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Mild Copper-Mediated Fluorination of Aryl Stannanes and Aryl Trifluoroborates

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Supporting Information

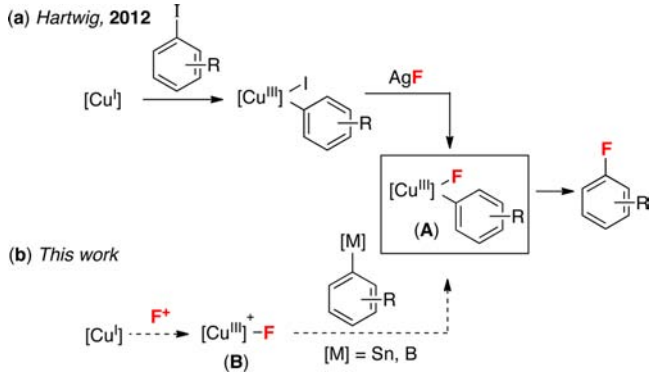
ABSTRACT: This communication describes a mild copper-mediated fluorination of aryl stannanes and aryl trifluoroborates with *N*-fluoro-2,4,6-trimethylpyridinium triflate. This protocol demonstrates broad substrate scope and functional group tolerance, and does not require the use of any noble metal additives. The reaction is proposed to proceed via an arylcopper(III) fluoride intermediate.

Aryl fluorides are extremely important structural motifs that feature prominently in pharmaceuticals, agrochemicals, organic materials, and biological imaging agents.[1] As a result, significant recent effort has focused on the development of new synthetic procedures for the generation of C_{Aryl}–F bonds.[2] Transition metal-mediated and/or catalyzed aryl–fluoride coupling reactions are of particular interest, because the rate, selectivity, and functional group tolerance of these transformations can often be modulated by changing the metal and its ligand environment.[3] Over the past 6 years, several different palladium[4] and silver-based protocols have been developed to effect aryl–fluoride bond formation via cross-coupling with aryl C–H bonds,[5,6] aryl triflates,[7] aryl stannanes,[8] aryl boronic acids,[9] and aryl silanes.[10] In several cases, these methods have been successfully applied to the late-stage fluorination of complex molecules. However, despite these significant advances, the reactions generally remain limited by the requirement for expensive and toxic noble metals.

A key unmet need in the field is a mild and general aryl fluorination protocol mediated by an earth abundant first row metal such as Cu.[11] In a seminal report in 2011, Ribas and co-workers demonstrated a proof-of-concept example of aryl–F bond formation at a macrocyclic aryl–Cu(III) complex.[12,13] More recently, Fier and Hartwig reported the Cu-mediated conversion of a broader scope of aryl iodides to aryl fluorides using AgF as the fluoride source at 140 °C.[14] As shown in Scheme 1a, this transformation is also believed to proceed via a Cu^{III}(aryl)(fluoride) intermediate **A** formed by oxidative addition of Ar–I to Cu(I) and subsequent reaction with AgF.

Inspired by these exciting advances, we sought to develop a milder and more versatile Cu(III)-mediated aromatic fluorination protocol. We hypothesized that an intermediate analogous to **A** could be formed under less forcing conditions via the combination of an electrophilic fluorinating reagent (F^+) and an aryl organometallic species (Scheme 1b).[5,15,16] Importantly, literature precedent in Pd- and Ag-catalyzed fluorination reactions has shown that F^+ reagents can serve as fluorine sources without introducing extra ligands that might lead to unproductive competing reductive elimination from the metal center.[4−6,8−10]

Scheme 1. Strategies for Cu-Mediated Aryl–F Coupling



To test this hypothesis, we initially explored the Cu-mediated fluorination of aryl stannane **1** with commercial electrophilic fluorinating reagents. These studies revealed that the combination of **1**, (^{t}BuCN)$_2$CuOTf, and *N*-fluoro-2,4,6-trimethylpyridinium triflate (NFTPT) in EtOAc at 25 °C for 12 h afforded modest (6%) yield of the desired product **1a** (Scheme 2a; see Tables S1–S4 for full optimization details). The major byproduct of this transformation is biaryl **1b** derived from unproductive homocoupling of the aryl stannane. We reasoned that its formation could be circumvented by initial oxidation of (^{t}BuCN)$_2$CuOTf with NFTPT to form putative Cu(III)–F intermediate **B** (Scheme 1) followed by addition of the stannane **1**. As shown in Scheme 2b, this sequential addition protocol resulted in dramatically improved yield of **1a** (74%) along with <4% of **1b**. Notably, the control reaction (in the absence of Cu) did not afford a detectable quantity of **1a**.

We next applied this room temperature fluorination protocol to a variety of different aryl stannanes. As shown in Scheme 3, aryl stannanes bearing electron-donating and withdrawing substituents underwent fluorination in good to excellent yields under these conditions. The presence of *ortho*-substituents was also well-tolerated. Notably, in all of the examples shown in Scheme 3, no fluorination products were detected in the absence of Cu (see Table S5 for the results of these control experiments).

With this proof of principle in hand, we next investigated replacing the aryl stannanes with less toxic aryl–boron reagents.

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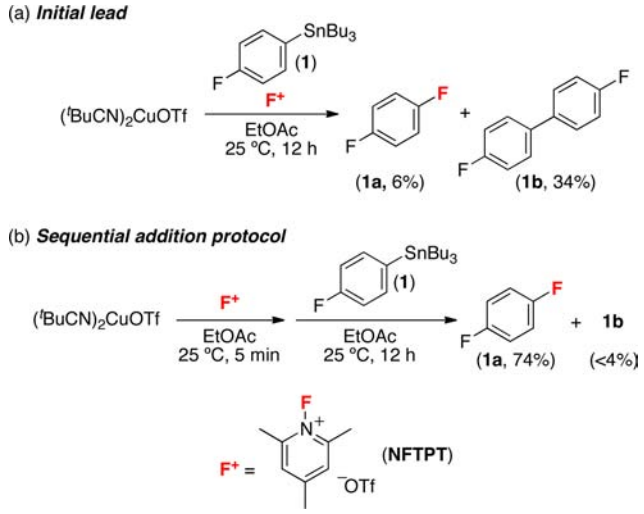
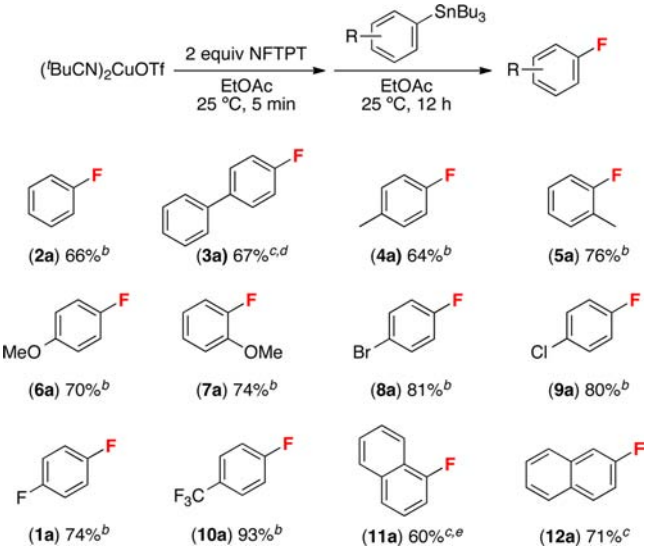
Scheme 2. Cu-Mediated Fluorination of Aryl Stannanes



Scheme 3. Substrate Scope for Cu-Mediated Fluorination of Aryl Stannanes[a]

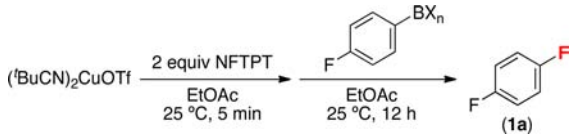


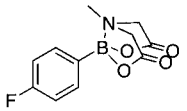
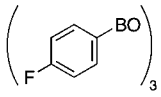
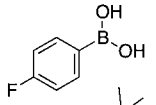
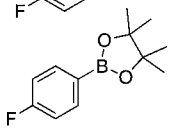
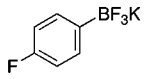
[a]General conditions: stannane (0.25 mmol, 1 equiv), (^{t}BuCN)$_2$CuOTf (1 equiv), NFTPT (2 equiv), EtOAc (0.1 M in stannane), 25 °C, 12 h. Copper salt and NFTPT were prestirred in solvent for 5 min, followed by addition of the stannane. [b]Yield determined by ^{19}F NMR spectroscopy. [c]Isolated yield. [d]Isolated product contained 8% of biphenyl (derived from protodestannylation). [e]1.2 equiv of (^{t}BuCN)$_2$CuOTf.

A series of *p*-FC$_6$H$_4$BX$_n$ derivatives were examined under identical conditions to those in Scheme 3. As shown in Table 1, the aryl boron reagents generally afforded low to modest yields under these conditions. In most cases, the major byproducts were either unreacted starting material or fluorobenzene from protodeboronation.[17] The best result (46% yield) was obtained with the aryl trifluoroborate substrate (entry 5). Optimization of this reaction showed that changing the solvent to MeCN resulted in an improvement in the yield to 58% (entry 6; see Tables S6–S9 for full optimization details).

The substrate scope for the copper-mediated fluorination of aryl trifluoroborates is shown in Scheme 4. Aryltrifluoroborates bearing electron-donating and electron-withdrawing substituents reacted to generate the aryl–F products in good yields.

Table 1. Cu-Mediated Fluorination of Aryl Boron Reagents[a]



Entry	Substrate	Yield
1		1%
2		3%
3		3%
4		7%
5		46%
6		58%[b]

[a]General conditions: stannane (0.025 mmol, 1 equiv), (^{t}BuCN)$_2$CuOTf (1 equiv), NFTPT (2 equiv), EtOAc (0.1 M in boron reagent), 25 °C, 12 h. Copper salt and NFPTP were prestirred in solvent for 5 min, followed by addition of the substrate. Yields determined by ^{19}F NMR spectroscopy. [b]Reaction conducted using MeCN as solvent.

Substrates containing *ortho*-substituents also underwent efficient fluorination under these optimized conditions. This protocol is compatible with a variety of common functional groups. Substrates bearing aryl aldehydes, ketones, amides, and esters produced the aryl fluorides in good yields. Control reactions (without added Cu) were conducted for all of the substrates in Scheme 4.[17] As shown in Table S10, the electron deficient aryl trifluoroborates showed no background reaction under these conditions. Furthermore, only traces of background fluorination products (2–6%) were observed with the electron rich substrates *p*-MeOC$_6$H$_4$BF$_3$K, MesBF$_3$K, and naphthylBF$_3$K.

In summary, this communication describes a new method for the Cu-mediated fluorination of aryl stannanes and aryl trifluoroborates with an electrophilic fluorinating reagent. The reactions proceed under very mild conditions (in many cases at room temperature) and exhibit a broad substrate scope and functional group tolerance.[18] A Cu(I/III) mechanism is proposed with a Cu^{III}(aryl)(fluoride) (**A** in Scheme 1) serving as a likely intermediate.[19] Importantly, this strategy takes advantage of the dual role of the electrophilic fluorinating reagent as both an oxidant for Cu(I) and a fluorine source.[20] Ongoing work is focused on effecting analogous fluorination reactions using alternative oxidants in conjunction with nucleophilic fluoride sources.[4a,e,21]

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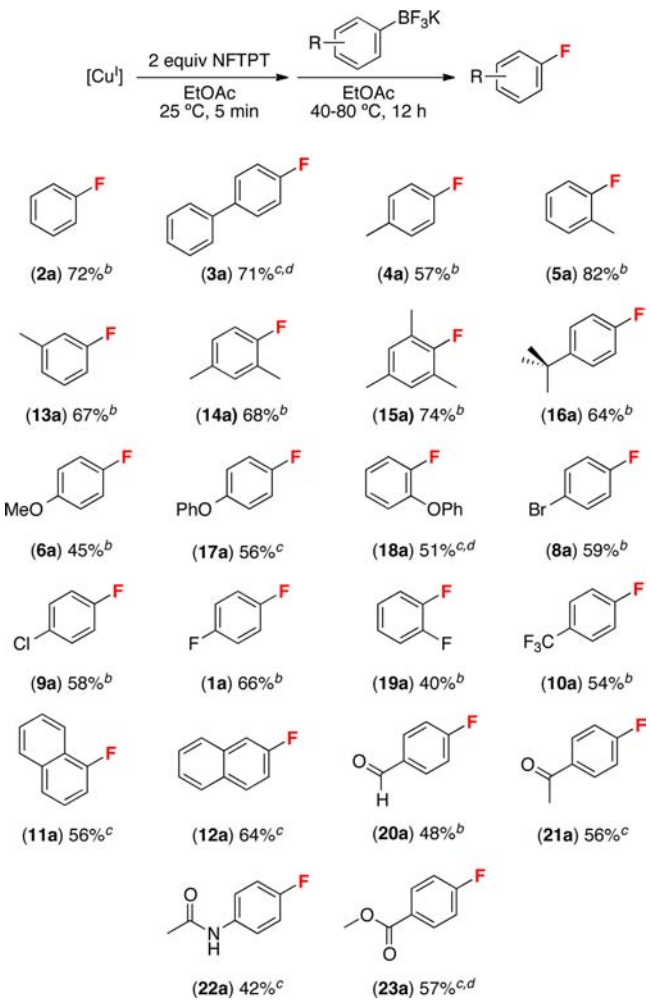
Scheme 4. Substrate Scope for Cu-Mediated Fluorination of Aryl Trifluoroborates[a]



[a]General conditions: substrate (0.25 mmol, 1 equiv), (^{t}BuCN)$_2$CuOTf or (MeCN)$_4$CuBF$_4$ (1 to 2 equiv), NFTPT (2 equiv), 40 or 80 °C, 12 h. Copper salt and NFTPT were prestirred in solvent for 5 min, followed by addition of the substrate. [b]Yield determined by ^{19}F NMR spectroscopy. [c]Isolated yield. [d]Isolated products contained small amounts (4−6%) of inseparable proto-deboronated side-products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic and analytical data for new compounds. 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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(19) ^{19}F NMR analysis of the reaction of (^{t}BuCN)$_2$CuOTf with NFTPT in EtOAc at room temperature shows a resonance at −123.0 ppm, which may correspond to a Cu(III)−F; however, this species is formed in low yield (∼1%), so it is unclear whether it is responsible for the observed reactivity. When this same reaction was conducted in the presence of 10 equiv of THF, the Cu(III) complex recently characterized by Hartwig [ref 15] was detected by ^{19}F NMR spectroscopy, albeit also in modest (∼18%) yield. See Supporting Information for relevant spectra. Ongoing efforts are focused on

gaining further insights into the organometallic intermediates and the mechanistic complexities of this transformation.
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