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

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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 aryl-boronate 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 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 Halex¹ 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 were obtained in many cases.³ Arylstannanes,⁴ arylsilver,⁵ arylpalladium,⁶ and arynickel⁷ 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 aryl-boronic acids (Ag, Pd) or aryl bromides (Ni). More recently, Ritter and coworkers 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 $(^t\text{BuCN})_2\text{CuOTf}$ and AgF .⁹

Arylboron reagents are valuable alternative sources of aryl groups for the synthesis of aryl fluorides because they are readily available, non-toxic, 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 those 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.

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Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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 conversion of arylboron nucleophiles to aryl fluorides (Scheme 3), we focused initially on the fluorination of pinacol-derived aryl-boronate 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

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 thermal and base-induced decomposition of the F^+ source. In addition, the ligating ability of 2,4,6-trimethylpyridine 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 $[\text{Me}_3\text{pyF}]\text{OTf}$.

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 significantly higher yields than those conducted with alkoxide bases. Reactions conducted with AgF as base occurred in significantly higher yields than reactions 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 Ar-BPin 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(I)F species.¹²

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 fluoride, 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 aryl-boronate esters. Substrates containing esters, ketones, aldehydes, amides, nitriles, aryl hldes, 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 *ortho*-anisylboronic ester (**1s**) also gave the aryl fluoride product, but in lower yield. 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 aryl-boron 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 proto-deborylation, a deuterium labeling experiment was conducted. The reaction of **1a** under the standard reaction conditions with two equivalents of added D₂O 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.

(1)

(2)

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 B₂Pin₂ 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.

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 pre-catalyst, B₂Pin₂, and KOAc¹⁵ 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.

4. Mechanistic Studies on the Fluorination of Arylboronate Esters

The mechanism of the copper-mediated fluorination of aryl-boronate esters was studied experimentally. Two simplified reaction pathways are shown in Scheme 4. One mechanism (Scheme 4, A) begins with transmetalation of the ArBPin to Cu(I), followed by reaction of the arylcopper(I) species with [Me₃pyF]PF₆. The second mechanism (Scheme 4, B) begins with formation of a Cu(III) species from reaction of a Cu(I) complex with an F⁺ source.

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 phenyl-copper¹⁶ with [Me₃pyF]PF₆, AgF and ^tBuCN in THF. After 18 h at 50 °C no fluorobenzene was detected by ¹⁹F NMR spectroscopy (eq 3). Furthermore, no reaction occurred between aryl pinacolboronate **1a** and (^tBuCN)₂CuOTf with added AgF in the absence of [Me₃pyF]PF₆ 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 Yet, 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 [Me₃pyF]PF₆ 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 product to form. Thus, the fluorination of aryl boronates with [Me₃pyF]PF₆ 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 2 occurs, we conducted a series of NMR spectroscopic measurements of the reaction of (tBuCN)₂CuOTf with [Me₃pyF]PF₆. The ¹⁹F NMR spectrum of (tBuCN)₂CuOTf consists of a sharp singlet at -77.7 ppm in THF. [Me₃pyF]PF₆ is insoluble in THF, and no ¹⁹F NMR signals were observed for a sample of [Me₃pyF]PF₆ suspended in THF.¹⁷ However, equimolar amounts of (tBuCN)₂CuOTf and [Me₃pyF]PF₆ in THF generated a colorless, homogenous solution within 5 min at room temperature (eq 5). A new species was formed, as determined by ¹H and ¹⁹F 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.

(5)

B. Spectroscopic Characterization of a Cu(III) Fluoride Intermediate—The ¹⁹F NMR spectrum of the reaction between equimolar amounts of (tBuCN)₂CuOTf and [Me₃pyF]PF₆ in THF at room temperature consisted of a doublet at -72.0 ppm due to the PF₆ 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 that we propose to correspond to a copper-bound fluoride (*J* = 66, 26 Hz). The chemical shift of the triflate peak in the new complex was 6.3 ppm downfield of the chemical shift of (tBuCN)₂CuOTf, suggesting that the triflate is bound to an electrophilic site, such as the Cu(III) center in the proposed product. Fluoride complexes of d⁸ transition metal centers containing weakly donating ligands have not been reported. The ¹⁹F NMR spectra of phosphine-ligated Pd(II)-F complexes typically contain resonances near -300 ppm. In contrast, the ¹⁹F NMR spectra of Pt(II)-F complexes contain signals as far downfield as -107.6 ppm for *trans*-[Pt(Ph)(F)(PPh₃)₂].¹⁸ The ¹⁹F chemical shifts of alkali-metal fluorides are near -150 ppm. Thus, the ¹⁹F 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 due to 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 ¹*J* 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 based on 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 $(^t\text{BuCN})_2\text{CuOTf}$ and $[\text{Me}_3\text{pyF}]\text{PF}_6$.

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 SI for the synthesis of 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).

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 ^1H NMR spectra of the new species reveals the identity of the dative nitrogen ligands bound to copper. The ^1H NMR spectrum of $(^t\text{BuCN})_2\text{CuOTf}$ in THF- d_8 consists of one singlet at 1.41 ppm (free $^t\text{BuCN}$ resonates at 1.32 ppm). The ^1H NMR spectrum of the new species in THF- d_8 contains a singlet at 1.33 ppm for free $^t\text{BuCN}$ 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_3py (δ 158.9, 151.3, 124.4, 20.0 and 17.4 ppm), which were distinct from those for free Me_3py (δ 158.1, 147.6, 121.3, 24.4, 20.7 ppm). These spectral data agree with the ^1H NMR spectral data indicating that Me_3py 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 $\nu_{\text{as}}(\text{SO})$ 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 $(^t\text{BuCN})_2\text{CuOTf}$ with $[\text{Me}_3\text{pyF}]\text{PF}_6$ was analyzed by ESI-MS under an inert atmosphere.²⁴ A 1:1 ratio of $(^t\text{BuCN})_2\text{CuOTf}$ and $[\text{Me}_3\text{pyF}]\text{PF}_6$ 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 minutes under an inert atmosphere with electrospray ionization. The ions $(^t\text{BuCN})_2\text{Cu}^+$ and $[(\text{Me}_3\text{py})(\text{THF})\text{Cu}(\text{F})(\text{OTf})]^+$ were observed as the major peaks in the mass spectrum (see SI). The signal attributed to the cation $[(\text{Me}_3\text{py})(\text{THF})\text{Cu}(\text{F})(\text{OTf})]^+$, has a mass to charge ratio of 424.10 for the base peak and the characteristic isotope pattern of copper. Together, these data indicate that the species formed from the reaction between $(^t\text{BuCN})_2\text{CuOTf}$ and $[\text{Me}_3\text{pyF}]\text{PF}_6$ has the general formula $[(\text{Me}_3\text{py})(\text{THF})\text{Cu}(\text{F})(\text{OTf})(\text{PF}_6)]$

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_3py trans and the triflate cis to THF is 9.3 kcal/mol more stable in the gas phase than the isomer with the Me_3py cis and the triflate trans to THF. These calculations also indicated that the ground state of $[(\text{Me}_3\text{py})(\text{THF})\text{Cu}(\text{F})(\text{OTf})(\text{PF}_6)]$ is approximately square pyramidal with hexafluorophosphate bound in the apical 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 analogs of the new species is clearly needed, binding of PF_6 or slow rotation to the THF would cause the complex to be chiral on the NMR time scale; this property would render the geminal protons at THF diastereotopic and chemically inequivalent. In the computed structure, the four inequivalent alpha 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 $^1J_{\text{HF}}$ coupling in the ^{19}F NMR spectra (*vide supra*). Studies toward analogs of this Cu(III) species that are sufficiently stable for isolation are ongoing.

B. 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 aryl-boron reagents to generate aryl-metal species has been shown to occur during palladium-catalyzed Suzuki cross-coupling.²⁵ Thus, the Cu(III)-fluoride could react directly with the aryl-boronate ester to generate an arylCu(III) species and F-BPin. However, the copper(III)-fluoride species (generated *in-situ*) did not undergo transmetalation with *p*-fluorophenylboronate **11**, as determined by ^{19}F NMR spectroscopy (eq 6). The reaction of $(^t\text{BuCN})_2\text{CuOTf}$ with $[\text{Me}_3\text{pyF}]\text{PF}_6$ and **11** in the absence of AgF did not lead to any detectable conversion of the arylboronate ester over 18 h at 50 °C.

(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 aryl-copper(III)fluoride. However, no new copper species from the reaction between the copper(III)-fluoride intermediate and AgF in THF after 18 h at 50 °C was detected by ^{19}F NMR spectroscopy (eq 7). 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 $[\text{Me}_3\text{pyF}]^+$ 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

(7)

Finally, the reaction of *p*-fluorophenylboronate **11** with $(^t\text{BuCN})_2\text{CuOTf}$, $[\text{Me}_3\text{pyF}]\text{PF}_6$ 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 minutes of the reaction of *p*-fluorophenylboronate **11** with $(^t\text{BuCN})_2\text{CuOTf}$ at 50 °C showed that greater than 90% of the arylboronate ester was converted to a new species. 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 aryl-boronate 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 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 aryl boronate ester), fluorobenzene (formed by pro-to-deborylation), 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.

The new species formed from the reaction between aryl-boronate **11**, $(^t\text{BuCN})_2\text{CuOTf}$, $[\text{Me}_3\text{pyF}]\text{PF}_6$ and AgF was further characterized by ^1H NMR spectroscopy. The aryl protons of the boronate ester **11** resonate at 7.76 ppm and 7.07 ppm in $\text{THF-}d_8$. The aromatic protons of the new species resonated further upfield at 7.68 ppm, 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 $^t\text{BuCN}$ (δ 1.33 ppm). These chemical shifts are similar to those of the trimethylpyridine ligand in $[(\text{Me}_3\text{py})\text{Cu}(\text{F})(\text{OTf})(\text{THF})(\text{PF}_6)]$ (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 **11** (δ 1.32 ppm).

The ^{11}B NMR spectrum of the reaction between aryl-boronate **11**, $(^t\text{BuCN})_2\text{CuOTf}$, $[\text{Me}_3\text{pyF}]\text{PF}_6$ and AgF under the standard reaction conditions showed >90% conversion of **11** (δ 30.4 ppm) to a new species within 20 minutes 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 **11** with $(^t\text{BuCN})_2\text{CuOTf}$, $[\text{Me}_3\text{pyF}]\text{PF}_6$ 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).

We propose the arylboronate-Cu(III)-fluoride complex undergoes rate-limiting transmetallation of the aryl group to copper. The aryl-Cu(III)-fluoride complex formed from transmetallation 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 macrocyclic aryl-Cu(III) complex with fluoride to form a macrocyclic fluoroarene.²⁶

Scheme 5 shows a mechanism for the fluorination of aryl-boronate esters with $(^t\text{BuCN})_2\text{CuOTf}$, $[\text{Me}_3\text{pyF}]\text{PF}_6$ and AgF that is consistent with our data. Our data indicate that the fluorination of aryl boronate 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 arylboronic ester. Rate-limiting transmetallation 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.

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 $(^t\text{BuCN})_2\text{CuOTf}$ and $[\text{Me}_3\text{pyF}]\text{PF}_6$ 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 transmetallation to form an arylcopper(III) fluoride, which undergoes reductive elimination to form the aryl fluoride product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Electrophilic Fluorine (F⁺) Reagents.

Figure 2. Fluoride peaks in the ^{19}F NMR spectrum of the reaction between $(^t\text{BuCN})_2\text{CuOTf}$ and $[\text{Me}_3\text{pyF}]\text{PF}_6$ in $\text{THF-}d_2$

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

Figure 4.
Computed ground state structure of $[(\text{Me}_3\text{py})(\text{THF})\text{Cu}(\text{F})(\text{OTf}))\text{PF}_6]$ in a THF solvent continuum.

Figure 5.
Proposed Structure of Arylboronate-Cu(III)-Fluoride Intermediate. L is 2,4,6-trimethylpyridine.

Scheme 1.
Conventional Routes to Fluoroarenes.

Scheme 2.
Transition-Metal Mediated Aryl Fluorination.

Scheme 3.
Copper Mediated Fluorination of $\text{ArB}(\text{OR})_2$.

Scheme 4.

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

Scheme 5.

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

Table 1Screen of F⁺ Reagents for the Fluorination of **1a** with (tBuCN)₂CuOTf and AgF.

$\text{1a} \xrightarrow[\text{THF, 50 } ^\circ\text{C, 18 h}]{\begin{matrix} (\text{tBuCN})_2\text{CuOTf (2 equiv)} \\ \text{F}^+ \text{ Source (3 equiv)} \\ \text{AgF (2 equiv)} \end{matrix}} \text{2a}$

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	[Cl ₂ pyF]OTf	100	100	0
5	[pyF]OTf	100	87	1
6	[Me ₃ pyF]BF ₄	84	9	56
7	[Me ₃ pyF]OTf	82	13	64
8	[Me ₃ pyF]PF ₆	88	12	75
9	[Me ₃ pyF]PF ₆	97	57	24
10	[Me ₃ pyF]PF ₆	100	39	38

^aReactions 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.

^bReactions were performed with KF in place of AgF.

^cReactions were performed with CsF in place of AgF.

Table 2

Fluorination of ArBPins with $(^t\text{BuCN})_2\text{CuOTf}$ and $[\text{Me}_3\text{pyF}]\text{PF}_6$ ^a

^aReactions 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.

^bIsolated yield from a reaction with 0.5 mmol of ArBPins.

^cReactions were conducted at 80 °C.

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

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	Neopentylglycol	15	70
6	Pinacol	12	75

^aReactions were performed with 0.1 mmol of aryl-boron 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.

Table 4

Fluorination of Arenes via C-H Borylation.

^aReactions were performed with 0.1 mmol of arene. Yields were determined by ¹⁹F NMR spectroscopy with 1-bromo-4-fluorobenzene as an internal standard added after the reaction.

^bThe borylation reaction was performed with 1.5% [Ir] and 3.0% dtbpy.

^cThe borylation reaction was performed with 0.5% [Ir] and 1.0% dtbpy.

^dThe fluorination reaction was performed at 80 °C for 18 h.

Table 5

Fluorination of Aryl Bromides via Pd-Catalyzed Borylation.

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