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Communication

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$Cu(OTf)_2$-Mediated Fluorination of Aryltrifluoroborates with Potassium Fluoride

Yingda Ye,[†] Sydonie D. Schimler,[†] Patrick S. Hanley,[‡] and Melanie S. Sanford*,[†]

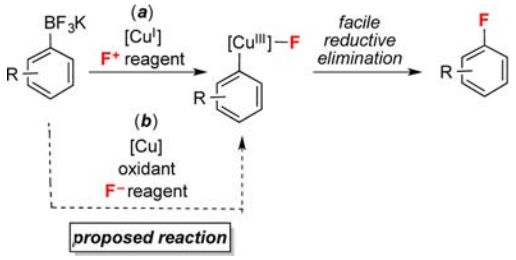
[†]Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States
[‡]Process Science, Dow Chemical Company, 1710 Building, Midland, Michigan 48674, United States

Supporting Information

ABSTRACT: This Communication describes the $Cu(OTf)_2$-mediated fluorination of aryltrifluoroborates with KF. The reaction proceeds under mild conditions (at 60 °C over 20 h) and shows a broad substrate scope and functional group tolerance. The Cu is proposed to play two separate roles in this transformation: (1) as a mediator for the aryl−F coupling and (2) as an oxidant for accessing a proposed Cu^{III}(aryl)(F) intermediate.

Fluorinated aromatic molecules are finding increasingly wide application in the pharmaceutical and agrochemical development pipelines[1] as well as in specialty materials and PET imaging reagents.[2] As a result, there is high demand for efficient, mild, and inexpensive procedures for the construction of aryl−fluoride bonds. Classical methods for aryl−F bond formation include the substitution of highly electron-deficient aryl halides with alkali metal fluorides (MF) via S_NAr pathways[3] and the reaction of aryldiazonium reagents with tetrafluoroborate.[4] More recently, significant effort has been devoted to the development of milder, safer, and more general alternatives to these methods starting from aryl halides,[5,6] aryl triflates,[7] diaryliodonium salts,[8] aryl organometallics,[9,10] aryl C−H bonds,[11] and phenols.[12]

Arylboron reagents are particularly attractive starting materials for C−F bond-forming reactions.[13] This functional group is typically readily synthetically accessible, nontoxic, and stable to many common organic reagents.[13] Several research groups have recently reported methods for the fluorination of organoboron compounds, including transformations mediated by Pd,[14] Ag,[10c] and Cu.[10a,b] While many of these reactions proceed in high yield and with reasonable substrate scope, they all remain fundamentally limited by the requirement for electrophilic fluorinating reagents as the source of fluorine (for an example of a Cu-mediated transformation of this type, see eq 1a). These reagents (e.g., Selectfluor, *N*-fluoropyridinium salts) are prohibitively expensive for large-scale applications;[15] furthermore, they are generally less desirable than fluoride salts for PET imaging applications, because their ^{18}F analogues are available in much lower specific activity.[2]



(1)

As part of an ongoing research program in transition metal-promoted fluorination chemistry, we sought to develop a mild nucleophilic fluorination of aryl boron compounds. We selected Cu as the metal of choice based on recent reports that high valent Cu^{III} complexes can undergo facile aryl−fluoride bond-forming reductive elimination reactions (eq 1a).[5b,6a,8a,10,16] We reasoned that the combination of the appropriate Cu salt, oxidant, and nucleophilic fluoride source could enable the fluorination of aryl boron derivatives (eq 1b). We report herein the development of a remarkably mild and general Cu-mediated fluorination of aryltrifluoroborates with potassium fluoride. The optimization and scope of this transformation are discussed in detail; furthermore, a preliminary mechanistic proposal is presented.

We hypothesized that AgF might be capable of serving as both a fluoride source and an oxidant for the Cu-mediated fluorination of aryltrifluoroborates. As such, we initially probed the fluorination of 4-fluorophenyltrifluoroborate (**1**) with AgF, mediated by a variety of different Cu salts. While most [Cu] sources provided no detectable fluorination, $Cu(OTf)_2$[17] promoted the desired reaction to afford moderate yield of **1a** after 20 h at 60 °C (57% yield, Table 1, entry 6). As a control, we next examined the analogous $Cu(OTf)_2$-mediated reaction using the non-redox-active fluoride source KF. Remarkably, this inexpensive alkali metal fluoride[18] afforded a high yield of **1a** (70%) under otherwise identical conditions (entry 9).[19] Similar results were also obtained with NaF and CsF (entries 8 and 10), whereas LiF was ineffective for this reaction (entry 7). The initial optimization studies were conducted on a 0.025 mmol scale; however, the KF reaction also proceeded in comparable (67%) yield on a 0.5 mmol scale. In addition, the reaction time could be shortened considerably by conducting this transformation at higher temperature. For example, at 100 °C the reaction proceeded to 56% yield within 15 min.

The optimized reaction conditions using KF were next applied to a series of different p-$FC_6H_4BX_2$ derivatives. As summarized in Table 2, the corresponding pinacol ester provided a 56% yield. Importantly, aromatic pinacol esters are readily available via Ir-catalyzed C−H functionalization,[20] setting up the possibility for previously unprecedented

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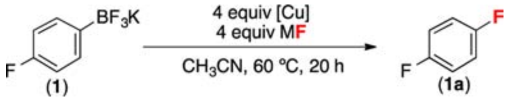
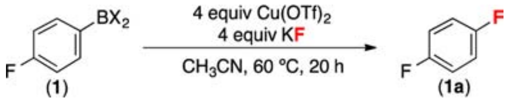
Table 1. Cu-Mediated Nucleophilic Fluorination of 1[a]

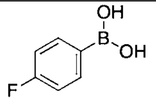
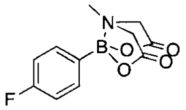
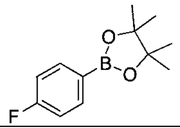


entry	[Cu]	MF	yield **1a** (%)
1	Cu(OTs)$_2$	AgF	nd
2	(CuOTf)$_2$·C$_6$H$_6$	AgF	nd
3	CuF$_2$	AgF	nd
4	Cu(OAc)$_2$	AgF	nd
5	(^{t}BuCN)$_2$Cu(OTf)	AgF	nd
6	Cu(OTf)$_2$	AgF	57
7	Cu(OTf)$_2$	LiF	nd
8	Cu(OTf)$_2$	NaF	62
9	Cu(OTf)$_2$	KF	70
10	Cu(OTf)$_2$	CsF	65

[a] General conditions: **1** (0.025 mmol, 1 equiv), [Cu] (4 equiv), MF (4 equiv), CH$_3$CN (0.083 M), 60 °C, 20 h. Yield determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. nd = no product was detected.

Table 2. Scope of Aryl Boron Reagents[a]



entry	Substrate	yield 1a
1		3%
2		9%
3		56%

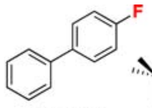
[a] General conditions: *p*-FC$_6$H$_4$BX$_2$ (0.025 mmol, 1 equiv), Cu(OTf)$_2$ (4 equiv), KF (4 equiv), MeCN (0.083 M), 60 °C, 20 h. Yield determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture.

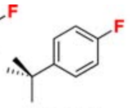
sequential C−H borylation/nucleophilic fluorination reactions.[21] In addition, the boronate esters are more suitable substrates for PET applications than the trifluoroborates, since they preclude the possibility of ^{19}F exchange and contamination. In contrast to the moderate yields observed for fluorination of the pinacol ester, the corresponding boronic acid and MIDA ester showed poor reactivity.

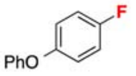
We next evaluated the fluorination of a diverse set of aryl- and heteroaryltrifluoroborate salts. As shown in Table 3, this Cu(OTf)$_2$-promoted fluorination with KF was applicable to both electron-deficient and electron-rich aryltrifluoroborates. All products with boiling points higher than 170 °C were isolated in ≥97% purity. Where noted, some aryl fluorides were isolated along with traces (2−3%) of an inseparable protodeboronated side product (**3a**, **5a**, **6a**, **9a**, **14a**).[22] This reaction shows excellent compatibility with carbonyl functional groups, including ketones, esters, and aldehydes (**11a**−**14a**). In addition, several different heterocyclic compounds, including pyridine derivatives, underwent fluorination to form **15a**−**17a**.

Table 3. Substrate Scope of Cu(OTf)$_2$-Mediated Fluorination of Aryltrifluoroborates with KF[a]

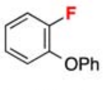

(2a) 48%[b]


(3a) 48%[c]

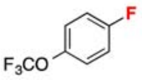

(4a) 55%[b]



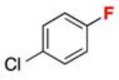
(5a) 45%[c]



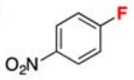
(6a) 66%[c]



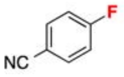
(7a) 71%[b]



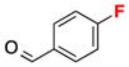
(8a) 70%[b,d]

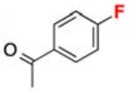


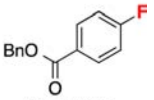
(9a) 65%[c]



(10a) 63%

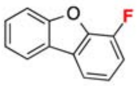

(11a) 57%

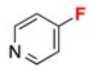

(12a) 60%

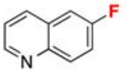


(13a) 68%


(14a) 66%[c]


(15a) 67%


(16a) 21%[b]


(17a) 36%

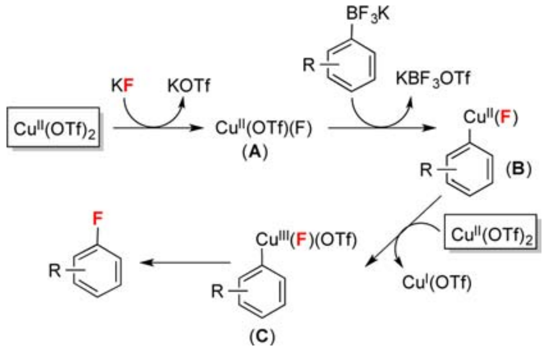
[a] General conditions: potassium aryltrifluoroborate (0.5 mmol, 1 equiv), Cu(OTf)$_2$ (4 equiv), KF (4 equiv), CH$_3$CN (0.083 M), 60 °C, 20 h. Unless otherwise noted, isolated yields are reported. [b] Yield determined by ^{19}F NMR spectroscopy. [c] Isolated product was ≥97% pure but contained traces of inseparable protodeboronated side products. [d] 4% of 1,4-dichlorobenzene was also observed as a side product.

While the yield of pyridine fluorination remains modest (21%),[23] this reaction is significant because fluoropyridines are prevalent in diverse agrochemicals[24] and pharmaceuticals.[25]

One current limitation of this method is that chloride-, bromide-, and iodide-containing substrates are susceptible to competing halodeboronation under the reaction conditions. For example, 4-chlorophenyltrifluoroborate reacted to form the desired fluorinated product **8a** in 70% yield along with 4% of 1,4-dichlorobenzene. Although this is a relatively minor side reaction, the byproducts can be challenging to separate.

A possible mechanism for this transformation is proposed in Scheme 1, in which Cu(OTf)$_2$ plays the dual role of a promoter of C−F bond formation and as an oxidant. The mild conditions employed in the reaction indicate that C−F coupling has a low activation barrier; as a result, we propose that this step occurs from a highly reactive Cu^{III} intermediate like **C**.[5b,10a,b] We hypothesize that this Cu^{III} species may be formed via a disproportionative reaction in which 1 equiv of a Cu^{II} aryl

Scheme 1. Possible Mechanism



intermediate like **B** is oxidized by 1 equiv of $Cu^{II}(OTf)_2$. This would provide an explanation for the high effectiveness of $Cu(OTf)_2$ in this transformation, since a strongly oxidizing Cu source would be required for this step. Consistent with the proposed dual role of Cu, the reaction yield falls off sharply upon the use of <2 equiv of $Cu(OTf)_2$ (to 15% with 1 equiv of [Cu] under otherwise identical conditions).[26] Further investigations will be required to establish a more detailed picture of the reaction mechanism.[27]

In summary, this Communication describes a mild Cu-mediated fluorination of aryl boron compounds with potassium fluoride. This transformation exhibits broad substrate scope. Furthermore, preliminary studies (Table S8) show that these reactions do not require rigorous exclusion of air and moisture. We propose that the Cu plays a dual role in this transformation: first, it serves to coordinate both the aryl and fluoride ligands and promote their coupling; second, it serves as an oxidant to generate the key reactive Cu^{III} intermediate. Further investigations of mechanism, scope, and applications of this method are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete experimental and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

mssanfor@umich.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(15) The current price for Selectfluor reagent is ~\$1100/mol, determined based on the largest quantity available from Sigma-Aldrich on Jul 10, 2013 (100 g/\$328). The current price for 1-fluoro-2,4,6-trimethylpyridinium triflate is ~\$3700/mol, determined based on the largest quantity available from TCI America on Jul 10, 2013 (25 g/\$317).

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(17) $Cu(OTf)_2$ can be prepared in a single step from $CuCO_3$ and HOTf. See: Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843.

(18) KF is at least 2 orders of magnitude less expensive than AgF. For example, the current price of KF is ~\$14/mol, determined based on the largest quantity available of the material used for our experiments (99% purity, spray dried) from Sigma-Aldrich on Aug 8, 2013 (1 kg/\$252). The current price for AgF is ~\$3600/mol, determined based on the largest quantity available (99% purity) from Sigma-Aldrich on Aug 8, 2013 (25 g/\$723).

(19) The major side products were fluorobenzene (derived from protodeboronation) and *N*-(4-fluorophenyl)acetamide (derived from coupling of the acetonitrile solvent with the fluoroarene). Similar side products were observed in all of the reactions in Table 3.

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(21) For an example of sequential C−H borylation/electrophilic fluorination transformations, see ref 10b.

(22) Significantly larger quantities of protodeboronated products were observed in Cu-mediated fluorination of organoboron compounds using electrophilic fluorinating reagents. For example, see ref 10b.

(23) The yield of **16a** can be increased to 49% by using 10 equiv of $Cu(OTf)_2$.

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(26) Preliminary efforts to use $Cu(OTf)_2$ as a catalyst in the presence of air as a terminal oxidant (in analogy to the work reported by Ribas[5b] and Wang[11c]) did not result in catalyst turnover.

(27) Preliminary ^{19}F NMR studies of this reaction did not show the presence of detectable diamagnetic Cu intermediates. See Supporting Information for relevant spectra.