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Synthesis of ^{18}F-Labeled Aryl Fluorosulfates via Nucleophilic Radiofluorination

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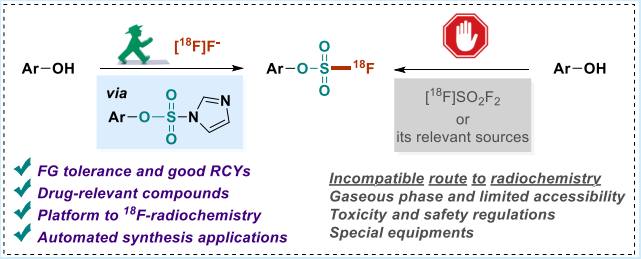
ABSTRACT: Sulfuryl fluoride gas is a key reagent for SO_2F transfer. However, conventional SO_2F transfer reactions have limited ^{18}F-radiochemistry translation, due to the inaccessibility of gaseous [^{18}F]SO_2F_2. Herein, we report the first SO_2F_2-free synthesis of aryl [^{18}F]fluorosulfates from both phenolic and isolated aryl imidazylate precursors with cyclotron-produced $^{18}F^-$. The radiochemical yields ranged from moderate to good with excellent functional group tolerance. The reliability of our approach was validated by the automated radiosynthesis of 4-acetamidophenyl [^{18}F]fluorosulfate.



Organosulfur compounds can exhibit diverse electronic profiles depending on the oxidation state of sulfur. In particular, S(II) compounds are typically soft nucleophiles while S(VI) compounds can act as electrophiles. These distinct properties enable the synthesis of a broad range of organosulfur derivatives. Interestingly, compared to sulfonyl halides, the stability of the $-OSO_2F$ moiety toward hydrolysis, thermolysis, and reduction is unique.[1] Biochemical probes can be obtained through the selective and orthogonal coupling of phenolic hydroxy groups with $-SO_2F$ groups.[2] In sulfur(VI) fluoride exchange (SuFEx), the fluoride atom functions as a leaving group to provide new connectivity.[3] A recent study by Zheng et al.[4] demonstrated adequate *in vivo* stability of aryl [^{18}F]fluorosulfate as a positron emission tomography (PET) imaging probe, making aryl [^{18}F]fluorosulfate an attractive candidate for image-based drug development. Therefore, facilitation of SO_2F transfer reactions is highly desirable. Since the first report of sulfurylative activation of a phenolic hydroxy group,[5] several methods have been developed for the preparation of aryl fluorosulfate (Figure 1a).[6] Sharpless and Dong[7] identified a fluorosulfuryl imidazolium salt as a stable FSO_2^+ fragment donor. De Borggraeve et al.[8] reported the *ex situ* generation of SO_2F_2 using a special two-chamber apparatus that obviated the direct handling of gaseous SO_2F_2.[9] Ende et al.[10] developed a $-SO_2F$ transfer method using a bench-stable [4-(acetylamino)phenyl]imidodisulfuryl difluoride (AISF) reagent. Despite these developments, none of the aforementioned methods can be readily translated into ^{18}F-radiochemistry.

The cyclotron-produced [^{18}F]fluoride ion is an essential radionuclide for PET, a noninvasive diagnostic modality for visualizing physiochemical processes *in vivo*.[11] However, it is present as the heavily hydrated form $^{18}F^-(H_2{}^{18}O)_n$ in target water. Its nucleophilicity is significantly compromised by hydration, and it has a short physical half-life ($t_{1/2}$) of 109.8 min.[12] These factors must be considered when translating

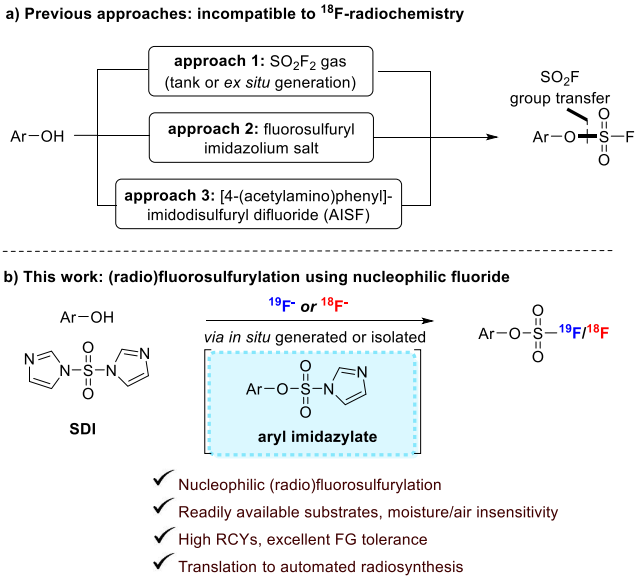


Figure 1. Synthesis of ^{18}F/^{19}F-aryl fluorosulfates.

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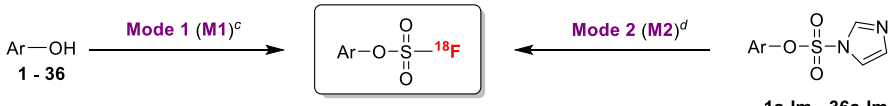
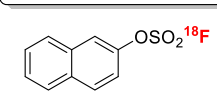
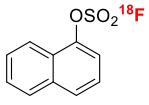
Scheme 1. Substrate Scope for the Radiofluorosulfurylation of Phenols[a,b]



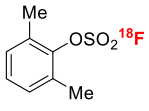
Simple Aromatics



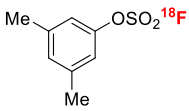
[^{18}F]**1b**
(41 ± 12%; 63 ± 9%)



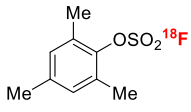
[^{18}F]**2b**
(29 ± 9%; 60 ± 10%)



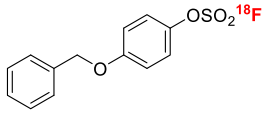
[^{18}F]**15b**
(59 ± 3%; 63 ± 3%)



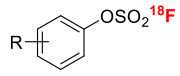
[^{18}F]**16b**
(44 ± 14%; 77 ± 9%)



[^{18}F]**17b**
(46 ± 16%; 37 ± 12%)



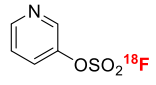
[^{18}F]**18b**
(54 ± 3%; 62 ± 5%)



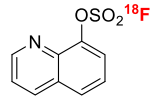
[^{18}F]**3b** - [^{18}F]**14b**

4-F-;	[^{18}F]**3b** (57 ± 7%; 80 ± 3%)	2-MeO-;	[^{18}F]**9b** (55 ± 10%; 69 ± 15%)
4-CF_3-;	[^{18}F]**4b** (37 ± 4%; 46 ± 1%)	3-MeO-;	[^{18}F]**10b** (52 ± 10%; 67 ± 14%)
3-I-;	[^{18}F]**5b** (39 ± 5%; 62 ± 10%)	4-MeO-;	[^{18}F]**11b** (73 ± 4%; 66 ± 2%)
2-CN-;	[^{18}F]**6b** (26 ± 2%; 25 ± 6%)	2-Ph-;	[^{18}F]**12b** (53 ± 7%; 75 ± 10%)
3-CN-;	[^{18}F]**7b** (15 ± 9%; 42 ± 5%)	3-Ph-;	[^{18}F]**13b** (45 ± 8%; 65 ± 1%)
4-CN-;	[^{18}F]**8b** (27 ± 9%; 48 ± 2%)	4-Ph-;	[^{18}F]**14b** (44 ± 4%; 70 ± 10%)

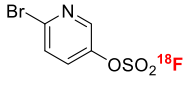
Heteroaromatics



[^{18}F]**19b**
(38 ± 3%; 40 ± 5%)

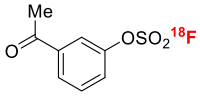


[^{18}F]**20b**
(47 ± 5%; 61 ± 2%)

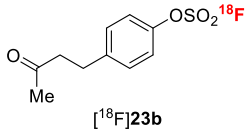


[^{18}F]**21b**
(16 ± 2%; 38 ± 3%)

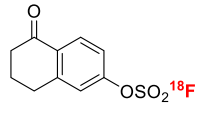
Functionalized Aromatics



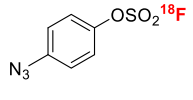
[^{18}F]**22b**
(25 ± 13%; 68 ± 4%)



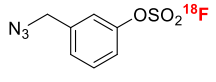
[^{18}F]**23b**
(47 ± 5%; 60 ± 5%)



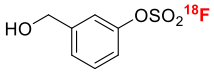
[^{18}F]**24b**
(8 ± 6%; 58 ± 2%)



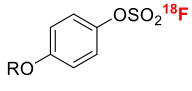
[^{18}F]**25b**
(31 ± 4%; 68 ± 4%)



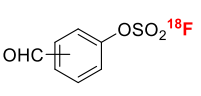
[^{18}F]**26b**
(10 ± 6%; 57 ± 4%)



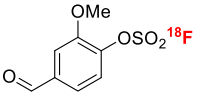
[^{18}F]**27b**
(23 ± 9%; 33 ± 13%)



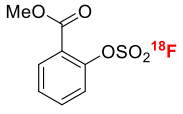
R = SO_2F: [^{18}F]**28b** (8 ± 3%)[e]
= SO_2Im: [^{18}F]**28b'** (65 ± 4%)[e]



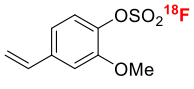
3-CHO; [^{18}F]**29b** (9 ± 6%; 42 ± 11%)
4-CHO; [^{18}F]**30b** (15 ± 6%; 45 ± 6%)



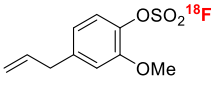
[^{18}F]**31b**
(62 ± 4%; 52 ± 2%)



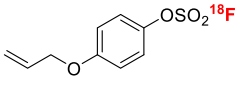
[^{18}F]**32b**
(33 ± 4%; 65 ± 8%)



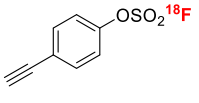
[^{18}F]**33b**
(15 ± 5%; 52 ± 2%)



[^{18}F]**34b**
(41 ± 17%; 55 ± 7%)



[^{18}F]**35b**
(46 ± 9%; 70 ± 7%)



[^{18}F]**36b**
(13 ± 3%; 47 ± 7%)

[a][^{18}F]F^-, 18-Crown-6 (2.6 mg, 9.8 μmol), K_2CO_3 (0.7 mg, 4.9 μmol), DMF (2 mL). [b]RCY was determined based on radio-HPLC chromatogram and expressed as average ± SD (n = 3). See, Section VII in the SI for details on the RCY determination. [c]Aryl alcohol (10 μmol), SDI (10 μmol), 140 °C, 10 min. [d]Aryl imidazylate (10 μmol), 100 °C, 10 min. [e]Mode 2 reaction with **28b′** produced two radiolabeled products ([^{18}F]**28b** and [^{18}F]**28b′**).

conventional fluorination protocols using $^{19}F^-$ to radiochemical fluorination with $^{18}F^-$. The use of radioactive fluorine-18 to produce PET radiotracers warrants the development of an automated radiosynthetic module to avoid unnecessary radiation exposure.[13] Such measures are generally unnecessary when using nonradioactive fluorine-19. Therefore, current conventional methods for the incorporation of $-SO_2F$ subunits do not appear suitable for ^{18}F-labeling applications. For example, De Borggraeve's[8] two-chamber apparatus used to generate gaseous SO_2F_2 is not compatible with commercially available radiosynthesizers. The translation of synthetic chemistry procedures developed for gaseous sulfuryl fluoride to ^{18}F-radiochemistry faces additional hurdles.

To overcome these limitations, we developed reliable and reproducible radiosynthetic approaches for aryl [^{18}F]-fluorosulfate without the need for specialized equipment.

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$-SO_2F$ groups were generated from readily available metal fluorides rather than from cumbersome gaseous fluorosulfuryl sources. Unlike the fluoride−chloride exchange using sulfonyl chloride, the nucleophilic fluorination of chlorosulfate with a metal fluoride such as KF has been relatively unexplored.[14] Herein, we report the first direct synthesis of ^{18}F-labeled aryl fluorosulfates (Figure 1b) from both phenols and isolated aryl imidazole sulfonates (imidazylates). We devised two strategies for ^{18}F-radiochemistry adaptation. The first involved the one-pot radiofluorosulfurylation of phenols using 1,1′-sulfonyldiimidazole (SDI) and $^{18}F^-$. The second strategy focused on the radiofluorination of isolated imidazylate precursors by incorporating $^{18}F^-$ into their sulfonyl moieties. At the outset, our protocols offered several distinct advantages over previously reported methods. First, (radio)fluorination could be achieved with a readily available nucleophilic fluoride source. Second, conventional synthetic approaches could be adapted without the need for specialized equipment or additional safety precautions. Finally, our protocols are readily transferrable to the efficient radiosynthesis of ^{18}F-labeled aryl fluorosulfates. Thus, our approach is expected to enable the rapid screening of pharmaceutical candidates along with exquisite PET imaging.

At the beginning of our studies, we focused on non-radioactive fluorosulfurylation to assess the practicality of our methods. We evaluated the formation of $-OSO_2F$ group directly from a phenolic substrate. Initially, we attempted to generate 2-naphthyl fluorosulfate (**1b**) by reacting 2-naphthol, SDI, and silver fluoride (AgF) in a one-pot reaction under neutral conditions (see Table S1, Section III in the Supporting Information (SI) for the detailed procedures). This process provided 2-naphthyl fluorosulfate (**1b**) with 54% yield. We carefully characterized the reaction mixture and identified an imidazylate derivative of 2-naphthol. Assuming that the $-OSO_2F$ group formed via such an imidazylate intermediate, we speculated that the imidazylate itself could be a viable labeling precursor. Next, we evaluated a series of common metal fluorides to identify the ideal fluoride source for imidazylate radiofluorination (see Table S2, Section III in the SI). Silver fluoride afforded the highest yield of 2-naphthyl fluorosulfate (**1b**). Nucleophilic fluorination of naphthol imidazylate (**1a-Im**) generated 2-naphthyl fluorosulfate (**1b**) in up to 90% isolated yield. The substrate scope of these two methods was evaluated, and the corresponding aryl fluorosulfates were formed in moderate to high yields (see Sections III and VI in the SI).

Next, we applied these $-SO_2F$ transfer reactions in ^{18}F-radiochemistry systems. While aryl fluorosulfate production was efficient in the presence of AgF, the implementation of $Ag^{18}F$ for routine ^{18}F-radiochemistry was problematic. In addition to fairly low radiochemical yields (RCYs), the $Ag^{18}F$ complex generated from Ag_2CO_3 adhered to the wall of the reaction vial, compromising the overall labeling efficiency. Therefore, we used the $^{18}F/K_2CO_3$/18-crown-6 complex as a phase-transfer agent during radiofluorosulfurylation. This provided the highest RCY of radiosulfurylated 4-fluorophenol [^{18}F]**3b** (see Section VIII in the SI). Using a one-pot method, we successfully radiolabeled phenol with $^{18}F^-$ to afford 4-fluorophenyl [^{18}F]fluorosulfate ([^{18}F]**3b**). A close examination of the HPLC-UV chromatogram revealed the presence of the corresponding imidazylate intermediate that was previously observed in the nonradioactive reaction mixture (see Section X in the SI). We postulated that the formation of this intermediate during radiofluorination was inevitable in a one-pot reaction. Similar to the direct fluorination of the imidazylate using the nonradioactive protocol, the aryl [^{18}F]fluorosulfate could be obtained from the bench-stable, isolated imidazylate precursor.[15]

Then, using these optimized radiochemical conditions, we focused our efforts on broadening the substrate scope (Scheme 1). We systematically compared two different radiofluorination modes: the direct one-pot radiofluorosulfurylation of phenolic precursors (Mode 1) and the radiofluorination of isolated imidazylates (Mode 2). We hypothesized that Mode 2 would afford higher RCYs while diminishing the formation of nonradioactive byproducts. As expected, [^{18}F]fluorosulfurylated products were achieved with both methods, although the RCYs differed between Modes 1 and 2. With both methods, the radiofluorosulfurylation of simple phenols bearing electron-withdrawing (4-F, 4-CF_3, 3-I, and CN) and electron-donating (MeO) substituents afforded [^{18}F]**3b**−[^{18}F]**11b** in 15% to 80% RCYs, regardless of the position of the substituent on the ring. Interestingly, the electronic nature of the ring did not significantly influence the overall outcome of radiofluorination using either Mode 1 or 2. Moderate to high RCYs were obtained with other electron-rich phenolic substrates. These included naphthyls (2-naphthyl [^{18}F]**1b** and 1-naphthyl [^{18}F]**2b**), biphenyls [^{18}F]**12b**−[^{18}F]**14b**, xylenols (2,6-xylenol [^{18}F]**15b** and 3,5-xylenol [^{18}F]**16b**), mesityl [^{18}F]**17b**, and benzylic ether [^{18}F]**18b**. No discernible substituent effects occurred with respect to the position and number of methyl substituents in the xylenolic systems. Heteroaromatic systems produced their corresponding fluorosulfated heteroarenes [^{18}F]**19b**−[^{18}F]**21b**. Halogen-substituted pyridine [^{18}F]**21b** was obtained in 38% RCY from the corresponding imidazylate **21a-Im**. This is particularly noteworthy as [^{18}F]**21b** provides a reactive synthetic handle for potential coupling operations.

Other functionalized phenols also produced aryl fluorosulfates. Ketone-bearing phenols [^{18}F]**22b**−[^{18}F]**24b** with enolizable α-protons were radiofluorinated via their imidazylates in 58−68% RCYs without the formation of radioactive tautomeric isomers. Azide-functionalized aryl fluorosulfates [^{18}F]**25b** and [^{18}F]**26b** were obtained from imidazylates **25a-Im** and **26a-Im** in 68% and 57% RCYs, respectively. Remarkably, 3-hydroxybenzyl fluorosulfate [^{18}F]**27b** was obtained from 3-hydroxybenzyl alcohol. The sulfurylative activation of benzyl alcohol with SDI led to the selective functionalization of the phenolic hydroxy group, leaving the alkyl hydroxy intact. Radiofluorination of imidazylate **27a-Im** also afforded the corresponding fluorosulfate [^{18}F]**27b** with higher RCY under basic labeling conditions ($^{18}F/K_2CO_3$/18-crown-6). No competing radiofluorination was observed at the benzylic position. A hydroquinone with two imidazyl sites (**28a-Im**) was prepared stoichiometrically. Unsurprisingly, the radiofluorination of this substrate occurred at only one of the imidazyl sites to produce [^{18}F]**28b′** (see Section IX in the SI for details). This was consistent with $^{18}F^-$ being a limiting agent in ^{18}F-radiochemistry. Unlike the previous results, [^{18}F]**28b** and [^{18}F]**28b′** were produced from radiofluorination of **28b′** in 8% and 65% RCYs, respectively. The formation of the major radiolabeled product [^{18}F]**28b′** might presumably stem from $^{19}F/^{18}F$ isotopic exchange, which has been recently reported.[4,16] Aryl fluorosulfates with aldehydic functionalities ([^{18}F]**29b**−[^{18}F]**31b**) were obtained in good RCYs from both phenols and their imidazylate derivatives. As prosthetic

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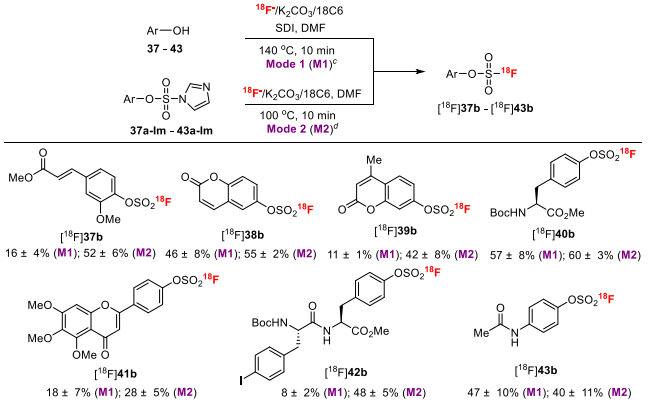
synthons, functionalized aldehydic aryl fluorosulfates enable the downstream modification of complex molecules. Ester-functionalized aryl fluorosulfate [^{18}F]**32b** was produced in 65% RCY via Mode 2 without basic hydrolysis. Vinyl, allylic, and alkynyl moieties gave their corresponding fluorosulfates [^{18}F]**33b**−[^{18}F]**36b**. The alkynyl radiosynthon potentially allows for concomitant click conjugation with an azide partner as a means of labeling biomacromolecules.[17]

Then we extended this methodology to radiolabeled natural products and drug-relevant compounds (Scheme 2). Methyl ferulate was radiolabeled via Mode 2 to afford [^{18}F]**37b** in 52% RCY. The remarkable tolerance to functional group variation within a structure containing both vinyl and ester functionalities was particularly noteworthy. Coumarin derivatives were radiofluorosulfurylated via Modes 1 and 2 to produce [^{18}F]**38b** and [^{18}F]**39b**, respectively, in RCYs of 11−55%. The same methods were employed to obtain radiolabeled derivatives of tyrosine ([^{18}F]**40b**), flavone ([^{18}F]**41b**), dipeptide ([^{18}F]**42b**), and acetaminophen ([^{18}F]**43b**) in RCYs ranging from 8% to 60%.

Finally, we evaluated the suitability of our radiolabeling approach in actual radiotracer production using the TracerLab Fx_{FN} automatic radiosynthesis module (Scheme 3). Acetaminophen **43** was chosen as a model substrate to assess the adaptability of our protocols to automated radiosynthesis. The RCYs and molar activities of the resulting aryl [^{18}F]-fluorosulfate [^{18}F]**43b** were determined after isolation via semipreparative radio-HPLC. The overall radiosynthesis was completed within 60 min. Purified 4-acetamidophenyl [^{18}F]-fluorosulfate [^{18}F]**43b** was obtained in 9% to 22% RCYs (Modes 1 and 2). Using the imidazylate derivative as the substrate instead of the phenol, [^{18}F]**43b** was obtained in a higher RCY. The molar activity of aryl [^{18}F]fluorosulfate was 42 to 55 GBq/μmol, adequate for PET imaging.[18] There were no significant differences between the molar activity of [^{18}F]**43b** from the phenol (Mode 1) and that of [^{18}F]**43b** from the imidazylate precursor (Mode 2).

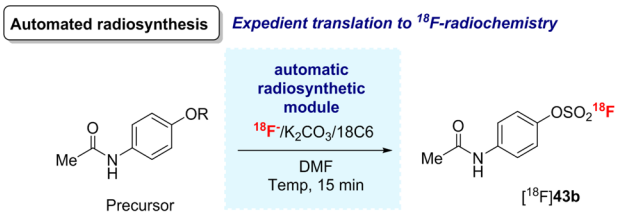
In summary, we developed two radiolabeling methods, starting from phenols and their derivatives, to rapidly generate aryl [^{18}F]fluorosulfates in good to high RCYs. Both the direct nucleophilic fluorination of aryl imidazylates and one-pot SO_2F transfer reactions using K^{18}F unequivocally provided ^{18}F-labeled aryl fluorosulfates. These synthetic methods tolerated a wide range of functional groups within (hetero)arenes and were applicable to biologically relevant complex molecules with moisture and air insensitivity. The efficacy of these methods was highlighted through the automated synthesis of a radiofluorosulfurylated acetaminophen derivative. This study helps expand the boundaries of radiochemistry.

Scheme 2. Radiofluorosulfurylation of Natural Products or Drug-Relevant Compounds[a,b]



[a]18-Crown-6 (2.6 mg, 9.8 μmol), K_2CO_3 (0.7 mg, 4.9 μmol), DMF (2 mL). [b]RCY was determined based on radio-HPLC chromatogram and expressed as average ± SD (n = 3). See, Section VII in the SI for details on the RCY determination. [c]Aryl alcohol (10 μmol) and SDI (10 μmol). [d]Aryl imidazylate (10 μmol).

Scheme 3. Automated Radiolabeling of Acetaminophen Derivatives[a]



Reactions	RCY[b], molar activity (Am)
Mode 1:[c] R = H (**43**), SDI, 140 °C	9 ± 2% 42 ± 11 GBq/μmol
Mode 2:[d] R = SO_2Im (**43a-Im**), 100 °C	22 ± 8% 55 ± 29 GBq/μmol

[a]18-Crown-6 (4.0 mg, 15 μmol), K_2CO_3 (1.0 mg, 7.2 μmol), precursor (10 μmol), DMF (1 mL). For details regarding the radioactivity of the isolated product, see Section XI in the SI. [b]RCY was determined based on the decay-corrected activity of isolated [^{18}F]**43b** and expressed as average ± SD. [c]n = 2. [d]n = 3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01868.

Detailed experimental procedures, NMR (^{1}H, ^{13}C, and ^{19}F) spectra, optimization studies, and radio-HPLC and selected radio-TLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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