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Rapid and Efficient Radiosyntheses of *meta*-Substituted [^{18}F]Fluoroarenes from [^{18}F]Fluoride Ion and Diaryliodonium Tosylates within a Microreactor

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Effective methods for the introduction of the short-lived positron-emitter fluorine-18 ($t_{1/2}$ = 109.7 min) at high specific radioactivity into fluoroarenes are valuable for the development of radiotracers for molecular imaging with positron emission tomography. We have explored the scope of the radiofluorination of diaryliodonium salts with no-carrier-added (NCA) [^{18}F]fluoride ion for the preparation of otherwise difficult to access *meta*-substituted [^{18}F]fluoroarenes. A microfluidic reaction platform was used to establish optimal radiochemical yields. Rapid, high yielding and selective radiofluorinations were achieved in unsymmetrical diaryliodonium tosylates (ArI$^+$Ar′TsO$^-$), in which Ar carried either a *meta* electron-withdrawing (CN, NO_2, CF_3) or electron-donating (Me or MeO) group, and in which the partner aryl group (Ar′) was relatively electron-rich, such as Ph, 3-MeC_6H_4, 4-MeOC_6H_4, 2-thienyl, or 5-Me-2-thienyl. The radiofluorination of appropriate diaryliodonium tosylates is therefore a generally useful method for the preparation of simple [^{18}F]*m*-fluoroarenes ([^{18}F]ArF).

Introduction

The short-lived positron-emitter, fluorine-18 ($t_{1/2}$ = 109.7 min), has gained great importance as a radiolabel for probes used with positron emission tomography (PET)[1] – a molecular imaging technique that is widely applied both in clinical research[2] and in drug development.[3–8] Expansion of the utility of PET depends on the development and availability of radioactive probes that are specific to particular biochemical targets or pathways. Radioligands bind to specific protein targets such as enzymes, channels, receptors, or transporters to enable their concentrations to be determined in vivo.[9] Yet other radiotracers may act as enzyme substrates and so permit other types of measurement, such as [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) for measuring glucose metabolism.[10] Fluorine-18 is attractive as a radiolabel for several reasons. These include that (i) fluorine may to some extent mimic a hydrogen atom or hydroxy group in an organic molecule, (ii) the half-life of fluorine-18 is well suited to monitoring kinetics in vivo over an acceptably short scanning session, and (iii) fluorine-18 can be produced with a moderate energy cyclotron in very high activities and specific activities through the ^{18}O(p,n)^{18}F reaction on ^{18}O-enriched water.[11,12] The ease of production of high amounts of fluorine-18 coupled with its almost 2 h half-life also allows this isotope to be distributed over distances that may be covered in a few hours to sites where a production cyclotron is unavailable. Hence, some useful ^{18}F-labeled radiotracers, such as [^{18}F]FDG, have become commercially available for clinical application through a network of regional distribution centers.

The ^{18}O(p,n)^{18}F reaction on ^{18}O-enriched water provides the fluorine-18 as aqueous fluoride ion. Therefore, all radiochemistry with fluorine-18 from this method of production must first involve a reaction of fluoride ion. In general, this usually implies an aliphatic or aromatic nucleophilic substitution reaction.[13] Labeling at aliphatic carbon atoms can be accomplished efficiently. However, fluorine-18 bonded to aliphatic carbon may be prone to defluorination in vivo, giving rise to [^{18}F]fluoride ion, which then binds avidly to bone. Defluorination can be problematic for PET scanning. For example, the uptake of [^{18}F]fluoride ion by skull may compromise PET measurements with the parent radiotracer in nearby brain. For this reason, attachment of fluorine-18 to an aryl carbon atom is often more attractive, since tendency for radiodefluorination is usually greatly reduced.

Several methods for preparing ^{18}F-labeled aryl fluorides have been evaluated and applied. These include the Balz–Schiemann reaction,[14] the Wallach reaction,[15] and classical aromatic nucleophilic substitution[13,16,17] (Scheme 1). The Balz–Schiemann reaction suffers from low maximal theoretical radiochemical yield (25%), which in practice may be very much lower on complex substrates, and also dilution of specific radioactivity due to the co-production on non-radioactive fluoro product from the usual tetrafluoroborate anion. The latter problem may be circumvented by

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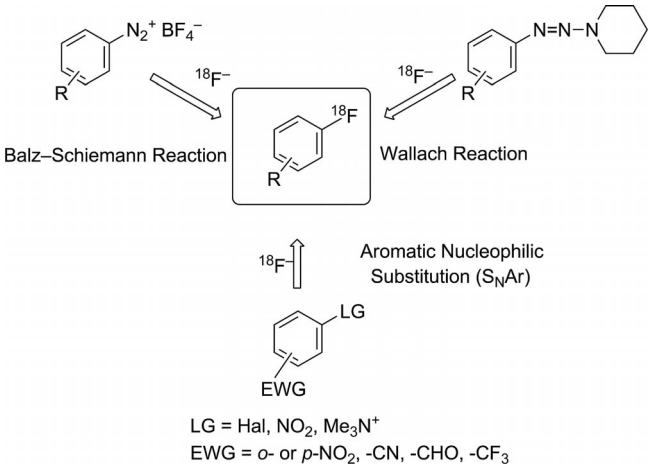
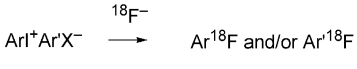
use of non-fluorine-containing anions, but the process is difficult, and radiochemical yields remain low.[18] The Wallach reaction may be performed at high specific radioactivity but again radiochemical yields tend to be very low on complex substrates. Over recent decades, classical aromatic nucleophilic substitution has become the most established and popular method for preparing [^{18}F]fluoroarenes at high specific radioactivity.[13,16,17] High radiochemical yields can be obtained, especially when deploying nitro or trimethylamino as the leaving group. Nevertheless, this method also has some limitations. In particular, an electron-withdrawing group, generally in *ortho* or *para* position to the leaving group, is required on the ring to be fluorinated.



Scheme 1. Well-explored approaches to the radiosyntheses of [^{18}F]-fluoroarenes from [^{18}F]fluoride ion.

A more recently explored method for the preparation of [^{18}F]fluoroarenes is the reaction of [^{18}F]fluoride ion with diaryliodonium salts (Scheme 2).[19–23] This method permits the introduction of [^{18}F]fluoride ion not only into electron-deficient but also into electron-rich rings, and into *ortho*,[24] *meta* or *para* position to substituents. A mechanism that is wholly distinct from classical aromatic nucleophilic substitution probably accounts for these useful features.[24,25] Despite the great potential of this labeling method, its scope has not been studied systematically. Here, we take advantage of the benefits of a microfluidic apparatus[26–29] for performing sequential small-volume radiofluorination reactions under well-controlled conditions as we described previously,[24,30,31] in order to study the reactions of diaryliodonium salts with [^{18}F]fluoride ion to prepare *meta*-substituted [^{18}F]fluoroarenes. We show that these [^{18}F]fluoroarenes can be obtained rapidly and in high radiochemical yield regardless of the electron-donating or withdrawing nature of the *meta* substituent, provided that the partner ring in the diaryliodonium salt is relatively electron-rich.



Scheme 2. Synthesis of [^{18}F]fluoroarenes from the radiofluorination of diaryliodonium salts.

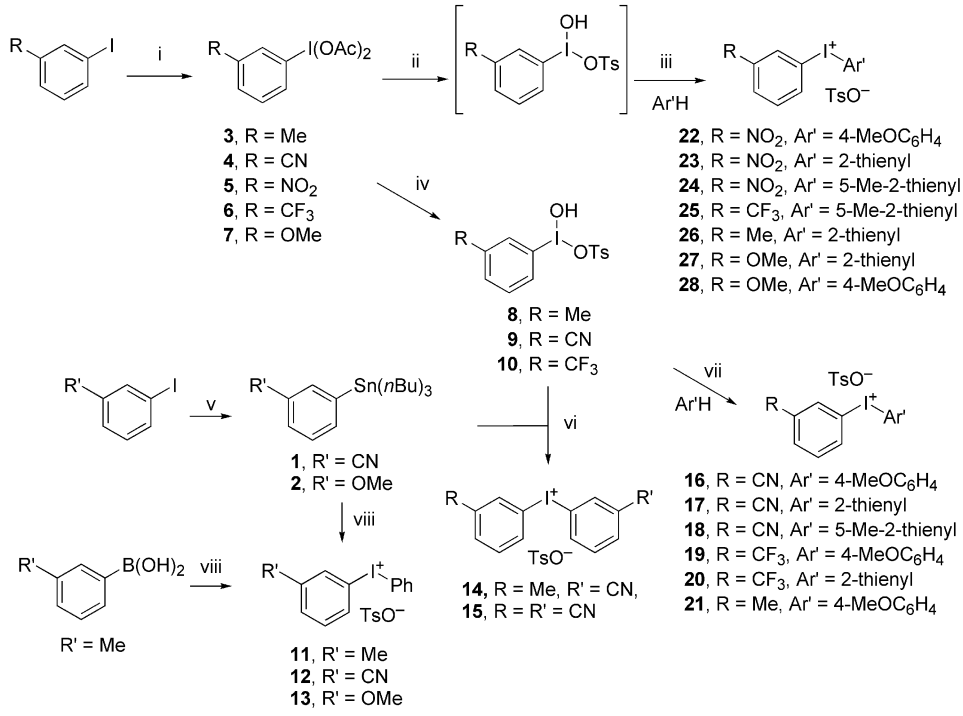
Results and Discussion

Our aim was to study the reactivity of no-carrier-added (NCA) [^{18}F]fluoride ion towards diaryliodonium salts ($ArI^+Ar'X^-$) bearing one of five *meta* substituents (OMe, Me, CN, CF_3, or NO_2) in one ring (Ar), where this ring is partnered in the salt with another relatively electron-rich ring (Ar′) selected from Ph, 3-MeC_6H_4, 4-MeOC_6H_4, 2-thienyl, or 5-Me-2-thienyl. It was necessary to prepare each of these salts, with poorly nucleophilic tosylate as the preferred counter anion (X^- = TsO^-).

Synthesis of Diaryliodonium Salts

Essentially three methods were used to prepare the diaryliodonium salts required for this study. These methods are based on the use of an isolated or in-situ generated *meta*-substituted [hydroxy(tosyloxy)iodo]arene (HTIA) with (i) an electron-rich arene, (ii) an arylboronic acid,[32] or (iii) an aryltri-*n*-butylstannane[33] (Scheme 3).

The *meta*-substituted (diacetoxyiodo)arenes **3**–**7**, required to prepare HTIAs as reactive intermediates, were obtained by oxidation of the corresponding iodoarenes with peracetic acid in acetic acid in generally moderate to high yields (16–75%). The required *meta*-substituted HTIAs were then prepared by treating the appropriate substituted (diacetoxyiodo)arene with tosic acid monohydrate in acetonitrile. The HTIAs bearing a *meta*-Me (**8**), -CN (**9**), or -CF_3 (**10**) substituent were isolated in high yields (72–91%), and in some examples these were also prepared and used in situ. HTIAs with a *meta*-NO_2 or -MeO group were prepared and used in situ only. Regiospecific control was required for the synthesis of unsymmetrically substituted diaryliodonium salts, in which each aromatic ring is differently substituted. The direct treatment of reactive electron-rich arenes, such as anisole, thiophene and 2-methylthiophene, with HTIAs was found to be regiospecific and produced the 4-methoxyphenyl, 2-thienyl and 5-methyl-2-thienyl aryliodonium tosylates, respectively. In this manner, we produced the diaryliodonium tosylates **16**–**21** from isolated HTIAs in moderate to high yields (36–86%) and **22**–**28** from in-situ generated HTIAs in high yields (81–98%). In the syntheses of other diaryliodonium salt, regioselectivity was conferred by treatment of a substituted arylboronic acid or a substituted aryltri-*n*-butylstannane with the appropriate HTIA.[32,33] Thus, (3-methylphenyl)(phenyl)-iodonium tosylate (**11**) was obtained from 3-tolylboronic acid in low but useful yield (20%). Aryltri-*n*-butylstannanes gave the iodonium tosylates **12**–**15** in low to moderate yields (25–59%). The requisite 1-cyano-3-(tri-*n*-butylstannyl)benzene (**1**) and 1-methoxy-3-(tri-*n*-butylstannyl)benzene (**2**) were readily obtained from the corresponding iodoarenes with hexabutylditin in moderately high yields (73%). All prepared diaryliodonium salts were stable to long-term storage at 4–5 °C under argon.



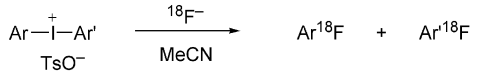
Scheme 3. Preparation of *meta*-substituted diaryliodonium tosylates **11**–**28**. Reagents, conditions and yields: (i) peracetic acid, AcOH, room temp., 4 h for **3** (46%), 14 h for **4** (75%), 6 h for **5** (59%), 6 h for **6** (43%), 1 h for **7** (16%); (ii) TsOH·H_2O, MeCN; (iii) $CHCl_3$, reflux, 3 h for **22** (87%), **23** (82%), **24** (90%), **25** (98%), **26** (90%), **27** (86%), **28** (81%); (iv) TsOH·H_2O, MeCN for **8** (72%), **9** (79%), **10** (91%); (v) Sn_2Bu_6, $Pd(PPh_3)_4$, toluene, reflux, 14 h for **1** (73%), **2** (73%); (vi) CH_2Cl_2, reflux, 4 h for **14** (25%), **15** (59%); (vii) $CHCl_3$, reflux, 4 h for **16** (54%), **17** (69%), **18** (36%), **19** (85%), **20** (86%), **21** (85%); (viii) Koser's reagent, CH_2Cl_2; 30 min, room temp. for **11** (20%), 4 h, reflux for **12** (32%), **13** (59%).

Radiochemistry

All radiochemistry was performed in a microfluidic apparatus. We have recently described the construction and operation of this apparatus.[24] In essence, the apparatus has a coiled silica glass capillary tube micro-reactor with an internal volume of 31.4 μL. This reactor is housed in a heater which can be thermostatted to any set temperature up to 200 °C. The reactor can be infused simultaneously with two solutions, a solution of diaryliodonium salt and a solution of the [^{18}F]fluoride ion reagent, each from a separate reservoir at a set flow rate. The reaction time is taken to equate to the residence time of reagents in the micro-reactor, which is the internal volume of the reactor divided by its effluent flow rate. Decay-corrected radiochemical yields (RCYs) were estimated from the reverse-phase HPLC analysis of reactor effluent based on the percentage of radioactivity in the radiochromatogram represented by radioactive product. All injected radioactivity was found to elute from the HPLC column. The HPLC measurement was subsequently corrected for the proportion of used radioactivity not recovered from the micro-reactor apparatus, which was assumed to be adsorbed [^{18}F]fluoride ion. Radioactivity recovery was moderate and variable (48 ± 27%, n = 19). Adsorption is a common phenomenon in reactions of dry NCA [^{18}F]-fluoride ion, regardless of reactor material (e.g., glass, glassy carbon or platinum).[34]

The microfluidic apparatus allows radiofluorination reactions to be performed in rapid sequence under very controlled conditions of reagent concentrations, residence time and temperature. Therefore, we tested each reaction under different conditions, in a search for the optimal radiochemical yield of [^{18}F]*m*-fluoroarenes. Usually, between 10 and 14 different conditions were tried, involving several different reaction temperatures. Decay-corrected radiochemical yields are reported for conditions found to give the highest incorporation of [^{18}F]fluoride ion into [^{18}F]fluoroarenes. The diaryliodonium tosylates were adequately soluble in acetonitrile, and this was chosen as a suitable polar aprotic reaction medium. Acetonitrile is widely used for reactions with [^{18}F]fluoride ion, particularly aliphatic nucleophilic substitution reactions, since the [^{18}F]fluoride ion is readily solubilized in the presence of K^+-K 2.2.2 (K 2.2.2 = 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane) as counter anion. In general, acetonitrile solutions of diaryliodonium salts were infused into the reactor at a concentration of 10 mM and at an infusion rate equal to that of the acetonitrile solution of NCA [^{18}F]fluoride ion K^+-K 2.2.2 complex. Thus, the concentration of salt within the micro-reactor was generally 5 mM. These concentrations are similar to those used in our preceding study of the radiofluorination of *ortho*-substituted diaryliodonium salts.[24] Reaction times were generally less than 5 min.

Table 1. RCYs of [^{18}F]*m*-fluoroarenes (Ar^{18}F) from the NCA radiofluorination of diaryliodonium tosylates bearing a *meta* electron-withdrawing substituent.

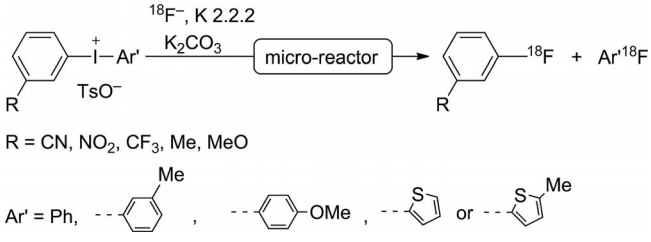


Entry	Diaryliodonium salt (ArI$^+$Ar′TsO$^-$)			*T*	*t*[a]	RCY of [^{18}F]fluoroarene [%][b]			Selectivity for Ar^{18}F
		Ar	Ar′	[°C]	[s]	Total	Ar^{18}F	Ar′^{18}F	
1	**15**	3-NCC$_6$H$_4$	3-NCC$_6$H$_4$	160	189	55	55		n.a.
2	**12**	3-NCC$_6$H$_4$	Ph	130	146	26	25	< 1	> 25
3	**16**	3-NCC$_6$H$_4$	4-MeOC$_6$H$_4$	130	146	93	82	11	7
4	**14**	3-NCC$_6$H$_4$	3-MeC$_6$H$_4$	160	189	81	76	5	15
5	**17**	3-NCC$_6$H$_4$	2-thienyl	160	189	60	58	2	29
6	**18**	3-NCC$_6$H$_4$	5-Me-2-thienyl	180	189	79	78	1	78
7	**22**	3-O$_2$NC$_6$H$_4$	4-MeOC$_6$H$_4$	130	191	65	58	7	8
8	**23**	3-O$_2$NC$_6$H$_4$	2-thienyl	130	140	35	31	4	8
9	**24**	3-O$_2$NC$_6$H$_4$	5-Me-2-thienyl	160	189	39	37	2	19
10	**19**	3-F$_3$CC$_6$H$_4$	4-MeOC$_6$H$_4$	190	189	54	53	< 1	> 53
11	**20**	3-F$_3$CC$_6$H$_4$	2-thienyl	180	236	66	66	0	> 66
12	**25**	3-F$_3$CC$_6$H$_4$	5-Me-2-thienyl	190	189	57	57	0	> 57

[a] Residence time in micro-reactor. [b] Decay-corrected, optimized yield chosen from 10–14 different runs. n.a. = not applicable.

Micro-reactor effluents were quenched by dilution in acetonitrile/water (1:1, v/v) at room temperature and then analyzed by reverse-phase HPLC with radioactivity detection. Radiochromatograms were in all cases simple, showing only separated [^{18}F]fluoride ion at or near the solvent front and either one or two later-eluted [^{18}F]fluoroarenes. The [^{18}F]*m*-fluoroarenes were identified by their comobility in HPLC with reference fluoroarenes.

We first investigated whether the radiofluorination of diaryliodonium salts was a viable route to [^{18}F]fluoroarenes bearing an electron-withdrawing *meta* substituent (Table 1). The reactions of 12 salts were studied (Scheme 4). These carried a *meta*-CN, -NO$_2$, or -CF$_3$ group on one ring. The other ring was relatively electron-rich: phenyl, 3-tolyl, 4-anisyl, 2-thienyl, or 5-Me-2-thienyl, or in one case 3-NCC$_6$H$_4$ in a symmetrical salt.

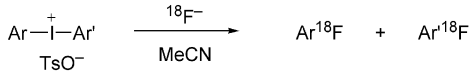


Scheme 4. Preparation of [^{18}F]*m*-fluoroarenes from NCA radiofluorination of diaryliodonium salts within a micro-reactor.

Radiofluorination of the symmetrical salt (**15**) produced [^{18}F]*m*-fluorobenzonitrile as the only radioactive product at 160 °C in 55% RCY in just over 3 min (Table 1, Entry 1). Use of the unsymmetrical salt in which one ring was phenyl (**12**) reduced the RCY of [^{18}F]*m*-fluorobenzonitrile to 25% at 130 °C (Table 1, Entry 2). The selectivity for this product was, however, very high (> 25). When the *m*-cyanophenyl ring was partnered with a more electron-rich aryl ring, substantially improved RCYs (58–82%) of [^{18}F]*m*-fluorobenzonitrile were obtained with generally high selectivities (Table 1, Entries 3–6). The radiofluorination of diaryliodonium salts having an electron-rich aryl ring (4-MeOC$_6$H$_4$, 2-thienyl, or 5-Me-2-thienyl) and a phenyl ring bearing a *meta*-NO$_2$ (**22**–**24**) or -CF$_3$ group (**19**, **20**, **25**) also produced *meta*-substituted [^{18}F]fluoroarenes in moderate to quite high RCYs (31–66%) and with high selectivities (Table 1, Entries 7–12). RCYs varied somewhat with the nature of the electron-rich ring, especially for the *m*-nitro salts. Overall, these results showed that diaryliodonium tosylates can be effective precursors for the rapid (< 5 min) preparation of [^{18}F]fluoroarenes bearing *meta* electron-withdrawing substituents. Hence, this method is a useful adjunct to classical aromatic nucleophilic substitution with [^{18}F]fluoride ion in arenes carrying a leaving group in *meta* position to a nitro group.[35–37]

We next studied the radiofluorination of diaryliodonium tosylates bearing *meta* electron-donating methyl or methoxy substituents in one ring, and in which the partner ring was electron-rich Ph, 2-thienyl, or 4-methoxyphenyl (Table 2). The reactions of 6 salts were studied (Scheme 4). RCYs of [^{18}F]*m*-fluoroarenes and product selectivities greatly depended on the nature of the non-*meta*-substituted electron-rich ring. Where this ring was phenyl as in **11**, the RCY of [^{18}F]*m*-fluorotoluene was low (12%) and less than that of [^{18}F]fluorobenzene (15%) (Table 2, Entry 1). By contrast, the RCY of [^{18}F]*m*-fluoroanisole from the phenyl compound **13** was exceptionally high (87%), and co-production of [^{18}F]fluorobenzene was low (6% RCY) (Table 2, Entry 5). Use of 2-thienyl as the electron-rich ring partner gave low RCYs of the target *meta*-substituted [^{18}F]fluoroarenes but with acceptable selectivity (Table 2, Entries 3 and 6). Use of 4-methoxyphenyl as electron-rich ring partner gave [^{18}F]*m*-fluorotoluene from **21** in moderately high RCY (47%) and good selectivity (Table 1, Entry 2), and gave

Table 2. RCYs of [^{18}F]*m*-fluoroarenes (Ar^{18}F) from the NCA radiofluorination of diaryliodonium tosylates bearing a *meta* electron-donating substituent.



Entry	Diaryliodonium salt (ArI$^+$Ar′TsO$^-$)			T	t[a]	RCY of [^{18}F]fluoroarene [%][b]			Selectivity for Ar^{18}F
		Ar	Ar′	[°C]	[s]	Total	Ar^{18}F	Ar′^{18}F	
1	**11**	3-MeC$_6$H$_4$	Ph	160	236	27	12	15	1
2	**21**	3-MeC$_6$H$_4$	4-MeOC$_6$H$_4$	180	236	52	47	5	9
3	**26**	3-MeC$_6$H$_4$	2-thienyl	190	236	27	26	< 1	> 26
4[c]	**26**	3-MeC$_6$H$_4$	2-thienyl	200	236	82	82	0	> 82
5	**13**	3-MeOC$_6$H$_4$	Ph	150	236	93	87	6	15
6	**27**	3-MeOC$_6$H$_4$	2-thienyl	200	314	10	9	1	9
7	**28**	3-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	180	236	37	36	1	36

[a] Residence time in micro-reactor. [b] Decay-corrected, optimized yield chosen from 10–14 different runs. [c] Reaction performed in DMF.

[^{18}F]*m*-fluoroanisole from **28** in moderately high RCY (36%) with very high selectivity (Table 2, Entry 7). These results show that the treatment of diaryliodonium salts with [^{18}F]fluoride ion can rapidly produce simple [^{18}F]*m*-fluoroarenes with electron-donating substituents in impressively high yields under selected conditions. Diaryliodonium tosylates that have 4-methoxyphenyl as one of the aryl rings gave generally moderate to high RCYs with high product selectivity. Thus, the reactions of appropriately designed diaryliodonium salts with [^{18}F]fluoride ion is a uniquely effective method for the rapid preparation of NCA [^{18}F]fluoroarenes bearing *meta* electron-donating groups, such as Me or OMe.

In this study, we did not systematically study the influence of solvent on RCY; the vast majority of reactions were conducted in acetonitrile, which in the microfluidic apparatus could be used well above its boiling point. The RCY of [^{18}F]*m*-fluoroanisole from the 2-thienyl salt **26** was dramatically improved to 82% when the reaction was conducted in DMF instead of acetonitrile (Table 2, Entry 4). Thus, reaction outcomes might well be influenced by solvent (compare Entries 4 and 3 in Table 2), and this may warrant a further detailed study. In our previous study on the radiofluorination of *ortho*-substituted diaryliodonium salts, we mainly used DMF (with trace water) as a solvent with impressive results.[24]

In a previous study, the free radical scavenger TEMPO was reported to be beneficial for improved yield and reproducibility in the reactions of fluoride ion with diaryliodonium salts.[23] As in our previous study of the radiofluorination of *ortho*-substituted diaryliodonium salts with NCA [^{18}F]fluoride ion in the same microfluidic apparatus,[24] here we observed high and consistent RCYs in the absence of TEMPO; this is possibly because photoinitiated decomposition of the salt is avoided.

Conclusions

This study demonstrates that the radiofluorination of unsymmetrical diaryliodonium tosylates (ArI$^+$Ar′TsO$^-$), in which Ar′ is 3-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-thienyl, or 5-Me-2-thienyl, is a rapid and effective method for producing simple NCA [^{18}F]*m*-fluoroarenes with either electron-withdrawing or electron-donating *meta* substituents from [^{18}F]fluoride ion.

Experimental Section

General Methods: ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR at 100 MHz and ^{19}F NMR at 376 MHz. No-carrier-added (NCA) [^{18}F]fluoride ion was obtained through the ^{18}O(p,n)^{18}F nuclear reaction by irradiating [^{18}O]water (95 atom-%) for 90–120 min with a proton beam (17 MeV; 20 μA) produced by a PETrace cyclotron. MP-1 or QMA anion exchange cartridges for [^{18}F]fluoride ion trapping and release were supplied by ORTG (Oakdale, TN). ***Precaution:*** Peracetic acid (32 wt.-%) is a strong oxidant and may cause explosions in the presence of reducing agents and organic materials.

Syntheses of Arylstannanes

3-(Tri-*n*-butylstannyl)benzonitrile (1): 3-Iodobenzonitrile (2.2 mmol, 0.50 g) was mixed with hexabutylditin (2.5 mmol, 1.45 g) and a catalytic amount of tetrakis(triphenylphosphane)palladium (0.5 mol-%, 15 mg) in anhydrous toluene (20 mL) under argon. The resulting mixture was refluxed overnight (ca. 14 h). Palladium catalyst was filtered off and toluene was removed in a rotary evaporator. The crude oily product was purified by column chromatography on silica gel (10% EtOAc/hexane; R_f = 0.42) to give **1** as a pale yellow oil (0.63 g, 73%). ^{1}H NMR ($CDCl_3$): δ = 7.72 (t, J = 0.8 Hz, 1 H), 7.68 (dt, J = 0.8, 4.4 Hz, 1 H), 7.57 (dt, J = 1.6, 5.6 Hz, 1 H), 7.40 (t, J = 7.8 Hz, 1 H), 1.48–1.54 (m, 6 H), 1.27–1.36 (m, 6 H), 1.01–1.05 (m, 6 H), 0.88 (t, J = 7.2 Hz, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 144.2, 140.5, 139.6, 131.4, 128.1, 119.5, 112.1, 28.9, 27.3, 13.6, 9.7 ppm.

1-Methoxy-3-(tri-*n*-butylstannyl)benzene (2): 3-Iodoanisole (3 mmol, 0.7 g) was mixed with hexabutylditin (3.5 mmol, 2.1 g) and tetrakis(triphenylphosphane)palladium (0.5 mol-%, 17 mg) in anhydrous toluene (20 mL) under argon. The reaction mixture was refluxed overnight (ca. 12 h). Palladium catalyst was filtered off and toluene was removed in a rotary evaporator. Crude product was separated by column chromatography on silica gel (10% EtOAc/hexane; R_f = 0.46) to give **2** as a colorless oil (0.87 g, 73%). ^{1}H NMR ($CDCl_3$):

δ = 7.29–7.22 (m, 1 H), 7.01–6.96 (m, 2 H), 6.85–6.82 (m, 1 H), 3.80 (s, 3 H), 1.57–1.52 (m, 6 H), 1.38–1.28 (m, 6 H), 1.07–1.03 (m, 6 H), 0.89 (t, J = 7.2 Hz, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 158.9, 143.4,128.8, 128.7, 122.1, 112.9, 55.0, 29.1, 27.4, 13.7, 9.6 ppm.

Syntheses of (Diacetoxyiodo)arenes

3-(Diacetoxyiodo)toluene (3): Peracetic acid (33 mmol; 32 wt.-%, diluted in AcOH, 7 mL) was added dropwise to 3-iodotoluene (8.0 mmol, 1.74 g) at 0 °C. The reaction mixture was then slowly warmed to room temp. and stirred for ca. 4 h; H_2O (ca. 1 mL) was then added, and the white precipitate was filtered off, washed with Et_2O, and dried in air to give **3** as a white solid (1.25 g, 46%); m.p. 156–159 °C (ref.[38] m.p. 150–152 °C). ^{1}H NMR ($CDCl_3$): δ = 7.92–7.89 (m, 2 H), 7.40–7.38 (m, 2 H), 2.43 (s, 3 H), 2.01 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 176.6, 141.6, 135.6, 132.9, 132.3, 130.9, 121.7, 21.6, 20.6 ppm.

1-Cyano-3-(diacetoxyiodo)benzene (4): Peracetic acid (9.5 mmol; 32 wt.-%, diluted in AcOH, 2 mL) was added dropwise to 3-iodobenzonitrile (3.0 mmol, 0.68 g) while cooled in an ice bath. The reaction mixture was then slowly warmed to room temp. and stirred overnight (ca. 14 h). The resulting white precipitate was filtered off, washed with Et_2O, and dried in air to give **4** as a white solid (0.78 g, 75%); m.p. 188–190 °C (ref.[39] m.p. 188–189 °C). ^{1}H NMR ($CDCl_3$): δ = 8.37 (t, J = 1.4 Hz, 1 H), 8.31 (dt, J = 1.2, 6.4 Hz, 1 H), 7.89 (dt, J = 1.0, 8.8 Hz, 1 H), 7.66 (t, J = 7.8 Hz, 1 H), 2.04 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 176.8, 138.9, 138.1, 137.1, 131.3, 120.9, 116.7, 115.1, 20.4 ppm.

1-(Diacetoxyiodo)-3-nitrobenzene (5): Peracetic acid (33 mmol; 32 wt.-%, diluted in AcOH, 7 mL) was added dropwise with vigorous stirring to 1-iodo-3-nitrobenzene (7.0 mmol, 1.74 g) cooled in an ice bath. The reaction mixture was stirred below 5 °C for 1 h and then gradually warmed to room temp. Reaction progress was monitored by TLC. After 6 h, the white precipitate was filtered off, washed with H_2O (20 mL) followed by Et_2O (20 mL), and dried in air to give **5** as a white solid (1.5 g, 59%); m.p. 155–158 °C (ref.[39] m.p. 148–150 °C). ^{1}H NMR ($CDCl_3$): δ = 8.95 (t, J = 2 Hz, 1 H), 8.44 (m, 1 H), 8.40 (m, 1 H), 7.23 (t, J = 8 Hz, 1 H), 2.04 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 176.8, 148.7, 140.4, 131.5, 130.1, 126.3, 120.6, 20.3 ppm.

1-(Diacetoxyiodo)-3-(trifluoromethyl)benzene (6): The procedure described for **5** was applied; 1-iodo-3-(trifluoromethyl)benzene (10 mmol, 2.72 g) with peracetic acid (23.7 mmol; 32 wt.-%, diluted in AcOH, 5 mL) gave **6** as a white solid (1.69 g, 43%); m.p. 138–139 °C (ref.[40] m.p. 146–147 °C). ^{1}H NMR ($CDCl_3$): δ = 8.33 (br. s, 1 H), 8.28 (d, J = 8.4 Hz, 1 H), 7.85 (dd, J = 0.4, 8 Hz, 1 H), 7.65 (t, J = 8 Hz, 1 H), 2.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 176.6, 138.1, 133.0 (q, J = 34 Hz), 131.8 (q, J = 4 Hz), 131.2, 131.0, 128.5 (q, J = 4 Hz), 124.2, 121.4, 121.0, 20.3 ppm. ^{19}F NMR ($CDCl_3$): δ = –62.8 ppm.

1-(Diacetoxyiodo)-3-methoxybenzene (7): Peracetic acid (33 mmol; 32 wt.-%, diluted in AcOH, 7 mL) was added dropwise to 3-iodoanisole (15 mmol, 3.51 g) in an ice/salt bath (ca. –10 °C). The reaction mixture was gradually warmed to room temp. and became a strong yellow solution over 1 h. H_2O (10 mL) was added to quench the reaction, and the aqueous mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The resulting yellow oil was triturated with Et_2O, and the generated white solid was filtered off, washed with Et_2O, and dried in air to give **7** as a pale yellow solid (0.84 g, 16%); m.p. 128–130 °C (ref.[38] m.p. 129–131 °C). ^{1}H NMR ($CDCl_3$): δ = 7.68–7.64 (m, 2 H), 7.42 (t, J = 8.4 Hz, 1 H), 7.11 (dq, J = 0.8, 2.8 Hz, 1 H), 3.87 (s, 3 H), 2.02 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 176.5, 160.5, 131.6, 127.1, 121.4, 120.5, 118.0, 55.8, 20.4 ppm.

Synthesis of [Hydroxy(tosyloxy)iodo]arenes

3-[Hydroxy(tosyloxy)iodo]toluene (8): Prepared according to a published method[41] (0.74 g, 72%); m.p. 126–129 °C. ^{1}H NMR ([D$_6$]-DMSO): δ = 9.75 (br. s, 1 H), 8.06–8.00 (m, 2 H), 7.51–7.47 (m, 4 H), 7.12 (dd, J = 0.4, 8.4 Hz, 2 H), 2.38 (s, 3 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 145.4, 141.1, 137.8, 134.7, 133.1, 131.7, 130.8, 128.1, 125.5, 123.4, 20.8, 20.7 ppm.

1-Cyano-3-[hydroxy(tosyloxy)iodo]benzene (9): pTsOH·H_2O (1.1 mmol, 0.2 g) in MeCN (10 mL) was added portion-wise to a solution of **4** (1.0 mmol, 0.35 g) in hot MeCN (10 mL) to give a yellow solution. A white solid precipitated when the solution was cooled to room temp. The precipitate was filtered off, washed with Et_2O (20 mL), and dried to give **4** as a slightly yellow solid (0.328 g, 79%); m.p. 142–144 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 9.98 (s, 1 H, br.), 8.72 (s, 1 H), 8.50 (d, J = 8 Hz, 1 H), 8.16 (d, J = 7.6 Hz, 1 H), 7.80 (t, J = 7.6 Hz, 1 H), 7.47 (d, J = 7.6 Hz, 2 H), 7.12 (d, J = 7.6 Hz, 2 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 145.3, 138.7, 137.9, 137.5, 135.9, 131.9, 128.2, 125.5, 123.4, 117.2, 113.5, 20.8 ppm. HRMS: calcd. for C_7H_5INO [M – OTs]$^+$ 245.9416; found 245.9411.

1-[Hydroxy(tosyloxy)iodo]-3-(trifluoromethyl)benzene (10): Prepared according to a published method[42] (1.67 g, 91%); m.p. 154–156 °C (ref.[42] m.p. 158–162 °C). ^{1}H NMR ([D$_6$]DMSO): δ = 9.94 (br. s, 1 H), 8.60 (s, 1 H), 8.49 (d, J = 8 Hz, 1 H), 8.06–8.04 (m, 1 H), 7.83 (t, J = 7.6 Hz, 1 H), 7.49 (dd, J = 1.6, 6.4 Hz, 2 H), 7.13 (d, J = 8 Hz, 2 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 145.0, 138.1, 132.1, 131.1, 130.7 (q, J = 3 Hz), 128.9 (q, J = 3 Hz), 128.2, 125.5, 124.5, 123.7, 121.8, 20.8 ppm. ^{19}F NMR ([D$_6$]-DMSO): δ = –61.2 ppm. HRMS: calcd. for $C_7H_5F_3IO$ [M – OTs]$^+$ 288.9337; found 288.9345.

Synthesis of Diaryliodonium Salts

By Reaction of [Hydroxy(tosyloxy)iodo]arenes with an Arylboronic Acid [32]

(3-Methylphenyl)(phenyl)iodonium Tosylate (11): 3-Tolylboronic acid (4 mmol, 0.54 g) was added portion-wise to a suspension of Koser's reagent {[hydroxy(tosyloxy)iodo]benzene; 4.0 mmol, 1.57 g} in CH_2Cl_2 (20 mL) at 0 °C. The resulting mixture became a yellow solution at room temp. over 30 min. CH_2Cl_2 was removed in vacuo, and the resulting brown oil was treated with Et_2O (20 mL). The resulting solid was filtered off, washed with Et_2O, air-dried and recrystallized from MeOH/Et_2O to give **11** as a white solid (0.36 g, 20%); m.p. 182–184 °C (ref.[43] m.p. 169–170 °C). ^{1}H NMR ($CDCl_3$): δ = 7.94 (d, J = 7.6 Hz, 2 H), 7.77 (s, 1 H), 7.72 (d, J = 8 Hz, 1 H), 7.51–7.48 (m, 3 H), 7.51–7.27 (m, 3 H), 7.21 (t, J = 7.6 Hz, 1 H), 7.02 (d, J = 7.6 Hz, 2 H), 2.30 (s, 3 H), 2.28 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 142.2, 139.3, 135.5, 135.1, 132.5, 132.2, 131.6, 131.5, 131.3, 128.4, 126.0, 115.3, 115.1, 21.3, 21.2 ppm. HRMS: calcd. for $C_{13}H_{12}I$ [M – OTs]$^+$ 294.9984; found 294.9986.

By Reaction of [Hydroxy(tosyloxy)iodo]arenes with Aryltri-*n*-butylstannanes

(3-Cyanophenyl)(phenyl)iodonium Tosylate (12): The 3-cyano derivative of Koser's reagent (**9**; 1.0 mmol, 0.39 g) was added portion-wise to a solution of **1** (1.0 mmol, 0.39 g) in CH_2Cl_2 (20 mL) at room temp. The mixture was refluxed for 4 h. Solvent was removed in vacuo, and the resulting yellow oil was triturated with Et_2O (10 mL). The solid was filtered off, washed with Et_2O, dried in air and recrystallized from MeOH/Et_2O to give **12** as a white solid (0.15 g, 32%); m.p. 154–155 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 8.86

(s, 1 H), 8.58 (d, J = 8.4 Hz, 1 H), 8.29 (d, J = 7.6 Hz, 2 H), 8.15 (d, J = 8 Hz, 1 H), 7.75–7.68 (m, 2 H), 7.56 (t, J = 8 Hz, 2 H), 7.47 (d, J = 8 Hz, 2 H), 7.15 (d, J = 8 Hz, 2 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 139.7, 138.4, 137.9, 137.3, 135.7, 135.3, 132.4, 132.3, 131.9, 128.0, 125.5, 117.0, 115.8, 113.9, 20.8 ppm. HRMS: calcd. for $C_{13}H_9IN$ [M – OTs]$^+$ 305.9780; found 305.9775.

(3-Methoxyphenyl)(phenyl)iodonium Tosylate (13): The procedure described for **12** was applied; **2** (2.2 mmol, 0.87 g) with Koser's reagent (2.5 mmol, 0.98 g) gave **13** as a white solid (0.63 g, 59%); m.p. 136–139 °C (ref.[33] m.p. 147–152 °C). ^{1}H NMR ($CDCl_3$): δ = 7.96 (dd, J = 1.2, 8.4 Hz, 2 H), 7.59 (t, J = 2 Hz, 1 H), 7.50–7.47 (m, 3 H), 7.41 (dd, J = 0.4, 7.2 Hz, 1 H), 7.33 (t, J = 7.6 Hz, 2 H), 7.21 (t, J = 8.4 Hz, 1 H), 7.02–6.97 (m, 3 H), 3.73 (s, 3 H), 2.30 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 141.6, 138.3, 134.2, 130.9, 130.5, 127.4, 125.9, 124.9, 119.1, 117.7, 114.4, 114.3, 54.8, 20.3 ppm. HRMS: calcd. for $C_{13}H_{12}IO$ [M – OTs]$^+$ 310.9933; found 310.9926.

By Reaction of Isolated HTIAs with Aryltri-*n*-butylstannanes

(3-Cyanophenyl)(3-methylphenyl)iodonium Tosylate (14): Isolated HTIA **8** (1.7 mmol, 0.69 g) was added portion-wise to a solution of **1** (1.7 mmol, 0.70 g) in CH_2Cl_2 (20 mL). The reaction mixture was refluxed for 4 h, and solvent was removed in vacuo. The resulting crude oil was triturated with Et_2O and the generated solid washed with Et_2O and dried in air to give **14** as a white solid (0.21 g, 25%); m.p. 185–188 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 8.84 (t, J = 1.6 Hz, 1 H), 8.57 (dq, J = 0.8, 8.4 Hz, 1 H), 8.15–8.13 (m, 2 H), 8.09 (dd, J = 0.4, 8 Hz, 2 H), 7.72 (t, J = 8 Hz, 1 H), 7.51–7.42 (m, 4 H), 7.11 (d, J = 7.6 Hz, 2 H), 2.35 (s, 3 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 145.8, 141.9, 139.6, 138.4, 137.5, 135.6, 135.4, 133.0, 132.4, 132.3, 131.6, 128.0, 125.5, 116.9, 116.7, 116.5, 113.8, 20.8 ppm. HRMS: calcd. for $C_{14}H_{11}IN$ [M – OTs]$^+$ 319.9936; found 319.9931.

Bis(3-cyanophenyl)iodonium Tosylate (15): The procedure described for **14** was applied; **1** (1.0 mmol, 0.39 g) with **9** (1.0 mmol, 0.42 g) gave **15** as a white solid (0.63 g, 59%); m.p. 219–220 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 8.86 (t, J = 1.6 Hz, 2 H), 8.60 (dq, J = 0.8, 5.6 Hz, 2 H), 8.17 (dd, J = 1.2, 6 Hz, 2 H), 7.75 (t, J = 8 Hz, 2 H), 7.46 (d, J = 8 Hz, 2 H), 7.11 (d, J = 8 Hz, 2 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 139.8, 138.6, 137.6, 135.9, 132.5, 128.0, 125.5, 117.0, 116.9, 114.0, 20.8 ppm. HRMS: calcd. for $C_{14}H_8IN_2$ [M – OTs]$^+$ 330.9732; found 330.9734.

By Reaction of Isolated HTIAs with Electron-Rich Arenes

(3-Cyanophenyl)(4-methoxyphenyl)iodonium Tosylate (16): A mixture of anisole (0.5 mL, 4.6 mmol) and **9** (0.25 mmol, 0.11 g) in chloroform (10 mL) was refluxed for 4 h. After evaporation of solvent under vacuum, the resulting oil was treated with Et_2O. The generated solid was filtered off, washed with Et_2O and dried in air to give **16** as a white solid (69 mg, 56%); m.p. 172–175 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 8.80 (s, 1 H), 8.52 (d, J = 8 Hz, 1 H), 8.20 (d, J = 8.8 Hz, 2 H), 8.12 (d, J = 7.6 Hz, 1 H), 7.71 (t, J = 8 Hz, 1 H), 7.47 (d, J = 8 Hz, 2 H), 7.10 (t, J = 6.8 Hz, 4 H), 3.80 (s, 3 H), 2.28 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 162.1, 145.7, 139.4, 138.1, 137.6, 137.4, 135.5, 132.3, 128.0,125.5, 117.6, 117.1, 117.0, 113.7, 105.8, 55.7, 20.8 ppm. HRMS: calcd. for $C_{14}H_{11}INO$ [M – OTs]$^+$ 335.9885; found 335.9894.

(3-Cyanophenyl)(2-thienyl)iodonium Tosylate (17): The procedure described for **16** was applied; thiophene (50 mg, 6 mmol) with **9** (0.50 mmol, 0.21 g) gave **17** as a white solid (0.19 g, 78%); m.p. 151–152 °C. ^{1}H NMR ($CDCl_3$): δ = 8.29 (d, J = 8.4 Hz, 1 H), 8.12 (t, J = 1.2 Hz, 1 H), 7.87 (dd, J = 1.2, 4 Hz, 1 H), 7.67 (d, J = 1.2 Hz, 1 H), 7.56 (dd, J = 1.2, 4 Hz, 1 H), 7.42–7.35 (m, 3 H), 7.05–6.99 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 141.0, 140.1, 138.7, 137.2, 136.2, 134.5, 131.6, 129.6, 128.7, 125.8, 118.9, 116.5, 114.9, 100.0, 21.3 ppm. HRMS: calcd. for $C_{11}H_7INS$ [M – OTs]$^+$ 311.9344; found 311.9352.

(3-Cyanophenyl)(5-methyl-2-thienyl)iodonium Tosylate (18): The procedure described for **16** was applied; 2-methylthiophene (0.7 mmol, 68 mg) with **9** (0.50 mmol, 0.21 g) gave **18** as a white solid (90 mg, 36%); m.p. 146–148 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 8.23 (s, 1 H), 8.57 (d, J = 7.6 Hz, 1 H), 8.12 (d, J = 6.8 Hz, 1 H), 7.95 (s, 1 H), 7.72 (t, J = 7.2 Hz, 1 H), 7.47 (d, J = 7.2 Hz, 2 H), 7.12 (d, J = 6.8 Hz, 2 H), 6.92 (s, 1 H), 2.56 (s, 3 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 151.7, 145.5, 141.3, 139.1, 137.8, 135.6, 132.3, 128.3, 128.1, 125.5, 119.7, 117.0, 113.6, 97.4, 20.8, 15.0 ppm. HRMS: calcd. for $C_{12}H_9NSI$ [M – OTs]$^+$ 325.9500; found 325.9503.

(4-Methoxyphenyl)[3-(trifluoromethyl)phenyl]iodonium Tosylate (19): The procedure described for **16** was applied; anisole (2.7 mmol, 0.3 mL) in chloroform (2 mL) with **10** (1.5 mmol, 0.69 g) gave **19** as a white solid (0.70 g, 85%); m.p. 174–175 °C. ^{1}H NMR ($CDCl_3$): δ = 8.17 (d, J = 8 Hz, 1 H), 8.03 (s, 1 H), 7.84 (dd, J = 2, 6.8 Hz, 1 H), 7.59 (d, J = 8 Hz, 1 H), 7.36–7.30 (m, 3 H), 6.91 (d, J = 8 Hz, 1 H), 6.74 (dd, J = 2, 7.2 Hz, 2 H), 3.71 (s, 3 H), 2.22 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 162.4, 142.0, 139.6, 138.3, 137.6, 133.0 (q, J = 34 Hz), 131.6, 131.1 (q, J = 4 Hz), 128.5, 127.9 (q, J = 4 Hz), 125.8, 121.4, 117.4, 116.3, 104.6, 55.5, 21.2 ppm. ^{19}F NMR ($CDCl_3$): δ = –62.7 ppm. HRMS: calcd. for $C_{14}H_{11}F_3IO$ [M – OTs]$^+$ 378.9807; found 378.9804.

(2-Thienyl)[3-(Trifluoromethyl)phenyl]iodonium Tosylate (20): The procedure described for **16** was applied; thiophene (6.0 mmol, 0.5 mL) with **10** (1.5 mmol, 0.69 g) at room temp. (ca. 14 h) gave **20** as a white solid (0.68 g, 86%); m.p. 151–152 °C. ^{1}H NMR ($CDCl_3$): δ = 8.24 (d, J = 8.4 Hz, 1 H), 8.15 (s, 1 H), 7.85 (dd, J = 1.2, 3.6 Hz, 1 H), 7.66 (d, J = 8 Hz, 1 H), 7.53 (dd, J = 1.2, 5.2 Hz, 1 H), 7.42 (t, J = 7.6 Hz, 1 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.00–6.97 (m, 3 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 141.7, 140.8, 139.8, 138.0, 136.0, 133.0 (q, J = 31 Hz), 131.6, 130.9 (q, J = 3 Hz), 129.5, 128.5, 128.0 (q, J = 4 Hz), 125.7, 121.2, 118.8, 100.0, 21.2 ppm. ^{19}F NMR ($CDCl_3$): δ = –62.8 ppm. HRMS: calcd. for $C_{11}H_7F_3IS$ [M – OTs]$^+$ 354.9265; found 354.9254.

(4-Methoxyphenyl)(3-methylphenyl)iodonium Tosylate (21): The procedure described for **16** was applied; anisole (2.7 mmol, 0.3 mL) with **8** (0.7 mmol, 0.28 g) gave **21** as a white solid (0.70 g, 85%); m.p. 122–126 °C. ^{1}H NMR ($CDCl_3$): δ = 7.88 (d, J = 9.2 Hz, 2 H), 7.75 (s, 1 H), 7.70 (d, J = 8 Hz, 1 H), 7.50 (d, J = 8 Hz, 2 H), 7.27–7.16 (m, 2 H), 7.02 (d, J = 8 Hz, 2 H), 6.81 (d, J = 8.4 Hz, 2 H), 2.30 (s, 3 H), 2.26 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 162.2, 142.4, 142.0, 139.4, 137.3, 135.0, 132.3, 131.6, 131.2, 128.4, 126.0, 117.3, 115.5, 103.6, 55.5, 21.2 ppm. HRMS: calcd. for $C_{14}H_{14}IO$ [M – OTs]$^+$ 325.0089; found 325.0078.

By Reaction of In situ Generated HTIAs with Electron-Rich Arenes

(4-Methoxyphenyl)(3-nitrophenyl)iodonium Tosylate (22): *p*TsOH·H$_2$O (0.50 mmol, 95 mg) was added to a suspension of **5** (0.50 mmol, 0.18 g) in MeCN (5 mL). A yellow solution developed instantly and then a precipitate. Chloroform (15 mL) was added, followed by anisole (2.7 mmol, 0.3 mL). The mixture was refluxed for 3 h. MeCN/chloroform was then removed in vacuo, and the resulting brown oil was triturated with Et_2O (10 mL). The generated solid was filtered off, washed with Et_2O (20 mL), and dried in air to give **22** as a white solid (0.23 g, 87%); m.p. 167–169 °C (ref.[43] m.p. 175–180 °C). ^{1}H NMR ([D$_6$]DMSO): δ = 9.13 (s, 1 H), 8.61 (d, J = 8 Hz, 1 H), 8.44 (d, J = 8 Hz, 1 H), 8.27 (d, J = 9.2 Hz,

2 H), 7.79 (t, *J* = 8 Hz, 1 H), 7.47 (d, *J* = 8 Hz, 2 H), 7.12–7.09 (m, 4 H), 3.80 (s, 3 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 162.2, 148.2, 145.6, 140.9, 137.7, 132.7, 129.5, 128.1, 126.5, 125.5, 117.6, 116.9, 105.9, 55.7, 20.8 ppm. HRMS: calcd. for $C_{13}H_{11}INO_3$ [M – OTs]$^+$ 355.9784; found 355.9778.

(3-Nitrophenyl)(2-thienyl)iodonium Tosylate (23): The procedure described for **22** was applied; **5** (0.50 mmol, 0.18 g) with thiophene (1.2 mmol, 0.1 mL) in the presence of *p*TsOH·H$_2$O (0.50 mmol, 95 mg) gave **23** as a white solid (0.21 g, 82%); m.p. 143–146 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 9.18 (s, 1 H), 8.66 (d, *J* = 7.6 Hz, 1 H), 8.44 (d, *J* = 8 Hz, 1 H), 8.17 (d, *J* = 3.2 Hz, 1 H), 8.00 (d, *J* = 4.8 Hz, 1 H), 7.81 (t, *J* = 8.4 Hz, 1 H), 7.46 (d, *J* = 7.6 Hz, 2 H), 7.21 (t, *J* = 3.6 Hz, 1 H), 7.11 (d, *J* = 7.6 Hz, 2 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 148.2, 145.6, 141.1, 140.6, 137.9, 137.7, 132.7, 129.8, 129.3, 128.1, 126.7, 125.5, 119.2, 101.3, 20.8 ppm. HRMS: calcd. for $C_{10}H_7INO_2S$ [M – OTs]$^+$ 331.9242; found 331.9242.

(5-Methyl-2-thienyl)(3-nitrophenyl)iodonium Tosylate (24): The procedure described for **22** was applied; **5** (0.50 mmol, 0.18 g) with 2-methylthiophene (0.7 mmol, 68 mg) in the presence of *p*TsOH·H$_2$O (0.50 mmol, 95 mg) gave **24** as a white solid (0.23 g, 90%); m.p. 142–144 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 9.15 (s, 1 H), 8.64 (d, *J* = 7.6 Hz, 1 H), 8.43 (d, *J* = 8 Hz, 1 H), 7.99 (d, *J* = 3.6 Hz, 1 H), 7.80 (t, *J* = 8 Hz, 1 H), 7.46 (d, *J* = 7.6 Hz, 2 H), 7.11 (d, *J* = 7.6 Hz, 2 H), 6.93 (d, *J* = 2.4 Hz, 1 H), 2.56 (s, 3 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 151.8, 148.2, 145.5, 141.5, 140.5, 137.7, 132.7, 129.2, 128.3, 128.1, 126.7, 125.5, 119.4, 20.8, 15.0 ppm. HRMS: calcd. for $C_{11}H_9NO_2SI$ [M – OTs]$^+$ 345.9399; found 345.9409.

(5-Methyl-2-thienyl)[3-(trifluoromethyl)phenyl]iodonium Tosylate (25): The procedure described for **22** was applied; **6** (2.0 mmol, 0.78 g) with 2-methylthiophene (2.5 mmol, 0.24 g) in the presence of *p*TsOH·H$_2$O (2.2 mmol, 0.42 g) gave **25** as a white solid (1.03 g, 98%); m.p. 140–142 °C. ^{1}H NMR (CDCl$_3$): δ = 8.22 (d, *J* = 8.4 Hz, 1 H), 8.10 (s, 1 H), 7.68–7.63 (m, 2 H), 7.75–7.27 (m, 3 H), 7.01 (d, *J* = 4.4 Hz, 2 H), 6.65 (dd, *J* = 1.2, 3.6 Hz, 1 H), 2.53 (s, 3 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (CDCl$_3$): δ = 152.0, 141.8, 141.4, 139.7, 137.6, 132.9 (q, *J* = 34 Hz), 131.5, 130.6 (q, *J* = 3 Hz), 128.5, 128.0, 125.8, 123.9, 121.2, 118.9, 21.2, 15.4 ppm. ^{19}F NMR (CDCl$_3$): δ = –62.8 ppm. HRMS: calcd. for $C_{12}H_9F_3IS$ [M – OTs]$^+$ 368.9422; found 368.9412.

(3-Methylphenyl)(2-thienyl)iodonium Tosylate (26): The procedure described for **22** was applied; **3** (0.5 mmol, 0.17 g) with thiophene (1.2 mmol, 0.1 mL) in the presence of *p*TsOH·H$_2$O (0.5 mmol, 95 mg) gave **26** as a white solid (0.21 g, 90%); m.p. 146–147 °C (ref.[44] m.p. 151–154 °C). ^{1}H NMR (CDCl$_3$): δ = 7.77–7.76 (m, 2 H), 7.73 (d, *J* = 8 Hz, 1 H), 7.56 (dd, *J* = 1.2, 5.6 Hz, 1 H), 7.51 (d, *J* = 8 Hz, 2 H), 7.28 (s, 1 H), 7.21 (t, *J* = 8 Hz, 1 H), 7.06–7.01 (m, 3 H), 2.32 (s, 3 H), 2.29 (s, 3 H) ppm. ^{13}C NMR (CDCl$_3$): δ = 142.3, 142.2, 140.3, 139.5, 135.9, 134.4, 132.4, 131.2, 131.1, 129.6, 128.5, 126.0, 118.9, 21.4, 21.3 ppm. HRMS: calcd. for $C_{11}H_{10}IS$ [M – OTs]$^+$ 300.9548; found 300.9539.

(3-Methoxyphenyl)(2-thienyl)iodonium Tosylate (27): The procedure described for **22** was applied; **7** (1 mmol, 0.35 g) with thiophene (6.0 mmol, 0.5 mL) in the presence of *p*TsOH·H$_2$O (1 mmol, 0.19 g) gave **27** as a white solid (0.42 g, 86%); m.p. 155–157 °C (ref.[45] m.p. 161 °C). ^{1}H NMR ([D$_6$]DMSO): δ = 8.08 (dd, *J* = 1.6, 4 Hz, 1 H), 7.97 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.94–7.93 (m, 1 H), 7.79 (dt, *J* = 0.4, 2 Hz, 1 H), 7.79–7.42 (m, 3 H), 7.21–7.16 (m, 2 H), 7.13 (d, *J* = 7.60 Hz, 2 H), 3.79 (s, 3 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 160.3, 145.6, 140.4, 137.7, 132.4, 129.6, 128.1, 126.6, 125.5, 120.1, 119.3, 117.8, 100.9, 55.9, 20.8 ppm. HRMS: calcd. for $C_{11}H_{10}IOS$ [M – OTs]$^+$ 316.9497; found 316.9492.

(3-Methoxyphenyl)(4-methoxyphenyl)iodonium Tosylate (28): The procedure described for **22** was applied; **7** (0.3 mmol, 0.13 g) with anisole (4.6 mmol, 0.5 mL) in the presence of *p*TsOH·H$_2$O (0.4 mmol, 76 mg) gave **28** as a white solid (0.15 g, 81%); m.p. 131–133 °C. ^{1}H NMR (CDCl$_3$): δ = 7.89 (dd, *J* = 2, 6.8 Hz, 2 H), 7.58 (t, *J* = 2 Hz, 1 H), 7.54 (dd, *J* = 1.6, 6.4 Hz, 2 H), 7.41 (dt, *J* = 0.8, 7.2 Hz, 1 H), 7.20 (t, *J* = 8 Hz, 1 H), 7.21 (d, *J* = 8 Hz, 2 H), 6.96 (dd, *J* = 0.8, 2.4 Hz, 1 H), 6.83 (dd, *J* = 2, 7.2 Hz, 2 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (CDCl$_3$): δ = 162.4, 161.0, 142.7, 139.3, 137.4, 131.9, 128.5, 126.2, 126.0, 119.5, 118.2, 117.4, 115.7, 103.6, 55.9, 55.6, 21.3 ppm. HRMS: calcd. for $C_{14}H_{14}IO_2$ [M–OTs]$^+$ 341.0039; found 341.0045.

Microfluidic NCA Radiofluorination of Diaryliodonium Salts

The detailed configuration and operation of the microfluidic device are described in our previous publications.[24,30] Cyclotron-produced NCA [^{18}F]fluoride ion (100–200 mCi) in [^{18}O]water (225–350 μL) was first adsorbed onto an anion exchange resin (i.e., MP-1 or QMA) cartridge within the CE module of a NanoTek apparatus (Advion) and then released with a solution of K_2CO_3 (0.8 mg; 5 μmol) plus K 2.2.2 (4.5 mg; 11 μmol) in MeCN/H$_2$O (9:1 v/v; 150 μL) into a 5 mL V-vial. The solution was dried by two cycles of azeotropic evaporation with MeCN (0.45 mL) at 100 °C. Dry ^{18}F$^-$-K 2.2.2-K$^+$ complex (70–150 mCi) was dissolved in MeCN or DMF (350 μL). A 10 mM solution of diaryliodonium salt was prepared in the same solvent. Each of the two solutions (255 μL) was loaded into a separate storage loop of the microfluidic apparatus. For radiofluorination reactions, each solution (10–15 μL) was infused simultaneously into the 4 m long coiled silica glass tube micro-reactor of the apparatus at a set flow rate in the range 5–10 μL/min and at different temperatures. The reaction product exiting the micro-reactor was quenched with MeCN/H$_2$O (1:1, v/v; 1 mL). Amounts of precursor, temperature and flow rates were varied to optimize RCYs. RCYs of [^{18}F]*m*-fluoroarenes were measured by reverse-phase radio-HPLC on a Luna C18 column (250 × 4.6 mm i.d.; 10 μm) eluted at 1.75 mL/min with a gradient of MeCN/H$_2$O with the percentage of MeCN increased linearly from 60 to 90% over 7 min. Retention times were 4.5, 5.6, 3.3, 4.0, 6.2, 5.4, 4.3, 5.0 and 5.1 min for [^{18}F]fluorobenzene, [^{18}F]3-fluorotoluene, [^{18}F]3-fluorobenzonitrile, [^{18}F]3-fluoronitrobenzene, [^{18}F]1-fluoro-3-(trifluoromethyl)benzene, [^{18}F]3-fluoroanisole, [^{18}F]-4-fluoroanisole, [^{18}F]2-fluorothiophene, [^{18}F]2-fluoro-5-methylthiophene, respectively. When the gradient was altered to increase MeCN from 20 to 90% over 11 min, [^{18}F]fluorobenzene and [^{18}F]-3-fluoroanisole eluted with retention times of 10.9 and 12.2 min, respectively, and when altered to increase MeCN from 55 to 90% over 7 min, [^{18}F]3-fluoroanisole and [^{18}F]4-fluoroanisole eluted at 5.4 and 5.0 min, respectively. These products were identified by their comobility with the respective reference fluoro compounds.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H, ^{13}C and ^{19}F NMR spectroscopic data and sample radiochromatograms.

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