

Copper-Catalyzed [¹⁸F]Fluorination of (Mesityl)(aryl)iodonium Salts

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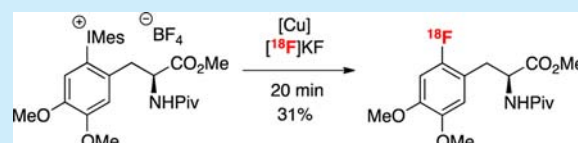
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S Supporting Information

ABSTRACT: A practical, rapid, and highly regioselective Cu-catalyzed radiofluorination of (mesityl)(aryl)iodonium salts is described. This protocol utilizes [¹⁸F]KF to access ¹⁸F-labeled electron-rich, -neutral, and -deficient aryl fluorides under a single set of mild conditions. This methodology is applied to the synthesis of protected versions of two important radiotracers: 4-[¹⁸F]-fluorophenylalanine and 6-[¹⁸F]fluoroDOPA.

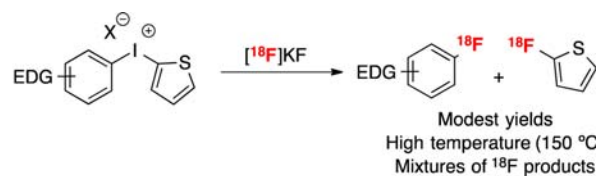


Positron emission tomography (PET) is a powerful and minimally invasive medical imaging technique that provides kinetic physiochemical information.¹ The most commonly used radioisotope for PET is ¹⁸F, which offers the advantages of high-resolution imaging, a relatively long lifetime ($t_{1/2} = 110$ min), and minimal perturbation of radioligand binding. Despite these advantages, the development of novel ¹⁸F radiotracers is currently impeded by a paucity of general and effective radiofluorination methods. There are currently few robust synthetic procedures for the incorporation of ¹⁸F into organic molecules with sufficient speed, selectivity, yield, radiochemical purity, and reproducibility to provide clinical imaging materials. Direct methods for the late stage nucleophilic [¹⁸F]fluorination of electron-rich aromatic substrates remains an especially long-standing challenge.² A target of particular interest in this regard is 6-[¹⁸F]fluoroDOPA.^{3,4}

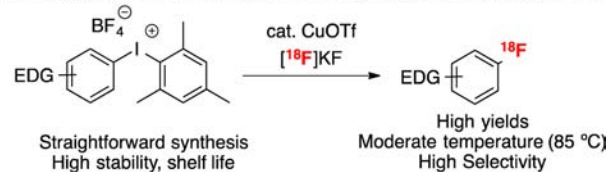
The classical radiofluorination methods for electron-rich aryl rings utilize electrophilic fluorinating reagents derived from [¹⁸F]F₂.² However, [¹⁸F]F₂ production typically requires ¹⁹F₂ as a carrier gas, which leads to low specific activity (SA) radiotracers (typically <1.0 Ci/mmol) and requires specialized facilities. The development of [¹⁸F]KF production from [¹⁸O]water has provided the means to synthesize high SA radiotracers (>1000 Ci/mmol) through nucleophilic substitution (typically S_N2 or S_NAr).¹ However, the use of [¹⁸F]KF is generally limited to the formation of primary sp³-C–F bonds or sp²-C–F bonds on electron-deficient (hetero)aromatics.

Two main strategies have been used to address these limitations. The first involves radiofluorination of powerful electrophiles such as diaryliodonium salts.⁵ Diaryliodonium salts bearing the 2-thienyl group have been shown to react with [¹⁸F]KF at elevated temperatures (often ≥150 °C) to afford [¹⁸F]fluororarenes (Scheme 1a).⁶ In these systems, the 2-thienyl group directs radiofluorination to the other aromatic ligand on iodine with moderate to good selectivity.⁶ However, the

Scheme 1. Radiofluorination of Diaryliodonium Salts



(b) Cu-Catalyzed Radiofluorination of Mesityl Iodonium Salts (this work)



[(thienyl)(aryl)I⁺] starting materials are often challenging to prepare, suffer from low stability, and have a limited shelf life.⁷ Furthermore, with electron-neutral or -rich substrates, these transformations frequently require high temperatures, exhibit modest regioselectivity, demonstrate limited functional group tolerance, and provide low radiochemical yields.⁶ With the exception of recent work by DiMaggio,⁸ it has proven challenging to access many important radiotracers using this method.

A second strategy applies transition metal catalysts and/or reagents to achieve radiofluorination with [¹⁸F]KF.^{9,10} Transition-metal catalysis offers opportunities for accelerating radiofluorination reaction rates as well as enhancing selectivity and reactivity. For instance, Hooker and Ritter have made progress in the radiofluorination of arenes using Pd^{9a,b} and Ni^{9c} complexes.

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We sought to develop a general, mild, high-yielding, and user-friendly procedure for the radiofluorination of diverse aromatic substrates by merging transition-metal catalysis with the fluorination of diaryliodonium reagents (Scheme 1b). We have recently demonstrated that Cu salts catalyze the fluorination of stable and synthetically accessible mesityl-substituted diaryliodonium salts.¹¹ Here, the mesityl group directs oxidative addition and fluorination to the smaller aryl group on iodine, regardless of its electronic properties. In this paper, we demonstrate that this Cu-catalyzed fluorination method can be translated to a high specific activity radiofluorination of electron-rich, -neutral, and -deficient arene substrates. Furthermore, this protocol enables the radiofluorination of protected versions of 4-^[18F]fluorophenylalanine, and 6-^[18F]fluoroDOPA.

Our initial studies focused on the Cu-catalyzed radiofluorination of [4-OMePh-I-Mes]BF₄ (**1**). This substrate was selected because the radiosynthesis of electron-rich fluoroarenes such as ^[18F]fluoroanisole remains a challenge.¹² Gratifyingly, the use of Cu(OTf)₂ as the catalyst, DMF as the solvent, and ^[18F]KF-18-crown-6 as the fluoride source resulted in 36% radiochemical conversion (RCC) to 4-^[18F]fluoroanisole in 20 min (Table 1, entry 1). High selectivity was observed for 4-

(Tables S1–S4, Supporting Information). Optimal conditions were as follows: 6 μmol loading of **1**, 1:1 molar ratio of CuOTf to **1**, 85 °C, 20 min, in a total volume of 750 μL of DMF. Under these conditions, **1** was obtained in 79 ± 8% radiochemical conversion (*n* = 38, entry 6). Notably, >50% RCC was obtained under most of the conditions examined, indicating that this transformation is remarkably insensitive to the reaction conditions (a particularly attractive attribute when translating this chemistry to use by nonexperts).

One concern in the radiofluorination of **1** is the possibility for isotopic dilution via ^{18F}/^{19F} exchange between the BF₄ counterion and the [^{18F}]KF.¹³ In principle, this issue can be addressed by changing the counterion;¹⁴ however, an evaluation of different [4-OMePh-I-Mes]X salts (X = TsO, PF₆, TfO) showed that the best conversion was obtained with BF₄ (Table 1, entries 6–9). To test whether isotopic dilution from the BF₄ counterion is, indeed, a problem, we compared the specific activity (SA) of the 4-^[18F]fluoroanisole product obtained from [4-OMePh-I-Mes]BF₄ to that from [4-OMePh-I-Mes]OTs. Automated syntheses were conducted in a standard module with 1500 mCi initial activity of ^{18F}. Under automated conditions, [4-OMePh-I-Mes]BF₄ afforded a RCC of 40 ± 10% and a SA of 1800 ± 800 Ci/mmol (*n* = 3), while [4-OMePh-I-Mes]OTs afforded 10 ± 2% RCC with a comparable SA of 3000 ± 1000 Ci/mmol (*n* = 3). These results indicate that isotopic dilution is not a significant problem under these reaction conditions.¹⁵

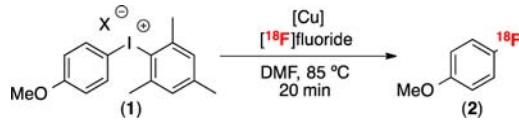
Importantly for the user, this transformation is performed under ambient conditions without the requirement for a drybox or extensive drying of reagents and glassware. The reaction mixture is homogeneous, and the remainder of ^{18F} appears to be sequestered as inorganic fluoride salts. The copper catalyst is commercially available and is stable in solution over at least 4 h; for instance, a 77% RCC was obtained using a solution of (CH₃CN)₄CuOTf in DMF that was allowed to stand for 4 h under ambient conditions prior to use. Finally, **1** and the other (mesityl)(aryl)iodonium salts described herein are colorless, free-flowing solids that are shelf stable for months under ambient conditions when protected from intense light. Thus, this method is highly practical and amenable to routine automated synthesis.

These radiofluorination conditions were next applied to a diverse series of (mesityl)(aryl)iodonium tetrafluoroborate salts (Table 2). In all cases, modest to excellent radiochemical conversion was obtained *without further optimization of the reaction conditions*. All of the reactions in Table 2 were highly selective for a single ^{18F}-containing product, with ≤2% fluoromesitylene detected. Furthermore, for all of the substrates examined, ≤2% of the corresponding fluoroarene product was observed in the absence of Cu catalyst, confirming that Cu is vital for accelerating the reaction rate as well as controlling selectivity.

This protocol can be used for the radiofluorination of arenes containing multiple electron-donating methoxy substituents (Table 2, entries 2 and 3). Remarkably, even the highly electron-rich product 1-^[18F]fluoro-3,4,5-trimethoxybenzene (**4**) was obtained in 14% RCC using this nucleophilic fluorination protocol. Steric factors do impact the radiochemical conversion; for instance, while 4-^[18F]fluoroanisole was obtained in 79% RCC, the corresponding 2-^[18F]fluoroanisole was formed in 30% RCC.

Electron-neutral and electron-deficient aryl rings also underwent radiofluorination in high yield and selectivity using this method (entries 6–10). A variety of functional groups, including amide NH bonds (**6**), ketones (**8**), aryl iodides (**9**), esters (**10**),

Table 1. Optimization of Radiofluorination of **1 To Form 4-^[18F]Fluoroanisole**

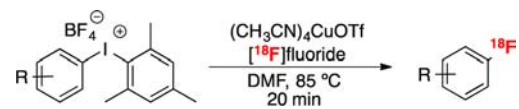












entry	[Cu]	X	RCC 2 ^a (%)
1 ^b	Cu(OTf) ₂	BF ₄	36 ± 19 (<i>n</i> = 15)
2 ^b	CuCO ₃ ·Cu(OH) ₂	BF ₄	10 ± 6 (<i>n</i> = 3)
3 ^b	CuOTf·toluene	BF ₄	43 ± 15 (<i>n</i> = 3)
4 ^b	(CH ₃ CN) ₄ CuOTf	BF ₄	70 ± 11 (<i>n</i> = 11)
5 ^b	none	BF ₄	<1
6 ^c	(CH ₃ CN) ₄ CuOTf	BF ₄	79 ± 8 (<i>n</i> = 38)
7 ^c	(CH ₃ CN) ₄ CuOTf	PF ₆	53 ± 7 (<i>n</i> = 3)
8 ^c	(CH ₃ CN) ₄ CuOTf	OTs	45 ± 26 (<i>n</i> = 3)
9 ^c	(CH ₃ CN) ₄ CuOTf	OTf	15 ± 12 (<i>n</i> = 3)

^aRadiochemical conversion was determined by radio-TLC (average of *n* runs). The identity of 4-^[18F]fluoroanisole was confirmed by HPLC.

^bConditions: [4-OMePh-I-Mes]BF₄ (6 μmol), [Cu] (3 μmol), [^{18F}]KF-18-crown-6·K₂CO₃ complex in DMF (250 μL, 300–700 μCi), total volume 750 μL. ^cConditions: [4-OMePh-I-Mes]X (6 μmol), [Cu] (6 μmol). [^{18F}]KF-18-crown-6·K₂CO₃ complex in DMF (250 μL, 300–700 μCi), total volume 750 μL.

^[18F]fluoroanisole, and <1% of ^[18F]fluoromesitylene was detected by radio-TLC or radio-HPLC. While the radiochemical conversion was reasonable, the reaction showed modest reproducibility (±19% yield over *n* = 15). To address this issue, we sought an alternate Cu precursor to catalyze the radiofluorination. A variety of Cu^I and Cu^{II} complexes were examined (for examples, see entries 2–4). Commercially available and bench stable (CH₃CN)₄CuOTf proved optimal, providing high radiochemical conversion and improved reproducibility (70 ± 11% RCC over *n* = 11, entry 4). A control experiment in the absence of Cu provided no detectable 4-^[18F]fluoroanisole and only 6% RCC to ^[18F]fluoromesitylene (entry 5). A number of other variables were examined to optimize the radiofluorination including the ratio of [Cu] to **1**, concentration of **1**, temperature, counterion, and reaction time

Table 2. [¹⁸F]Fluorination of (Mesityl)(aryl)iodonium Salts^b


entry	product	RCC ^a
1	 (2)	79 ± 8% (n = 38)
2	 (3)	51 ± 6% (n = 5)
3	 (4)	14 ± 1% (n = 5)
4	 (5)	30 ± 8% (n = 6)
5	 (6)	66 ± 2% (n = 3)
6	 (7)	51 ± 8% (n = 3)
7	 (8)	67 ± 2% (n = 3)
8	 (9)	35 ± 8% (n = 3)
9	 (10)	58 ± 4% (n = 3)
10	 (11)	35 ± 1% (n = 3)

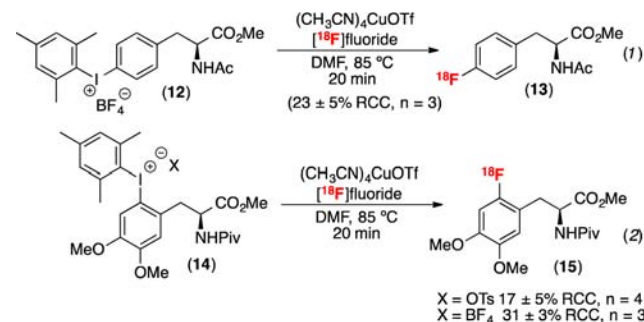
^aRadiochemical conversion were determined by radio-TLC (average of n runs). The identity of each product was confirmed by HPLC.

^bReaction conditions: precursor (6 μmol), Cu catalyst (6 μmol), [¹⁸F]KF·18-crown-6·K₂CO₃ complex in DMF (250 μL, 300–700 μCi). Total reaction volume 750 μL.

and aldehydes (11), were well tolerated. This enabled the preparation of several known PET prosthetic groups, including 4-[¹⁸F]fluoroiodobenzene (entry 8),¹⁶ methyl [¹⁸F]-fluorobenzoate (entry 9),¹⁷ and [¹⁸F]fluorobenzaldehyde (entry 10).¹⁸

Having demonstrated that a diverse range of [¹⁸F]arylfluorides can be accessed via this methodology, the radiofluorination of several molecules of clinical relevance was investigated. Two (mesityl)(aryl)iodonium salts derived from aromatic amino acids (12 and 14) were prepared and subjected to the radiofluorination protocol (Scheme 2). Without any substrate-specific optimization, the radiolabeled products 13 and 15 were obtained in acceptable yields. Importantly, 13 is a protected version of 4-[¹⁸F]fluorophenylalanine (F-PHE), a radiotracer originally developed in the 1970s as a probe of pancreatic and cerebral protein synthesis.¹⁹ However, clinical applications of F-PHE to tumor imaging have not been realized partially due to the lack of an acceptable radio-synthesis. The original doses of F-PHE were prepared in low specific activity (<0.01 Ci/mmol) and required a dose “approaching toxic levels in order to obtain adequate

Scheme 2. Amino Acid Derived Substrates



sample count rates.^{20,21} The current protocol affords protected F-PHE (13) in 23% RCC (eq 1).

Finally, protected 6-[¹⁸F]fluoroDOPA 15 was prepared in 17 ± 6% RCC with a tosylate counterion and 30 ± 3% RCC with a tetrafluoroborate counterion (eq 2). While there has been much activity in the radiofluorination community aimed at accessing 6-[¹⁸F]fluoro-L-DOPA,^{21,22} current methods suffer from drawbacks that limit routine production of this material. This molecule has been of great interest to the PET community since the 1970s due to its numerous clinical applications.^{3,4} However, despite decades of research, there is no routine automated synthesis of ¹⁸F-DOPA in clinical use.^{5,6} To further demonstrate the utility of this method, we have performed the automated synthesis of 15 from the shelf stable salt 14-OTs. Under our standard conditions, 14-OTs afforded 17 ± 2% RCC of 15 with a SA of 4000 ± 2000 Ci/mmol (n = 2).^{23,24}

In summary, this paper demonstrates a general, practical, and rapid Cu-catalyzed radiofluorination of diaryliodonium salts using [¹⁸F]KF. This method is compatible with a wide range of functional groups, is competent for electronically diverse aryl groups, and uniformly affords good selectivity for a single ¹⁸F-containing product. The synthesis of protected versions of clinically relevant tracers, 4-[¹⁸F]fluorophenylalanine and 6-[¹⁸F]fluoroDOPA, has been demonstrated. Application of this methodology to other molecules of clinical interest is ongoing and will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, optimization details, radio-TLC traces, HPLC traces, and spectral data for all new compounds. 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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(24) Salts **12** and **14** were prepared from L-PHE and L-DOPA respectively. Optimization of the radiosynthesis is ongoing and to date ee's have not yet been determined.