THF is 9.3 kcal/mol more stable in the gas phase than the isomer with the Me$_3$py cis and the triflate trans to THF. These calculations also indicated that the ground state of $[(\mathrm{Me_3py})(\mathrm{THF})\mathrm{Cu}(\mathrm{F})(\mathrm{OTf})(\mathrm{PF_6})]$ is approximately square pyramidal with hexafluorophosphate bound in the apical

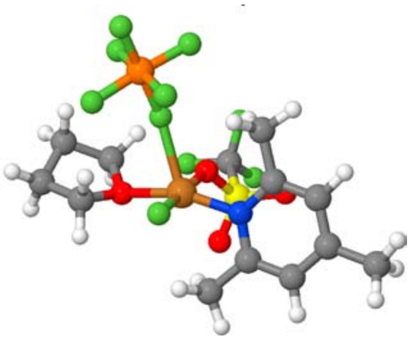


Figure 4. Computed ground-state structure of $[(Me_3py)(THF)Cu(F)(OTf)(PF_6)]$ in a THF solvent continuum.

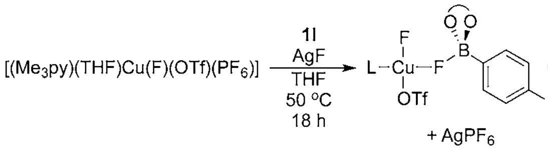
position (Figure 4). Calculations performed with a THF solvent continuum indicated that the neutral complex containing a bound PF_6 anion is more stable than the separated ions by $\Delta H = 14.2$ kcal/mol and $\Delta G = 2.1$ kcal/mol. Although further work on stable analogues of the new species is clearly needed, binding of PF_6 or slow rotation of the THF would cause the complex to be chiral; this property would render the geminal protons at THF diastereotopic and chemically inequivalent. In the computed structure, the four inequivalent α protons of the bound THF lie in an orientation with short (2.4 and 2.6 Å) H−F distances that are consistent with the observation of $^1J_{HF}$ coupling in the ^{19}F NMR spectra (vide supra). Studies toward analogues of this Cu(III) species that are sufficiently stable for isolation are ongoing.

C. Reactions of the Cu(III) Fluoride Intermediate with the Reaction Components. The reactivity of the cationic copper(III) fluoride species was investigated to assess the competence of this species to be an intermediate and to determine which reagents react with this complex to form the aryl fluoride product. The reaction of metal fluorides with arylboron reagents to generate arylmetal species has been shown to occur during palladium-catalyzed Suzuki cross-coupling.[25] Thus, the Cu(III) fluoride could react directly with the arylboronate ester to generate an $(aryl)Cu^{III}$ species and F-BPin. However, the copper(III) fluoride species (generated in situ) did not undergo transmetalation with *p*-fluorophenylboronate **1l**, as determined by ^{19}F NMR spectroscopy (eq 6). The reaction of $(^tBuCN)_2CuOTf$ with $[Me_3pyF]PF_6$ and **1l** in the absence of AgF did not lead to any detectable conversion of the arylboronate ester over 18 h at 50 °C.

$$\begin{array}{l}[(Me_3py)(THF)Cu(F)(OTf)]PF_6 \\ \quad + \ p\text{-}F(C_6H_4)BPin\ (\mathbf{1l})\end{array} \xrightarrow[\substack{50\ ^\circ C \\ 18\ h}]{THF} \begin{array}{c}\textbf{No} \\ \textbf{Transmetallation}\end{array} \qquad (6)$$

The potential that the copper(III) fluoride species reacts with AgF to form a copper(III) species containing two fluorides was also investigated. If formed, a copper(III) difluoride could react with the arylboronate ester to give an arylcopper(III) fluoride. However, no new copper species from the reaction between the copper(III) fluoride intermediate and AgF in THF over 18 h at 50 °C was detected by ^{19}F NMR spectroscopy. The reaction of the copper(III) fluoride with the more reactive, and more soluble, tetrabutylammonium fluoride (TBAF) resulted in the rapid formation of paramagnetic copper(II) species, as determined by characteristic broad peaks in the NMR spectrum. The formation of Cu(II) could result from N−F reductive elimination of $[Me_3pyF]^+$ from an unstable Cu(III) difluoride to form a copper(I) fluoride. Copper(I) fluoride complexes are known to disproportionate rapidly to Cu(0) and CuF_2, and this disproportionation would account for the paramagnetic species observed in the ^{19}F NMR spectrum.[12]

Finally, the reaction of *p*-fluorophenylboronate **1l** with $(^tBuCN)_2CuOTf$, $[Me_3pyF]PF_6$, and AgF under the standard reaction conditions was monitored, and this reaction led to a new species that appears to be a second intermediate in the fluorination of arylboronate esters The ^{19}F NMR spectrum after 20 min of the reaction of *p*-fluorophenylboronate **1l** with $[(Me_3py)(THF)Cu(F)(OTf))PF_6)]$ and AgF at 50 °C showed that greater than 90% of the arylboronate ester was converted to a new species (eq 7). New resonances in the ^{19}F NMR spectrum were observed. A new signal corresponding to the *p*-fluorine atom on the aryl ring (−115.7 ppm) resonated upfield of that on the starting, free arylboronate ester (−108.7 ppm). The peak corresponding to the Cu^{III}−F species described above was quickly consumed and was replaced by a broad peak at −138 ppm. The intensity of the peak at −138 ppm was twice that of the peak from the fluorine atom on the aryl group. The resonance from the triflate was observed at −76 ppm, and this peak was sharper and was located upfield of the triflate peak of the cationic Cu(III) fluoride (−71.4 ppm, broad). The other peaks observed in the ^{19}F NMR spectrum were 1,4-difluorobenzene (the product of fluorination of the arylboronate ester), fluorobenzene (formed by protodeborylation), internal standard, and F-BPin. F-BPin and 1,4-difluorobenzene were formed in concert with consumption of the copper species corresponding to the resonances at −115.7 and −138 ppm.



(7)

The new species formed from the reaction between arylboronate **1l**, $(^tBuCN)_2CuOTf$, $[Me_3pyF]PF_6$, and AgF was further characterized by ^1H NMR spectroscopy. The aryl protons of the boronate ester **1l** resonate at 7.76 and 7.07 ppm in THF-d_8. The aromatic protons of the new species resonated further upfield at 7.68 and 6.99 ppm. The ^1H NMR spectrum of the reaction solution also contained resonances for ligated trimethylpyridine at δ 7.49, 2.63, and 2.46 ppm and for free ^tBuCN at δ 1.33 ppm. These chemical shifts are similar to those of the trimethylpyridine ligand in $[(Me_3py)Cu(F)(OTf)(THF)(PF_6)]$ (δ 7.49, 2.66, and 2.48 ppm). The proton resonances for the pinacolate group (δ 1.25 ppm) were shifted upfield of those for the pinacolate group of **1l** (δ 1.32 ppm).

The ^{11}B NMR spectrum of the reaction between arylboronate **1l**, $(^tBuCN)_2CuOTf$, $[Me_3pyF]PF_6$, and AgF under the standard reaction conditions showed >90% conversion of **1l** (δ 30.4 ppm) to a new species within 20 min at 50 °C. This new species corresponded to a ^{11}B resonance at 4.5 ppm. As the reaction progressed, the peak at 4.5 ppm decayed in concert with the formation of F-BPin (0.6 ppm). The chemical shift of 4.5 ppm is consistent with the formation of a four-coordinate anionic arylboronate. These results suggest that the Ar−B bond is present in the observed species.

We propose that the copper complex formed from the reaction of *p*-fluorophenylboronate **1l** with $(^tBuCN)_2CuOTf$, $[Me_3pyF]PF_6$, and AgF is a neutral arylboronate Cu(III) fluoride. A potential structure of this complex is shown in

Figure 5. We propose that the two fluorine atoms give rise to a single broad ^{19}F resonance due to a combination of stereoisomerism and transfer of the boron center from one fluorine to the other. This species was formed in 90% yield (based on the conversion of ArBPin).

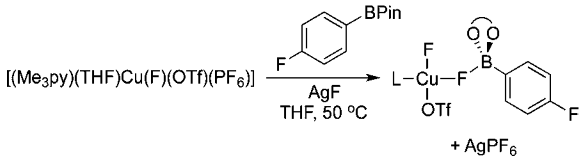
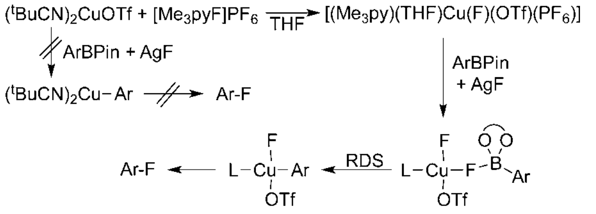


Figure 5. Proposed structure of the arylboronate Cu(III) fluoride intermediate. L is 2,4,6-trimethylpyridine.

We propose that the arylboronate Cu(III) fluoride complex undergoes rate-limiting transmetalation of the aryl group to copper. The aryl Cu(III) fluoride complex formed from transmetalation would then undergo fast reductive elimination of the Ar–F product. Fast reductive elimination of an aryl fluoride is consistent with a recent report by Ribas and coworkers in which an aryl Cu(III) fluoride complex was proposed to be formed as an unobserved, reactive intermediate during the reaction of a macrocylic aryl Cu(III) complex with fluoride to form a macrocyclic fluoroarene.[26]

Scheme 5 shows a mechanism for the fluorination of arylboronate esters with (^{t}BuCN)$_2$CuOTf, [Me$_3$pyF]PF$_6$, and AgF that is consistent with our data. Our data indicate that the fluorination of arylboronate esters does not occur by the formation of arylcopper(I) species. Instead, the fluorination reactions appear to occur by generation of a cationic copper(III) fluoride intermediate that reacts with the combination of fluoride and arylboronate ester. Rate-limiting transmetalation of the aryl group to Cu(III) is proposed to form an aryl Cu(III) fluoride from which rapid reductive elimination of the Ar–F product occurs.

Scheme 5. Proposed Mechanism for the Fluorination of ArBPin with (^{t}BuCN)$_2$CuOTf and Me$_3$pyF-PF$_6$



SUMMARY AND CONCLUSIONS

In summary, we have developed an operationally simple, direct method for the fluorination of arylboronate esters and revealed the formation of two copper(III) fluoride intermediates. This reaction occurs with readily available reagents under mild conditions. Electron-rich, electron-deficient, ortho-substituted, and diversely functionalized arylboronate esters undergo fluorination in good yield. In addition, sequential, one-pot processes allow the fluorination of arenes and aryl bromides to occur through arylboronate ester intermediates generated in situ. We provide evidence that the fluorination of arylboronate esters with (^{t}BuCN)$_2$CuOTf and [Me$_3$pyF]PF$_6$ occurs by facile formation of a cationic copper(III) fluoride complex, which reacts with AgF and ArBpin to form a neutral fluoroarylboronate complex. This fluoroarylboronate undergoes transmetalation to form an arylcopper(III) fluoride, which undergoes reductive elimination to form the aryl fluoride product.

ASSOCIATED CONTENT

Supporting Information

Text, figures, and tables giving experimental procedures, characterization data for new compounds, and details of the calculations. 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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