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Note

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Chemoselective radiosyntheses of electron-rich [^{18}F]fluoroarenes from aryl(2,4,6-trimethoxyphenyl)iodonium tosylates

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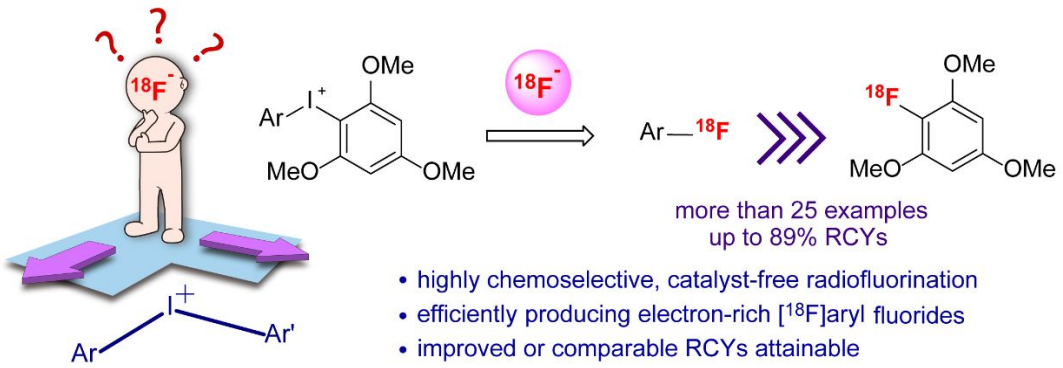


Abstract

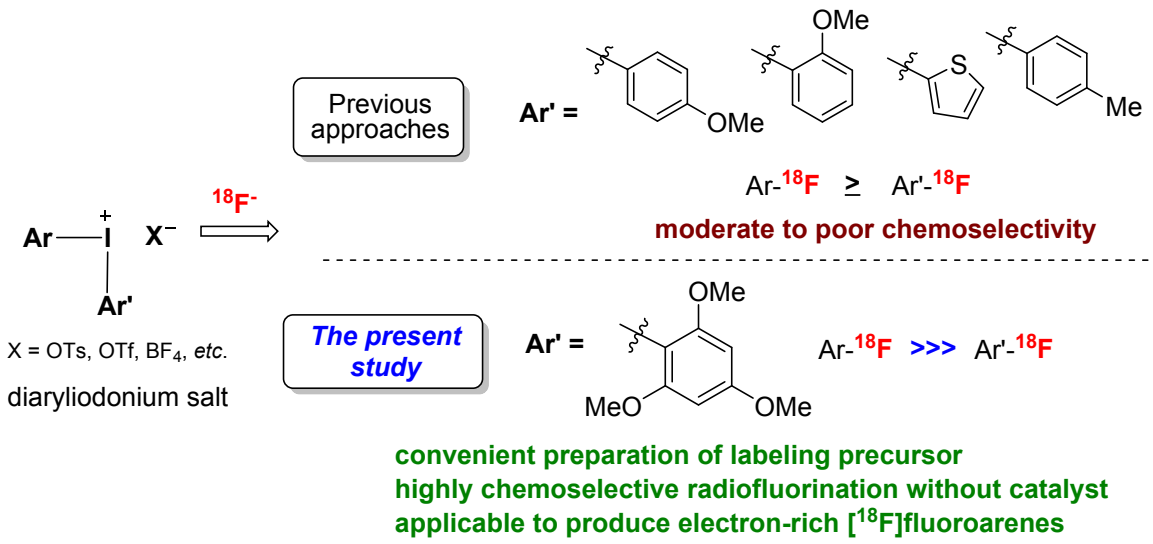
Hypervalent diaryliodonium salts have been used to produce various [^{18}F]fluoroarenes. The iodonium salt approach as a labeling precursor has been established to equally afford complex ^{18}F-fluorinated molecules. Because of the inherent two-aryl ring system connected to a central iodine atom, safeguarding the chemoselectivity during radiofluorination using diaryliodonium salts is important. Herein, we introduce a superior chemoselective radiosynthesis of [^{18}F]fluoroarenes using an aryl(2,4,6-trimethoxyphenyl)iodonium tosylate as a precursor for ^{18}F-incorporation, even on electron-rich aryl rings.

Fluoroaromatic compounds are an important class of organic compounds because of their unique physiochemical and biological properties.[1] Extensive effort has been devoted to developing a reliable approach to constructing aromatic C–F bonds to exploit the inherently strong C–F bond in fluoroaromatic systems. In radiochemistry associated with fluorine-18 for positron emission tomography (PET) imaging modality, the aromatic C–^{18}F bond is known to offer various advantages over other aliphatic ^{18}F-radiotracers. One such advantage is the metabolic stability of aromatic ^{18}F-radiotracers, which ameliorates radiodefluorination under physiological conditions during image acquisition.[2] Widely employed methods for aromatic radiofluorination include the use of various classes of hypervalent compounds,[3] arylborons,[4] arylstannanes,[5] and *N*-arylsydnones.[6] Among them, diaryliodonium salts and iodonium ylides offer catalyst-free radiofluorination, which relieves the downstream quality-control burden of PET tracers produced for human use.

Recently, different research groups have used diaryliodonium salts to exploit the unique aryl-group transfer ability. This approach has encouraged synthetic chemists to focus on developing an efficient method to chemoselectively transfer aryl groups onto the desired chemical skeleton.[7] In fluorine-18 radiochemistry, the use of diaryliodonium salts is now a well-established approach to the single-step introduction of a [^{18}F]fluoride ion onto electron-rich aryl rings and complex radiopharmaceuticals with an aromatic chemical entity, which is difficult to achieve through conventional nucleophilic aromatic fluorination.[3] Simple aryl rings can be radiofluorinated via symmetrical iodonium salts;[8] however, the synthesis of symmetric iodonium salts can be challenging, particularly when the desired ring has a complex structure. Consequently, unsymmetrical diaryliodonium salts are widely preferred for radiotracers, although awareness of chemoselectivity in radiofluorination is important because of the competition between two aryl rings for the incoming ^{18}F-nucleophile. The radiofluorination with a diaryliodonium salt can produce two ^{18}F-fluorinated aryl rings in a non-chemoselective

manner when the iodonium salt bears two electronically similar aryl rings. One method to overcome this limitation is to use an electron-rich aryl ring to direct the ^{18}F-nucleophile onto the desired aromatic moiety; 4-anisyl-, 2-anisyl-, 2-thienyl-, 4-tolyl-, and, less frequently, phenyl-rings have been used as spectator aryl rings.[3a,9–11] DiMagno *et al.* demonstrated that cyclophane efficiently modulates the direction of nucleophile incorporation.[12] The synthesis of this class of iodonium salts for routine use without adversely affecting their excellent chemoselectivity is challenging, particularly when dealing with complex substrates.

Scheme 1. ^{18}F-Directing Aryl Rings Used for Diaryliodonium Salts



Recently, 1,3,5-trimethoxybenzene (TMB) has been used as counterpart aryl rings in iodonium salts to selectively transfer the aryl group to the desired chemical entity in an organic synthesis, thereby enabling chemoselective arylation with nucleophiles containing C, N, O, and/or S atoms.[13] Because the rapid and reliable incorporation of ^{18}F ($t_{1/2}$ = 109.8 min) is required to produce ^{18}F-labeled tracers, chemoselective radiofluorination is ideal to produce clinical PET tracers for imaging purposes. In addition, facile separation of the radioactive

byproduct is important to achieve the radiochemical purity required for PET radiopharmaceuticals. Such facile separation might be achievable with the aryl(2,4,6-trimethoxyphenyl)iodonium salt as a ^{18}F-directing aryl partner. Herein, we show that, compared with other spectator aryl rings, the 2,4,6-trimethoxyphenyl (TMP) group in a diaryliodonium tosylate confers excellent chemoselectivity to produce electron-rich aryl fluorides as well as improved radiochemical yield (RCY) in radiofluorinations (Scheme 1).

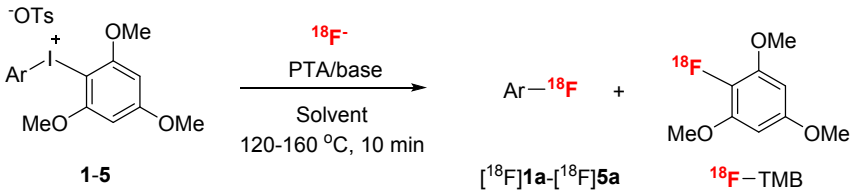
Aryl(TMP)iodonium tosylates were prepared using the modified *meta*-chloroperbenzoic acid (*m*CPBA)-mediated single-pot method established by Stuart[14] and Olofsson.[15] Using symmetric TMB as the electron-rich aryl ring partner advantageously prevents the formation of isomeric byproducts during the iodonium salt synthesis. Thus, unsymmetrical iodonium tosylates with a TMP group as a spectator ring were obtained in 10–90% yields and were used for subsequent radiofluorination.

Initially, we selected mesityl(TMP)iodonium tosylate (**1**) to gain insight into the radiofluorination medium required to produce [^{18}F]fluoroarenes from aryl(TMP)iodonium tosylates. Common aprotic organic solvents–acetonitrile, *N*-methyl-2-pyrrolidone, 1,4-dioxane, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and *N*,*N*-dimethylacetamide (DMA)–were screened for their suitability. Different phase-transfer agents (PTAs) were also compared to identify the ideal PTA solution for radiofluorination. The initial radiofluorination of **1** under different reaction conditions revealed that K 2.2.2 was the best PTA for our purposes (see Supporting Information for details); however, we subsequently found that this condition was not generally applicable to all substrates.

Next, we examined the selectivity between electron-rich aryl rings during radiofluorination. For comparison, we selected five electron-rich aryl rings to assess the ring selectivity: 4-anisyl, 2-anisyl, 2-thienyl, 4-tolyl, and mesityl, the last of which is employed in

Cu-catalyzed aromatic radiofluorination. The electron-rich aryl rings **1**–**4** were selectively fluorinated against the 2,4,6-TMP ring, demonstrating excellent chemoselectivity, even among the electron-rich aromatic systems (Table 1). Most commonly formed 4-[^{18}F]fluoroanisole was obtained at a 29% RCY (Entry 2, Table 1). Other electron-rich aryl rings were also efficiently radiofluorinated with up to 89% RCY (Entries 1 and 3–5, Table 1). Oddly, [^{18}F]fluorothiophene was not observed in the radio-HPLC analysis of **5** (Entry 5, Table 1). The characterization of the resulting [^{18}F]fluorothiophene is known to be problematic when a thienyl iodonium salt is used as a radiolabeling precursor,[10] presumably because this system is too electron-dense for the incoming [^{18}F]fluoride ion to join either ring. Strikingly, the peak for [^{18}F]F-TMB was barely noticeable in the radio-HPLC chromatogram, indicating that this moiety is the ideal aryl ring partner for controlling the chemoselectivity of ^{18}F-incorporation into the electron-rich aryl system. Unlike the chemically unstable [^{18}F]fluorothiophene and somewhat volatile [^{18}F]fluoroanisole byproducts, the [^{18}F]F-TMB coproduct in the fluorination mixture could be readily traced to assess the fluorination integrity in PET radiotracer production.

Table 1. Comparison of Fluorine-18 Incorporation among Electron-rich Aryl Rings[a,b]

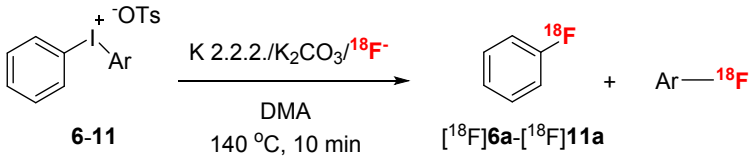


entry	Substrate[c] #; Ar	condition[d]	RCY (%)[e] ^{18}F-Ar	RCY (%)[e] ^{18}F-TMB
1	**1**; Mesityl	A	89 ± 4	N.O.[g]
2	**2**; 4-MeOC$_6$H$_4$	B	29 ± 9[f]	<1
3	**3**; 2-MeOC$_6$H$_4$	C	39 ± 6	N.O.
4	**4**; 4-MeC$_6$H$_4$	C	36 ± 1	N.O.
5	**5**; 2-Thienyl	D	0	N.O.

[a] K 2.2.2. (3.7 mg, 9.7 μmol), K_2CO_3 (0.7 mg, 4.8 μmol); or $TBAHCO_3$ (10 μL, 13.2 μmol; 40% aq solution). [b] Solvent (2 mL). [c] Substrate (3 mM). [d] A: K 2.2.2./K_2CO_3/DMSO/120 °C; B: $TBAHCO_3$/DMSO/160 °C; C: K 2.2.2./K_2CO_3/DMA/160 °C; D: K 2.2.2./K_2CO_3/DMA/160 °C. [e] Average ± SD (n = 2). [f] n = 4. [g] N.O. = not observed.

After initially comparing the chemoselectivity, we radiofluorinated a series of phenyl(aryl)iodonium tosylates with various electron-rich aryl groups to determine whether the RCY could be improved in addition to the demonstrated selectivity. As a model compound to produce [^{18}F]fluorobenzene, phenyl(TMP)iodonium tosylate (**11**) was prepared along with other phenyl(aryl)iodonium tosylates (aryl = 2-anisyl (**6**), 4-anisyl (**7**), 4-tolyl (**8**), mesityl (**9**), and 2-thienyl (**10**)); these iodonium tosylates were radiofluorinated under the same reaction conditions (in DMA at 140 °C for 10 min) to enable a direct comparison (Table 2). Notably, **11** gave the highest RCY with the expected excellent chemoselectivity (Entry 6, Table 2). From these controlled experiments, we found that [^{18}F]fluorobenzene was exclusively produced in a selective manner over the other electron-rich aryl rings. This chemoselectivity is a substantial improvement over that afforded by anisole and thiophene, which are often used as aryl partners with diaryliodonium salts.

Table 2. Radiofluorination of Phenyl(aryl)iodonium Tosylates to Produce [^{18}F]Fluorobenzene with Different Electron-rich Aryl Rings[a]



6-11 [^{18}F]**6a**-[^{18}F]**11a**

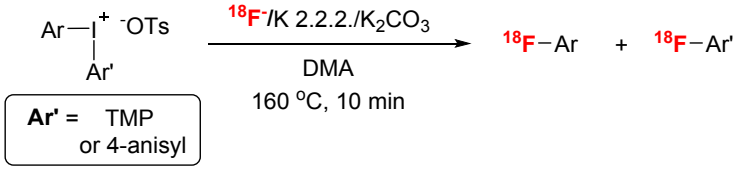
entry	substrate (#; Ar)	RCY (%)[b] ^{18}F-Ph	RCY (%)[b] ^{18}F-Ar	Selectivity for ^{18}F-Ph[c]
1	**6**; 2-$MeOC_6H_4$	7 ± 2	<1	>7

2	**7**; 4-$MeOC_6H_4$	25 ± 0	<1	>25
3	**8**; 4-MeC_6H_4	20 ± 8	6 ± 3	3.3
4	**9**; Mesityl	8 ± 0	29 ± 2	0.3
5	**10**; 2-Thienyl	6 ± 3	<1	>6
6	**11**; TMP	36 ± 7	N.O.[d]	>36

[a] Substrate (3 mM), K 2.2.2. (3.7 mg, 9.7 μmol), K_2CO_3 (0.7 mg, 4.8 μmol), DMA (2 mL). [b] Average ± SD (n = 2). [c] Selectivity: ^{18}F-Ph/^{18}F-Ar. [d] N.O.= not observed.

In addition to the advantageous chemoselectivity of aryl(TMP)iodonium tosylate, aryl(TMP)iodonium and aryl(4-anisyl)iodonium tosylates were compared to investigate whether improved or comparable RCYs were attainable (Table 3). The selected iodonium tosylates (TMP- and 4-anisyl-iodonium tosylates) were radiofluorinated under the same conditions (solvent, temperature, and PTA/base) to directly compare their efficiency. In the comparison of TMP-iodonium tosylate **1** and 4-anisyl-iodonium tosylate **12**, 4-[^{18}F]fluoromesitylene was produced at a higher RCY when the TMP-iodonium tosylate was radiofluorinated. 2-[^{18}F]Fluoroanisole was also produced at a higher RCY with **3** than with the 4-anisyl-iodonium tosylate (**13**). Overall, the aryl(TMP)iodonium tosylates were found to provide higher RCYs than the 4-anisyl-iodonium tosylates. Note that 4-[^{18}F]fluoroanisole was detected using radio-HPLC, whereas little or no [^{18}F]F-TMB was observed in the reaction mixture (see the radio-HPLC chromatogram in Supporting Information). In our study, all of the radioactive products formed by radiofluorination separated well, which might improve the implementation of this methodology for the production of PET radiotracers for clinical study.

Table 3. Comparison between Aryl(TMP)iodonium and Aryl(4-anisyl)iodonium Tosylates for the Radiosynthesis of [^{18}F]Fluoroarenes[a]



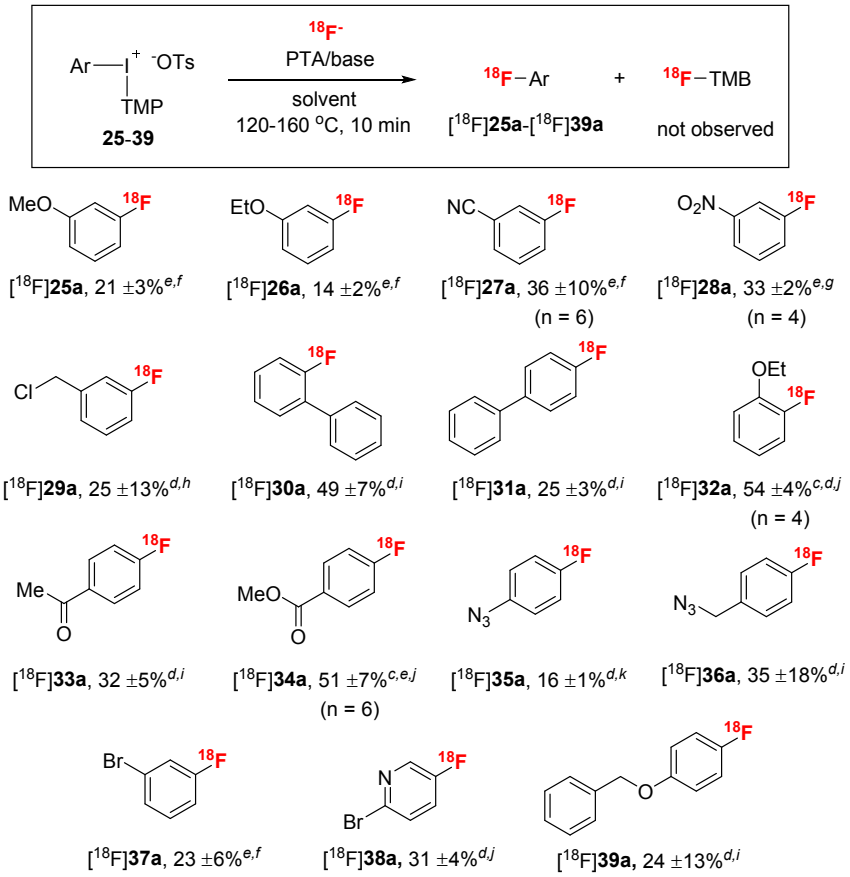
entry	Ar	#	Ar' = 4-anisyl RCY (%)[b]		#	Ar' = TMP RCY (%)[b]	
			^{18}F-Ar	^{18}F-anisole		^{18}F-Ar	^{18}F-TMB
1	Mesityl	**12**	25 ± 2	<1	**1**	85 ± 7	N.O.[c]
2	2-MeOC$_6$H$_4$	**13**	9 ± 2	4 ± 1	**3**	39 ± 6	N.O.
3	2-MeOCH$_2$C$_6$H$_4$	**14**	39 ± 21	N.O.	**15**	48 ± 5	N.O.
4	4-MeC$_6$H$_4$	**16**	31 ± 9	6 ± 2	**4**	36 ± 1	N.O.
5	3-MeC$_6$H$_4$	**17**	26 ± 9	1.3 ± 0.8	**18**	34 ± 17	N.O.
6	2-MeC$_6$H$_4$	**19**	53 ± 13	<1	**20**	68 ± 7	N.O.
7	4-EtOCO-C$_6$H$_4$	**21**	22 ± 5	<1	**22**	42 ± 16	N.O.
8	3-EtOCO-C$_6$H$_4$	**23**	20 ± 2	<1	**24**	35 ± 9	N.O.

[a] Substrate (3 mM), K 2.2.2. (3.7 mg, 9.7 μmol), K_2CO_3 (0.7 mg, 4.8 μmol), DMA (2 mL). [b] Average ± SD (n = 2). [c] N.O.= not observed.

Next, we extended the applicability of the TMP-aryl iodonium tosylates to the synthesis of more functionalized [^{18}F]fluoroarenes (Scheme 2). As demonstrated in the radiofluorination of **1**, one reaction condition could not be accommodated when different substrates were used in radiofluorination. An investigation using TMP-iodonium tosylates revealed that *meta*-[^{18}F]fluoroarenes were produced with excellent chemoselectivity in comparison with the chemoselectivity[16] previous reported for anisyl- and thienyl-aryl rings. The electron-donating methoxy (**25**) and ethoxy (**26**) groups were well tolerated to give 3-[^{18}F]fluoroanisole and 3-[^{18}F]fluorophenetole at 21% and 14% RCY, respectively ([^{18}F]**25a** and [^{18}F]**26a**, Scheme 2). TMP-iodonium tosylates such as CN– (**27**) or NO_2– (**28**) with an electron-withdrawing group at the *meta*-position produced the corresponding [^{18}F]fluoroarenes at 36% and 33% RCY, respectively ([^{18}F]**27a** and [^{18}F]**28a**, Scheme 2). *Meta*-[^{18}F]fluorobenzyl

chloride as a potential [^{18}F]fluoro-alkylating agent was also produced in a single step with a useful RCY ([^{18}F]**29a**, Scheme 2) (see ref. 18f for *para*-[^{18}F]fluorobenzyl chloride from aryl(TMP)iodonium tosylate, which was produced in a microfluidic system). The electron-rich *ortho*- or *para*-substituted [^{18}F]fluoroarenes were obtained at 25–54% RCYs ([^{18}F]**30a**–**32a**, Scheme 2). Notably, little [^{18}F]F-TMB was observed in any of the resultant radiofluorination mixtures except for **32**. [^{18}F]Fluoroarenes with *para*-electron-withdrawing substituents were obtained at useful RCYs ([^{18}F]**33a** and [^{18}F]**34a**, Scheme 2). Azide-functionalized click-labeling synthons were produced in a single step at 16% and 35% RCY ([^{18}F]**35a** and [^{18}F]**36a**, Scheme 2, respectively). Halogen-functionalized homoaromatic and heteroaromatic [^{18}F]fluoroarenes were produced at 23% and 31% RCY ([^{18}F]**37a** and [^{18}F]**38a**, Scheme 2, respectively) as well as [^{18}F]fluorobenzyl ether ([^{18}F]**39a**, 24% RCY).

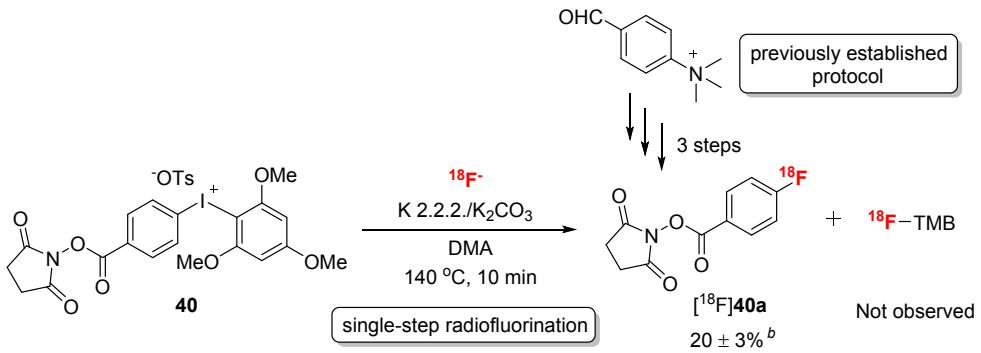
Scheme 2. Radiosynthesis of Functionalized [^{18}F]Fluoroarenes Using Various Aryl(TMP)iodonium Tosylates[a,b]



[a] K 2.2.2. (3.7 mg, 9.7 μmol)/K_2CO_3 (0.7 mg, 4.8 μmol), solvent (2 mL), 10 min. [b] RCYs in parenthesis are average ± SD (n = 2), otherwise specified. [c] $TBAHCO_3$ (10 μL, 13.2 μmol; 40% aq solution). [d] Substrate (3 mM). [e] Substrate (7.5 mM). [f] DMSO, 140 °C. [g] DMSO, 160 °C. [h] DMA, 140 °C. [i] DMA, 160 °C. [j] DMSO, 120 °C. [k] DMA, 120 °C.

Lastly, the radiosynthesis of *N*-succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB; [^{18}F]**40a**)[17a] was demonstrated from a TMP-iodonium precursor, which was previously established in three synthetic steps (Scheme 3). This single-step radiosynthesis[17b,c] of an ^{18}F-fluorinated labeling agent using aryl(TMP)iodonium tosylate could facilitate the subsequent production of protein- and peptide-labeling agents.

Scheme 3. Radiofluorination to Produce the Complex Labeling Building Block [^{18}F]SFB[a]



[a] Substrate (3 mM), K 2.2.2. (3.7 mg, 9.7 μmol), K_2CO_3 (0.7 mg, 4.8 μmol), DMA (2 mL). [b] Average ± SD (n = 3).

In conclusion, the highly chemoselective radiosynthesis of electron-rich [^{18}F]fluoroarenes was realized using aryl(TMP)iodonium tosylates as radiolabeling precursors. Various unsymmetrical TMP-iodonium tosylates were prepared via single-pot *m*CPBA-mediated synthesis to afford 2,4,6-trimethoxyphenyl as a spectator aryl group. The remarkable chemoselectivity for directing the [^{18}F]fluoride ion to electron-rich aryl rings implies that aryl(TMP)iodonium tosylates can provide efficient and reliable radiosynthetic routes to potential PET radiopharmaceuticals, particularly when iodonium salts are used as labeling precursors.

EXPERIMENTAL SECTION

General Information. Reaction progress was monitored by TLC, and TLC spots were visualized under 254 nm UV light. Crude products were purified on a column chromatography using silica gel (0.060–0.020 mm, 60 A). Melting points were recorded using 1101D Mel-Temp® Digital Melting Point Apparatus (Cole-Parmer Ltd, Stone, Staffordshire, UK) and uncorrected. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker Avance III HD 300 spectrometer (300 MHz), installed at Yonsei Center for Research Facilities (YCRF at Yonsei

University, Seoul, Republic of Korea). The chemical shifts for ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, were reported in δ units (ppm) relative to the residual protonated solvent resonance, and the coupling constants (*J*) were given in Hz. FT-IR spectra were recorded on Vertex 70 (Bruker, Billerica, MA, USA), and only major peaks were reported. Electrospray ionization (ESI) high resolution mass spectrometry (HRMS) using a time-of-flight mass spectrometer was performed at Korea Basic Science Institute (KBSI), Ochang, Republic of Korea. The Ultimate 3000 spectra HPLC system (Thermo Scientific, Waltham, MA, USA) comprised a reverse phase column (Luna®, 5 μm, C18(2), 100 Å, 250 × 4.6 mm i.d.; Phenomenex, Torrance, CA, USA) and a radioactivity detector (PMT; Flow-count; Bioscan, Washington, DC, USA). Radioactivity was determined with a CRC®-712M dose calibrator (Capintec, Ramsey, NJ, USA).

Materials. An aluminum-backed plate with silica gel 60 F_{254} for thin-layer chromatography (TLC) analysis was purchased from Macherey-Nagel GmbH & Co. KG (Düren, North Rhine-Westphalia, Germany). Sep-Pak® Light QMA cartridge (carbonate form, part no. 186004540) was purchased from Waters (Milford, MA, USA). 2-Fluorophenetole, 3-fluorophenetole, 3'-fluoroacetophenone, 3-iodobenzyl chloride and 1-(benzyloxy)-4-fluorobenzene were purchased from Combi-Blocks (San Diego, CA, USA). *N*-Succinimidyl 4-fluorobenzoate and 40% aq tetrabutylammonium hydrogen carbonate solution were purchased from FutureChem (Seoul, Republic of Korea). Oxygen-18 enriched water was acquired from Rotem (Beer Sheva, Israel). *Meta*-chloroperbenzoic acid (*m*CPBA) was obtained from Sigma-Aldrich (St. Louis, MO, USA) and used without further treatment. *m*CPBA used in this study has 70–77% active peroxy content and is stabilized with H_2O and *meta*-chlorobenzoic acid. All other chemicals were purchased from Sigma-Aldrich, ACROS organics (Waltham, MA, USA), and Alfa Aesar (Ward Hill, MA, USA) and used as received.

The following iodo- or fluoro-arenes were prepared as described previously: 2-iodophenetole,[18a] 3-iodophenetole,[18a] 1-azido-4-iodobenzene,[18b] 1-azido-4-fluorobenzene,[18b] 4-iodobenzyl azide,[18b] 4-fluorobenzyl azide,[18b] 1-methoxymethyl-2-iodobenzene,[18c] 1-methoxymethyl-2-fluorobenzene,[18d] 2-iodo-1,3,5-trimethoxybenzene,[18e] 2-fluoro-1,3,5-trimethoxybenzene,[18f] and *N*-succinimidyl 4-iodobenzoate.[18g] 2-(Diacetoxyiodo)thiophene was prepared according to the literature method.[18h] The following diaryliodonium tosylates were synthesized according to the known procedures: 2-methoxyphenyl(phenyl)iodonium tosylate (**6**),[18i] 4-methoxyphenyl(phenyl)iodonium tosylate (**7**),[18i] 4-methylphenyl(phenyl)iodonium tosylate (**8**),[18j] 2,4,6-trimethylphenyl(phenyl)iodonium tosylate (**9**),[18i] 2-thienyl(phenyl)iodonium tosylate (**10**),[18i] 2,4,6-trimethylphenyl(4-methoxyphenyl)iodonium tosylate (**12**),[18i] 4-methylphenyl(4-methoxyphenyl)iodonium tosylate (**16**),[18k] 3-methylphenyl(4-methoxyphenyl)iodonium tosylate (**17**),[16] 2-methylphenyl(4-methoxyphenyl)iodonium tosylate (**19**),[18k] 4-ethoxycarbonylphenyl(4-methoxyphenyl)iodonium tosylate (**21**),[18k] and 3-ethoxycarbonylphenyl(4-methoxyphenyl)iodonium tosylate (**23**).[18l]

Syntheses of Diaryliodonium Tosylates. *2-Thienyl(2,4,6-trimethoxyphenyl)iodonium tosylate* (**5**). To a solution of 2-(diacetoxyiodo)thiophene (0.49 g, 1.5 mmol) in dichloromethane (15 mL) was added *p*-TsOH·H_2O (0.31 g, 1.6 mmol) and 1,3,5-trimethoxybenzene (0.29 g, 1.7 mmol). The reaction mixture was stirred at rt for 30 min, and evaporated under reduced pressure. After removal of solvent, the crude oil was triturated with Et_2O. The solid precipitate was filtered, washed with Et_2O (30 mL x 2) and dried in air to give **5** (0.080 g, 10%) as a white solid; m.p. 192–193 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.67 (m, 3 H), 7.50 (d, J = 5.3 Hz, 1 H), 7.10 (d, J = 8.0 Hz, 2 H), 6.98 (dd, J = 5.3, 3.8 Hz, 1 H), 6.12 (s, 2 H), 3.92 (s, 6 H), 3.84 (s, 3 H), 2.33 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 167.0, 159.9, 143.1, 139.6, 139.4, 135.2, 129.1, 128.6, 126.2, 91.7, 77.4, 57.2, 56.1, 21.6.

IR (KBr): 2977, 2946, 1579, 1227, 1176, 1122, 1011, 679 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{14}IO_3S^+$ $[M - OTs]^+$ 376.9708; found 376.9708.

2-Methoxyphenyl(4-methoxyphenyl)iodonium tosylate (**13**). A solution of 2-methoxyiodobenzene (0.23 g, 1.0 mmol) and *m*CPBA (0.34 g, 1.5 mmol) in chloroform (15 mL) was stirred at rt for 4 h. After adding *p*-$TsOH \cdot H_2O$ (0.21 g, 1.1 mmol) and anisole (0.54 g, 5.0 mmol) to the mixture, the reaction mixture was stirred at 40 °C for 2 h, and evaporated under reduced pressure. After removal of solvent, the crude oil was triturated with Et_2O. The solid precipitate was filtered, washed with Et_2O (30 mL x 2) and dried in air to give **13** (0.41 g, 80%) as a white solid; m.p. 141–143 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, J = 9.0 Hz, 2 H), 7.60–7.47 (m, 4 H), 7.06 (d, J = 8.1 Hz, 2 H), 7.01–6.93 (m, 2 H), 6.87 (d, J = 9.1 Hz, 2 H), 3.92 (s, 3 H), 3.81 (s, 3 H), 2.31 (s, 3 H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 162.5, 156.6, 142.8, 139.3, 137.7, 135.4, 134.2, 128.5, 126.1, 123.8, 117.5, 112.4, 104.8, 101.9, 56.9, 55.7, 21.3. IR (KBr): 2946, 2843, 1573, 1480, 1298, 1256, 1187, 1120, 1009, 754, 679 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{14}IO_2^+$ $[M\text{-}OTs]^+$ 341.0038; found 341.0039.

2-Methoxymethylphenyl(4-methoxyphenyl)iodonium tosylate (**14**). Treating 1-methoxymethyl-2-iodobenzene (0.37 g, 1.5 mmol) according to the synthetic procedure for compound **13** gave compound **14** (0.53 g, 67%) as a white solid; m.p. 124–127 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, J = 8.8 Hz, 2 H), 7.58 (d, J = 8.0 Hz, 2 H), 7.43–7.20 (m, 4 H), 7.04 (d, J = 7.8 Hz, 2 H), 6.90 (d, J = 8.8 Hz, 2 H), 4.67 (s, 2 H), 3.82 (s, 3 H), 3.54 (s, 3 H), 2.30 (s, 3 H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 162.8, 143.1, 139.2, 138.7, 138.3, 132.5, 131.3, 131.1, 130.4, 128.5, 126.1, 117.8, 115.6, 101.8, 74.9, 58.8, 55.7, 21.3. IR (KBr): 3070, 2975, 2927, 1491, 1257, 1195, 1091, 1029, 1008, 818, 677 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{16}IO_2^+$ $[M - OTs]^+$ 355.0195; found 355.0195.

General Procedure for Synthesis of Aryl(TMP)iodonium Tosylate from Iodoarene. The following diaryliodonium tosylates were prepared by the modified synthetic

procedure established by Stuart[14] and Olofsson.[15] This series of TMP-iodonium tosylates seemed to have shelf stability for several months when stored in amber vials at 4–8 °C.

Mesityl(2,4,6-trimethoxyphenyl)iodonium tosylate (**1**).[15] A solution of 2-iodomesitylene (0.49 g, 2.0 mmol) and *m*CPBA (0.52 g, 2.3 mmol) in dichloromethane (15 mL) was stirred at rt for 4 h. After adding *p*-TsOH·H_2O (0.42 g, 2.2 mmol) and 1,3,5-trimethoxybenzene (0.50 g, 3.0 mmol) to the mixture, the reaction mixture was stirred at rt for 30 min, and evaporated under reduced pressure. After removal of solvent, the crude oil was triturated with Et_2O. The solid precipitate was filtered, washed with Et_2O (30 mL x 2) and dried in air to give **1** (0.98 g, 84%) as a white solid; m.p. 186–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.1 Hz, 2 H), 7.04 (d, J = 7.9 Hz, 2 H), 6.90 (s, 2 H), 6.12 (s, 2 H), 3.83 (s, 3 H), 3.82 (s, 6 H), 2.61 (s, 6 H), 2.31 (s, 3 H), 2.26 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 166.4, 160.4, 143.4, 142.6, 142.4, 138.9, 129.5, 128.3, 126.0, 122.4, 91.7, 81.9, 56.7, 56.1, 26.6, 21.3, 20.9. HRMS (ESI): calcd. for $C_{18}H_{22}IO_3^+$ [M - OTs]$^+$ 413.0614; found 413.0612.

The following compounds (**2**−**4**, **11**, **15**, **18**, **20**, **22**, and **24**−**40**) were prepared similarly from the appropriate iodoarene and 1,3,5-trimethoxybenzene.

4-Methoxyphenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**2**). Yield (0.33 g, 39%) as a white solid; m.p. 209–212 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 7.87 (d, J = 7.8 Hz, 2 H), 7.68 (d, J = 7.4 Hz, 2 H), 7.19 (d, J = 7.6 Hz, 2 H), 6.97 (d, J = 7.9 Hz, 2 H), 6.38 (s, 2 H), 3.97 (s, 6 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 2.34 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, CD_3OD): δ = 168.6, 164.0, 161.3, 143.6, 141.6, 138.0, 129.8, 126.9, 118.3, 104.5, 92.8, 86.8, 57.7, 56.6, 56.2, 21.3. IR (KBr): 2948, 2842, 1585, 1487, 1230, 1158, 1029, 680 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{18}IO_4^+$ [M - OTs]$^+$ 401.0250; found 401.0247.

2-Methoxyphenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**3**). Yield (0.48 g, 84%) as a pale yellow solid; m.p. 159–161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, J = 7.9 Hz, 2 H), 7.40 (t, J = 7.6 Hz, 1 H), 7.19 (d, J = 7.8 Hz, 1 H), 7.03 (d, J = 7.8 Hz, 2 H), 6.94 (d, J =

8.2 Hz, 1 H), 6.87 (t, *J* = 7.6 Hz, 1 H), 6.16 (s, 2 H), 3.89 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 6 H), 2.29 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ = 167.2, 160.7, 156.3, 143.7, 138.9, 132.9, 132.4, 128.4, 126.1, 123.7, 112.2, 103.4, 91.9, 81.3, 57.2, 57.0, 56.2, 21.4. IR (KBr): 3010, 2975, 2943, 1582, 1478, 1221, 1175, 1123, 1009, 681 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{18}IO_4^+$ $[M - OTs]^+$ 401.0250; found 401.0245.

4-Methylphenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**4**).[14] Yield (0.71 g, 64%) as a white solid; m.p. 200–202 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 7.81 (d, *J* = 8.3 Hz, 2 H), 7.68 (d, *J* = 8.1 Hz, 2 H), 7.26 (d, *J* = 8.2 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 6.40 (s, 2 H), 3.96 (s, 6 H), 3.88 (s, 3 H), 2.36 (s, 3 H), 2.35 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_3OD): δ = 168.7, 161.4, 144.3, 143.6, 141.6, 135.8, 133.4, 129.8, 126.9, 112.2, 92.8, 86.3, 57.7, 56.7, 21.29, 21.28. HRMS (ESI): calcd. for $C_{16}H_{18}IO_3^+$ $[M - OTs]^+$ 385.0301; found 385.0292.

Phenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**11**).[15] Yield (0.72 g, 89%) as a white solid; m.p. 214–216 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 7.94 (d, *J* = 7.7 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 2 H), 7.60 (t, *J* = 7.3 Hz, 1 H), 7.45 (t, *J* = 7.7 Hz, 2 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 6.40 (s, 2 H), 3.96 (s, 6 H), 3.88 (s, 3 H), 2.35 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_3OD): δ = 168.8, 161.4, 143.6, 141.6, 135.8, 133.0, 132.7, 129.8, 126.9, 115.9, 92.9, 86.2, 57.7, 56.7, 21.3. HRMS (ESI): calcd. for $C_{15}H_{16}IO_3^+$ $[M - OTs]^+$ 371.0144; found 371.0143.

2-Methoxymethylphenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**15**). Yield (0.29 g, 24%) as a white solid; m.p. 153–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.0 Hz, 2 H), 7.43–7.32 (m, 2 H), 7.23–7.14 (m, 2 H), 7.06 (d, *J* = 7.8 Hz, 2 H), 6.18 (s, 2 H), 4.69 (s, 2 H), 3.88 (s, 3 H), 3.84 (s, 6 H), 3.63 (s, 3 H), 2.31 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ = 167.3, 160.9, 144.0, 138.7, 138.2, 131.1, 130.9, 130.6, 129.7, 128.3, 126.1, 114.0, 91.9, 83.7, 74.8, 59.1, 57.2, 56.2, 21.3. IR (KBr): 3091, 2941, 2844, 1585, 1462, 1352, 1222, 1180, 1121, 1009, 681 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{20}IO_4^+$ $[M - OTs]^+$ 415.0406; found 415.0406.

3-Methylphenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**18**). Yield (0.82 g, 74%) as a pale yellow solid; m.p. 178–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.70 (m, 3 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.25–7.15 (m, 2 H), 7.10 (d, J = 7.9 Hz, 2 H), 6.16 (s, 2 H), 3.874 (s, 6 H), 3.865 (s, 3 H), 2.32 (s, 3 H), 2.30 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 167.1, 160.6, 143.4, 142.0, 139.1, 134.3, 132.2, 131.1, 130.8, 128.5, 126.1, 115.5, 91.7, 83.5, 57.0, 56.2, 21.4, 21.3. IR (KBr): 3090, 2942, 1584, 1238, 1183, 1119, 1009, 675 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{18}IO_3^+$ [M - OTs]$^+$ 385.0301; found 385.0300.

2-Methylphenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**20**).[13d] Yield (0.80 g, 72%) as a white solid; m.p. 189–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (dd, J = 7.8, 1.1 Hz, 1 H), 7.64 (d, J = 8.1 Hz, 2 H), 7.41–7.30 (m, 2 H), 7.08–7.03 (m, 3 H), 6.13 (s, 2 H), 3.88 (s, 6 H), 3.84 (s, 3 H), 2.68 (s, 3 H), 2.31 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 166.8, 160.4, 143.3, 141.3, 139.1, 137.2, 132.3, 131.3, 128.7, 128.4, 126.0, 121.4, 91.7, 83.7. 56.9, 56.1, 25.6, 21.3. HRMS (ESI): calcd. for $C_{16}H_{18}IO_3^+$ [M - OTs]$^+$ 385.0301; found 385.0302.

[4-(Ethoxycarbonyl)phenyl](2,4,6-trimethoxyphenyl)iodonium tosylate (**22**). Yield (0.96 g, 78%) as a white solid; m.p. 189–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (s, 4 H), 7.71 (d, J = 8.1 Hz, 2 H), 7.11 (d, J = 7.9 Hz, 2 H), 6.17 (s, 2 H), 4.36 (q, J = 7.1 Hz, 2 H), 3.87 (s, 3 H), 3.86 (s, 6 H), 2.33 (s, 3 H), 1.37 (t, J = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 167.3, 165.2, 160.6, 143.1, 139.3, 133.7, 133.0, 132.1, 128.5, 126.1, 120.4, 91.7, 84.3, 61.7, 57.0, 56.1, 21.4, 14.3. IR (KBr): 3096, 2949, 1710, 1585, 1227, 1182, 1120, 677 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{20}IO_5^+$ [M - OTs]$^+$ 443.0355; found 443.0360.

[3-(Ethoxycarbonyl)phenyl](2,4,6-trimethoxyphenyl)iodonium tosylate (**24**). Yield (0.64 g, 52%) as a white solid; m.p. 189–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (s, 1 H), 8.20 (d, J = 8.1 Hz, 1 H), 8.08 (d, J = 7.8 Hz, 1 H), 7.63 (d, J = 8.1 Hz, 2 H), 7.39 (t, J = 8.0 Hz, 1 H), 7.06 (d, J = 8.0 Hz, 2 H), 6.16 (s, 2 H), 4.34 (q, J = 7.1 Hz, 2 H), 3.88 (s, 6 H),

3.85 (s, 3 H), 2.31 (s, 3 H), 1.36 (t, J = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 167.2, 164.4, 160.6, 143.1, 139.3, 138.6, 134.8, 133.3, 132.1, 131.2, 128.5, 126.1, 115.8, 91.7, 84.5, 61.8, 57.0, 56.1, 21.4, 14.3. IR (KBr): 2984, 2940, 1729, 1580, 1225, 1179, 1122, 1010, 681 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{20}IO_5^+$ [M - OTs]$^+$ 443.0355; found 443.0356.

3-Methoxyphenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**25**). Yield (0.75 g, 65%) as a white solid; m.p. 156–158 ^oC. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 8.1 Hz, 2 H), 7.54–7.52 (m, 1 H), 7.29–7.25 (m, 1 H), 7.17 (t, J = 8.2 Hz, 1 H), 7.09 (d, J = 7.9 Hz, 2 H), 6.97–6.93 (m, 1 H), 6.19 (s, 2 H), 3.87 (s, 3 H), 3.86 (s, 6 H), 3.75 (s, 3 H), 2.32 (s, 3 H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 167.2, 160.9, 160.6, 143.4, 139.2, 131.8, 128.5, 126.1, 125.0, 119.0, 117.8, 115.5, 91.7, 83.5, 57.0, 56.2, 55.9, 21.3. IR (KBr): 3089, 2944, 1584, 1236, 1178, 1119, 987, 676 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{18}IO_4^+$ [M - OTs]$^+$ 401.0250; found 401.0240.

3-Ethoxyphenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**26**). Yield (0.79 g, 67%) as a white solid; m.p. 149–151 ^oC. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, J = 8.1 Hz, 2 H), 7.55–7.54 (m, 1 H), 7.26–7.25 (m, 1 H), 7.18–7.10 (m, 3 H), 6.96–6.93 (m, 1 H), 6.17 (s, 2 H), 3.97 (q, J = 7.0 Hz, 2 H), 3.87 (s, 9 H), 2.33 (s, 3 H), 1.36 (t, J = 7.0 Hz, 3 H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 167.2, 160.7, 160.3, 143.3, 139.2, 131.7, 128.5, 126.1, 124.9, 119.5, 118.3, 115.5, 91.7, 83.5, 64.3, 57.0, 56.2, 21.4, 14.6. IR (KBr): 2976, 2939, 1588, 1470, 1236, 1165, 1120, 1008, 680 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{20}IO_4^+$ [M - OTs]$^+$ 415.0406; found 415.0404.

3-Cyanophenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**27**).[14] Yield (0.44 g, 39%) as a pale yellow solid; m.p. 207–209 ^oC. ^1H NMR (300 MHz, CD_3OD): δ = 8.34 (t, J = 1.4 Hz, 1 H), 8.21 (d, J = 8.2 Hz, 1 H), 7.95 (d, J = 7.8 Hz, 1 H), 7.68–7.59 (m, 3 H), 7.20 (d, J = 8.0 Hz, 2 H), 6.43 (s, 2 H), 3.98 (s, 6 H), 3.90 (s, 3 H), 2.36 (s, 3 H). $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD): δ = 169.1, 161.4, 143.6, 141.6, 140.0, 138.8, 136.5, 133.4, 129.8, 126.9, 117.6, 116.2,

115.9, 93.0, 86.4, 57.8, 56.8, 21.3. HRMS (ESI): calcd. for $C_{16}H_{15}NIO_3^+$ [M - OTs]$^+$ 396.0097; found 396.0109.

3-Nitrophenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**28**). Yield (0.24 g, 21%) as a pale yellow solid; m.p. 210–212 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 8.77 (t, J = 1.9 Hz, 1 H), 8.43–8.40 (m, 1 H), 8.31–8.27 (m, 1 H), 7.73–7.64 (m, 3 H), 7.19 (d, J = 8.0 Hz, 2 H), 6.43 (s, 2 H), 3.99 (s, 6 H), 3.90 (s, 3 H), 2.35 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, CD_3OD): δ = 167.8, 160.1, 148.9, 142.3, 140.2, 139.8, 132.3, 129.0, 128.4, 126.2, 125.5, 114.2, 91.7, 85.1, 56.5, 55.4, 19.9. IR (KBr): 2978, 2940, 1585, 1347, 1214, 1164, 1125, 1009, 811, 681 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{15}NIO_5^+$ [M - OTs]$^+$ 415.9995; found 415.9996.

[3-(Chloromethyl)phenyl](2,4,6-trimethoxyphenyl)iodonium tosylate (**29**). Yield (0.52 g, 51%) as a white solid; m.p. 172–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (t, J = 1.7 Hz, 1 H), 7.80 (d, J = 8.2 Hz, 1 H), 7.71 (d, J = 8.2 Hz, 2 H), 7.48 (d, J = 7.7 Hz, 1 H), 7.29 (t, J = 8.0 Hz, 1 H), 7.11 (d, J = 7.9 Hz, 2 H), 6.17 (s, 2 H), 4.49 (s, 2 H), 3.88 (s, 6 H), 3.87 (s, 3 H), 2.33 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 167.2, 160.6, 143.2, 140.9, 139.3, 134.0, 133.5, 131.6, 131.3, 128.5, 126.1, 115.7, 91.7, 83.9, 57.0, 56.1, 44.8, 21.4. IR (KBr): 3006, 2969, 1588, 1467, 1412, 1340, 1191, 1121, 1040, 692 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{17}ICIO_3^+$ [M - OTs]$^+$ 418.9911; found 418.9911.

2-Biphenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**30**). Yield (0.58 g, 47%) as a white solid; m.p. 164–166 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 8.25 (dd, J = 8.1, 1.1 Hz, 1 H), 7.70–7.65 (m, 3 H), 7.54–7.41 (m, 5 H), 7.31–7.28 (m, 2 H), 7.20 (d, J = 7.9 Hz, 2 H), 6.23 (s, 2 H), 3.84 (s, 3 H), 3.69 (s, 6 H), 2.35 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, CD_3OD): δ = 168.5, 161.3, 147.0, 143.7, 142.5, 141.5, 139.0, 133.6, 132.7, 131.1, 130.4, 129.9, 129.8, 129.7, 126.9, 118.9, 92.5, 85.1, 57.4, 56.6, 21.3. IR (KBr): 2937, 2844, 1584, 1472, 1226, 1179, 1130, 1033, 815, 675 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{20}IO_3^+$ [M - OTs]$^+$ 447.0457; found 447.0464.

4-Biphenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**31**).[14] Yield (0.87 g, 71%) as a white solid; m.p. 196–198 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.6 Hz, 2 H), 7.73 (d, J = 8.1 Hz, 2 H), 7.51–7.38 (m, 7 H), 7.10 (d, J = 8.3 Hz, 2 H), 6.18 (s, 2 H), 3.90 (s, 6 H), 3.87 (s, 3 H), 2.30 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 167.1, 160.6, 144.4, 143.3, 139.2, 139.0, 134.4, 130.0, 129.1, 128.5, 127.2, 126.1, 114.1, 91.7, 83.9, 57.1, 56.2, 21.3. HRMS (ESI): calcd. for $C_{21}H_{20}IO_3^+$ [M - OTs]$^+$ 447.0457; found 447.0460.

2-Ethoxyphenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**32**). Yield (1.1 g, 90%) as a white solid; m.p. 179–181 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.2 Hz, 2 H), 7.43–7.37 (m, 1 H), 7.32 (dd, J = 8.0, 1.4 Hz, 1 H), 7.06 (d, J = 8.3 Hz, 2 H), 6.93–6.85 (m, 2 H), 6.16 (s, 2 H), 4.15 (q, J = 7.0 Hz, 2 H), 3.87 (s, 3 H), 3.83 (s, 6 H), 2.31 (s, 3 H), 1.46 (t, J = 7.0 Hz, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 167.1, 160.6, 155.7, 143.7, 138.8, 133.0, 132.9, 128.3, 126.1, 123.5, 112.9, 103.6, 91.8, 81.3, 65.7, 57.1, 56.1, 21.3, 14.6. IR (KBr): 2986, 1580, 1181, 1118, 1010, 679 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{20}IO_4^+$ [M - OTs]$^+$ 415.0406; found 415.0407.

4-Acetylphenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**33**). Yield (0.52 g, 44%) as a white solid; m.p. 204–206 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.03 (d, J = 8.5 Hz, 2 H), 7.95 (d, J = 8.5 Hz, 2 H), 7.46 (d, J = 7.9 Hz, 2 H), 7.10 (d, J = 7.8 Hz, 2 H), 6.48 (s, 2 H), 3.94 (s, 6 H), 3.87 (s, 3 H), 2.57 (s, 3 H), 2.28 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ = 197.4, 166.4, 159.4, 145.8, 138.8, 137.6, 134.4, 130.8, 128.0, 125.5, 120.9, 92.1, 87.1, 57.4, 56.2, 26.9, 20.8. IR (KBr): 2981, 2947, 2844, 1687, 1582, 1346, 1231, 1156, 1004, 681 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{18}IO_4^+$ [M - OTs]$^+$ 413.0250; found 413.0249.

[4-(Methoxycarbonyl)phenyl](2,4,6-trimethoxyphenyl)iodonium tosylate (**34**).[14] Yield (0.52 g, 48%) as a white solid; m.p. 195–197 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 8.05–7.99 (m, 4 H), 7.67 (d, J = 8.2 Hz, 2 H), 7.19 (d, J = 7.9 Hz, 2 H), 6.42 (s, 2 H), 3.97 (s, 6 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 2.34 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, CD_3OD): δ = 169.0, 166.8, 161.5,

143.6, 141.6, 135.8, 134.5, 133.2, 129.8, 126.9, 120.5, 93.0, 86.1, 57.8, 56.7, 53.1, 21.3. HRMS (ESI): calcd. for $C_{17}H_{18}IO_5^+$ [M - OTs]$^+$ 429.0199; found 429.0197.

4-Azidophenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**35**).[13b] Yield (0.53 g, 44%) as a white solid; m.p. 187–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, J = 8.9 Hz, 2 H), 7.69 (d, J = 8.2 Hz, 2 H), 7.10 (d, J = 7.9 Hz, 2 H), 6.92 (d, J = 8.9 Hz, 2 H), 6.16 (s, 2 H), 3.88 (s, 6 H), 3.86 (s, 3 H), 2.33 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 167.1, 160.5, 143.6, 143.2, 139.3, 135.9, 128.5, 126.1, 121.8, 109.7, 91.7, 84.5, 57.0, 56.1, 21.3. HRMS (ESI): calcd. for $C_{15}H_{15}N_3IO_3^+$ [M - OTs]$^+$ 412.0158; found 412.0159.

[4-(Azidomethyl)phenyl](2,4,6-trimethoxyphenyl)iodonium tosylate (**36**). Yield (0.58 g, 50%) as a white solid; m.p. 177–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.5 Hz, 2 H), 7.67 (d, J = 8.1 Hz, 2 H), 7.24 (d, J = 8.5 Hz, 2 H), 7.08 (d, J = 7.9 Hz, 2 H), 6.16 (s, 2 H), 4.34 (s, 2 H), 3.85 (s, 9 H), 2.31 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 167.2, 160.6, 143.2, 139.3, 134.3, 130.7, 128.5, 126.1, 115.0, 91.7, 84.0, 57.0, 56.1, 53.8, 21.4. IR (KBr): 2945, 2093, 1581, 1228, 1177, 1118, 1009, 679 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{17}N_3IO_3^+$ [M - OTs]$^+$ 426.0315; found 426.0315.

3-Bromophenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**37**). Yield (0.53 g, 43%) as a white solid; m.p. 175–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.89 (m, 2 H), 7.70 (d, J = 8.1 Hz, 2 H), 7.57 (d, J = 8.1 Hz, 1 H), 7.19 (t, J = 8.3 Hz, 1 H), 7.11 (d, J = 8.0 Hz, 2 H), 6.17 (s, 2 H), 3.88 (s, 6 H), 3.87 (s, 3 H), 2.33 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 167.2, 160.6, 143.1, 139.3, 136.0, 134.4, 132.8, 132.4, 128.6, 126.1, 123.9, 115.8, 91.8, 84.6, 57.1, 56.2, 21.4. IR (KBr): 3084, 2943, 1579, 1453, 1227, 1119, 1009, 817, 678 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{15}IBrO_3^+$ [M - OTs]$^+$ 448.9249; found 448.9253.

6-Bromopyridin-3-yl(2,4,6-trimethoxyphenyl)iodonium tosylate (**38**). Yield (0.78 g, 63%) as a white solid; m.p. 206–208 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 8.81 (d, J = 2.4 Hz, 1 H), 8.21 (dd, J = 8.5, 2.5 Hz, 1 H), 7.69 (d, J = 8.3 Hz, 3 H), 7.22 (d, J = 7.9 Hz, 2 H), 6.44

(s, 2 H), 4.00 (s, 6 H), 3.90 (s, 3 H), 2.37 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_3OD): δ = 169.1, 161.3, 155.0, 146.3, 145.6, 143.5, 141.6, 132.6, 129.8, 126.9, 114.0, 93.0, 86.2, 57.8, 56.7, 21.3. IR (KBr): 3163, 2943, 2845, 1585, 1344, 1232, 1119, 1009, 682 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{14}NIBrO_3^+$ $[M - OTs]^+$ 449.9202; found 449.9202.

[4-(Benzyloxy)phenyl](2,4,6-trimethoxyphenyl)iodonium tosylate (**39**). Yield (0.75 g, 60%) as a white solid; m.p. 191–193 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 7.87 (d, J = 9.0 Hz, 2 H), 7.68 (d, J = 8.1 Hz, 2 H), 7.41–7.29 (m, 5 H), 7.19 (d, J = 8.0 Hz, 2 H), 7.04 (d, J = 9.0 Hz, 2 H), 6.38 (s, 2 H), 5.10 (s, 2 H), 3.96 (s, 6 H), 3.87 (s, 3 H), 2.34 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_3OD): δ = 168.6, 163.1, 161.3, 143.6, 141.6, 138.0, 137.6, 129.8, 129.6, 129.2, 128.7, 126.9, 119.3, 104.8, 92.8, 86.7, 71.4, 57.7, 56.6, 21.3. IR (KBr): 2946, 2844, 1580, 1471, 1227, 1164, 1006, 807, 678 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{22}IO_4^+$ $[M - OTs]^+$ 477.0563; found 477.0562.

{4-[(2,5-Dioxopyrrolidinyloxy)carbonyl]phenyl}(2,4,6-trimethoxyphenyl)iodonium tosylate (**40**). The reaction was performed in accordance with the synthetic procedure for compound **1** with slight modification (reaction medium: MeCN, reaction temperature: 60 °C) to yield compound **40** (0.40 g, 30%) as a white solid; m.p. 143–145 °C. ^{1}H NMR (300 MHz, CD_3OD): δ = 8.18–8.11 (m, 4 H), 7.69 (d, J = 8.2 Hz, 2 H), 7.22 (d, J = 7.9 Hz, 2 H), 6.45 (s, 2 H), 3.99 (s, 6 H), 3.91 (s, 3 H), 2.90 (s, 4 H), 2.36 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_3OD): δ = 170.1, 167.8, 160.9, 160.1, 142.2, 140.3, 134.8, 132.4, 128.4, 128.3, 125.6, 121.1, 91.7, 84.7, 56.5, 55.4, 25.2, 19.9. IR (KBr): 2945, 1741, 1585, 1208, 1163, 1122, 1008, 680 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{19}INO_7^+$ $[M - OTs]^+$ 512.0206; found 512.0207.

Radiochemistry: A General Procedure. No-carrier-added $[^{18}F]$fluoride ion was produced via $[^{18}O(p,n)^{18}F]$ nuclear reaction by irradiation of $[^{18}O]H_2O$ on a GE PETtrace 16.5 MeV cyclotron (GE Healthcare, Madison, WI, USA). Typical irradiation parameters, including 40 μA for 3 min, resulted in 5.5 ± 0.7 GBq (150 ± 20 mCi) of $[^{18}F]$fluoride ion in $[^{18}O]H_2O$

target water. The cyclotron-produced [^{18}F]fluoride ion (1.0–1.5 GBq) in $H_2{}^{18}O$ was trapped on a QMA cartridge preconditioned with 10 mL H_2O, and the trapped [^{18}F]fluoride ion was released with a PTA solution (K 2.2.2. (15 mg, 39 μmol) and K_2CO_3 (2.7 mg, 19 μmol) in MeCN-H_2O (49:1 v/v; total 1200 μL); or $TBAHCO_3$ (40 μL, 53 μmol; 40% aq solution) in 1.0 mL MeCN). The residual target water was removed by azeotropic evaporation with MeCN at 110 °C for 10 min, then cooled to rt for 3 min. The resulting [^{18}F]fluoride ion complex was solubilized in organic solvent (DMF, DMA, or DMSO; 4.0 mL) by stirring at rt for 5 min. The iodonium tosylate precursor solution (*ca.* 3.0 or 7.5 mM) in the corresponding solvent (1.0 mL) was added to $^{18}F^-$/K 2.2.2./K_2CO_3 or $^{18}F^-$/$TBAHCO_3$ complex solution (1.0 mL). The radiofluorination was performed in a borosilicate glass vessel with silicone cap containing Teflon septum using conductively heated reactor[19] (Monowave 50, Anton Paar GmbH, Austria) at different temperatures (120–160 °C) for 10 min. Then the reaction mixture was cooled to 60 °C, and an aliquot (*ca.* 200 μL) was diluted with MeCN-H_2O (40:60 v/v, 3 mL) and subjected to reverse-phase radio-HPLC. RCYs of the [^{18}F]fluoroarenes were determined by radio-HPLC. The identity of [^{18}F]fluoroarenes was confirmed with coinjection of non-radioactive fluoro-standards.

ASSOCIATED CONTENT

Supporting Information

Screening of conditions for radiofluorination, radio-HPLC chromatograms, and ^{1}H and ^{13}C{^{1}H} NMR spectra (PDF) are available. The material is available free of charge on the ACS Publications website at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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