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Communication

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NHC-Copper Mediated Ligand-Directed Radiofluorination of Aryl Halides

Liam S. Sharninghausen,[†] Allen F. Brooks,[‡] Wade Winton,[‡] Katarina J. Makaravage,[†] Peter J. H. Scott*[‡] and Melanie S. Sanford*[†]

[†] Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States

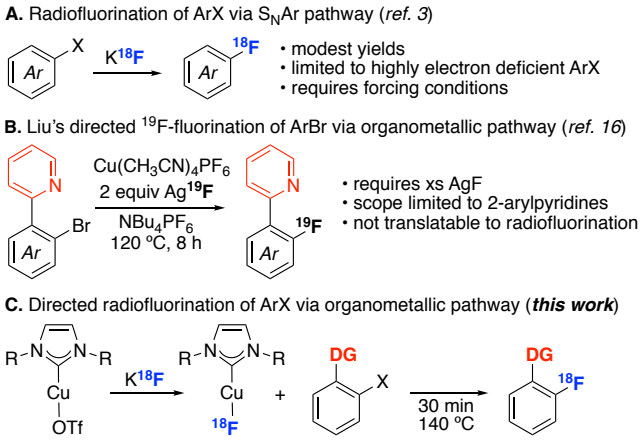
[‡] Department of Radiology, University of Michigan, 1301 Catherine, Ann Arbor, Michigan 48109, United States

Supporting Information Placeholder

ABSTRACT: [^{18}F]-labeled aryl fluorides are widely used as radiotracers for positron emission tomography (PET) imaging. Aryl halides (ArX) are particularly attractive precursors to these radiotracers, as they are readily available, inexpensive, and stable. However, to date, the direct preparation of [^{18}F]-aryl fluorides from aryl halides remains limited to S_NAr reactions between highly activated ArX substrates and K^{18}F. This report describes an aryl halide radiofluorination reaction in which the C(sp^2)–^{18}F bond is formed via a copper-mediated pathway. Copper *N*-heterocyclic carbene complexes serve as mediators for this transformation, using aryl halide substrates with directing groups at the *ortho* position. This reaction is applied to the radiofluorination of electronically diverse aryl halide derivatives, including the bioactive molecules vismodegib and PH-089.

Late-stage methods for constructing ^{18}F–(hetero)aryl bonds are highly valued for the synthesis of positron emission tomography (PET) radiotracers.[1,2] Historically, ^{18}F-labeled aromatic substrates have most commonly been prepared via S_NAr reactions between electron deficient aryl halide precursors and K^{18}F (Scheme 1A).[3,4] Aryl halides are particularly attractive radiofluorination precursors because they are abundant, stable, and synthetically accessible. However, the substrate scope of S_NAr (radio)fluorination reactions remains narrow, as resonance electron withdrawing substituents on the aromatic ring are required to stabilize Meisenheimer-type intermediates.[1,5] Furthermore, even with such highly activated substrates, S_NAr pathways often require long reaction times and forcing conditions, which renders them ill-suited for many late-stage radiofluorination applications.[6,7] As such, a key objective for the field is to develop complementary methods for the radiofluorination of (hetero)aryl–halides and pseudohalides.[8,9]

Scheme 1. Strategies for direct fluorination of aryl halides.

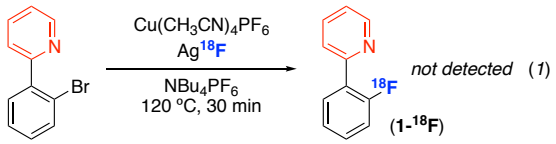


Our approach to this challenge has focused on developing Cu-mediated methods for C(sp^2)–^{18}F coupling reactions.[1,2b] Recent studies have shown that Cu salts such as Cu(OTf)$_2$ and Cu(CH$_3$CN)$_4$PF$_6$ mediate the nucleophilic radiofluorination of aryl stannane,[10] aryl boron,[11] diaryliodonium,[12] and aryl C–H substrates[13] with K^{18}F. In these systems the key C(sp^2)–^{18}F bond is formed via reductive elimination from an organometallic Cu(aryl)(^{18}F-fluoride) intermediate.[11f,14] This organometallic pathway is mechanistically distinct from an S_NAr reaction. As such, it enables the radiofluorination of a wide scope of electronically diverse aryl groups.

Despite this progress, analogous Cu mediators have proven ineffective at engaging aryl halide substrates in radiofluorination reactions. Two reports have documented the Cu-promoted nucleophilic ^{19}F-fluorination

of aryl halides (e.g., the work of Liu in Scheme 1B). However, both require superstoichiometric AgF as the fluoride source,[15,16] and neither has proven translatable to radiolabeling with $^{18}F^-$ (*vide infra*). This report describes the use of *N*-heterocyclic carbene (NHC) Cu complexes as mediators for ligand-directed aryl halide radiofluorination (Scheme 1C). The discovery of this transformation in the context of ^{19}F-fluorination and its subsequent translation to radiofluorination are described in detail.

Our initial studies attempted to translate Liu's ^{19}F-fluorination of 2-(2-bromophenyl)pyridine (Scheme 1B) to a radiolabeling protocol. However, as shown in eq. 1, under the standard conditions (with $Cu^I(CH_3CN)_4PF_6$, $Ag^{18}F$, and NBu_4PF_6 in CH_3CN at 120 °C), no trace of product **1-^{18}F** was detected by radio-TLC or radio-HPLC after 0.5 h. Furthermore, no improvement was observed upon variation of the ^{18}F source, solvent, additives, or temperature (Table S7). We note that, in contrast to the ^{19}F-fluorination, the radiofluorination reaction requires the use of $Ag^{18}F$ as the limiting reagent at sub-micromolar concentrations. We hypothesize that this renders $Cu^I(CH_3CN)_4PF_6$-mediated radiofluorination prohibitively slow relative to the decay of the radionuclide ($t_{1/2}$ ~110 min).

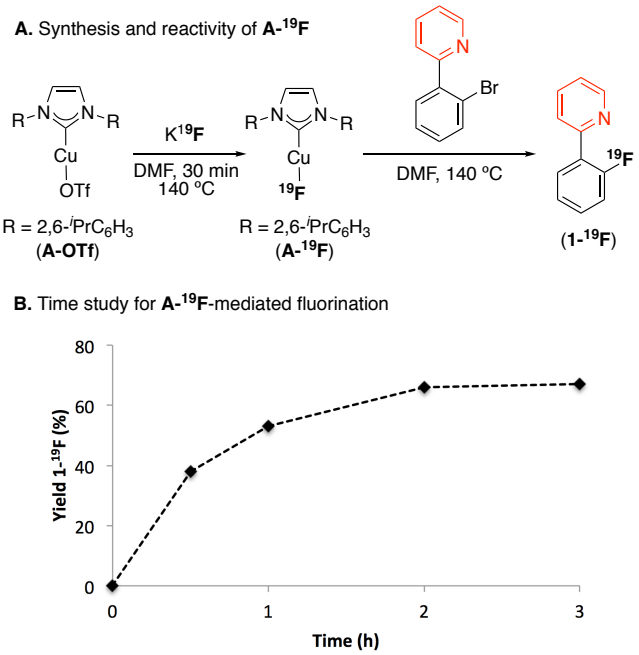


Literature reports suggest that aryl-bromide bond activation (via oxidative addition at Cu^I) is likely the slow step in this transformation.[16,17] We reasoned that the introduction of a strongly electron donating NHC ligand at the Cu^I center would accelerate this key step.[18,19] Furthermore, since $(NHC)Cu^I(F)$ complexes can be generated directly from KF,[20] this approach should eliminate the requirement for excess AgF. Finally, sterically bulky NHC ligands are known to stabilize Cu^I–fluoride complexes to dimerization or disproportionation,[19,21] which are likely competing decomposition pathways for the Cu mediator.[22]

To test this hypothesis, we initially examined the reactivity of a series of $(NHC)Cu^I(^{19}F)$ complexes with 2-(2-bromophenyl)pyridine (Scheme 2A). As summarized in Table S3, the yield of fluorinated product **1-^{19}F** varied from 3–65% as a function of the structure of the NHC ligand,[19,23] with 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidine (IPr) affording the optimal result. Notably, $(IPr)Cu^I(^{19}F)$ (**A-^{19}F**) is available in nearly quantitative yield from the reaction of $(IPr)Cu^I(OTf)$ (**A-OTf**) with $K^{19}F$ (Scheme 2A),[20] thus precluding the requirement for Ag salts in this transformation. Importantly, control studies revealed that other group 11 metal salts including $Cu^I(CH_3CN)_4PF_6$/KF, CuF_2,[24] or AgF afforded ≤3% of **1-^{19}F** under otherwise identical conditions (Table S4). Furthermore, no reaction was observed between the aryl bromide substrate and $K^{19}F$ under these conditions in the absence of copper.

A time study with **A-^{19}F** shows that the fluorination reaction is complete within 2 h at 140 °C and affords 40% yield after just 30 min (Scheme 2B). This suggests the feasibility of achieving radiofluorination with this system. Finally, a preliminary survey of substrates revealed that **A-^{19}F**-mediated fluorination has a significantly enhanced scope versus that of Liu's $Cu^I(CH_3CN)_4PF_6/Ag^{19}F$ system (Scheme 1B). For instance, the sterically hindered pyridine substrate 2-(2-(bromo)phenyl)-6-methylpyridine was unreactive under Liu's conditions, but affords **2-^{19}F** in 34% yield with **A-^{19}F** as the Cu mediator (Scheme 2C). Similarly, the oxazoline and imine substrates were unreactive under Liu's conditions, but afford 30% and 37% yield of **3-^{19}F** and **4-^{19}F**, respectively, using **A-^{19}F**.[25]

Scheme 2. NHC-Cu-mediated ^{19}F-fluorination of aryl bromides

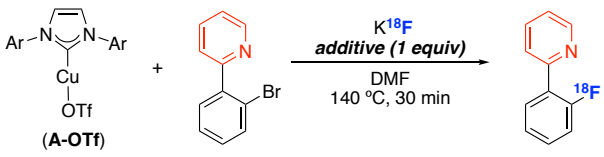


(A) Conditions: **A-OTf** (0.006 mmol, 1 equiv), KF (1.5 equiv), DMF (0.01 M), 140 °C for 30 min, then aryl bromide (0.006 mmol), 140 °C for 21 h. (B) Conditions: **A-^{19}F** (0.01 mmol, 1 equiv), aryl bromide (1 equiv), DMF

(0.015 M), 140 °C for 21 h. (C) Conditions: **A-^{19}F** (0.006 mmol, 1 equiv), aryl bromide (1 equiv), DMF (0.01 M), 140 °C for 21 h. Yields determined by ^{19}F NMR spectroscopic analysis of crude reaction mixtures.

We next focused on translating these preliminary results to radiofluorination. The reaction of (IPr)Cu^{I}(OTf) (**A-OTf**) with 2-(2-bromophenyl)pyridine and K^{18}F for 30 min at 140 °C in DMF afforded **1-^{18}F** in 10% radiochemical conversion (RCC) as determined by radio-TLC and radio-HPLC (Table 1, entry 1).[26,27] The reaction was optimized by exploring additives that have been shown to enhance yields in other Cu-mediated C(sp^2)–^{18}F coupling reactions (e.g., phase transfer reagents, nitrogen heterocycles, Table 1, entries 2–5).[1,11a,13,28] Of the surveyed additives, 1 equiv of 4-dimethylaminopyridine (DMAP) relative to the aryl bromide precursor proved optimal, affording **1-^{18}F** in 65% RCC.

Table 1. Cu-mediated radiofluorination of aryl halides.



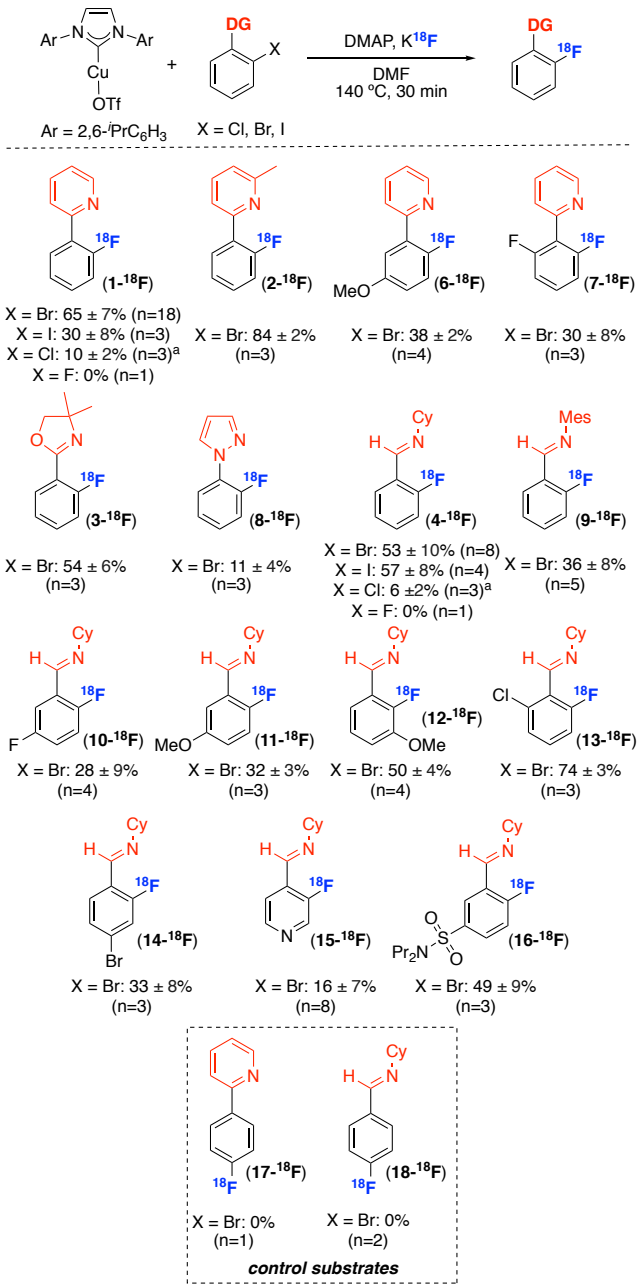
entry	Additive	RCC (%)
1	none	10
2	Kryptofix	26
3	pyridine	23
4	DBU	30
5	DMAP	65

Conditions: aryl bromide (0.005 mmol, 1 equiv), **A-OTf** (1 equiv), additive (1 equiv), K^{18}F, DMF (0.015 M), N_2 atmosphere, 140 °C, 30 min.[27] RCC determined by radio-TLC (n ≥ 2).

With these optimized conditions in hand, we next explored the scope of the **A-OTf**-mediated radiofluorination of aryl halides. As shown in Figure 1, the chloro-, bromo-, and iodo-2-phenylpyridine precursors all reacted to afford **1-^{18}F** in RCCs ranging from 10–65%. In contrast, no ^{19}F/^{18}F exchange was detected with **1-^{19}F** under these conditions. It is currently unclear why **1-I** affords lower yield than **1-Br**; however, this observation is in line with Liu's results for the Cu-catalyzed [^{19}F]-fluorination of halophenylpyridines.[16] Substitution on either the pyridine or aryl ring was tolerated to afford products such as **2-^{18}F**, **6-^{18}F**, and **7-^{18}F**. Other nitrogen-donors, including oxazoline, pyrazole, cyclohexyl imine, and mesityl imine, served as effective directing groups, affording **3-^{18}F**, **8-^{18}F**, **4-^{18}F**, and **9-^{18}F**, respectively. The scope of cyclohexyl imine derivatives was most thoroughly explored, as this directing group is straightforward to install and remove starting from readily available benzyaldehyde derivatives. Various substitution patterns on the (hetero)arene ring were well tolerated, affording compounds **10**–**16-^{18}F** in RCCs ranging from 16–74%. An intramolecular competition reaction between an *ortho*-chloride and bromide resulted in selective radiofluorination of the bromide to form **13-^{18}F**. This selectivity is consistent with that expected for a metal-mediated activation of a C(sp^2)–X bond.[29]

Importantly, a variety of control reactions were conducted in these systems. First, the 4-substituted aryl bromides in the pyridine and cyclohexyl imine series were subjected to the reaction conditions. These are electronically similar, but do not benefit from the directing effect. As shown in Figure 1, these substrates did not afford detectable **17-^{18}F** or **18-^{18}F** under the optimized conditions.[30] In addition, all of these reactions were conducted in the absence of Cu to test for background S_NAr reactivity. As shown in Table S12, ≤1% of compounds **1**–**16-^{18}F** were detected under these conditions. Finally, substituting simple Cu^{I} or Cu^{II} salts for (IPr)Cu^{I}(OTf) afforded yields of ≤5% for representative substrates (Table S11), underscoring the central role of the NHC ligand in these transformations.

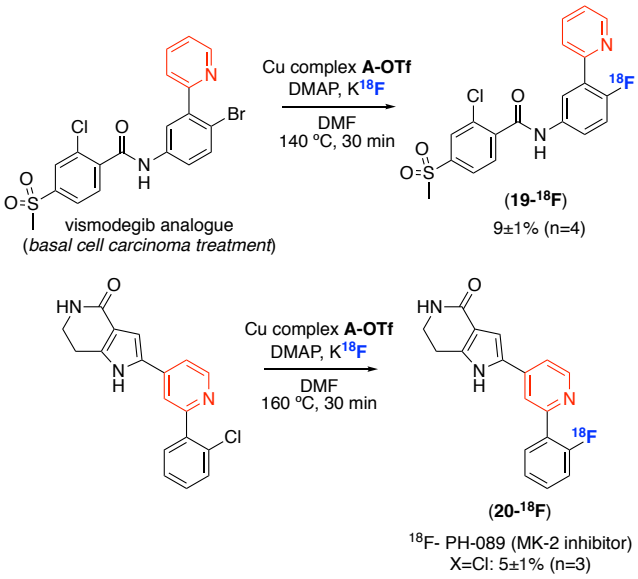
Figure 1. Substrate scope of Cu-mediated radiofluorination of aryl halides.



Conditions: aryl halide (0.005 mmol, 1 equiv), **A-OTf** (1 equiv), DMAP (1 equiv), $K^{18}F$, DMF (0.015 M), N_2 atmosphere, 140 °C for 30 min.[27] RCC determined by radio-TLC (n ≥ 3). [a]Reaction conducted at 160 °C.

^{18}F-analogues of several bioactive molecules could also be accessed using this approach. In a first example, the bromide analogue of vismodegib (**19-Br**), a basal cell carcinoma treatment,[31] underwent radiofluorination to afford **19-^{18}F** (Scheme 3). In a second example, ^{18}F-labeled PH-089 (**20-^{18}F** in Scheme 3), an MK-2 inhibitor,[32] was synthesized in 5% RCC from the chloride precursor.

Scheme 3. Radiofluorination of bioactive molecules.



A final set of studies focused on automating the radiosynthesis of **1-^{18}F** using a TRACERLab FX_{FN} synthesis module. Initial automated studies using 241.1 mCi (8.93 x 10^9 Bq) of $K^{18}F$ gave 57 ± 8 % radiochemical yield (RCY; n = 2), demonstrating the compatibility of the method with automation. Further investigations coupled automated synthesis with semi-preparative HPLC purification to afford **1-^{18}F** in 14.3 ± 3.2% RCY (decay-corrected; 119.9 mCi ± 28; n = 2) with good molar activity (1614 ± 353 Ci/mmol; n = 2) and radiochemical purity. While unoptimized, this result demonstrates the potential of this method for PET applications.

In conclusion, we have developed a Cu-mediated protocol for the ^{19}F- and ^{18}F-fluorination of diverse aryl halide substrates. Strategic design of the Cu mediator was necessary to achieve the reaction rates/yields required for efficient radiofluorination, and an NHC-ligated Cu complex ultimately proved optimal in this system. A wide scope of nitrogen-containing directing groups and substituted aryl halide derivatives underwent ^{18}F-fluorination, and the reaction proved effective for the synthesis of biologically relevant molecules such as **19-^{18}F** and **20-^{18}F**. More broadly, this work demonstrates that NHC-type ligands enable new C(sp^2)–F coupling reactions at Cu. As such, this work opens up opportunities for designing next-generation Cu mediators for the radiofluorination of currently inert substrates (e.g., aryl halides that lack a directing group).

ASSOCIATED CONTENT. Supporting Information. A listing of the contents of each file supplied as Supporting Information should be included.

AUTHOR INFORMATION

Corresponding Author

*Peter J. H. Scott. E-mail: pjhscott@umich.edu.
*Melanie S. Sanford. e-mail: mssanfor@umich.edu.

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[24] The following patent reported the stoichiometric fluorination of aryl halides with CuF_2 at 180 °C. However, minimal details are provided. Grushin, V. V. (DuPont & Co., USA) Process for Preparing Fluoroarenes from Haloarenes. U.S. Patent 7,202,388, May 10, 2007.

[25] In contrast, aryl halides without directing groups (e.g., 4-bromobiphenyl) afforded no detectable fluorinated products under these conditions (see SI, section 3.3 for complete details).

[26] Control reactions (in the absence of Cu or using various other Cu precursors) result in ≤1% RCC under analogous conditions (Tables S11 and S12).

[27] Procedure for radiofluorination involves initial combination of aryl halide, **A-OTf**, DMAP and DMF in a N_2 glove box. The reaction mixture is removed from the glovebox and a DMF solution of $K^{18}F$ is added to the reaction vial through a septa cap prior to heating. See SI, section 5.3 for full details.

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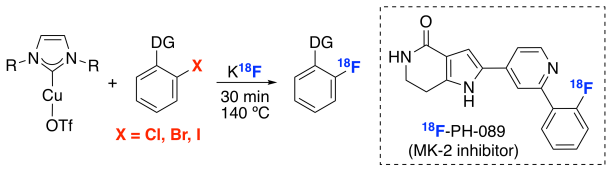
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18F
18F-PH-089
(MK-2 inhibitor)