

Cu-Mediated C–H ¹⁸F-Fluorination of Electron-Rich (Hetero)arenes

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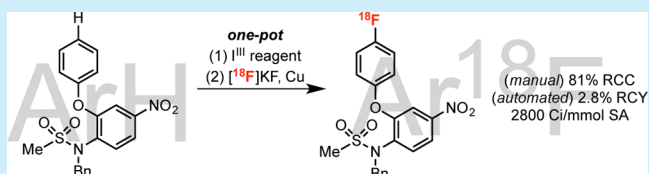
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Supporting Information

ABSTRACT: This communication describes a method for the nucleophilic radiofluorination of electron-rich arenes. The reaction involves the initial C(sp²)–H functionalization of an electron-rich arene with MesI(OH)OTs to form a (mesityl)-(aryl)iodonium salt. This salt is then used in situ in a Cu-mediated radiofluorination with [¹⁸F]KF. This approach leverages the stability and availability of electron-rich arene starting materials to enable mild late-stage radiofluorination of toluene, anisole, aniline, pyrrole, and thiophene derivatives. The radiofluorination has been automated to access a 41 mCi dose of an ¹⁸F-labeled nimesulide derivative in high (2800 ± 700 Ci/mmol) specific activity.



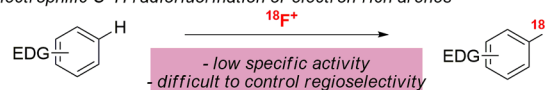
The development of methods for the nucleophilic radiofluorination of electron-rich (hetero)arene precursors represents a long-standing challenge for the radiochemistry community.^{1–3} Most existing routes to ¹⁸F-labeled electron-rich aromatics are limited by the requirement for prefunctionalization of the labeling site with, for example, a boron, tin, hypervalent iodine, or transition-metal substituent.^{3,4} These prefunctionalized precursors are often not commercially available and must be accessed via multistep synthesis and purification sequences.^{3a–c,e–k} Furthermore, a number of radiofluorination precursors (e.g., hypervalent iodine reagents and Ni/Pd complexes) have limited shelf lives, which precludes widespread clinical applications.⁵ Overall, methods for the direct nucleophilic radiofluorination of arene C–H bonds would help to address these challenges.⁶

Several methods have been reported for the *electrophilic* C–H radiofluorination of electron-rich arenes (Scheme 1A).^{1c,f} These involve the initial generation of an ¹⁸F⁺ source (e.g., [¹⁸F]F₂ or [¹⁸F]Selectfluor) and subsequent electrophilic aromatic substitution (S_EAr) between the ¹⁸F⁺ reagent and the arene substrate. This approach eliminates the need for prefunctionalization. However, the requirement for ¹⁸F⁺ reagents leads to three key limitations. First, ¹⁸F⁺ reagents afford radiofluorinated products with low specific activity due to the need to use carrier [¹⁹F]F₂ gas for their synthesis.⁷ Second, the production of ¹⁸F⁺ sources requires specialized facilities.⁸ Third, the high reactivity of electrophilic fluorinating reagents often results in poor site and chemoselectivity.⁹

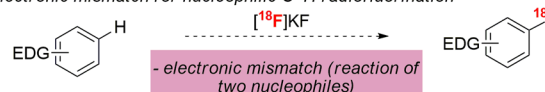
These limitations could be addressed through the development of a nucleophilic radiofluorination of (hetero)aryl C–H bonds (Scheme 1B), as this would enable the use of easily accessible bench-stable precursors in combination with high specific activity [¹⁸F]KF. The key challenge for this approach is

Scheme 1. Strategies for the C–H Radiofluorination of Electron-Rich Arenes

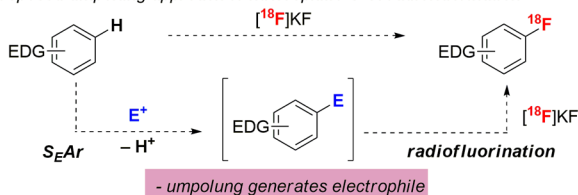
A. Electrophilic C–H radiofluorination of electron-rich arenes



B. Electronic mismatch for nucleophilic C–H radiofluorination



C. Proposed umpolung approach to nucleophilic C–H radiofluorination



the electronic mismatch between nucleophilic [¹⁸F]KF and the nucleophilic electron-rich arene substrate (Ar–H). We hypothesized that this could be overcome via an umpolung strategy that would invert the polarity of the arene substrate (Scheme 1C). Specifically, an initial S_EAr reaction with an electrophile (E⁺) would functionalize the C–H bond and generate an electrophilic coupling partner (Ar–E).¹⁰ Ar–E could then undergo in situ nucleophilic radiofluorination with [¹⁸F]KF. We demonstrate herein the realization of this approach using I^{III}-based electrophiles. This enables the

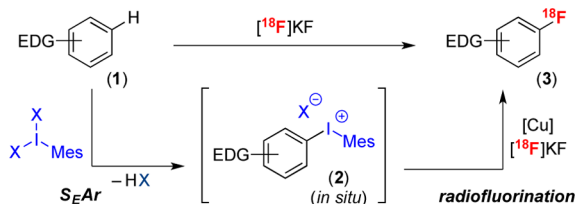
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selective radiofluorination of electron-rich aromatics, including toluene, anisole, aniline, pyrrole, and thiophene derivatives. Furthermore, it can be scaled to automated radiosynthesis modules and used to access high specific activity ^{18}F -labeled products.

The approach in Scheme 1C is predicated on the identification of an electrophile (E^+) that (i) undergoes site-selective $\text{S}_{\text{E}}\text{Ar}$ with diverse electron-rich (hetero)arenes and (ii) generates an intermediate ($\text{Ar}-\text{E}$) that can participate in a nucleophilic radiofluorination. Notably, it is not critical that $\text{Ar}-\text{E}$ be stable; indeed, a key advantage of this approach is that $\text{Ar}-\text{E}$ will be used in situ, thus precluding the need for isolation/storage of this intermediate. On the basis of these considerations, we selected I^{III} reagents as E^+ . As shown in Scheme 2, $\text{ArI}^{\text{III}}\text{X}_2$ salts are known to participate in

Scheme 2. Proposed Use of Hypervalent Iodine Reagents as E^+



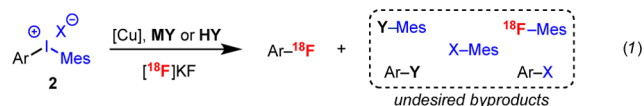
site-selective $\text{S}_{\text{E}}\text{Ar}$ reactions with electron-rich (hetero)arenes.^{11–13} Furthermore, these transformations yield diaryliodonium salts, which we have shown to undergo Cu-catalyzed radiofluorination with ^{18}F KF.^{3a,14} While electron-rich diaryliodonium salts are notoriously unstable,^{5a,15} this approach offers the advantage that they are generated in situ from stable and readily available C–H starting materials.

Our initial investigations focused on the reaction of anisole (1a) with $\text{MesI}(\text{OH})\text{OTs}$ (Table 1). These partners were selected because they are well-known to undergo $\text{S}_{\text{E}}\text{Ar}$ in the presence of Lewis or Brønsted acid activators¹⁶ (MY or HY, respectively, in eq 1) to form a single isomeric product, $[\text{4-MeOC}_6\text{H}_4\text{-I-Mes}]^+$ (2a). Furthermore, 2a is known to undergo Cu-catalyzed radiofluorination with ^{18}F KF.^{3a,13,14,17} There were two key considerations for our choice of arylidonium

Table 1. Optimization of the Radiofluorination of Anisole^a

entry	activator	base	RCC 3a ^b (%)
1	TsOH·H ₂ O		27 ± 4 (<i>n</i> = 4)
2	TsOH·H ₂ O	<i>i</i> Pr ₂ NEt (20 μmol)	61 ± 8 (<i>n</i> = 9)
3	TMSOTf		5 ± 2 (<i>n</i> = 5)
4	TMSOTf	<i>i</i> Pr ₂ NEt (10 μmol)	58 ± 0.4 (<i>n</i> = 3)
5	TMSOTf	<i>i</i> Pr ₂ NEt (20 μmol)	78 ± 4 (<i>n</i> = 3)
6 ^{c,d}	TMSOTf	<i>i</i> Pr ₂ NEt (20 μmol)	87 ± 4 (<i>n</i> = 13)

^aConditions: (1) 1a (10 μmol), $\text{MesI}(\text{OH})\text{OTs}$ (10 μmol), activator (10 μmol), CH_2Cl_2 (40 μL); (2) $(\text{MeCN})_4\text{CuOTf}$ (10 μmol), ^{18}F KF·18-crown-6· K_2CO_3 complex in DMF (100 μL, 80–1200 μCi), total volume 1.0 mL. ^bRCC was determined by radio-TLC (average of *n* runs). The identity of 3a was confirmed by HPLC. ^cQuinaldic acid (10 μmol) was included in step 2. ^d98:2 selectivity (3a/ ^{18}F fluoromesitylene) detected by radio-HPLC.



electrophile and activator for this one-pot radiofluorination. First, these reagents should not contain nucleophilic counterions (Y) (e.g., carboxylates), as these are susceptible to undesired coupling reactions with the diaryliodonium intermediate 2 (eq 1).¹⁸ Second, their byproducts should be compatible with the Cu-mediated radiofluorination step.

With these criteria in mind, we first examined the use of TsOH as the activator. The two-step procedure involved (1) stirring 1a, $\text{MesI}(\text{OH})\text{OTs}$, and TsOH (10 μmol) in CH_2Cl_2 for 18 h at 25 °C and then (2) adding the reaction mixture to a solution of $(\text{MeCN})_4\text{CuOTf}$ and ^{18}F KF·18-crown-6 in DMF and heating at 85 °C for 20 min. The reactions were assayed using radio-TLC and radio-HPLC, and these initial conditions afforded a 27% radiochemical conversion (RCC) to 4- ^{18}F fluoroanisole (3a) (Table 1, entry 1).^{3a} We hypothesized that the addition of a base in step 2 would quench the residual acid from the diaryliodonium formation step. This was expected to enhance the radiofluorination yield, as Cu-catalyzed nucleophilic fluorinations are known to be acid-sensitive.¹⁹ Indeed, a screen of bases revealed that *i*Pr₂NEt (20 μmol) increased the RCC to 61 ± 8% (*n* = 9, entry 2).^{20,21}

Trimethylsilyl trifluoromethanesulfonate (TMSOTf) also proved to be an effective activator for the $\text{S}_{\text{E}}\text{Ar}$ reaction. The use of this activator in step 1 coupled with *i*Pr₂NEt (20 μmol) in step 2 delivered 4- ^{18}F fluoroanisole (3a) in 78 ± 4% RCC (*n* = 3, entry 5). Finally, the evaluation of different additives revealed that the addition of quinaldic acid (10 μmol) to the Cu-mediated radiofluorination under otherwise identical conditions resulted in a RCC of 87 ± 4% (*n* = 13, entry 6).²² Notably, the RCC of this transformation of 1a to 3a (87%) is comparable to that reported using isolated $[\text{4-MeOC}_6\text{H}_4\text{-I-Mes}]^+$ as the substrate for Cu-catalyzed radiofluorination (79%).^{3a}

The site-selectivity of the reaction of anisole was determined by radio-HPLC analysis²³ via comparison to authentic standards of the three possible isomers (see the Supporting Information for complete details). The ^{18}F -fluorination proceeded to afford the *para*-isomer with >99:1 selectivity.^{12,13a–d} This high selectivity is fully consistent with that reported for $\text{S}_{\text{E}}\text{Ar}$ reactions between hypervalent iodine reagents and related electron-rich arene substrates.¹² Importantly, <2% of ^{18}F -fluoromesitylene was detected under any of the conditions examined.

We next evaluated the scope of this C–H radiofluorination (Figure 1).²⁴ A series of anisoles (3a–f), protected anilines (3g–i), and toluene (3j,k) derivatives reacted under the standard conditions to form ^{18}F -labeled arenes in >80% RCC. The transformation was tolerant of aryl halides (3c and 3o), esters and tertiary amides (3d, 3g, and 3m), sulfonamides (3h, 3o, and 3q), and nitro groups (3q) as well as substitution adjacent to the site of fluorination (3e). Protic functional groups (e.g., alcohols, amines, and amides) were not compatible and were thus protected prior to the reaction.²⁷ The radiofluorination of heterocycles, including thiophene, pyrrole, and uracil, required elevated temperature (105 °C) to afford 3l–n. Notably, the radiofluorination of these heterocycles proceeded with lower selectivity, and significant quantities of ^{18}F fluoromesitylene were observed in these systems. However, in all cases, this byproduct was readily separable by

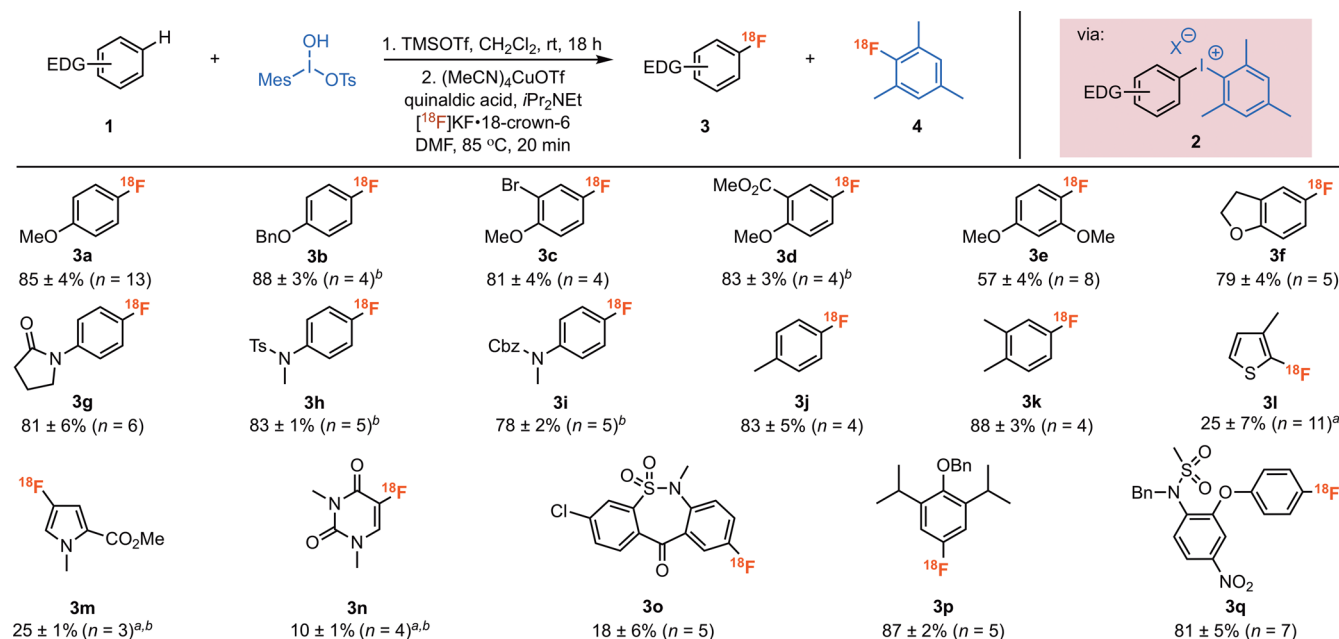


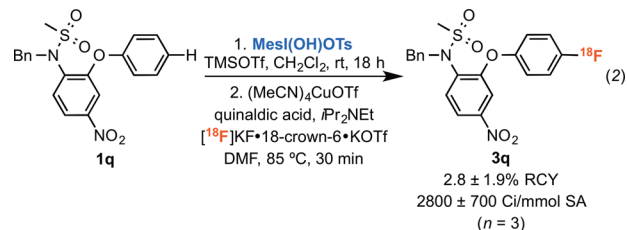
Figure 1. Cu-mediated C(sp²)-H radiofluorination of electron-rich arenes. Conditions: (1) **1** (10 μmol), MesI(OH)OTs (10 μmol), TMSOTf (10 μmol), CH₂Cl₂ (40 μL); (2) (MeCN)₄CuOTf (10 μmol), quinaldic acid (10 μmol), *i*Pr₂NEt (20 μmol), [¹⁸F]KF·18-crown-6·K₂CO₃ complex in DMF (100 μL, 80–1200 μCi), total volume 1.0 mL. Reported radiochemical conversions were measured by radio-TLC (average of *n* runs) and were corrected for presence of **4** (ratio of 3/4 determined by radio-HPLC). The identity of each product was confirmed by radio-HPLC. Key: (a) 105 °C; (b) TMSOTf (5 μmol).^{25,26}

HPLC.^{25,26} The formation of 2-[¹⁸F]fluoro-3-methylthiophene (**3l**) in 25% RCC is particularly noteworthy, as thiophenes are particularly challenging to radiofluorinate using other methods.^{1d–f,28} Indeed, thiophene is typically used as the inert ligand on diaryliodonium salts to direct radiofluorination to the other arene ligand.^{1d–f,29}

We next examined the late-stage C–H radiofluorination of fragments that appear in pharmaceuticals. In one example, the dibenzothiazepine fragment of tianeptine (Coaxil), underwent radiofluorination to yield **3o** in 18% RCC. Additionally, both *O*-Bn-protected propofol (an anesthetic and sedative) and *N*-Bn-protected nimesulide (a nonsteroidal anti-inflammatory) reacted under our standard conditions to yield ¹⁸F-analogues **3p** and **3q** in 87% and 81% RCC, respectively.

A final set of experiments focused on automation of this reaction on a TRACERLab FX_{FN} radiosynthesis module used for the preparation of clinical radiotracers.^{2b} Initial automated studies were conducted for anisole (**1a**) using ~1.5 Ci of [¹⁸F]fluoride ([¹⁸F]KF·18-crown-6·KOTf) and afforded 4-[¹⁸F]fluoroanisole (**3a**) in 56 ± 4% RCC and a specific activity of 2700 ± 1900 Ci/mmol (*n* = 4).^{20,30} We also automated the radiofluorination of *N*-Bn-protected nimesulide without any further optimization. Radiolabeling was conducted using ~1.5 Ci of [¹⁸F]fluoride, and the product was purified via semipreparative HPLC to yield a formulated 41 ± 31 mCi dose of **3q** in 2.8 ± 1.9% non-decay-corrected radiochemical yield (RCY) with 2800 ± 700 Ci/mmol specific activity (*n* = 3, eq 2). This proof-of-concept demonstration provides a foundation for the application of this method to the synthesis of other radiotracer targets.

In summary, this report describes a method for the nucleophilic radiofluorination of electron-rich arene C–H bonds that enables the late-stage C–H functionalization of (hetero)aromatic scaffolds. This approach eliminates the need to isolate/store prefunctionalized starting materials, instead leveraging the bench



stability and availability of electron-rich aromatic substrates. Current efforts are focused on the application of this C(sp²)-H to C–¹⁸F radiofluorination chemistry to clinically relevant targets.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01902.

Experimental and spectral data for all new compounds and all reactions (PDF)

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Notes

The authors declare no competing financial interest.

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- (20) For experimental details, see the [Supporting Information](#).
- (21) These conditions and others employing trifluoromethanesulfonic acid or trifluoroacetic anhydride for iodonium formation afforded low RCCs and/or did not prove to be general.
- (22) The RCC of isolated [4-MeOC₆H₄-I-Mes]⁺OTf⁻ (**2a**) was also improved to 85% with the addition of quinaldic acid (10 μmol) and iPr₂N⁺Et⁻ (10 μmol). At this time, the role of quinaldic acid in the radiofluorination is unknown.
- (23) The regioselectivity is set in the S_EAr reaction and was confirmed by ¹H NMR spectroscopic analysis of the iodonium salts generated under these conditions. See the [SI](#) for details.
- (24) For consistency, step 1 was allowed to run for 18 h. However, in many cases, the S_EAr reaction was complete after a shorter time.
- (25) In select examples, decreasing the amount of TMSOTf in the first step helped to eliminate minor ¹⁸F-labeled byproducts believed to originate from residual TMSOTf.
- (26) The RCCs of **3l–o** were lower due to formation of larger amounts of [¹⁸F]fluoromesitylene and other unidentified [¹⁸F] byproducts. See the [Supporting Information](#) for details.
- (27) A summary of unreactive or noncompatible arene substrates is available in the [Supporting Information](#).
- (28) Kilbourn, M. R. *Nucl. Med. Biol.* **1989**, *16*, 681.
- (29) In general, selectivity for **3** over **4** was greater than 95:5 in favor of **3**. The only exceptions were **3d**, **3l**, **3m**, **3n**, and **3o**. See the [Supporting Information](#) for details.
- (30) [¹⁸F]KF·18-crown-6·K₂CO₃ performed poorly as a [¹⁸F]fluoride source for the automated reactions. Improved reactivity was obtained using [¹⁸F]KF·18-crown-6·KOTf.