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Copper-Mediated Radiofluorination of Arylstannanes with [^{18}F]KF

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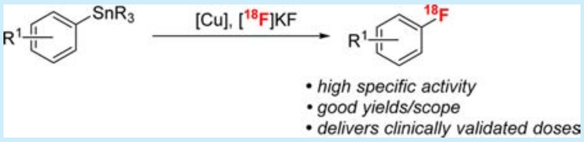
Supporting Information

ABSTRACT: A copper-mediated nucleophilic radiofluorination of aryl- and vinylstannanes with [^{18}F]KF is described. This method is fast, uses commercially available reagents, and is compatible with both electron-rich and electron-deficient arene substrates. This method has been applied to the manual synthesis of a variety of clinically relevant radiotracers including protected [^{18}F]F-phenylalanine and [^{18}F]F-DOPA. In addition, an automated synthesis of [^{18}F]MPPF is demonstrated that delivers a clinically validated dose of 200 ± 20 mCi with a high specific activity of 2400 ± 900 Ci/mmol.

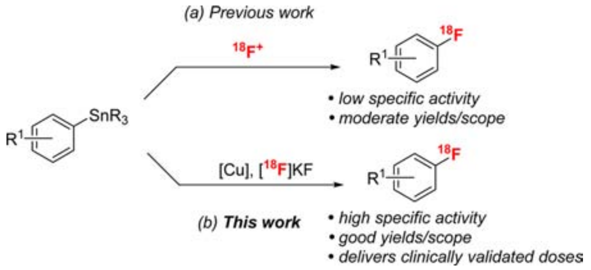


Positron emission tomography (PET) imaging is a noninvasive diagnostic imaging technique that provides in vivo physiochemical information.[1−4] Fluorine-18 (^{18}F) is the most commonly used radionuclide for PET, largely due to its attractive half-life of 110 min. This half-life enables the sophisticated synthesis of target molecules, allows distribution of ^{18}F-labeled tracers to facilities that lack cyclotrons, and facilitates in vivo pharmacokinetic studies.[2] With the increasing number of PET scans, there is a need for new, practical methods for the late-stage introduction of ^{18}F into bioactive molecules. Methods that enable the *nucleophilic* radiofluorination of readily accessible and stable precursors are in particularly high demand due to the availability of [^{18}F]fluoride from small medical cyclotrons.[5,6]

Arylstannanes are appealing precursors for PET radiolabeling for a number of reasons. First, they can be easily prepared from inexpensive starting materials,[7,8] and important examples are already known intermediates and/or commercially available (i.e., TriBoc-L-DOPA methyl ester).[9] Second, the Sn−C bond is stable to most functional group manipulations,[10,11] which enables flexible and modular syntheses of complex precursors that can then undergo selective late-stage radiofluorination. Third, arylstannanes have already been validated as precursors to radiopharmaceuticals for human clinical trials,[12−15] thereby mitigating concerns about toxicity and the feasibility of Sn removal. However, to date, the major limitation in this field is that existing methods for the fluorination[16,17] and radiofluorination[18,19] of arylstannanes require electrophilic fluorine sources (e.g., F_2, *N*-fluoropyridinium salts, *N*-fluorobenzenesulfonimide, Selectfluor) (Scheme 1a).[20] These reagents are much more expensive and less available than fluoride (particularly in the ^{18}F form). Furthermore, electrophilic radiofluorination methods result in products with dramatically lower specific activity (ratio of ^{18}F/^{19}F), which greatly reduces imaging sensitivity.[3]

We sought to address this limitation through the development of a method for the Cu-mediated nucleophilic radiofluorination of arylstannanes (Scheme 1b). This work builds on recent reports from our group[6e,21] and others[6c,f] demonstrating a related Cu-mediated (radio)fluorination of arylboron precursors. In addition to the generally attractive features of arylstannane precursors discussed above, we anticipated that they would be particularly well suited for Cu-mediated radiofluorination. Specifically, a key fundamental step of the Cu-mediated process, the transmetalation of the aryl group to Cu, is expected to proceed significantly faster from tin versus boron, which should result in faster reaction rates (crucial for radiolabeling applications) as well as fewer side reactions and higher yields.[22,23] We report herein the development, optimization, and scope of the Cu-mediated radiofluorination of arylstannanes with [^{18}F]KF. This transformation exhibits high functional group tolerance and has been applied to the late-stage radiofluorination of a number of complex molecules. Furthermore, it has been scaled to an automated synthesis module and used to prepare a clinically validated high specific activity dose of the radiotracer 2′-methoxyphenyl-(*N*-2′-pyridinyl)-*p*-^{18}F-fluorobenzamidoethylpiperazine ([^{18}F]MPPF).

Scheme 1. Radiofluorination of Arylstannanes



Our initial investigations focused on the Cu(OTf)$_2$-mediated fluorination of **1-SnBu$_3$** with KF under conditions analogous to those demonstrated for aryltrifluoroborate substrates.[21] After 18 h

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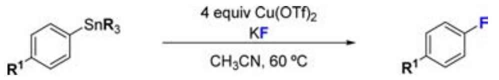
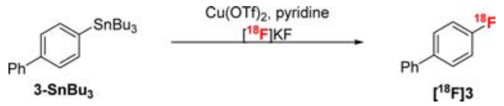
Table 1. Cu-Mediated Nucleophilic Fluorination of Arylstannanes in Acetonitrile with Excess Fluoride[a]



entry	R	R^1	time (h)	additive	KF (equiv)	yield (%)
1	Bu	F	18	none	4	42
2	Bu	F	18	18-crown-6	4	55
3	Bu	F	2	none	4	42
4	Bu	F	2	18-crown-6	4	53
5	Bu	F	0.25	18-crown-6	4	51
6	Bu	F	0.25	18-crown-6	0.5	15[b]
7	Bu	MeO	0.25	18-crown-6	4	23
8	Me	MeO	0.25	18-crown-6	4	24
9	Bu	Ph	0.25	18-crown-6	4	34
10	Me	Ph	0.25	18-crown-6	4	64
11	Bu	Ac	0.25	18-crown-6	4	57
12	Me	Ac	0.25	18-crown-6	4	65

[a] General conditions: Arylstannane (0.025 mmol, 1 equiv), Cu(OTf)$_2$ (4 equiv), KF, 18-crown-6 (4 equiv), CH$_3$CN (0.083 M), 60 °C. Yield determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture using 1,2-difluorobenzene as an internal standard. [b] Yield based on KF.

Table 2. Cu-Mediated Nucleophilic Fluorination of 3-SnBu$_3$ with [^{18}F]KF[a]



entry	solvent	temp (°C)	pyridine (equiv)	RCC[b] (%)
1	CH$_3$CN	60	0	nd
2	CH$_3$CN	60	50	nd
3	DMF	60	50	nd
4	DMF	110	50	22 ± 2
5	DMA	110	50	51 ± 1
6	DMA	110	15	53 ± 1
7	DMA	140	15	55 ± 10
8[c]	DMA	140	15	65 ± 2
9[d]	DMA	140	15	44 ± 1

[a] General conditions: **3-SnBu$_3$** (0.01 mmol, 1 equiv), Cu(OTf)$_2$ (2 equiv), pyridine (15 equiv), [^{18}F]KF, DMA (0.01 M), 140 °C, 30 min. RCC determined by radio-TLC ($n \geq 2$). [b] nd = no product detected by radio-TLC or HPLC. [c] Reaction time = 5 min. [d] **3-SnMe$_3$** used as substrate.

at 60 °C with 4 equiv of KF in CH$_3$CN, the fluorinated product **1** was obtained in 42% yield as determined by ^{19}F NMR spectroscopy (Table 1, entry 1). While this yield is lower than that reported with **1-BF$_3$K** under closely analogous conditions (70%, 20 h), the addition of 18-crown-6 as a phase-transfer catalyst could be used to boost the yield with **1-SnBu$_3$** to 55% (entry 2). Furthermore, as predicted, the fluorination of **1-SnBu$_3$** is significantly faster than that of **1-BF$_3$K**. For example, **1-SnBu$_3$** affords 51% yield after just 15 min under these conditions. In contrast, the analogous reaction of **1-BF$_3$K** requires more than 2 h to afford 50% yield. The faster rate with **1-SnBu$_3$** is highly desirable for PET applications. We also examined the sensitivity of this reaction to the stoichiometry of fluoride. This is another key consideration for translation because [^{18}F]fluoride is typically the limiting reagent during radiofluorination. We were encouraged to see that this reaction still proceeds (albeit in reduced yield) with KF as the limiting reagent (Table 1, entry 6).

We next applied this fluorination to a small set of arylstannanes (Table 1, entries 7–12) to establish the effectiveness of our 15 min nucleophilic fluorination protocol for electronically diverse arylstannanes and examine the impact of the alkyl substituents on tin (R) on the reaction. As shown in Table 1 (entries 7–12), stannanes bearing electron-donating (*p*-MeO), electron-neutral (*p*-Ph), and electron-withdrawing (*p*-Ac) substituents react to form fluorinated products in moderate to good yields within just 15 min at 60 °C. The *p*-MeO derivative is particularly noteworthy, as the corresponding aryltrifluoroborate is poorly reactive, affording <5% yield under any of the fluorination conditions examined.[21] Substitution of the alkyl group on the stannane had a significant impact on yield over this short reaction time, with the Me-substituted stannanes affording comparable or higher yield than the Bu derivatives in all cases. This likely reflects a faster rate of transmetalation from the less hindered tin center.[24]

We next focused on translating this nucleophilic fluorination to achieve the ^{18}F-fluorination of **3-SnBu$_3$**. As is common in the radiofluorination field,[3,25] significant reoptimization was required, as the best cold fluorination conditions afforded no detectable ^{18}F-labeled product (Table 2, entry 1). This is likely a consequence of the dramatic change in fluoride stoichiometry (from 0.3 M with KF to approximately 1 nM with [^{18}F]KF).[26] Three modifications were found to be critical for achieving radiofluorination in this system: (1) changing from CH$_3$CN to an amide-based solvent (DMF or DMA); (2) the addition of pyridine (which was also an important additive in related radiofluorinations of arylborons);[6e] and (3) increasing the reaction temperature to between 110 and 140 °C. The optimal radiofluorination conditions for **3-SnBu$_3$** were as follows: 2 equiv of Cu(OTf)$_2$, 15 equiv of pyridine in 0.1 M DMA at 140 °C. This afforded [^{18}F]**3** in 65 ± 2% radiochemical conversion (RCC) within just 5 min (entry 8).

The optimal conditions were applied to a series of aryl-, heteroaryl-, and vinylstannane precursors. As summarized in Figure 1, this method is compatible with aromatic substrates bearing electron-neutral (**3**), electron-withdrawing (**4**, **13**), and electron-donating substituents (**2**, **5–10**) as well as hetero-

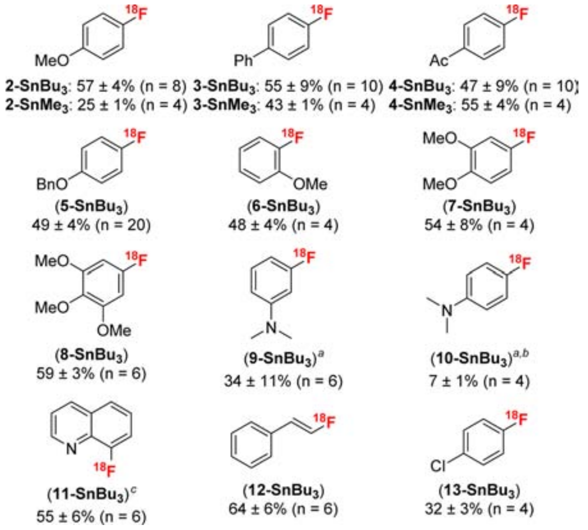


Figure 1. Scope of arylstannane substrates. Conditions: aryltributyltin substrate (0.01 mmol, 1 equiv), Cu(OTf)$_2$ (2 equiv), pyridine (15 equiv), [^{18}F]KF, DMA (0.01 M), 140 °C, 5–30 min. RCC determined by radio-TLC; (a) 100 °C; (b) 18-crown-6 (0.5 equiv); (c) 30 equiv of pyridine.

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aromatic (**11**) and vinylstannane (**12**) derivatives. Substrates such as **13-SnBu$_3$** include a functional handle that can be used for further elaboration. Ortho-substitution was well-tolerated, with the *o*-MeO substrate **6-SnBu$_3$** affording a yield comparable to that of the *p*-MeO substrate **2-SnBu$_3$** (RCC = 57% versus 48%, respectively). This is in contrast to other metal-mediated nucleophilic radiofluorinations, which typically afford much lower yields with *ortho*-substituted aromatic substrates (see Table S20). The electron-rich substrates (**2**, **5−10**) are noteworthy, as they are challenging to radiofluorinate using traditional S$_N$Ar.[1] Overall, the RCCs are comparable, and in many cases significantly higher, than those for the state-of-the-art metal-mediated radiofluorinations of analogous substrates (see Table S20 for a comparison of metal-mediated nucleophilic radiofluorination methods).

We next applied our method to the preparation of products currently being evaluated as radiotracers in clinical trials or already FDA approved.[27,37] Initial studies were conducted via manual synthesis, which provided useful RCCs (Figure 2). For instance, this method is effective for the synthesis of protected phenylalanine derivatives ([^{18}F]**14** and [^{18}F]**15**) for studying amino acid transport.[28] We also targeted 3-[^{18}F]fluoro-5-[(pyridin-3-yl)-ethynyl]benzonitrile ([^{18}F]F-PEB, [^{18}F]**18**), whose previous radiosyntheses suffer from low yields (1−5% RCY, nondecay corrected).[6e,29−31] Our new method, starting from the readily available and stable arylstannane precursor **18-SnBu$_3$**, delivers the product in 11 ± 2% RCC.

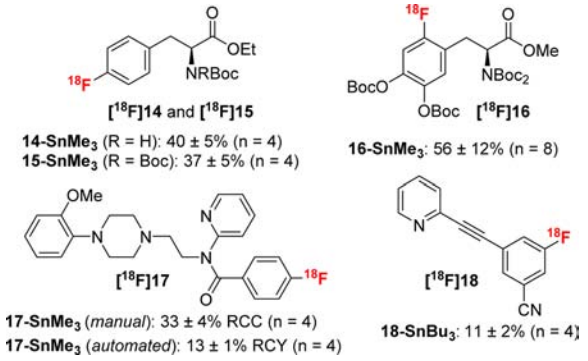
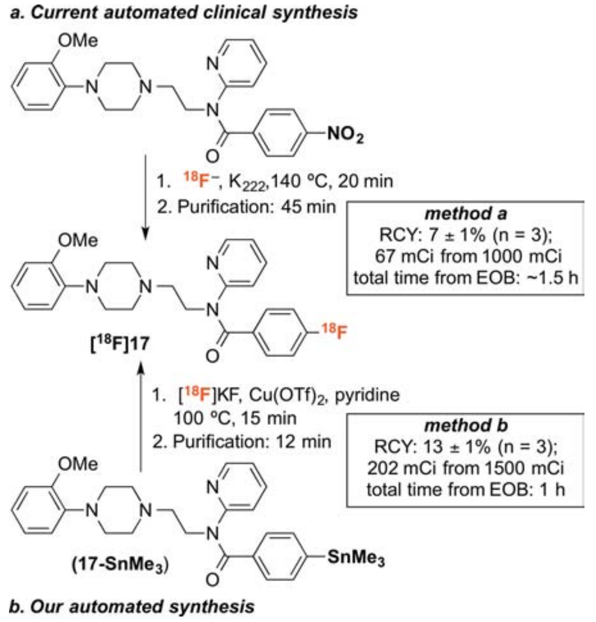


Figure 2. Substrate scope of relevant radiotracers.

This method is also effective for the radiofluorination of the protected L-DOPA stannane **16-SnMe$_3$**, affording [^{18}F]**16** in 56 ± 12% yield. This result is noteworthy for several reasons. First, nucleophilic methods for radiolabeling L-DOPA remain highly sought after,[1,28,32,33] and the obtained RCC is among the best reported for this type of transformation (see Figure S10 for a comparison of nucleophilic methods for [^{18}F]F-DOPA derivatives). Second, the precursor **16-SnMe$_3$** is a single step from a commercial stannane whose derivatives have been used in the clinical production of [^{18}F]F-DOPA via electrophilic radiofluorination.[12,13] As such, the successful radiofluorination of **16-SnMe$_3$** offers the potential for a direct nucleophilic replacement for this method.

Finally, we targeted [^{18}F]MPPF ([^{18}F]**17**), a serotonin receptor ligand currently synthesized by S$_N$Ar radiofluorination of the NO$_2$ precursor (Scheme 2a). Our manual Cu-mediated procedure from stannane **17-SnMe$_3$** delivered [^{18}F]**17** in 33 ± 4% RCC. The [^{18}F]MPPF synthesis was scaled and automated using a TRACERLab FX$_{FN}$ module (Scheme 2b). The reaction using 1500 mCi of initial activity afforded a formulated and validated 200 ± 20 mCi dose (13% RCY) after radiolabeling and HPLC purification.[34] The dose prepared by this method passed all cGMP quality control testing necessary for clinical use, as outlined in the US Pharmacopeia and 21CFR212, including residual Cu and Sn levels below the allowed limits specific in the ICH Guidelines (see the Supporting Information for complete information).[6g,35] As shown in Scheme 2, our new method affords nearly double the RCY and reduces the overall time from end of bombardment (EOB) to end of purification by one-third relative to the current commercial synthesis of this tracer.[36]

Scheme 2. Comparison of Current Methods To Synthesize [^{18}F]MPPF ([^{18}F]17)[36,37]



In conclusion, this paper discloses a mild, copper-mediated method for the nucleophilic fluorination and radiofluorination of arylstannanes. This method represents the first practical nucleophilic fluorination of stannanes using ^{18}F, is compatible with aryl, heteroaryl, and vinylstannanes, and fills an important gap in available late-stage fluorination methods. Furthermore, this process can be readily automated and scaled on a commercial radiochemistry synthesis module and applied to clinically relevant radiotracers. Finally, we have shown that the method is tolerant of a reasonable number of functional groups common in drug targets. To expand the utility further, exploration of the compatibility of this method with medicinal chemistry space is ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02911.

Experimental procedures, optimization details, radio-HPLC/TLC traces, and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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