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Copper-Mediated Oxidative Fluorination of Aryl Stannanes with Fluoride

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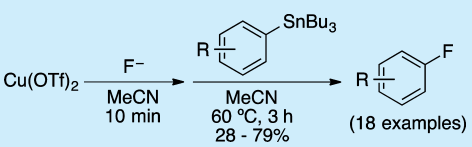
Supporting Information

ABSTRACT: A regiospecific method for the oxidative fluorination of aryl stannanes using tetrabutylammonium triphenyldifluorosilicate (TBAT) and copper(II) triflate is described. This reaction is robust, uses readily available reagents, and proceeds via a stepwise protocol under mild conditions (60 °C, 3.2 h). Broad functional group tolerance, including arenes containing protic and nucleophilic groups, is demonstrated.

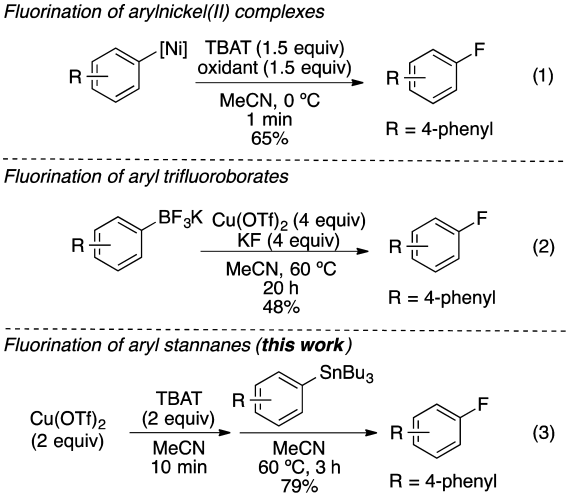


Numerous and valuable applications of fluorinated aromatic small molecules have stirred powerful interest within the chemistry community. As such, a remarkable increase in synthetic methodologies for C−F bond construction has been reported in the past decade.[1−3] Notable improvements in aryl fluoride bond formation have utilized transition metals to facilitate this transformation.[4−6] While early examples were focused on palladium[7−14] and silver[15−19] catalytic methods, lower cost metals such as copper[20−27] and nickel[28] have recently emerged as alternative mediators of C−F bond formation. Despite attention from many research groups, most modern fluorination methods use electrophilic fluorinating sources (e.g., Selectfluor, *N*-fluoropyridinium salts) or specialized precursors. These methods have considerably improved accessibility of fluorinated arenes yet they are not useful for applications in positron emission tomography (PET) due to the fact that ^{18}F is generated as nucleophilic [^{18}F]fluoride. While [^{18}F]F_2 and other electrophilic ^{18}F-fluorination reagents exist, their use in the synthesis of PET radiotracers results in low specific activity, namely $^{18}F/^{19}F$ ratio and, consequently, are not broadly useful for molecular imaging applications.[29]

The development of an electrophilic fluorination reaction that utilizes a readily available nucleophilic fluoride source in combination with an external oxidant is a highly attractive approach that would be particularly valuable for translation into radiofluorination for PET imaging applications. Such oxidative fluorination transformations are conceptually challenging due to fluorine's inherent nature as the most oxidizing element present. In spite of this challenge few groups have reported oxidative fluorination transformations. Meng and Li reported a hypervalent iodine mediated method to provide *para*-fluorinated anilides in moderate to good yields[30] using similar conditions reported earlier for the synthesis of 4-fluorophenols via oxidative fluorination of 4-*tert*-butylphenols.[31] Studies by the Daugulis group utilized an 8-aminoquinoline directing group to demonstrate an oxidative C−H fluorination of benzoic acid derivatives via copper catalysis using super stoichiometric amounts of AgF and *N*-methylmorpholine (NMO).[32] While these methods demonstrate good yields, the substrate scopes are limited and directing groups are required.

The first example of oxidative fluorination with a first row transition metal, reported by the Ritter group in 2012, proceeds via an arylnickel(II) complex in the presence of a hypervalent iodine oxidant and tetrabutylammonium triphenyldifluorosilicate (TBAT) (Scheme 1, eq 1).[28] Subsequently, the Sanford group disclosed a copper mediated fluorination of aryl trifluoroborates with potassium fluoride using copper(II) triflate (4 equiv) (Scheme 1, eq 2).[26] In the context of ^{18}F-

Scheme 1. Oxidative Fluorination of Aryl Metal Complexes with Fluoride



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radiofluorination, synthesis of the PET probe [^{18}F]5-fluorouracil was reported for human doses via the nickel-mediated methodology.[33] Trifluoroborate substrates for ^{18}F-radiofluorination are likely to undergo isotopic dilution via ^{18}F/^{19}F exchange between the starting material and [^{18}F]KF; therefore, alternative aryl boron reagents have recently been investigated for applications in radiofluorination.[34] While these methods demonstrate broad substrate scope and high yields, they require synthesis of complex starting materials or long reaction times and a large excess of transition metal. Thus, improvement upon the current methods for oxidative fluorination is warranted.

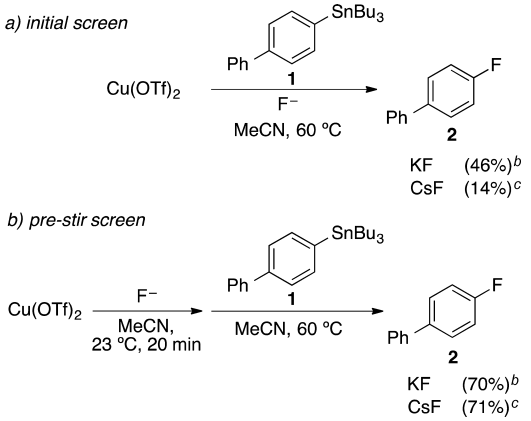
We sought to develop a mild, relatively quick fluorination reaction using nucleophilic fluoride and synthetically accessible starting materials. Reports confirming reductive elimination of high valent Cu(III) species[20−22,24,25] initiated our interest in utilizing this transition metal to enable aryl C−F bond formation with nucleophilic fluoride. Aryl stannanes have been reported from a wide scope of complex functionality[17] and can be accessed in one step from the halide or triflate. This synthetic accessibility in addition to stability and robustness attracted our attention to their use over other starting materials such as aryl iodonium precursors, which can be challenging to prepare and functionalize. Here, we report the oxidative fluorination of aryl stannanes, using nucleophilic fluoride and copper(II) triflate, under mild conditions (Scheme 1, eq 3).

Copper-based methods for arene C−F bond formation and mechanistic studies have seen a dramatic increase since Ribas' initial report of a Cu(III) isolated complex.[20,35] In particular, mechanistic studies from the Sanford group suggest that copper plays the dual role of transition metal mediator for aryl-F coupling as well as the oxidant to access the Cu(III) intermediate, requiring excess copper(II) triflate (4 equiv).[26] The proposed mechanism involves transmetalation of a Cu(II)(OTf)(F) complex and subsequent oxidation by another equivalent of copper(II) triflate to generate the highly reactive Cu(III) species. In agreement with this proposed dual role of copper, our initial experiments exploring the fluorination of aryl stannanes required upward of 4 equiv of copper to obtain moderate yields that dramatically dropped off when less than 2 equiv were used. However, we hypothesized that initial formation of the Cu(II)(OTf)(F) complex might be capable of facilitating the transmetalation more efficiently. We tested this hypothesis by pre-stirring the fluoride source and copper(II) triflate briefly to potentially form the Cu(II)(OTf)(F) complex followed by addition of the aryl stannane. Remarkably, this stepwise protocol resulted in a significant increase in yield of the aryl fluoride, 70% yield compared to the 46% obtained from single addition (Scheme 2). Of note, the effects of the pre-stir were more apparent with CsF, which enabled the reaction to proceed with only 2 equiv of copper(II) triflate. Various oxidants were screened in an attempt to replace the second equivalent of copper, but little to no detectable fluorination was observed (see Supporting Information (SI)).

We next evaluated the effects of solvent on the reaction. Consistent with Sanford's findings, our initial solvent screen revealed that the fluorination failed in all solvents other than acetonitrile (Table 1). A report from the Wang group demonstrating copper-mediated C−H fluorination of azacalix[1]arene[3]pyridines suggests that acetonitrile may play a key role in facilitating a facile reductive elimination via stabilization of the Cu(I) ion that is ejected during this step.[21] We hypothesized that MeCN-ligation may be required to stabilize the copper intermediates for the fluorination reaction to proceed. To test this hypothesis, we screened the reaction in various solvents spiked with acetonitrile (Table 1). As predicted, the reaction proceeds in all solvents screened except DMF, with as little as 10% acetonitrile in the solvent mixture. Noncoordinating solvents such as dichloromethane gave higher yields whereas coordinating solvents such as DMF gave no product, presumably due to interference with MeCN-ligation to the copper center. Other nitriles such as propionitrile and isobutyronitrile were also able to facilitate fluorination albeit in lower yields (see SI). Attempts to isolate an acetonitrile-coordinated copper fluoride intermediate were unsuccessful.

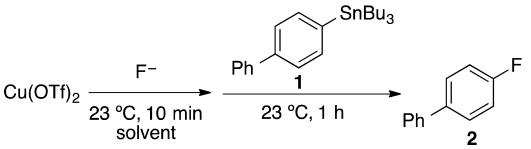
In our evaluation of fluoride sources, TBAT gave the highest yields; therefore, optimized conditions using this reagent via the stepwise protocol were applied to a series of aryl stannanes to examine the substrate scope for this reaction (Scheme 3). Both electron-deficient and electron-rich aryl stannanes underwent oxidative fluorination in good to excellent yields. This reaction demonstrates broad compatibility, as fluorination can proceed in the presence of common functionality including esters, nitriles, aldehydes, ketones, ethers, sulfones, and alcohols.

Scheme 2. Effects of Pre-stir towards Oxidative Fluorination of Aryl Stannanes[a]



[a]Yields determined by ^{19}F NMR spectroscopy with 1-fluoro-3-nitrobenzene as an internal standard. [b]$Cu(OTf)_2$ (4 equiv), KF (4 equiv), 1 h. [c]$Cu(OTf)_2$ (2 equiv), CsF (2 equiv), 3 h.

Table 1. Dependence of Fluorination on MeCN[a]



entry	solvent	yield (%)	yield (%)[b]
1	MeCN	58	58
2	Et_2O	0	33
3	THF	0	28
4	DCM	0	53
5	toluene	0	18
6	DMF	0	0
7	EtOAc	0	42
8	1,4-dioxane[d]	0	47[c]
9	toluene[d]	0	47[c]

[a]Conditions: $Cu(OTf)_2$ (2 equiv) and KF (2 equiv), solvent (300 μL). Yields were determined by ^{19}F NMR spectroscopy with 1-fluoro-3-nitrobenzene as an internal standard added after the reaction. [b]30 μL of MeCN added. [c]200 μL of MeCN added. [d]200 μL of solvent used.

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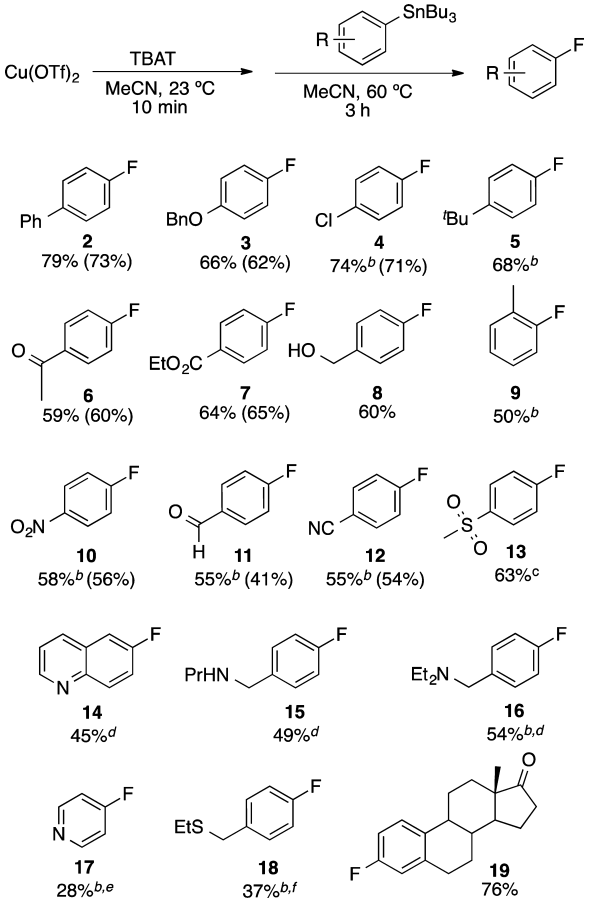
Scheme 3. Oxidative Fluorination of Aryl Stannanes with $Cu(OTf)_2$ and TBAT[a]



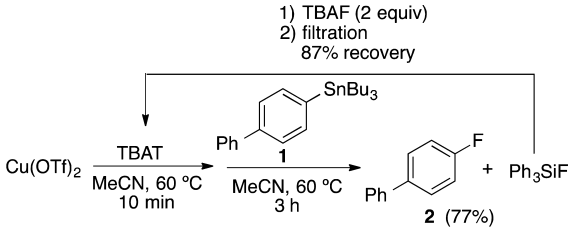
[a]Reaction conditions: $Cu(OTf)_2$ (2 equiv), TBAT (2 equiv), MeCN (0.083 M), 23 °C, 3 h. Copper salt and TBAT were pre-stirred in MeCN for 10 min followed by addition of the stannane. Unless otherwise noted, isolated yields are reported. Yields using CsF (2 equiv) as a fluoride source, determined by ^{19}F NMR, are reported in parentheses. [b]Yields were determined by ^{19}F NMR spectroscopy with 1-fluoro-3-nitrobenzene as an internal standard added after the reaction. Pre-stir was conducted at 60 °C. [c]Stirred for 5 h. [d]$Cu(OTf)_2$ (4 equiv). [e]80 °C, 3 h. [f]$Cu(OTf)_2$ (3 equiv), TBAT (3 equiv).

Substrates containing pyridine derivatives or substituted amines were amenable to fluorination, albeit in modest yield. Notably, arenes bearing protic groups as well as nucleophilic thioethers participated in fluorination, which has been consistently challenging for fluorination methodologies using nucleophilic fluoride sources.

The use of less than 2 equiv of TBAT resulted in a decrease in yield. We hypothesized that the byproduct, fluorotriphenylsilane, could be utilized to regenerate excess reagent. With the addition of TBAF after completion of the reaction and subsequent filtration, TBAT could be regenerated in 87% yield, effectively recovering most of the excess reagent used in the transformation. The recovered TBAT was recycled and provided the aryl fluoride in comparable yield (77% vs 79%) (Scheme 4). Alternatively, CsF, which outperforms KF in the context of alkali metal fluoride sources, can be used in place of TBAT to give similar fluorination yields (Scheme 3).

In summary, we report a regiospecific oxidative fluorination of aryl stannanes with copper(II) triflate and nucleophilic fluoride. This transformation proceeds under mild conditions

Scheme 4. TBAT Regeneration



to afford fluoro arenes with broad functional group tolerance including protic and nucleophilic groups. Use of a stepwise protocol enables a lower copper loading than previously reported for aryl trifluoroborates, and recovery of nearly 1 equiv of TBAT allows for recycling of the fluoride source. Our studies support the previously suggested mechanism in which copper acts as both an oxidant and a mediator of carbon−fluorine bond formation. Presumably, initial formation of a copper(II) fluoride complex via a stepwise protocol facilitates transmetalation to efficiently afford aryl fluorides. We propose that acetonitrile plays a key role in stabilization of the copper center, possibly to promote rapid transmetalation and to support reductive elimination of the arylcopper(III) intermediate. Investigations of this methodology for applications in ^{18}F-radiochemistry are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02125.

Experimental procedures, optimization screens, compound characterization, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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