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Research Article

Comparison of pathways to the versatile synthon of no-carrier-added 1-bromo-4-[^{18}F]fluorobenzene

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Summary

The availability of no-carrier-added (n.c.a.) 1-bromo-4-[^{18}F]fluorobenzene with high radiochemical yields is important for ^{18}F-arylation reactions using metallo-organic 4-[^{18}F]fluorophenyl compounds (e.g. of lithium or magnesium) or Pd-catalyzed coupling. In this study, different methods for the preparation of 1-bromo-4-[^{18}F]fluorobenzene by nucleophilic aromatic substitution reactions using n.c.a. [^{18}F]fluoride were examined. Of six pathways compared, symmetrical *bis*-(4-bromphenyl)iodonium bromide proved most useful to achieve the title compound in a direct, one-step nucleophilic substitution with a radiochemical yield (RCY) of 65% within 10 min. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: ^{18}F-fluorination; 1-bromo-4-[^{18}F]fluorobenzene; iodonium leaving group; fluorine-18; [^{18}F]fluoromethane

Introduction

Methods for the introduction of fluorine-18 into aromatic ring systems play an important role in the development of new radiopharmaceuticals for positron emission tomography. There are two common pathways for the ^{18}F-labelling of the arene system. However, electrophilic ^{18}F-substitution leads only to carrier-added products because of the unavoidable addition of elemental fluorine to the target gas. In spite of several recent attempts to improve the electrophilic pathway by less addition of carrier[1–3] the specific activity using electrophilic substitution is often too low for labelling, e.g. of receptor ligands.

The other pathway via nucleophilic displacement of adequate leaving groups (e.g. NO_2 or $N^+(CH_3)_3$) which are activated by electron withdrawing

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substituents (e.g. CHO, $COCH_3$, COOMe, NO_2, CN, etc.) by no-carrier-added (n.c.a.) [^{18}F]fluoride is generally used for the preparation of ^{18}F-labelled, electron deficient arenes. However, in limited cases a direct one step synthesis of n.c.a. electron rich [^{18}F]fluoroarenes is even possible via an ^{18}F-fluorination reaction when using substituted diphenyliodonium salts, which was introduced into ^{18}F-radiochemistry by Pike and Aigbirhio.[4]

While only a few examples are described for direct nucleophilic ^{18}F-labelling of complex molecules[cf. 5–7] the n.c.a. ^{18}F-labelling of complex radiopharmaceuticals is performed in most cases starting from small, simple electron deficient arenes being subsequently converted into complex molecules via multi-step reactions (e.g. the synthesis of n.c.a. [^{18}F]fluoroamino acids[8] and n.c.a. [^{18}F]fluorometaraminol[9,10]).

Until now, there are only a few examples of synthetic methods using ^{18}F-labelled aromatic organometallic compounds. In order to enlarge the scope of n.c.a. ^{18}F-labelling via organometallic intermediates, the synthesis of n.c.a. 4-[^{18}F]fluorohalobenzene is an important key step. n.c.a. [^{18}F]fluorohaloarenes, especially the bromo and iodo derivatives, serve as synthon for ^{18}F-fluoroarylation reactions using 4-[^{18}F]fluorphenyl lithium or magnesium halide[11,12] or for palladium-catalyzed coupling reactions to [^{18}F]fluorophenylalkenes and -arenes.[13–15]

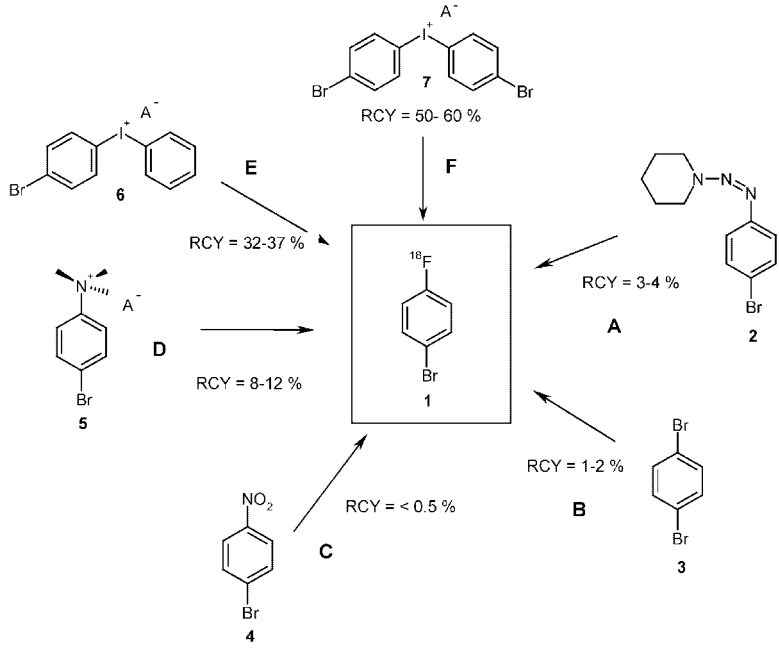
The aim of this study was to examine different methods for a facile, one-pot synthesis of 1-bromo-4-[^{18}F]fluorobenzene.

Results and discussion

Different methods can be taken into consideration for the synthesis of n.c.a. 1-bromo-4-[^{18}F]fluorobenzene **1**. Recently, Allain-Barbier *et al.*[13] and Forngren *et al.*[14] published a two-step procedure for the synthesis of 1-bromo-4-[^{18}F]fluorobenzene **1**. After a carbonyl activated ^{18}F-for-NO_2 substitution on 3-bromo-6-nitrobenzaldehyde the aldehyde group was removed by the Wilkinson catalyst to yield 40–66% radiochemical yield (RCY) of 1-bromo-4-[^{18}F]fluorobenzene **1**.

In Scheme 1 direct methods to 1-bromo-4-[^{18}F]fluorobenzene **1** as examined in this study are outlined, while most of these methods are also applicable for the synthesis of n.c.a. 1-[^{18}F]fluoro-4-iodobenzene.

Both [^{18}F]fluorohalo compounds offer the possibility of use of a variety of coupling conditions. For example, they can be converted either into corresponding lithium or magnesium compounds useful for ^{18}F-fluoroarylation reactions. Further, coupling reactions using palladium catalysts lead to [^{18}F]fluoroarylalkenes[16] or [^{18}F]fluoroaniline derivatives.[17] Both methods enlarge the scope of possibilities for the synthesis of PET radiopharmaceuticals.



Scheme 1. One-step reaction to n.c.a. 1-bromo-4-[^{18}F]fluorobenzene

Studies of the halogen-activated ^{18}F-for-halide and ^{18}F-for-nitro exchange and the Wallach reaction

The well-known Wallach reaction (Scheme 1, pathway **A**) was applied in ^{18}F-chemistry for the labelling of spiro- and haloperidol.[18,19] In case of the decomposition of 1-piperidyldiazo-4-bromobenzene **2**, however, even using a wide variation of several parameters (temperature, concentration of precursor, ^{19}F-carrier, solvent, different sulfonic acids for decomposition) not more than 3–4% RCY of 1-bromo-4-[^{18}F]fluorobenzene **1** was achieved.

Former studies of a direct nucleophilic aromatic substitution reaction using an ^{18}F-for-halide exchange showed contradicting results.[20,21] Therefore, as depicted in pathway **B**, a nucleophilic exchange reaction was examined using halides simultaneously as weak activating and leaving group. The well-known and efficient Kryptofix®2.2.2. phase transfer catalyst in combination with K_2CO_3[22] served as anion activation system. However, nucleophilic ^{18}F-substitution led only to 1–2% RCY of 1-bromo-4-[^{18}F]fluorobenzene using DMSO at up to 160 °C reaction temperature and a concentration of 15–20 mmol/l of 1,4-dibromobenzene **3**.

In earlier studies, Shiue *et al.*[23] showed that ^{18}F-labelling of bromo- and chloronitrobenzene as precursors using Rb_2CO_3 as anion activator and temperatures higher than 160 °C for 15 min yielded 10–50% RCY of [^{18}F]fluoro-4-nitrobenzene. A detailed reinvestigation in this study (Pathway **C)** of the halogen activated ^{18}F-for-NO_2 exchange on 1-bromo-4-nitroarene **4**

yielded likewise only 0.5% of 1-bromo-4-[^{18}F]fluorobenzene **1** and more than 40% of 1-[^{18}F]fluoro-4-nitrobenzene using the efficient Kryptofix 2.2.2/K_2CO_3 as anion activator and DMSO as solvent at less drastic conditions of 80°C within 5 min.These results are in agreement with a recently published study on the synthesis of ^{18}F-labelled 6-nitroquipazine.[24] There, an RCY of 30% of 1-[^{18}F]fluoro-2-nitrobenzene was found for the nitro-activated and microwave-assisted ^{18}F-labelling of an *ortho* substituted bromo precursor.

Studies of the ^{18}F-for-$N^+(CH_3)_3$ substitution; formation of [^{18}F]fluoromethane

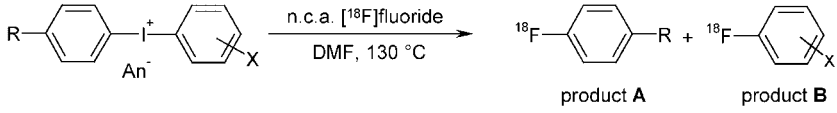
Based on earlier results an ^{18}F-for-$N^+(CH_3)_3$ substitution on 4-halo-*N*,*N*,*N*-trimethyl-ammonium triflates appeared to be a promising synthetic pathway for the synthesis of n.c.a. 4-[^{18}F]fluoro-1-haloarenes. At first the trimethylammonium function was considered as the best leaving group for an activated nucleophilic ^{18}F-substitution reaction on arenes.[25] In contrast to an earlier publication,[26] however, the ^{18}F-for-$N^+(CH_3)_3$ substitution with weakly activating halides, e.g. in 4-bromo-*N*,*N*,*N*-trimethylammonium triflate **5** (pathway **D**), led only to a radiochemical yield of 8–15% of 1-bromo-4-[^{18}F]fluorobenzene[27] **1**. These results were confirmed by another group[13] and could be explained by the formation of volatile methyl [^{18}F]fluoride, which has also been produced instead of the [^{18}F]fluoroarene on *ortho* $N^+(CH_3)_3$-substituted acetophenone derivatives.[28] Furthermore, formation of [^{18}F]CH_3F was observed by Maeda *et al.*[29] when investigating the dimethylsulfonium group as a leaving group for nucleophilic aromatic ^{18}F-fluorination reactions.

Studies on-4-halophenyliodonium salts

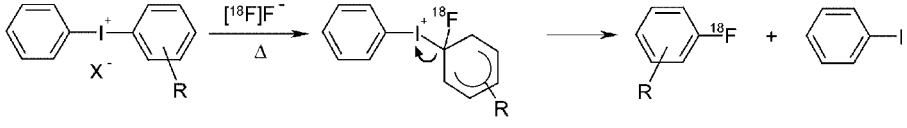
The use of iodonium salts as precursors for n.c.a. [^{18}F]fluoroarenes[4,30] offers the possibility of direct nucleophilic ^{18}F-fluorination of weakly activated arenes. Using bromine as substituent R (see Table 1), the decomposition of the corresponding iodonium salts leads to a mixture of [^{18}F]fluorobenzene and [^{18}F]fluorobromobenzene and the corresponding iodoarenes, respectively (cf. also Scheme 2).

As listed in Table 1, a radiochemical yield of about 50% of n.c.a. 1-[^{18}F]fluoro-4-bromobenzene **1** was found after 10 min reaction time in dimethylformamide (DMF) as solvent. The formation of 1-[^{18}F]fluoro-4-bromobenzene **1** is preferred to the formation of [^{18}F]fluorobenzene. This was also described in the literature[30] and reflects expectations based on the classic S_NAr mechanism for nucleophilic aromatic substitution. An increase in the electronegativity of R causes a decrease in the electron density of the aromatic ring, resulting in a better nucleophilic attack of the [^{18}F]fluoride ion forming preferably the 1-[^{18}F]fluoro-4-bromobenzene **1** (Scheme 2).

Table 1. RCY of n.c.a. bromo-[^{18}F]fluoroarene by thermal decomposition of diaryliodonium salts



Cpd.	R	X	Anion	RCY (%)	Ratio	
					Product **A**	Product **B**
6	Br	H	triflate	50 ± 5	70	30
7a	Br	4-Br	bromide	65 ± 10	100	0
7b	Br	4-Br	triflate	55 ± 10	100	0
7c	Br	4-Br	tosylate	65 ± 10	100	0
8	CH_3O	3-Br	triflate	43 ± 5	98	2



Scheme 2. General mechanism of the nucleophilic decomposition of diphenyliodonium salts with [^{18}F]fluoride

The principal drawback of the approach of a mono-substituted (4-bromophenyl)phenyliodonium salt as precursor for the synthesis of 1-bromo-4-[^{18}F]fluorobenzene is that the maximum radiochemical yield is limited by the additional formation of 30% [^{18}F]fluorobenzene (cf. Table 1).

Thus, to simplify the synthesis of n.c.a. 1-bromo-4-[^{18}F]fluorobenzene **1** and to improve the RCY, symmetrically substituted *bis*-(4-bromophenyl)iodonium salts **7** were used as starting material (pathway **F**). The major advantage of this precursor lies in the exclusive formation of 1-bromo-4-[^{18}F]fluorobenzene **1** as ^{18}F-labelled product in contrast to the (4-bromophenyl)phenyliodonium salts **6**. Nevertheless, the formation of ^{18}F-labelled arenes using iodonium salt is accompanied by the formation of macroscopic amounts of iodoarenes (Scheme 2), while the starting iodonium-precursor is completely decomposed under the reaction conditions used for ^{18}F-labelling.

There are different possibilities for a preparative purification of 1-bromo-4-[^{18}F]fluorobenzene **1**. The decision for one of the purification procedures is depending on the desired following reaction. For Pd-catalyzed reactions, like Stille[13] or Sonogashira[15] coupling or for the magnesium- or lithium reactions[12] it is not necessary to remove the iodobenzenes formed by the decomposition of the iodonium salt. Here, a simple purification procedure via a silica gel cartridge is probably the easiest way to remove the solvent DMF, the phase

transfer catalyst and [^{18}F]fluoride. Furthermore, this method offers the best conditions to establish a fully automated synthesis. To obtain n.c.a. 1-bromo-4-[^{18}F]fluorobenzene **1** in high radiochemical and chemical purity, a GC-procedure appears the best way for purification, but it is hard to automate and leads to a lower yield which is due to more purification steps (see experimental part). Nevertheless, both methods are useful when the subsequent reaction step demands the absence of moisture. As a third method for purification a simple distillation was introduced by Forngren *et al.*[14]

In Figure 1, the time course of 1-bromo-4-[^{18}F]fluorobenzene **1** using *bis*-(4-bromophenyl)iodonium bromide **7a** as precursor is depicted; the saturation yield is reached at 10–15 min. The concentration of precursor was optimized (not shown here) and the best concentration was found to be $\sim$25 mmol/l. Earlier used concentrations of Kryptofix® 2.2.2 and potassium carbonate (molar ratio 2:1)[26] as phase transfer catalyst proved also optimal for this reaction.

Variation of solvent had a strong influence on the radiochemical yields of the ^{18}F-fluorinated products. It was possible to obtain n.c.a. 4-bromo-[^{18}F]fluorobenzene **1** in radiochemical yields of up to 65% with bromide or tosylate as counter ion within 10 min reaction time, using DMF or DMF/dioxane as solvent and a reaction temperature of 130°C. In the case of DMAA the radiochemical yields obtained were found to be only half of those in DMF. Unexpectedly, no labelling reaction was observed in dimethyl sulfoxide (DMSO) which may be due to redox processes during the ^{18}F-labelling. In contrast to other studies[30] the ^{18}F-fluorination in acetonitrile at 100°C yielded only 1–5% RCY. These low yields were also found in the nucleophilic

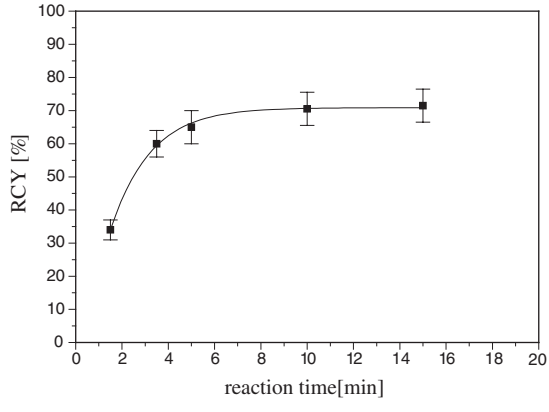


Figure 1. Time course of n.c.a. [^{18}F]fluoride substitution on *bis*-(4-bromophenyl) iodonium bromide reaction conditions: [*bis*-(4-bromophenyl)iodonium bromide] = 90 mmol/l, [K $\subset$ 2.2.2.] = 33.25 mmol/l, [K_2CO_3] = 16.63 mmol/l, 0.55 ml DMF, 130°C, (n = 3)

^{18}F-synthesis of 1-iodo-4-[^{18}F]fluorobenzene using *bis*-(4-iodophenyl)iodonium salts.[15]

The influence of the counter ion of symmetrically substituted *bis*-(4-bromophenyl)iodonium salts (cf. Table 1) differed from the results previously described for diphenyliodonium salts,[31] where an increasing RCY was found in the sequence tosylate < iodide < triflate < chloride < bromide. Using symmetric *bis*-(4-bromophenyl)iodonium salts no significant difference is observed between the sulfonate anions (tosylate and triflate) and bromide, even though the solubility of the sulfonate derivatives in DMF is better than the solubility of the bromide derivative.

The optimization studies described above were determined via aliquots taken from the reaction mixture and analyzed by HPLC. Interestingly, it is recommendable to increase the amount of precursor to 90 mmol/l and using 130°C reaction temperature to improve the preparative yield of n.c.a. 4-bromo-[^{18}F]fluorobenzene **1**, when using the separation by a silica gel column. The preparative RCY after separation was found to be 40 ± 5%. The GC-procedure again delivered only 20 ± 5% RCY, but a high chemical and radiochemical purity. The specific activity was determined to > 14.8 TBq/mmol via the GC-procedure starting from 185 MBq n.c.a. [^{18}F]fluoride.

Additionally, an alternative strategy was examined for the formation of n.c.a. 1-bromo-3-[^{18}F]fluorobenzene via unsymmetrically substituted diphenyliodonium salts as precursors (cf. Scheme 3) by increasing the relative reactivity of the bromophenyl moiety.

(3-Bromophenyl)-(4-methoxyphenyl)iodonium triflate was chosen as precursor, because the positive mesomeric and inductive effect of the methoxy group was expected to direct the ^{18}F-labelling reaction to the formation of 1-bromo-3-[^{18}F]fluorobenzene. Indeed, only 2–4% RCY of 4-[^{18}F]fluoroanisole and more than 40% RCY of 1-bromo-3-[^{18}F]fluorobenzene were found using DMF at 100°C within 6 min. However, the total yield could not compete with 65% RCY which is due to the twofold statistical chance in the symmetrically substituted *bis*-(4-bromophenyl)-iodonium precursor.

Scheme 3. Preparation of n.c.a. 1-bromo-3-[^{18}F]fluorobenzene via (3-bromophenyl)-(4-methoxyphenyl)iodonium triflate

Conclusion

In conclusion, six methods were compared for the one-step synthesis of n.c.a. 1-bromo-4-[^{18}F]fluorobenzene. The best results were obtained using *bis*-(4-bromophenyl)iodonium salts as precursors yielding up to 65% RCY of the title compound **1**, whereas unsymmetrically substituted 4-bromophenyliodonium and (3-bromophenyl)-(4-methoxyphenyl)iodonium salts led to only 35 and 40% RCY of the desired product accompanied with corresponding [^{18}F]fluorobenzenes, respectively. The other methods examined, like substitution on dihalobenzenes or the Wallach reaction, were even less efficient because of the low activation of the aromatic ring system for aromatic nucleophilic substitution reaction when using the weakly activating halides. Even the use of the trimethylammonium moiety as leaving group led to only 10–15% RCY of 1-bromo-4-[^{18}F]fluorobenzene with the weakly activating halide while more than 70% RCY was found for [^{18}F]fluoromethane.

Experimental

Materials and methods

Reagents and anhydrous solvents were purchased from Aldrich (Steinheim, Germany) or Merck (Darmstadt, Germany), *N*,*N*-dimethyl-4-fluoroaniline from PurChem (Karlsruhe, Germany) and fluoromethane from Heraeus (Karlsruhe, Germany). They were used without further purification. Oxygen-18 enriched water (> 95% enriched) was supplied by Chemotrade (Leipzig, Germany). Sep-Pak^{TM} C-18 plus-cartridges were purchased from Waters (Eschborn, Germany), EN-cartridges, glass column (LiChrolut^{TM} 65 × 10 mm) and LiChrolut^{TM} RP-18 from Merck (Darmstadt, Germany).

Thin layer chromatography (TLC) was run on precoated plates of silica gel 60_{F254} (Merck). The compounds were detected at 254 nm. Analytical HPLC was performed on the following systems: HPLC Sykam (S1000) pump, Knauer UV/VIS-detector (type 97) with a constant wavelength of 254 nm and an EG&G ACE Mate^{TM} radioactivity detector. Gas chromatography was performed on a Hewlett Packard HP 5890 Series II equipped with a TCD. RadioTLC chromatograms were detected on a Packard Instant Imager^{TM}. ^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded on a Bruker Avance 200 spectrometer with samples dissolved in $CDCl_3$ or d_6-DMSO. All shifts are given in δ ppm using the signals of the appropriate solvent as a reference. Mass spectra were obtained from a Finnigan Automass Multi mass spectrometer with an electron beam energy of 70 eV. High resolution mass spectra were recorded on a Finnigan MAT 900 ST apparatus (University of Cologne). Melting points are uncorrected and were determined on a Mettler FP-61 apparatus in open capillaries.

Precursor synthesis

Further compounds were synthesized according to literature methods: 1-piperidyldiazo-4-bromobenzene **2**[11], (4-bromophenyl)trimethylammonium triflate **5**[26], (4-bromophenyl)phenyliodonium triflate **6**[32], *bis*-(4-bromphenyl) iodonium bromide **7a**[33].

Bis-(4-bromphenyl)iodonium triflate 7b and (3-bromophenyl)-(4-methoxyphenyl)iodonium triflate 8. 4-Bromodiacetoxyiodo(III)benzene and 3-bromodiacetoxyiodo(III)benzene were synthesized according to literature methods[34,35] and used without further purification. Trifluoromethanesulfonic acid (0.36 ml/4.07 ml) was added slowly at –20°C to a stirred solution of the corresponding bromodiacetoxyiodo(III)benzene (2.05 mmol) and further stirred for 1 h at room temperature. Then, the solution was cooled to –10°C and the aromatic compound (2.2 mmol) was added dropwise. The reaction mixture was stirred for 24 h at room temperature. After evaporation of the solvent, diethyl ether was added to crystallize the residue. The solids were filtered, washed with diethyl ether and recrystallized from methanol.

Bis-(4-bromphenyl)iodonium triflate **7b** (yield 0.56 g, 43%): mp.: 198°C; ^{1}H-NMR (d_6-DMSO): 8.2 ppm (4 H, m, Ar-H), 7.8 ppm (4 H, m, ArH); ^{13}C-NMR (d_6-DMSO): 116.2 ppm (=C-Br), 127.2 ppm (=C-I), 135.6 ppm (=C-H), 137.9 ppm (=C-H); ^{19}F-NMR (d_6-DMSO): −78.16 ppm (3F, s, -SO_3CF_3); IR (KBr, cm^{-1}): 3075, 1553, 1471, 1273, 1165, 637; LC/MS-mode (*m*/*z*): (M^+ = 439); HR-MS (*m*/*z*): $C_{12}H_8Br_2I$; exact mass calculated (g/mol): [M^+] 436.804; measured: 436.803.

(3-Bromophenyl)-(4-methoxyphenyl)iodonium triflate **8** (yield 0.31 g, 39%): mp.: 128–129°C; ^{1}H-NMR (d_6-DMSO): 8.55 ppm (1 H, t, ArH), 8.23 ppm (3 H, d, ArH), 7.85 ppm (1 H, m, Ar-H), 7.49 ppm (1 H, t, Ar-H), 7.11 ppm (2 H, d, Ar-H), 3.82 ppm (3 H, s, -OCH_3); ^{13}C-NMR (d_6-DMSO): 162.97 ppm (=C-O), 144.88 ppm (=C-I), 138.2 ppm (=C-H), 137.48 ppm (=C-H), 135.68 ppm (=C-H), 134.54 ppm (=C-H), 134.24 ppm (=C-H), 123.97 ppm (=C-Br), 118.46 ppm (=C-I), 106.52 ppm (=C-H), 56.59 ppm (-CH_3); ^{19}F-NMR (d_6-DMSO): −78.74 ppm (3F, s, -SO_3CF_3); HR-MS (*m*/*z*): $C_{13}H_{11}^{77}BrIO$; exact mass calculated (g/mol): [M^+] 388.904; measured: 388.902; LC–MS-Mode (*m*/*z*): (M^+=390).

Bis-(4-bromphenyl)iodonium tosylate 7c. *Bis*-(4-bromphenyl)iodonium hydrogensulfate[33] (0.9 g/2 mmol) was dissolved in 15 ml methanol and mixed with 0.38 g (2 mmol) toluenesulfonic acid monohydrate. The solution was heated to reflux and 0.82 g (2.5 mmol) lead(II)carbonate were added. After 2 h the reaction mixture was further stirred for 4 h at RT. After removal of the solvent, addition of diethyl ether gave the raw product, which was crystallized in ethanol/diethyl ether. Yield 0.6 g, 96%.

mp: 203°C; ^{1}H-NMR (d_6-DMSO): 8,2 ppm (4 H, m, Ar-H), 7,8 ppm (4 H, m, ArH), 7.5 ppm (2 H, m Ar-H), 7.1 ppm (2 H, m Ar-H), 2.3 ppm (3 H, s, C_3), ^{13}C-NMR (d_6-DMSO): 21.7 ppm (-CH_3), 116.4 ppm (=C-Br), 126.4 (=CH), 127,1 ppm (=C–I), 128,9 (=CH), 135,4 ppm (=C-H), 138.0 ppm (=C-H) 144.9 (=C-), 146.4 (=C-); IR (KBr, cm^{-1}): 3075, 1553, 1471, 1273, 1165, 637; LC/MS-mode (*m*/*z*): (M^+ = 439); HR-MS (*m*/*z*): $C_{12}H_8Br_2I$; exact mass calculated (g/mol): [M^+] 436.804; measured: 436.803.

Radiochemistry

For all substitution experiments [^{18}F]fluoride was produced by the $^{18}O(p,n)^{18}F$ nuclear reaction via bombardment of an isotopically enriched [^{18}O]water (1.3 ml) target with a 17 MeV proton beam from the BC 1710 Baby Cyclotron. The [^{18}F]fluoride (148–222 MBq) in 10–20 µl water, 10 mg (26.5 µmol) Kryptofix® 2.2.2 and 13.25 µl of a 1 M K_2CO_3 in a 5 ml Wheaton glass vial were dried two times by azeotropic evaporation with 1 ml anhydrous acetonitrile at 80°C.

Studies on the Wallach reaction. The details of these studies were described earlier in detail.[11] In brief: to dried [^{18}F]fluoride (37–74 MBq), 30 mg (112 µmol) of 1-piperidyldiazo-4-bromobenzene and 350 µmol of toluenesulfonic acid or methanesulfonic acid together with 500 µl CCl_4 were added and heated to 100°C for 15 min. After the reaction the solution was cooled, filtered and analyzed by HPLC.

Standard conditions for the ^{18}F-fluorination exemplified by the synthesis of 1-bromo-4-[^{18}F]fluorobenzene via dibromodiphenyliodonium salt. The closed reaction vial containing dry [^{18}F]fluoride was heated to 130°C by an oil bath and a solution of the 4,4′-dibromodiphenyliodonium salt dissolved in 0.8 ml DMF (25 mmol/l) was added. At the appropriate time (10 min) aliquots of the reaction mixture (20 µl) were quenched in 300 µl acetonitrile and analyzed by reversed phase HPLC using a µ-Bondapak column (4 × 250 mm). Radioactivity measurement was performed by a NaI(Tl) well-type scintillation detector on-line connected with the outlet of the u.v.-photometer.

The same procedure was applied for the halogen-activated ^{18}F-for-halide studies using a precursor concentration of 15–20 mmol/l in 1 ml DMSO at 160°C and for the ^{18}F-for-NO_2 exchange using 40–50 mmol/l of precursor in 1 ml DMSO at 80°C.

GC isolation of 1-bromo-4-[^{18}F]fluorobenzene. The organic components of the reaction mixture were separated from the solvent and the salts by a solid phase extraction on SEP-PAK® C-18 cartridges. Then, the cartridge was washed

with 10 ml water and afterwards dried by a stream of air. By rinsing the cartridge with 2 ml diethyl ether 1-bromo-4-[^{18}F]fluorobenzene was coeluted with 1,4-diiodobenzene and the whole eluate was passed through a cartridge filled with anhydrous $MgSO_4$ for drying. The volume of the solution was then reduced in the cold to about 1 ml by using a stream of argon. After that, the solution was gas chromatographically separated as described below, and the n.c.a. 1-bromo-4-[^{18}F]fluorobenzene was trapped in dry form in a nitrogen cooled trap. Afterwards the labelled product was dissolved in 1–5 ml dry diethyl ether. From end of synthesis this separation took 40 min.

Gas-chromatographic separation was performed on Chromosorb W-AW-DMCS (60–80 mesh) with 6% bentone and 20% DC 200 in a glass column (4 m × 8 mm) and with a helium gas flow of 150 ml/min. The injector was heated to 240°C. A TCD detector was used for the detection of the reference compounds. At the outlet of the GC, a heated 1/16″ stainless steel line lead to a Valco valve oven (HVEC-220 V, heated to 200°C) with two outlets. One outlet was connected to a cooling trap cooled by liquid nitrogen by another heated 1/16″ stainless steel line to collect the labelled product. The parameters of the temperature program were:

Starting temperature:	140°C
Start of heating:	5 min
Heating rate:	15°C/min
Reset:	50 min
k′(1-bromo-4-fluorobenzene)	4.53

Column chromatographic isolation of 1-bromo-4-[^{18}F]fluorobenzene. After finishing the labelling reaction the whole reaction mixture was given on top of a small glass column (120 × 10 mm) for column chromatography. The stationary phase consisted of silica Si-60 (0.063–0.200 mm) conditioned by dry diethyl ether. Thereby the whole reaction mixture (0.8 ml DMF) was separated within 10 min in which the first 2.5 ml eluate were discarded (diethyl ether). The following 3 ml contained about 95% of the whole n.c.a. 4-bromo-[^{18}F]fluorobenzene. Owing to the strong adsorption of DMF on silica it was relatively easy to separate the aromatic compounds from the dipolar aprotic solvent.

Conditions for the examination of [^{18}F]fluoromethane formation. The ^{18}F-labelling of bromophenyltrimethylammonium triflate (**5**) was carried out according to the procedure described above using 16 mmol/l of precursor in 0.8 ml DMSO at 120°C. The reaction mixture was cooled in an ice bath, the activity of the closed vial was measured and after that the gas phase of the vial

was qualitatively analyzed by gas chromatography using the following conditions:

Column:	4 m × 8 mm glass column
Material:	Porapack P
Temperature:	30°C
k′([^{18}F]fluoromethane)	2.18

For its quantification [^{18}F]fluoromethane was removed from the organic phase by a stream of argon (10 min). The ^{18}F-labelled arenes were separated by silica gel column chromatography (1 × 15 cm) using diethyl ether as solvent. The activity of the diethyl ether solution was measured to obtain the yield of [^{18}F]fluoroarenes. The purity of the [^{18}F]fluoroarenes was checked by reversed-phase HPLC using a μ-Bondapak column (4 × 250 mm).

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