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Copper-Mediated Fluorination of Aryl Iodides

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S *Supporting Information*

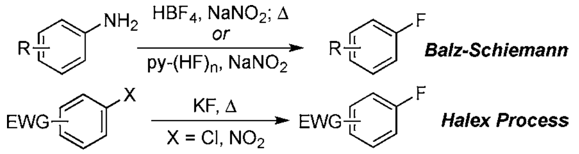
ABSTRACT: The synthesis of aryl fluorides has been studied intensively because of the importance of aryl fluorides in pharmaceuticals, agrochemicals, and materials. The stability, reactivity, and biological properties of aryl fluorides can be distinct from those of the corresponding arenes. Methods for the synthesis of aryl fluorides, however, are limited. We report the conversion of a diverse set of aryl iodides to the corresponding aryl fluorides. This reaction occurs with a cationic copper reagent and silver fluoride. Preliminary results suggest this reaction is enabled by a facile reductive elimination from a cationic arylcopper(III) fluoride.

The unique stability, reactivity, and biological properties of fluorinated compounds make them useful in many chemical disciplines. Compounds containing an aryl fluoride moiety are common in pharmaceuticals and agrochemicals because the site containing fluorine is stable toward degradation, and this stability improves biological activity.

The conditions typically used to form aryl−fluorine bonds are harsh; thus the fluorine is usually introduced into the arene ring at the beginning of a synthesis or as part of a building block. Improved methods for late-stage aromatic fluorination would be important for diversification in medicinal chemistry. Moreover, methods for aromatic fluorination with simple sources of anionic fluoride would be valuable for the preparation of ^{18}F-labeled compounds used in positron emission tomography (PET) imaging. Yet, no method has been reported for the fluorination of electron-neutral to electron-rich aryl halides.

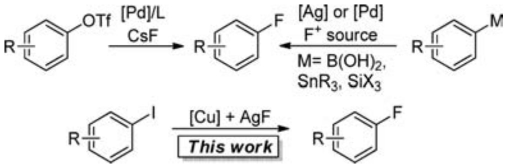
Instead, aryl fluorides have been prepared by the Balz−Schiemann reaction involving the decomposition of aryldiazonium salts (Scheme 1).[1] The acidic conditions, the toxicity of the reagents, and the potential for explosions limit the synthetic utility of the Balz−Schiemann reaction.[1] Alternatively, aryl fluorides bearing electron-withdrawing groups have been prepared by the halogen exchange (halex) process in which electron-deficient aryl chlorides or nitroarenes undergo nucleophilic aromatic substitution with fluoride at high temperatures (Scheme 1).[2] However, this reaction occurs only with substrates that are activated toward nucleophilic attack.

Scheme 1. Conventional Routes to Fluoroarenes



Recently, transition metal complexes have been used to prepare fluoroarenes.[3] Palladium-catalyzed fluorination of aryl triflates has been reported (Scheme 2).[4] Although these findings demonstrated that aryl electrophiles can undergo fluorination in the presence of a transition metal catalyst, the formation of a single product occurred only with substrates bearing electron-withdrawing groups.[4] The triflates for this reaction are formed from phenols, and a reagent for the conversion of phenols to aryl fluorides was reported more recently.[5] Methods for the conversion of aryl stannanes,[6] boronic acids,[7] and silanes[8] to aryl fluorides with silver or palladium and an electrophilic fluoride source also have been published, but the aryl nucleophiles in these reactions are often prepared from the aryl halide. Therefore, a method to convert aryl halides to the corresponding aryl fluorides would be more direct than the reactions of main group−aryl reagents.

Scheme 2. Metal-Mediated Aryl Fluorination



Here, we report the fluorination of a set of functionally diverse aryl iodides with a simple copper reagent and fluoride source. The success of this reaction with a nucleophilic fluoride reagent rests on the identification of an appropriate ligand for copper. With the proper choice of ligand and source of fluoride, the rapid decomposition of copper(I) fluorides is avoided.

Having recently developed copper-mediated fluoroalkylations[9] of arenes, including reactions through unstable fluoroalkyl intermediates, we studied copper systems for the fluorination of aryl iodides. The strong metal−fluorine bond causes C−F reductive elimination to be slower than competing side reactions.[3,10] However, Ribas and co-workers have shown that a macrocyclic arylcopper(III) complex undergoes C−F bond formation, suggesting that copper-mediated fluorination of aryl electrophiles through high-valent copper is feasible.[11] We hypothesized that reductive elimination from an arylcopper(III) fluoride species would be facilitated by a non-coordinating counterion and weakly donating ligands. Based on

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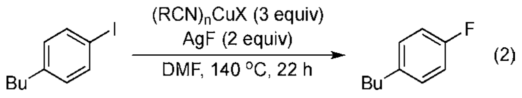
this logic, we found that the reaction of 4-butyl-1-iodobenzene with $(MeCN)_4CuBF_4$ and AgF gave detectable amounts of aryl fluoride. No reaction occurred in the absence of copper, demonstrating that a direct reaction between AgF and ArI is not occurring.

This initial result led us to investigate the effect of nitrile ligands and counterions on the halogen exchange reaction. Cationic copper complexes ligated by nitriles can be prepared in multigram quantities within minutes from the reaction of Cu_2O with strong acids in the nitrile solvent (eq 1). By this

$$Cu_2O + HX \xrightarrow[rt]{RCN} (RCN)_4CuX \quad (1)$$

route, we prepared copper complexes containing different nitriles and counterions (see Supporting Information (SI)). These complexes were tested as mediators of the fluorination of 1-butyl-4-iodobenzene with AgF (eq 2). Reactions of this aryl

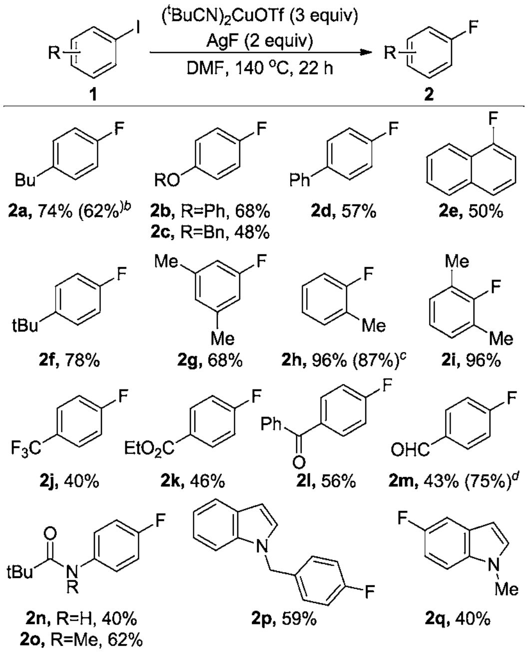


iodide with AgF in the presence of the complexes ligated by ^tBuCN occurred in higher yields than those conducted with complexes ligated by MeCN, ^iPrCN, and PhCN. Reactions conducted with copper complexes containing SbF_6 and OTf as counterion occurred in higher yields than those conducted with copper complexes containing BF_4 and PF_6. Reactions conducted with ^tBuCN-ligated CuOTf were more reproducible than those conducted with ^tBuCN-ligated $CuSbF_6$. An excess of copper, relative to AgF, was critical for the reaction to occur in high yields (see SI). Reactions conducted with CsF in place of AgF gave the same aryl fluoride product, but in a 34% yield with 30% of the arene side product.

^tBuCN-ligated CuOTf was prepared in multigram quantites from Cu_2O, triflic acid, and ^tBuCN (*vide supra*). When the ^tBuCN-ligated CuOTf complex is prepared, four nitriles are bound in a tetrahedral geometry.[12] However, placing the solid under vacuum at room temperature resulted in the loss of two nitriles to give a compound with the formula $(^tBuCN)_2CuOTf$, as determined by elemental analysis[13] and X-ray crystallography.[14] This complex is stable to oxygen and absorbs moisture from the air only slowly. Thus, this species can be weighed quickly on the benchtop.

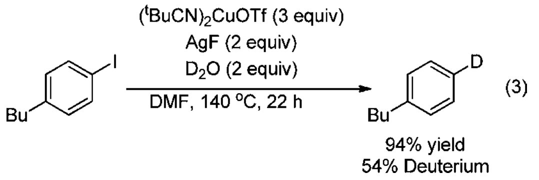
Reactions of the combination of $(^tBuCN)_2CuOTf$ and AgF with a range of aryl iodides are shown in Table 1. These data show that electron-rich and electron-poor iodoarenes react to form the aryl fluorides in good yields, as determined by NMR spectroscopy. Sterically hindered aryl iodides (**1h**, **1i**) reacted to provide nearly quantitative yields of the aryl fluoride. Esters, amides, aldehydes, ketones, and indole heterocycles were tolerated under the reaction conditions. Reactions conducted with AgF as the limiting reagent and an excess of aryl iodide provided high yields of the aryl fluoride **2m**. Conditions for conducting fluorinations with limiting fluoride are important for the use of this process to provide ^{18}F-labeled product for PET imaging. The aryl fluoride **2a** was isolated in good yield on a 0.5 mmol scale. The greatest challenge in the current reactions is the separation of the major aryl fluoride product from the arene side product. Methods for separation from the arene and conditions for minimizing formation of the arene are currently being studied.

Table 1. Fluorination of Aryl Iodides with $(^tBuCN)_2CuOTf$ and AgF[a]



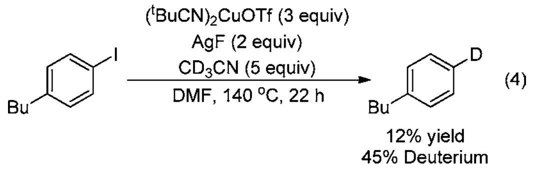
[a]Reactions were performed with 0.1 mmol of aryl iodide to determine yields by ^{19}F NMR spectroscopy with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. ^{19}F NMR chemical shifts were compared with those of the authentic aryl fluorides. [b]Isolated yield from a reaction with 0.5 mmol of ArI. [c]Reactions were conducted with 1 equiv of ArI, 2 equiv of $(^tBuCN)_2CuOTf$, and 1 equiv of of AgF. [d]Reactions were conducted with 3 equiv of ArI, 2 equiv of $(^tBuCN)_2CuOTf$ and 1 equiv of AgF.

The source of hydride leading to the arene side product was investigated by deuterium-labeling experiments. The reaction between **1a**, $(^tBuCN)_2CuOTf$, and AgF with 2 equiv of D_2O formed the arene in 94% yield, with 54% incorporation of deuterium into this product (eq 3). These data suggest that



adventitious water is one source of the hydro-dehalogenation product, despite the use of anhydrous DMF[15] and oven-dried glassware. Indeed, the rigorous exclusion of water is essential for high yields.

The reaction of **1a** under the standard conditions with 5 equiv of CD_3CN produced 12% of the arene side product with 45% incorporation of deuterium into this arene (eq 4). This

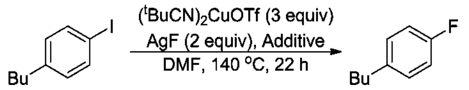


finding shows that the alpha proton of the nitrile is also a source of hydride in the hydro-dehalogenation process. Thus, the higher yields from reactions mediated by complexes of

^{t}BuCN than from those of the other nitriles can be attributed, in part, to the absence of acidic protons on the ligand. The arene side product from reactions run in DMF-d_7 did not contain deuterium, showing that arene does not form by hydrogen atom abstraction from the solvent.

Lower yields and conversions were obtained when the reactions were conducted with an excess of AgF, relative to $({}^{t}\mathrm{BuCN})_2\mathrm{CuOTf}$ (see SI). To understand the deleterious effect of excess AgF, we conducted reactions under the standard conditions, but with added AgOTf and with added CsF (Table 2). Reactions run with 1 or 2 equiv of added AgOTf proceeded in much lower yields and lower conversions than those without added AgOTf (Table 2). However, reactions run under the standard conditions with 1 or 2 equivs of added CsF were not as inhibited as the reactions with added AgOTf. These findings suggest that the lower yields in the presence of excess AgF result from the silver ion, rather than fluoride. The AgF may mediate an unproductive redox reaction with copper to generate a copper(0) or copper(II) species that does not mediate the fluorination of aryl iodides.

Table 2. Effect of Added AgOTf and CsF on Aryl Iodide Fluorination[a]

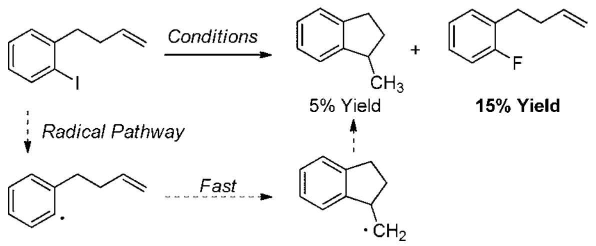


entry	additive	ArF (%)	ArH (%)	conversion (%)
1	AgOTf (1 equiv)	18	13	60
2	AgOTf (2 equiv)	5	22	51
3	CsF (1 equiv)	71	23	100
4	CsF (2 equiv)	59	25	92

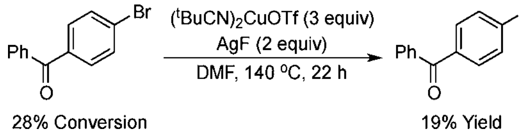
[a] Reactions were performed with 0.1 mmol of **1a** in 0.5 mL of DMF for 22 h. Yields were determined by gas chromatography with 1-bromo-4-fluorobenzene as an internal standard added after the reaction.

Reactions of aryl halides with Cu(I) species have been proposed in some cases to occur by radical intermediates[16] and in other cases to occur through Cu(III) intermediates formed by oxidative addition of organic halides to a Cu(I) species.[17] To probe the potential intermediacy of aryl radicals during this fluorination reaction, we conducted the process with *o*-(3-butenyl)iodobenzene (Scheme 3). The corresponding aryl radical undergoes 5-exo-trig cyclization with a rate constant of $10^8\ \mathrm{s}^{-1}$ to form 1-methylindane after hydrogen atom abstraction.[18] The reaction of *o*-(3-butenyl)iodobenzene under the standard conditions gave <5% of the cyclized product, with 15% of the aryl fluoride product; the remaining mass balance consisted of 4-phenyl-1-butene. This finding suggests that the formation of aryl fluoride does not occur through an aryl radical intermediate because the rate of cyclization should be much faster than the intermolecular reaction of a Cu(II) intermediate with the fluoride source. However, a fraction of the aryl iodide appears to react through a radical pathway, as deduced by the observation of some cyclized product. We suggest that this radical pathway is due to the formation of a copper side product during the reaction.[19]

Scheme 3. Probe for Aryl Radical Intermediates



To gain additional data on whether this fluorination process occurs through an initial electron-transfer reaction, we tested the fluorination of 4-bromobenzophenone. The reduction potential of this bromoarene is higher than that of some of the aryl iodides in Table 1.[20] Thus, the formation of an aryl radical by an outer-sphere electron transfer with this aryl bromide should occur at a rate that is comparable to the rate of the reactions of aryl iodides.[20] However, the aryl bromide reacted to <30% conversion and formed the aryl fluoride in only 19% yield (eq 5). A higher conversion of the aryl bromide would be expected if the copper system reacted with the aryl halide by a single-electron-transfer pathway.



(5)

Additional data were consistent with the absence of aryl radicals. The reaction of 1-butyl-4-iodobenzene under the standard fluorination conditions, but with 1 equiv of TEMPO as a free radical trap, yielded the aryl fluoride in 74% yield with 93% conversion of the aryl iodide. In addition, reactions in DMF-d_7 did not lead to incorporation of deuterium into the arene side product. If an aryl radical were formed, hydrogen atom abstraction from the solvent, rather than from adventitious water (*vide supra*), would be expected because DMF is present in higher concentrations and has weaker X−H bonds than those in water. Reactions run in the dark gave identical results to those run in room light.

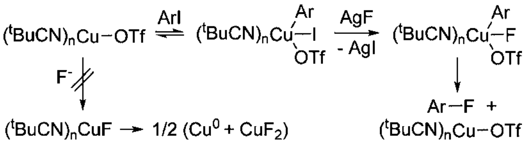
Nucleophilic attack of fluoride on an aryl iodide coordinated to copper through the π system is an alternative mechanism. However, the observation of arene side product suggests that protonolysis of an arylcopper species occurs. Such a protonolysis would not be expected to occur during nucleophilic attack on a π-coordinated arene.[17d,21]

Finally, fluorinations of aryl halides could occur through a benzyne intermediate. Grushin and Marshall reported a fluorination of aryl triflates with tetramethylammonium fluoride, which resulted in constitutional isomers that were consistent with an aryne intermediate.[22] We detected only one isomer in each reaction, and the fluorination of 2,6-dimethyliodobenzene occurred in high yield. These data are inconsistent with reaction through an aryne intermediate.

A copper(I) fluoride species is a potential intermediate in the fluorination of aryl iodides. Unligated copper(I) fluoride is unstable toward rapid and exothermic decomposition to Cu(0) and $\mathrm{CuF_2}$,[23] and only two copper(I) fluorides have been reported. Both of these complexes contain strongly bound ancillary ligands.[24] To test the properties of a ^{t}BuCN-ligated copper(I) fluoride, $({}^{t}\mathrm{BuCN})_2\mathrm{CuOTf}$ and AgF were combined in DMF and allowed to react between room temperature and 140 °C. No new species were observed by ^{19}F NMR spectroscopy over the course of 8 h at room temperature, 80, 100, or 140 °C. The reaction between $({}^{t}\mathrm{BuCN})_2\mathrm{CuOTf}$ and the more reactive anhydrous tetra-*n*-butylammonium fluoride led to rapid decomposition of the nitrile-ligated copper triflate at room temperature without formation of a species that could be detected by ^{19}F NMR spectroscopy. The higher yields obtained with AgF than with other fluorides might be due, at least in part, to the low solubility of this fluoride source. The slow background reaction of AgF with $(^t\mathrm{BuCN})_2\mathrm{CuOTf}$ leads to a lower concentration of the copper(I) fluoride and thus a lower rate of decomposition.

A proposed reaction mechanism that is consistent with our data and known chemistry of copper is shown in Scheme 4. In this pathway, reversible oxidative addition of an aryl iodide to a nitrile-ligated CuOTf forms an arylcopper(III) iodide containing a coordinated or loosely bound triflate. The rate and equilibrium for oxidative addition are likely faster for copper complexes containing the more donating ^{t}BuCN than for those containing other nitriles, and this expectation is consistent with the higher yields from reactions conducted with this ligand than from those conducted with other nitriles. The electrophilicity of a Cu(III) triflate might favor transmetalation of AgF with this species, and we propose this reaction occurs to form an arylcopper(III) fluoride that undergoes C−F bond formation.

Scheme 4. Proposed Mechanism for the Fluorination of 1 with $(^t\mathrm{BuCN})_2\mathrm{CuOTf}$ and AgF



In summary, we have developed an operationally simple fluorination of aryl iodides with readily available reagents. This reaction tolerates ether, amide, ester, ketone, and aldehyde functional groups and occurs with some heterocyclic systems. Moreover, it occurs in high yield with sterically hindered aryl iodides. We propose that this reaction occurs by oxidative addition to form a Cu(III) intermediate and C−F reductive elimination from an arylcopper(III) fluoride. Work is ongoing to extend the work described here to the synthesis of ^{18}F-labeled compounds for PET imaging.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization of all new compounds, and crystallographic data (CIF) for $(^t\mathrm{BuCN})_4\mathrm{CuOTf}$ and $(^t\mathrm{BuCN})_2\mathrm{CuOTf}$. 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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(12) See SI.

(13) Calcd: C, 34.87; H, 4.79; N, 7.39. Found: C, 34.96; H, 4.88; N, 7.53.

(14) See the SI for the influence of the ratio of ^{t}BuCN:Cu on the fluorination of aryl iodides.

(15) Anhydrous DMF was purchased from Acros and stored over molecular sieves, water content <0.005%.

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