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^{18}F Radiochemistry

^{18}F Labeling of Arenes

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aryl fluorides · fluorine-18 · heterocycles · positron emission tomography · radiochemistry

Molecular imaging has witnessed an upsurge in growth, with positron emission tomography leading the way. This trend has encouraged numerous synthetic chemists to enter the field of ^{18}F-radiochemistry and provide generic solutions to address the well-recognized challenges of late-stage fluorination. This Minireview focuses on recent developments in the ^{18}F-labeling of aromatic substrates.

1. Introduction

The incorporation of fluorine into aromatic systems is well known to purvey beneficial properties to a potential drug candidate.[1] The demand of medicinal chemists for selective methods of fluorination has driven the field of organofluorine chemistry forward at a spectacular rate, with important milestones reached, particularly in recent years. Molecular imaging has also promoted the field of late-stage fluorination. The unnatural radionuclide ^{18}F has unique properties that are ideally suited to positron emission tomography (PET), one of the leading imaging modalities used in the clinic. With a half-life of 109.7 min, ^{18}F allows for the multistep synthesis of complex radiotracers and for transport of [^{18}F]fluoride and ^{18}F radiotracers such as [^{18}F]fluorodeoxyglucose[2] away from the site of production to research facilities and hospitals. The decay profile of ^{18}F by positron emission (97%) and electron capture (3%) is an additional advantage. The emitted low-energy (0.635 MeV) positron has a maximum range in water of 2.4 mm, which results in high-resolution PET images. The huge potential of PET in personalized medicine and drug discovery[3] has encouraged the development of a range of new "cold" fluorination methods, but translation to ^{18}F radiolabeling has been slow.[4] The intrinsic challenges of ^{18}F radiochemistry are significant and require tailored conceptual innovation. A major obstacle is the half-life, which requires reactions to be completed within minutes rather than hours. Radioisotopes are typically produced in a nano- or picomolar concentration, with precursors commonly present in large excess (millimolar concentration). This stoichiometry is very different to "cold" fluorinations, where it is commonplace for the fluoride source to be present in excess. In addition, the necessity of lead hot cells to shield users from radiation makes performing "hot" reactions more difficult from a practical consideration than performing "cold" experiments in an organic synthesis laboratory. This Minireview is focused solely on the ^{18}F radiolabeling of arenes, which is a sought-after motif in radiotracer design, in part because of the metabolic robustness of fluorinated aromatic compounds in vivo. The ideal radiosynthesis would incorporate the radiolabel as late in the synthesis as possible, with any subsequent and purification steps being very rapid and high yielding. We have opted not to discuss in this Minireview ^{18}F targets requiring post-fluorination chemical transformations.

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2. Synthesis of [^{18}F]Fluoroaromatic Compounds with [^{18}F]Fluoride

2.1. Production of [^{18}F]Fluoride[5]

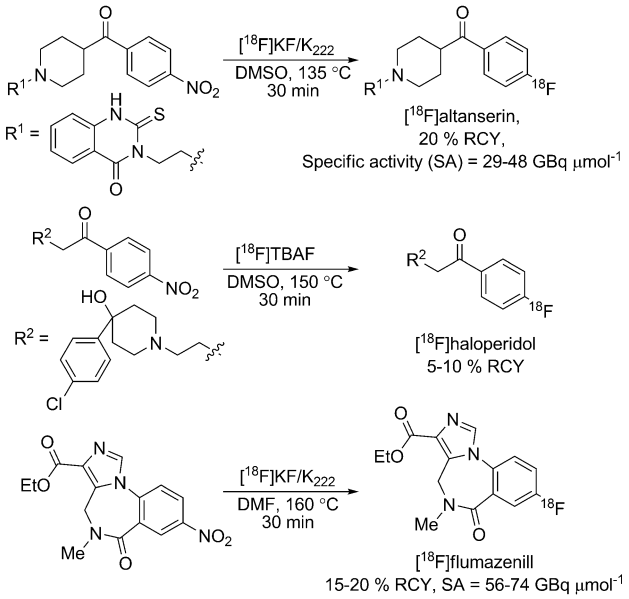
[^{18}F]Fluoride is most commonly produced in cyclotrons by the nuclear reaction ^{18}O(p,n)^{18}F; in practical terms, this involves irradiating (proton bombardment) [^{18}O]water, a process that delivers aqueous [^{18}F]fluoride. The associated cationic species is likely to be a metal ion from the cyclotron target. The [^{18}F]fluoride in [^{18}O]water can be drained from the cyclotron and easily transported to another site. As no ^{19}F is introduced at any stage in the production of [^{18}F]fluoride, the specific activity (SA)[4a] is high, reaching up to 5500 GBq μmol^{-1}.[5] Aqueous [^{18}F]fluoride is not a competent nucleophile[6] and is, therefore, subjected to dehydration prior to use by loading onto an ion-exchange column. [^{18}F]Fluoride is then eluted with a countercation (either a metal ion with a cryptand or a tetraalkylammonium salt) dissolved in MeCN/H_2O, followed by azeotropic drying to produce a reactive [^{18}F]fluoride source. The drying process can be performed manually on a conventional heating plate, but the majority of research centers use an automated synthesis unit that minimizes the radiation dose to the research worker.

[^{18}F]Fluoride is favored over [^{18}F]F_2 as the source of ^{18}F because it is easier to produce and handle, and furthermore is available with higher specific activity.

2.2. Nucleophilic Aromatic Substitution

Nucleophilic aromatic substitution (S_NAr) is frequently used for the synthesis of radiolabeled aryl fluorides.[7] These reactions require the presence of activating electron-withdrawing substituents in the *ortho* or *para* positions relative to the leaving group.[8] If these groups are not desired in the final product, additional steps after the ^{18}F fluorination are required to remove these activating groups, but this set of additional reactions may decrease the radiochemical yield (RCY) dramatically. More elegantly, these activating group(s) may be transformed after the ^{18}F fluorination to construct molecular complexity, thereby allowing easy access to ^{18}F radiotracers not amenable to direct nucleophilic ^{18}F fluorination.[9] The trimethylammonium and nitro groups are most widely used for displacement with [^{18}F]fluoride, although the substitution of halogens and sulfonium salts has been documented.[10] The trimethylammonium leaving group can be advantageous, as the excess precursor is more easily separated from the product.[11] However, this precursor does lead to competitive fluorodemethylation and the release of [^{18}F]methyl fluoride, a side reaction that reduces significantly the RCY.[12] Typical S_NAr reactions for ^{18}F labeling necessitate heating at high temperature (> 100 °C) in a polar aprotic solvent, a set of conditions which may preclude the presence of more-sensitive functionalities and applications to thermally unstable targets, such as some peptides and proteins. Despite some of the drawbacks associated with S_NAr reactions, various ^{18}F radiotracers have been prepared by relying on this reaction as the last step of the synthesis: these include [^{18}F]altanserin,[13] a radioligand for serotonin receptors, and [^{18}F]haloperidol, used for the measurement of dopamine D_2 receptors.[14] Notably,[^{18}F]flumazenil, a ligand that targets central benzodiazepine receptors was successfully prepared by S_NAr reactions from a precursor presenting with a *meta*-positioned activating group (Scheme 1).[15]

Aromatic precursors bearing activating electron-withdrawing groups *meta* to the leaving group are less suitable for S_NAr reactions. Pike and co-workers investigated the use of microwave technology to facilitate the ^{18}F fluorination of these more challenging substrates.[16] A series of *meta*-substituted arenes with an activating electron-withdrawing group (NO_2, CN, CF_3, Br) and a suitable leaving group (NO_2, F, $^+NMe_3$) were treated with [^{18}F]KF/K_{222} by applying either conventional heating or microwave conditions. Higher yields were obtained under microwave heating (90 W, 3 min) compared to conventional heating (150 °C, 10 min), but this trend is not general (Table 1).



Scheme 1. Syntheses of ^{18}F radiotracers by S_NAr reactions. TBAF = tetra-*n*-butylammonium fluoride, K_{222} = kryptofix = 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane.

The synthesis of the mGluR5 radioligand [^{18}F]3-fluoro-5-((2-methylthiazol-4-yl)ethynyl)benzonitrile ([^{18}F]FMTEB) was attempted under microwave conditions by halogen exchange of either Cl or Br with [^{18}F]fluoride. Isolated RCYs were found to be 4 and 8% for Cl and Br, respectively, thus indicating that the presence of the *meta*-positioned CN group is not sufficient for this reaction to be synthetically useful (Scheme 2).[17]

As a consequence of the harsh conditions required for nucleophilic fluorination, sensitive substrates such as peptides or proteins are normally labeled by coupling a prefunctionalized precursor with a ^{18}F-radiolabeled so-called prosthetic group.[18] [^{18}F]Fluorobenzaldehyde and *N*-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB) are most commonly used to

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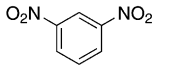
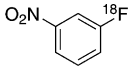
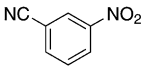
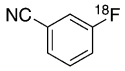
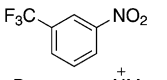
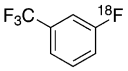
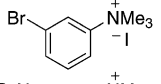
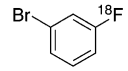
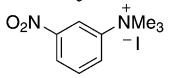
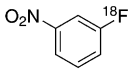
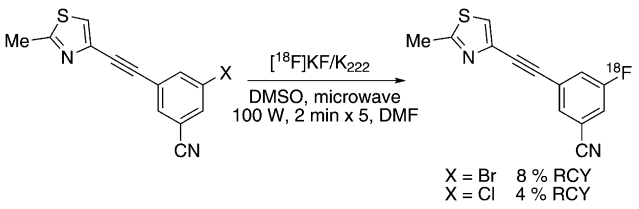
Véronique Gouverneur obtained a PhD from UCL (Belgium) with Prof. L. Ghosez. After a postdoctoral Fellowship with Prof. R. A. Lerner at the Scripps research Institute (USA), she accepted a position of Maître de Conférences at ULP (France). In 1998, she moved to the University of Oxford as University Lecturer and Tutorial Fellow at Merton College (UK). She became Professor of Chemistry in 2008. Her research aims at advancing fluorine chemistry in a broad sense.

Table 1: Synthesis of *meta*-substituted [^{18}F]fluoroarenes by S_NAr reactions.

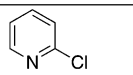
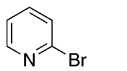
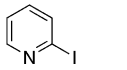
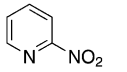
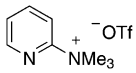
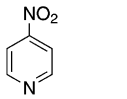
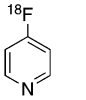
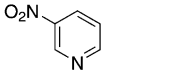
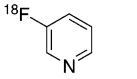
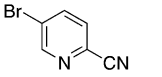
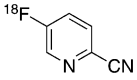
Entry	Precursor	Product	RCY [%] thermal[a]	RCY [%] microwave[b]
1			21	47
2			20	46
3			8	13
4			3	17
5			4	8

[a] [^{18}F]KF/K_{222}, 1-methyl-2-pyrrolidinone, 150 °C,10 min. [b] [^{18}F]KF/K_{222}, 1-methyl-2-pyrrolidinone, 90 W, 3 min.



Scheme 2. Microwave-mediated synthesis of [^{18}F]FMTEB.

Table 2: Synthesis of *ortho*-, *meta*-, and *para*-fluoropyridines by S_NAr reactions.

Entry	Precursor	Product	RCY [%] thermal[a]	RCY [%] microwave[b]
1			3	22
2			16	71
3			0	14
4			85	88
5			89	90
6			60[c]	72
7			1[c]	2
8			92[d]	N/A

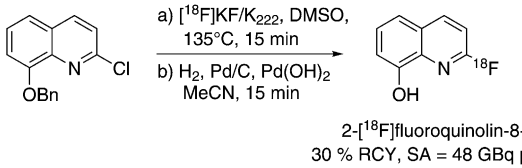
[a] [^{18}F]KF/K_{222}, DMSO, 150 °C,10 min. [b] [^{18}F]KF/K_{222}, DMSO, 100 W, 2 min. [c] [^{18}F]KF/K_{222}, DMSO, 145 °C, 10 min; [d] [^{18}F]KF/K_{222}, DMSO, 150 °C, 5 min. N/A = not applicable. OTf = trifluoromethanesulfonate.

acylate lysine residues and N-terminal amine groups. Whilst [^{18}F]fluorobenzaldehyde can be conveniently synthesized in a one-step S_NAr procedure from 4-formyl-*N*,*N*,*N*-trimethylbenzenaminium trifluoromethane sulfonate, attempts to synthesize [^{18}F]SFB directly from *N*-succinimidyl 4-nitrobenzoate with [^{18}F]KF/K_{222} were not successful.[19] This target, however, is accessible by applying one of the various multistep sequences reported in the literature, all featuring the introduction of the *N*-succinimidyl motif after ^{18}F fluorination.[20]

The ^{18}F labeling of heteroarenes with fluoride has been examined extensively, with an emphasis on the ^{18}F fluorination of pyridines, by Dollé and co-workers (Table 2). Pyridine, having a lower energy LUMO than benzene, is more amenable to nucleophilic aromatic substitution, and the presence of additional activating groups is, therefore, not a prerequisite. 2-[^{18}F]Fluoropyridine was selected as a model substrate to study the influence of the *ortho*-positioned leaving group on the radiochemical yield.[21] Upon conventional heating at 150 °C in DMSO with [^{18}F]KF/K_{222} for 10 minutes, 2-nitropyridine and (2-pyridyl)trimethylammonium triflate gave 2-[^{18}F]fluoropyridine in RCYs of 85 and 89 %, respectively (entries 4 and 5). Under these conditions 2-iodopyridine gave none of the desired product, whereas 2-chloro- and 2-bromopyridine gave RCYs of 3 and 16 %, respectively (entries 1–3). The same transformation under microwave conditions for 2 minutes led to similar yields for the nitro and trimethylammonium precursors, whereas the RCY of 2-[^{18}F]fluoropyridine from 2-bromopyridine was increased to 71 %. 4-[^{18}F]Fluoropyridine and 3-[^{18}F]fluoropyridine were prepared by S_NAr reactions of the corresponding nitro precursors in 72 and 2 % RCY, respectively (entries 6 and 7). Although 3-[^{18}F]fluoropyridine is not accessible by this method, it was demonstrated that the presence of a cyanide group at the 2-position and a Br leaving group in the 5-position allows for the synthesis of 5-[^{18}F]fluoropicolinonitrile in 92 % RCY (entry 8).[22] The labeling of pyridines by isotopic exchange has also been reported.[23] ^{18}F-Labeled pyridines have found widespread use as prosthetic groups for the indirect labeling of peptides, proteins, and oligonucleotides.[24]

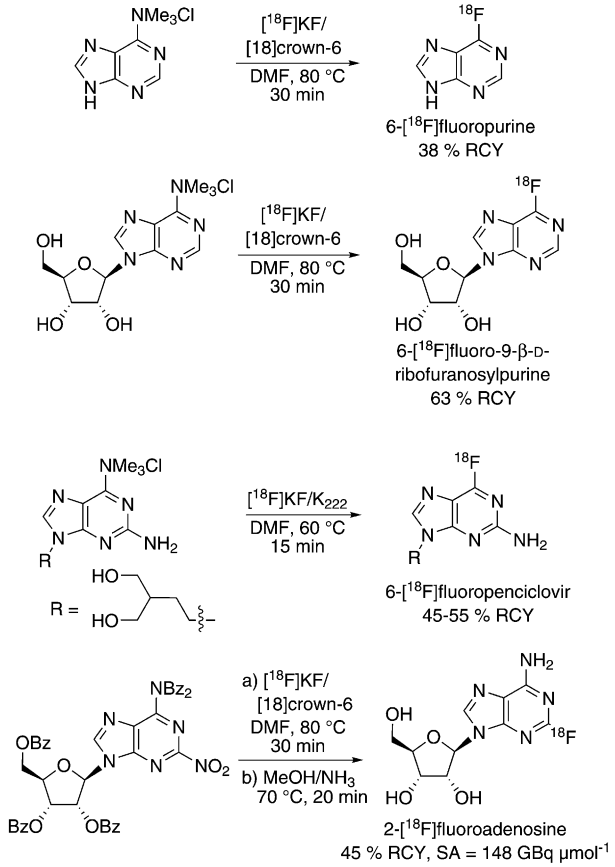
The synthesis of 2-[^{18}F]fluoroquinolin-8-ol by substitution of a chloride leaving group is possible, whereas attempts to synthesize 4-[^{18}F]fluoroquinolin-8-ol were unsuccessful (Scheme 3).[25]

Early work validated the synthesis of 6-[^{18}F]fluoropurine and 6-[^{18}F]fluoro-9-β-D-ribofuranosylpurine from trimethylammonium chloride precursors with RCYs of 38 and 63 %, respectively.[26] The PET probes 6-[^{18}F]fluoropenciclovir[27] and 2-[^{18}F]fluoroadenosines were synthesized by using the S_NAr method (Scheme 4).[28]



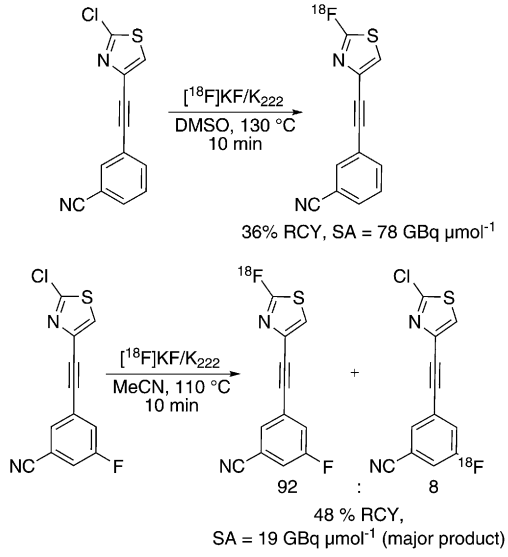
2-[^{18}F]fluoroquinolin-8-ol
30 % RCY, SA = 48 GBq μmol^{-1}

Scheme 3. Synthesis of 2-[^{18}F]fluoroquinolin-8-ol. Bn = benzyl.



Scheme 4. Synthesis of [^{18}F]purines. Bz = benzoyl.

Other heteroaromatic motifs, such as azabenzoxazoles[29] and 1,3-thiazoles,[30] have been labeled with [^{18}F]fluoride using S_NAr. The synthesis of 2-[^{18}F]fluoro-1,3-thiazoles by nucleophilic displacement of halogenated 1,3-thiazoles has been applied to a series of $mGlu_5$ radioligands (Scheme 5).[30]



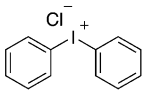
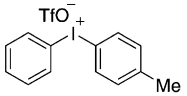
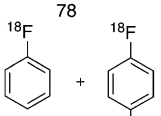
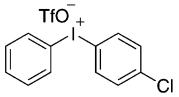
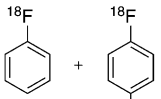
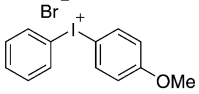
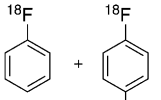
Scheme 5. Synthesis of 1,3-[^{18}F]thiazoles.

To the best of our knowledge, a single report discloses the synthesis of [^{18}F]fluorobenzene by a benzyne strategy. Treatment of benzenediazonium-2-carboxylate with [^{18}F]HF and [^{19}F]KF led to [^{18}F]fluorobenzene, although no yields or specific activities were reported.[31]

2.3. Diaryliodonium Salts

Diaryliodonium salts[32] have been of particular interest to radiochemists,[33] as they allow the nucleophilic fluorination of electron-rich arenes, a class of targets not accessible by a classical direct S_NAr reaction. In early studies pioneered by Pike and Aigbirhio,[33a] the fluorination of diaryliodonium salts was validated with both [^{18}F]KF/K_{222} and [^{18}F]CsF in MeCN. Good radiochemical yields of the desired [^{18}F]fluoroarenes were obtained within 40 minutes at 85 °C. A mixture of two possible [^{18}F]fluoroarenes was observed for unsymmetrically substituted diaryliodonium salts. In the examples studied, the regioselectivity was found to be dependent on the electron density of the aryl rings, with the fluorination occurring preferentially at the electron-poor arene (Table 3).

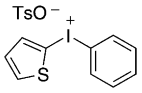
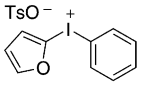
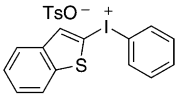
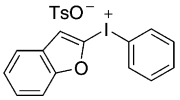
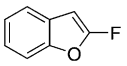
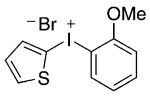
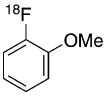
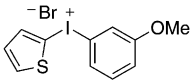
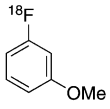
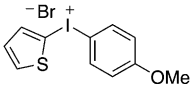
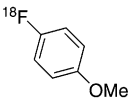
Table 3: Electronic effects on the fluorination of unsymmetrical diaryliodonium salts.

Entry	Precursor	Product distribution RCY [%]
1[a]		 78
2[b]		 3 : 2 68
3[c]		 2 : 3 14
4[b]		 100 : 0 88

[a] [^{18}F]KF/K_{222}, MeCN, 110 °C, 35 min. [b] [^{18}F]KF/K_{222}, MeCN, 85 °C, 40 min. [c] [^{18}F]KF/K_{222}, MeCN, 100 °C, 35 min.

The reactivity of unsymmetrical diaryliodonium salts bearing electron-rich heteroaromatic groups was further investigated (Table 4). Unsymmetrical phenylheteroaryliodonium salts were prepared with 2-substituted furan, *N*-methylpyrrole, and thiophenyl arenes.[34] For these substrates, nucleophilic fluorination with CsF gave fluorobenzene only. The presence of the 2-benzo[*b*]thiophene group led exclu-

Table 4: Electronic effects on the fluorination of unsymmetrical diaryliodonium salts.

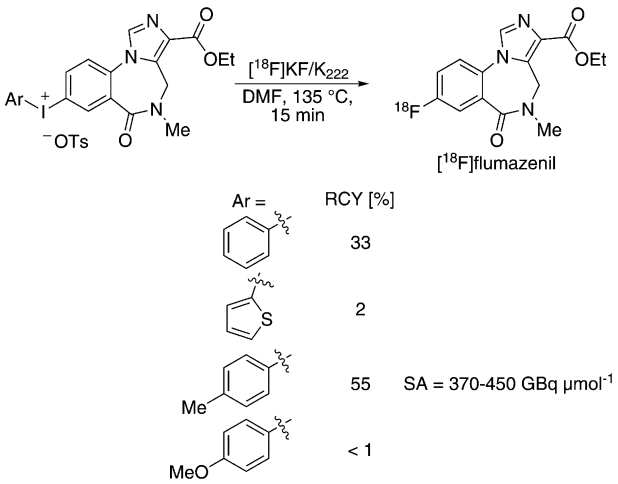
Entry	Precursor	Observed product	RCY [%]
1[a]			N/A
2[a]			N/A
3[a]			N/A
4[a]			N/A
5[b]			60
6[b]			20
7[b]			25-30

[a] CsF, MeCN, 80 °C, overnight. [b] [^{18}F]KF/K_{222}, DMF, 130 °C, 45 min. N/A = not applicable. OTs = *p*-toluenesulfonate.

sively to the formation of fluorobenzene, whereas a 2-benzo[*b*]furan gave selectively 2-fluorobenz[*b*]furan (entries 3 and 4). This work has been translated to ^{18}F labeling, with the 2-thienyl group effective at directing fluorination to electron-rich aromatic compounds such as anisole (entries 5–7). Coenen and co-workers synthesized 2-methoxyphenyl-, 3-methoxyphenyl-, and 4-methoxyphenyl(2-thienyl)iodonium bromide and treated these precursors with [^{18}F]KF/K_{222} in DMF at 130 °C for 45 minutes. The corresponding products, 2-[^{18}F]fluoroanisole, 3-[^{18}F]fluoroanisole, and 4-[^{18}F]fluoroanisole, were formed in RCYs of 60, 20, and 25–30 %, respectively. The counteranion of the iodonium salt was found to be very important, with RCYs following the order tosylates < iodides < triflates < bromides.[35]

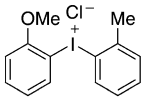
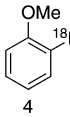
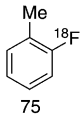
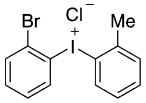
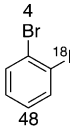
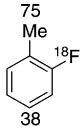
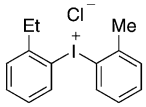
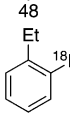
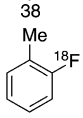
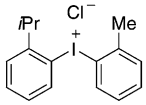
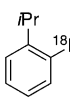
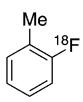
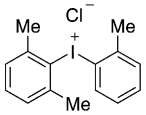
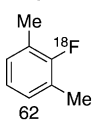
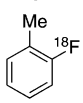
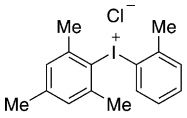
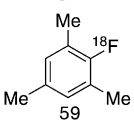
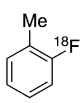
A series of unsymmetrical precursors was studied for the synthesis of [^{18}F]flumazemil: the 4-methyphenylmazenil iodonium tosylate gave higher yields than 2-thiophenyl- and 4-methoxyphenylmazenil iodonium triflates. Taken together, these data suggest that caution should be exercised when selecting a putative directing group (Scheme 6).[36]

Competition experiments were performed with unsymmetrical *ortho*-substituted diaryliodonium chlorides.[37] This study, undertaken by Pike and co-workers, was aimed at determining to what extent the so-called *ortho* effect[38] directs the fluorination of functionalized iodonium salts. The following order was deduced: 2,6-di-Me > 2,4,6-tri-Me > Br > Me > Et ≈ *i*Pr > H > OMe, a ranking suggesting that the *ortho* effect is not solely due to steric constraints (Table 5).[37]



Scheme 6. Synthesis of [^{18}F]flumazenil from diaryliodonium salts.

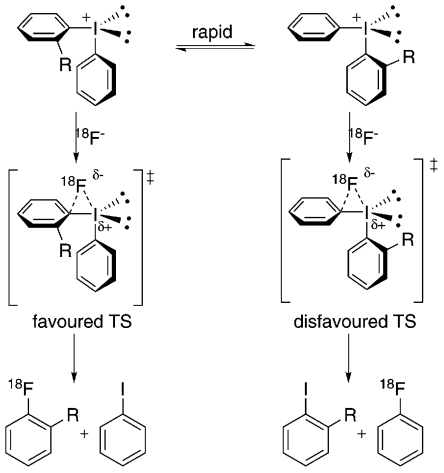
Table 5: *Ortho*-directing effect.

Entry	Diaryliodonium precursor	RCY of [^{18}F]fluoroarene [%]		Selectivity for main product
1[a]		 4	 75	18.8
2[b]		 48	 38	1.26
3[b]		 43	 52	1.21
4[b]		 40	 48	1.20
5[b]		 62	 11	5.56
6[c]		 59	 33	1.78

[a] [^{18}F]KF/K_{222}, DMF, 140 °C, 188 s. [b] [^{18}F]KF/K_{222}, DMF, 170 °C, 236 s. [c] [^{18}F]KF/K_{222}, DMF, 130 °C, 236 s.

A nucleophilic aromatic substitution mechanism has been proposed for the fluorination of diaryliodonium salts. In addition, an alternative mechanism whereby the [^{18}F]fluoride binds to iodine prior to formation of the aryl fluoride has also been proposed. In cross-over experiments, DiMagno and co-workers have reported that diaryliodonium salts can undergo fluoride-promoted ligand exchange, although this effect was dependent on the fluoride concentration.[39] Computational calculations were performed on the ground-state stabilities of

the model dialkynyliodonium fluorides instead of diaryl species. These calculations predict a "T"-shaped geometry, where fluorine occupies one of the axial positions. The electron-poor alkynyl group preferentially occupies the axial position, while the electron-rich alkynyl unit adopts the equatorial position *syn* to the fluorine atom. This would predict fluorination to occur on the more electron-rich unit, which is inconsistent with the experimental data. Calculation of the transition-state stabilities for C–F extrusion revealed an opposite preference, where the more electron-deficient alkynyl group preferentially occupies the equatorial position, thus corroborating the experimental results. This study revealed that iodonium fluorides may form stable dimers, which can provide a low-energy pathway for interconversion of axial/equatorial ligands.[40,41] It has been suggested that the reaction may adhere to the Curtin–Hammett principle, with the product ratio depending on the relative energy of the corresponding transition states (Scheme 7).[37]

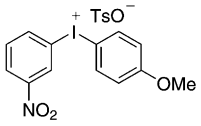
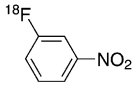
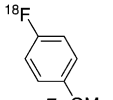
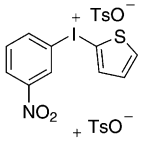
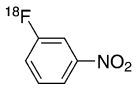
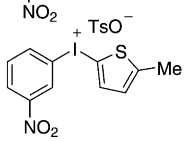
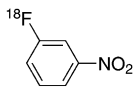
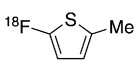
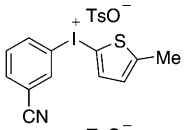
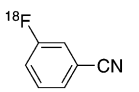
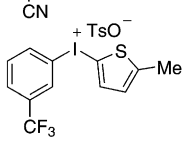
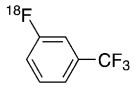


Scheme 7. Suggested mechanism for the fluorination of diaryl iodonium salts. TS = transition state.

The synthesis of *meta*-substituted [^{18}F]fluoroarenes is possible from iodonium precursors (Table 6).[42] Unsymmetrical diaryliodonium tosylates were synthesized with a *meta*-CN, NO_2, or CF_3 group on one of the aromatic rings, the other ring being an electron-rich heteroarene (e.g. 4-anisyl, 2-thienyl, or 5-Me-2-thienyl). By using [^{18}F]KF/K_{222} in MeCN at elevated temperatures, the desired products were formed in 31–78% RCY, with the lower yields being for the *meta*-nitro-substituted [^{18}F]fluoroarenes.

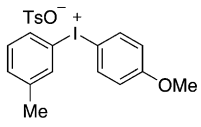
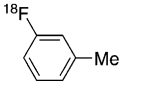
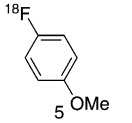
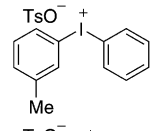
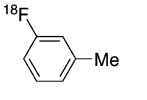
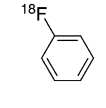
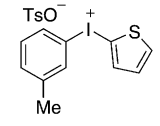
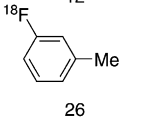
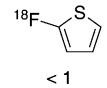
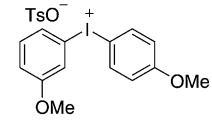
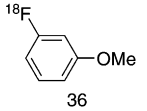
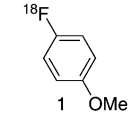
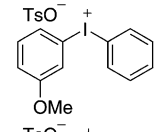
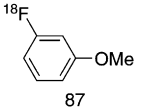
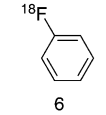
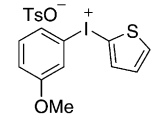
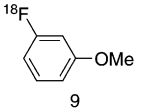
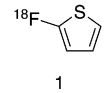
Diaryliodonium salts with electron-donating groups in the *meta* position were prepared, with the 2-thienyl, 4-methoxyphenyl, or phenyl acting as the regiodirecting group. [^{18}F]*meta*-Fluoroanisole was formed in 87% RCY from the phenyliodonium tosylate, whereas the corresponding 2-thienyl and 4-methoxyphenyl gave yields of 9 and 36%, respectively. Conversely, *meta*-[^{18}F]fluorotoluene was delivered in 12% RCY from the phenyliodonium precursor, while the 2-thienyl and 4-methoxyphenyl analogues gave yields of 26 and 47%, respectively (Table 7).

Table 6: Synthesis of electron-poor *meta*-substituted [^{18}F]aryl fluorides.

Entry	Precursor	Product distribution RCY [%]	
1[a]		 58	 7
2[a]		 31	 4
3[a]		 37	 2
4[b]		 78	 1
5[c]		 57	 0

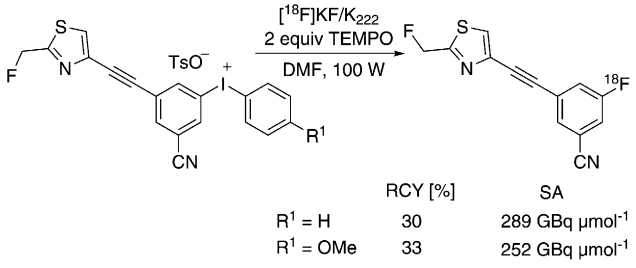
[a] [^{18}F]KF/K_{222}, MeCN, 130°C, 191 s. [b] [^{18}F]KF/K_{222}, MeCN, 180°C, 189 s. [c] [^{18}F]KF/K_{222}, MeCN, 190°C, 189 s.

Table 7: Synthesis of electron-rich *meta*-substituted [^{18}F]aryl fluorides.

Entry	Precursor	Product distribution RCY [%]	
1[a]		 47	 5
2[b]		 12	 15
3[c]		 26	 < 1
4[d]		 36	 1
4[e]		 87	 6
5[f]		 9	 1

[a] [^{18}F]KF/K_{222}, MeCN, 180°C, 236 s. [b] [^{18}F]KF/K_{222}, MeCN, 160°C, 236 s. [c] [^{18}F]KF/K_{222}, MeCN, 190°C, 236 s. [d] [^{18}F]KF/K_{222}, MeCN, 180°C, 236 s. [e] [^{18}F]KF/K_{222}, MeCN, 150°C, 314 s; [f] [^{18}F]KF/K_{222}, MeCN, 200°C, 314 s.

This method was applied to the synthesis of mGluR5 radioligands with specific activities in the range of 252–289 GBq μmol^{-1} (Scheme 8).[17] Addition of the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) has been reported to give higher RCYs and more consistent results (Scheme 8).[43]



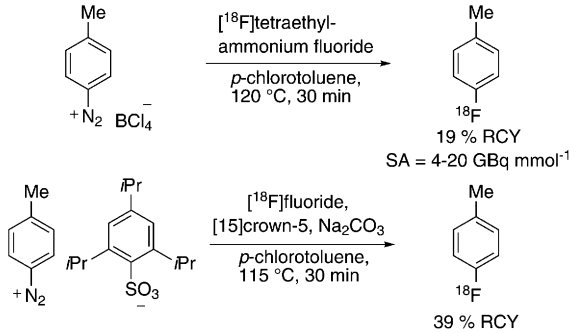
Scheme 8. Synthesis of [^{18}F]mGlu5 PET ligands from diaryliodonium tosylates.

The utility of aryliodonium salts is further highlighted by the synthesis of 3-[^{18}F]fluoropyridine and 3-[^{18}F]fluoroquinoline, whereby incorporation of [^{18}F]fluoride to the *meta* position occurred in 55–63% and 22–25% RCY, respectively.[44]

Taken together, the data available on the fluorination of iodonium salts demonstrate that this reaction provides a useful way to label arenes not easily accessible by traditional S_NAr.

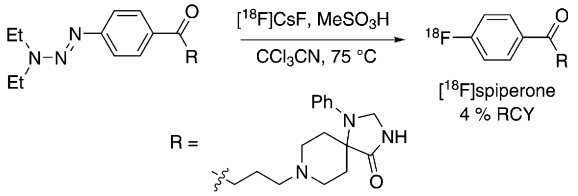
2.4. Dediazoniation Reactions

The conventional Balz–Schiemann transformation has not seen widespread use in the preparation of ^{18}F radiotracers, despite being the first method reported for the incorporation of [^{18}F]fluoride into aromatic systems.[45] The use of a tetrafluoroborate anion is not desirable in a radiochemical setting since its use translates to the formation of radiotracers of low specific activity. The tetrachloroborate anion was examined as an alternative. The fluorination of *p*-toluidyldiazonium tetrachloroborate yielded *p*-[^{18}F]fluorotoluene with an optimized RCY of 19% and SA in the range 4–20 GBq mmol^{-1}.[46] Subsequent studies identified 2,4,6-triisopropylbenzenesulfonate as the optimal diazonium counterion, giving *p*-[^{18}F]fluorotoluene in up to 39% RCY; the scope of this reaction was not further investigated (Scheme 9).[47]



Scheme 9. ^{18}F Labeling by fluorodediazonation.

The sparse literature on the use of the Balz–Schiemann reaction for the preparation of radiotracers reflects the low efficiency of the process. The Wallach triazene reaction could serve as a viable alternative. Triazenes are relatively stable, but decompose upon heating in the presence of an acid to give the corresponding diazonium salt, which can subsequently react with [^{18}F]fluoride.[48] Aryldiazonium ions break down through heterolytic and/or homolytic pathways, depending on the reaction solvent and redox potentials of the reactants.[49] The use of chlorinated solvents such as CCl_4 or Cl_3CCN minimizes undesired protodediazoniation. The synthesis of ^{18}F-labeled spiperone from the corresponding diethyltriazene with [^{18}F]CsF and methanesulfonic acid gave < 0.5% RCY in CH_3CN, in comparison to 4% RCY in Cl_3CCN (Scheme 10).[50] Pages and Langlois found trifluoroethanol to be a very effective solvent for the Wallach reaction, with aryl fluorides obtained in high yields with CsF and trifluoromethanesulfonic acid. However, translation of these conditions to a radiochemical transformation gave no trace of the desired ^{18}F-labeled substrate.[51]



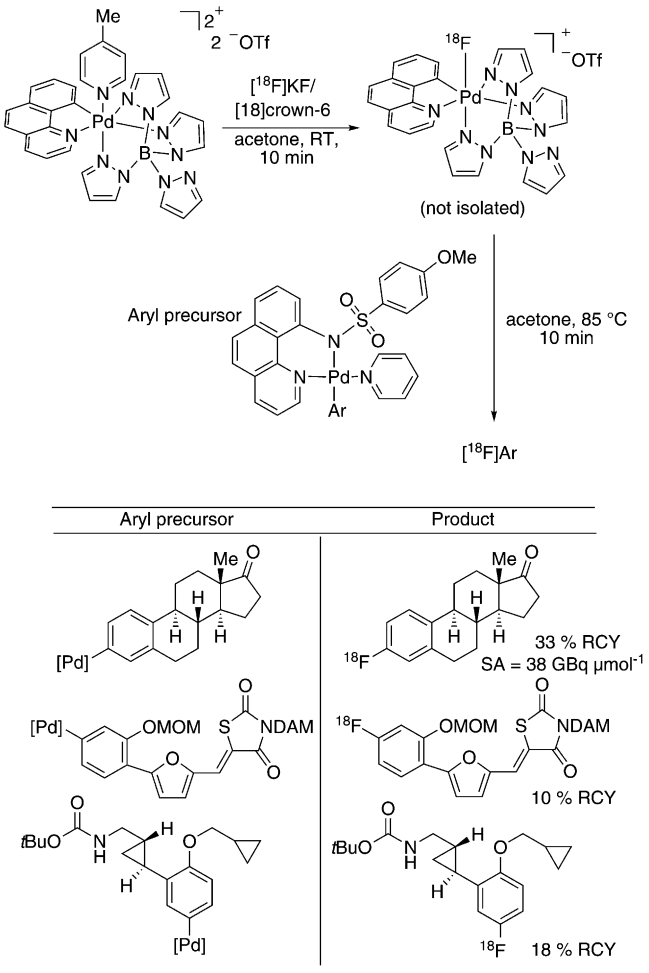
Scheme 10. Synthesis of [^{18}F]spiperone.

A solid-phase-supported variant of the Wallach reaction has recently been developed based on 1-(aryldiazenyl)piperazines bound to a Merrifield-type resin; a single substrate was ^{18}F labeled in 14% RCY.[52] The radiochemical fluorination of solid-supported aryldiazonium sulfonates proceeded in low RCYs because of adsorption of [^{18}F]fluoride on to the resin. Although selected radiotracers have been synthesized from triazene precursors, the products are formed in low RCY, but with high specific activity. As a consequence of the poor RCYs, the Wallach reaction is not employed as a routine radiochemical procedure.

2.5. [^{18}F]Fluoride Umpolung Strategies

A method allowing for the direct oxidation of [^{18}F]fluoride to an electrophilic [^{18}F]fluorine species (fluoride umpolung) would allow for the production of a large range of radiotracers with no compromise of specific activity. On the basis of redox potentials, this avenue appears prohibitively challenging. Recently, Ritter and co-workers provided an innovative solution to this problem with a no-carrier added synthesis of an ^{18}F-labeled electrophilic fluorinating reagent derived from [^{18}F]fluoride.[53] Carefully designed studies led to the development of a highly fluorophilic Pd^{IV} complex, which upon treatment with [^{19}F]KF gave a Pd^{IV} fluoride in 90% yield. The judicious selection of benzo[*h*]quinolyl and tetrapyrazole borate ligands confers sufficient stability to this

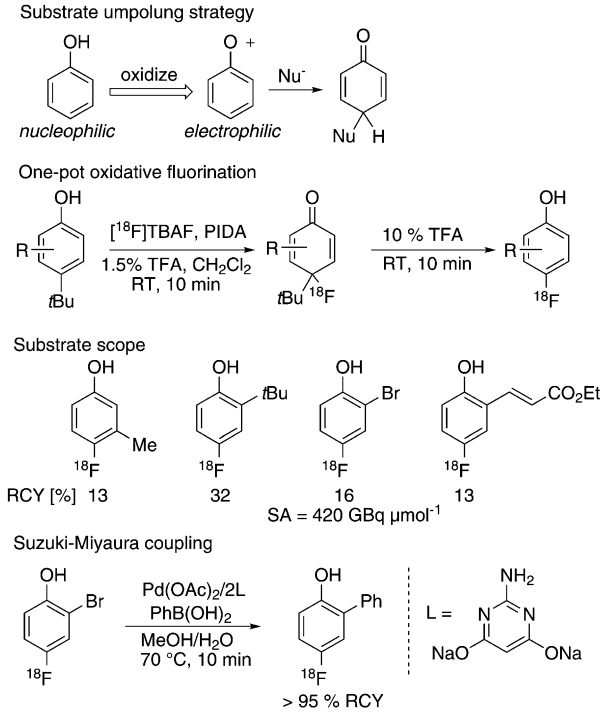
novel complex by preventing undesired reaction pathways such as reductive elimination. The authors reasoned that nucleophilic attack would occur at the only accessible antibonding palladium–fluorine orbital ($\sigma^*_{Pd\text{-}F}$), a hypothesis consistent with DFT calculations. In effect, this is an S_N2 reaction at the fluorine atom, with palladium acting as the leaving group, thus reflecting the net electrophilic nature of this Pd^{IV} complex. The reaction of a series of palladium(II)–aryl precursors[54] with this newly designed $Pd^{IV}F$ complex led to the desired aryl fluorides within 10 minutes at 85 °C. The [^{18}F]Pd^{IV} complex was subsequently synthesized from [^{18}F]KF/[18]crown-6 in 10 min at room temperature. This complex was not isolated or characterized, but mixed directly with the required palladium(II)–aryl precursor; the mixture was then heated to 85 °C for 10 minutes. By using this procedure, three functionalized [^{18}F]aryl fluorides could be accessed in RCYs ranging from 10 to 33 %. The specific activity on a selected example was in the range of 40 GBq μmol^{-1} (Scheme 11).



Scheme 11. Palladium-mediated fluoride umpolung. DAM = bis(4-methoxyphenyl)methyl, MOM = methoxymethyl.

2.6. Aryl Umpolung Strategies

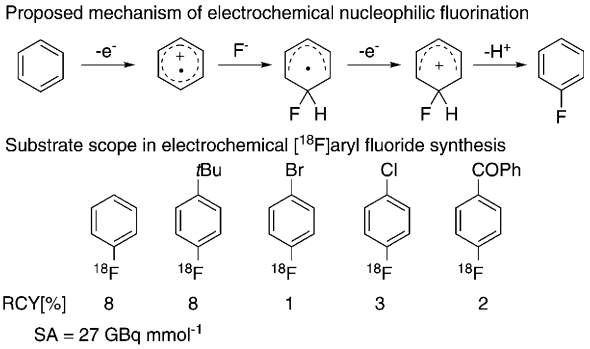
Gouverneur and co-workers developed an alternative umpolung strategy for the radiochemical synthesis of aryl fluorides. Conceptually, it was hypothesized that the fluorination of electron-rich aromatic compounds with [^{18}F]fluoride could be achieved oxidatively, with the oxidation event targeting the electron-rich substrate (aryl umpolung) rather than the [^{18}F]fluoride. A series of phenols bearing a 4-positioned *tert*-butyl leaving group were selected as model substrates since the fluorophenol motif is prevalent in many radiotracers. Treatment of these phenol precursors with [^{18}F]tetra-*n*-butylammonium fluoride ([^{18}F]TBAF)/1.5 % trifluoroacetic acid (TFA) in the presence of bis(acetoxy)iodobenzene (PIDA) in CH_2Cl_2 (10 min at room temperature) followed by rearomatization with TFA (10 min at room temperature), yielded the desired 4-[^{18}F]fluorophenols in RCYs of the isolated products of up to 32 %. The transformation tolerates substitution in the *ortho* and *meta* positions of the aromatic substrate. This procedure is sufficiently rapid that subsequent post-fluorination steps could be performed. The authors demonstrated that 2-bromo-4-[^{18}F]fluorophenol was amenable to a palladium-mediated Suzuki–Miyaura coupling with benzylboronic acid, thereby expanding the scope of this method to prosthetic group chemistry. This oxidative fluorination was also adapted for use on an automated microfluidic device, which is an important consideration for further developments towards clinical applications (Scheme 12).[55]



Scheme 12. Oxidative ^{18}F fluorination of phenols.

2.7. Electrochemical Radiofluorination

Fluoride may be introduced into organic molecules by electrochemical oxidative fluorination. For aromatic substrates, the mechanism is thought to proceed by formation of the aryl radical cation, with a subsequent nucleophilic attack of fluoride on this species generating an aryl radical. Oxidation of this radical gives an aryl cation that undergoes rearomatization by loss of a proton.[56] Reischl et al. developed this method towards the synthesis of [^{18}F]aryl fluorides. Oxidation of benzene in an electrolysis cell, using $Et_3N{\cdot}3HF$ and $Et_3N{\cdot}HCl$ in MeCN as the electrolyte, in the presence of [^{18}F]fluoride gave [^{18}F]fluorobenzene in 17% RCY. When the protocol used lower quantities of $Et_3N{\cdot}3HF$, the specific activity was found to be 27 GBq mmol^{-1}, consistent with a carrier-added synthesis, although the RCY was reduced to 8%.[57] This method was extended to simple monosubstituted benzenes and phenylalanine derivatives, but RCYs were poor (Scheme 13).[58]



Scheme 13. Electrochemical radiofluorination.

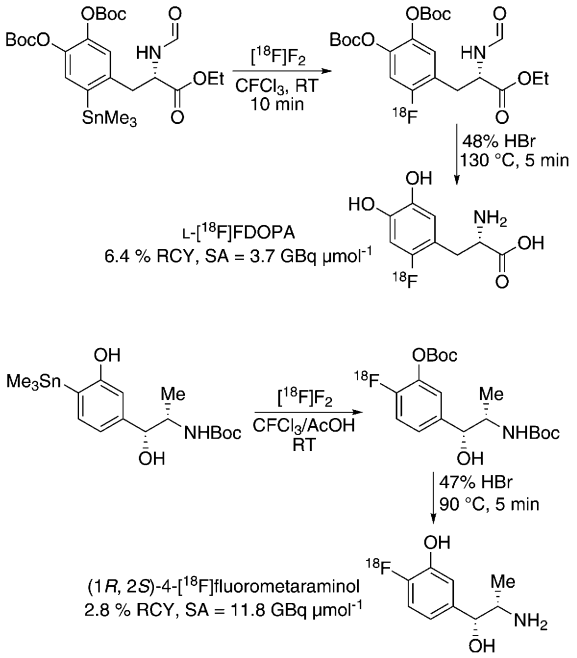
3. Electrophilic [^{18}F]Fluorination of Aromatic Compounds

3.1. Production of [^{18}F]F_2[5]

[^{18}F]F_2 is typically produced by the nuclear reaction $^{18}O(n,p)^{18}F$, using [^{18}O]O_2 as the target. Following initial irradiation, and subsequent addition of [^{19}F]F_2 (0.2%), a second irradiation delivers [^{18}F]F_2, with specific activities in the region of 1 GBq μmol^{-1}. An improved procedure using a smaller quantity of [^{19}F]F_2 gives access to [^{18}F]F_2 with improved specific activities of up to 55 GBq μmol^{-1}.[71] The use of [^{18}F]F_2 leads to a theoretical maximum RCY of 50%, with the remaining activity lost as [^{18}F]fluoride; this stands true for electrophilic [^{18}F]OF- and [^{18}F]NF-type reagents prepared from [^{18}F]F_2. These disadvantages combined with the handling of gaseous [^{18}F]F_2 are well-recognized by radiochemists and it is, therefore, not surprising that [^{18}F]F_2 is only considered for radiolabeling in cases of targets which are not accessible from [^{18}F]fluoride. To date, the radiotracers that fall within this category are more often electron-rich arenes, for example 6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine ([^{18}F]-L-FDOPA), which today is still produced clinically from [^{18}F]F_2.[59]

3.2. Labeling with [^{18}F]F_2 and [^{18}F]OF Reagents

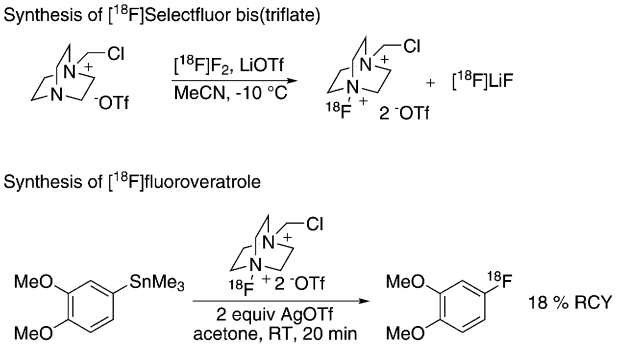
The reactivity profile of [^{18}F]F_2 and [^{18}F]OF reagents (e.g. [^{18}F]perchloryl fluoride[60] and [^{18}F]acetyl hypofluorite[61]) is such that their use in the direct fluorination of arenes more often produces a mixture of products.[62] To some extent, control over product selectivity has been addressed by using prefunctionalized organometallic aryl precursors.[63] 2-[^{18}F]Fluoroanisole, 3-[^{18}F]fluoroveratrole, and 2-[^{18}F]fluoroaniline were produced in RCYs of 34, 21, and 24%, respectively, by subjecting the corresponding *ortho*-lithiated precursors to fluorination with [^{18}F]perchloryl fluoride ([^{18}F]$FClO_3$). When the same reactions were performed with [^{18}F]F_2, the desired reaction products were formed in lower RCYs; a spectrum of side reactions took place, as testified by the presence of a number of unidentified radioactive signals upon analysis of the crude reaction mixtures.[60a] It is noteworthy that perchloryl fluoride is not able to mediate the electrophilic fluorodestannylation of aryl stannanes. In contrast, [^{18}F]F_2 and [^{18}F]AcOF are competent reagents for the synthesis of [^{18}F]FDOPA.[59] Currently, the clinical production of this radiotracer more often relies on fluorodestannylation with [^{18}F]F_2 followed by a single deprotection step (Scheme 14). The fluorodestannylation method was also applied to other radiotracers, including [^{18}F]fluoro-*meta*-tyrosine[64] and (1*R*,2*S*)-4-[^{18}F]fluorometaraminol.[65] Only isolated cases of direct fluorination of heteroarenes with electrophilic [^{18}F]F_2 have been reported, but none are practical. This includes the synthesis of trace amount of 8-[^{18}F]fluoroguanines (< 1% RCY).[66]



Scheme 14. ^{18}F Fluorodestannylation of electron-rich arenes with high specific activity post-target [^{18}F]F_2. Boc = *tert*-butoxycarbonyl.

3.3. Labeling with [^{18}F]NF Reagents

The development of NF reagents was driven by the desire for a nonhazardous electrophilic fluorine source of tamed reactivity, which should allow for better control over product selectivity. The first electrophilic [^{18}F]NF reagents reported were [^{18}F]-*N*-fluoropyridinium triflate[67] and 1-[^{18}F]-fluoro-2-pyridone.[68] A limited substrate scope was shown for both reagents, with only a single example of aromatic fluorination. Phenylmagnesium chloride was converted into [^{18}F]fluorobenzene with [^{18}F]-*N*-fluoropyridinium triflate in 62% RCY. A series of *N*-[^{18}F]fluoro-*N*-alkylsulfonamides were synthesized and their reactivity towards arylmagnesium bromides and aryllithium compounds studied.[69] Of the sulfonamides investigated, [^{18}F]-*N*-fluoro-*endo*-norbornyl-*p*-tolylsulfamide was found to give the best results. The most commonly employed NF reagents in modern synthetic fluorine chemistry are *N*-fluorobenzenesulfonimide (NFSi) and 1-chloromethyl-4-fluorodiazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor), as these commercially available reagents display very advantageous reactivity profiles that allow for the fluorination of a wide range of substrates. Gouverneur and co-workers reported the synthesis of both *N*-[^{18}F]fluorobenzenesulfonimide[70] and [^{18}F]Selectfluor bis(triflate),[71] with the latter reagent being prepared from high specific activity [^{18}F]F_2.[72] The fluorodestannylation of a series of electron-rich arenes was examined. Under the conditions used, NFSi was not sufficiently reactive to provide the desired aryl fluorides. Fluorodestannylation with [^{18}F]Selectfluor bis(triflate) was successful in MeCN within 20 minutes at room temperature in the presence of 2 equivalents of AgOTf. Under these conditions, [^{18}F]fluoroveratrole was obtained in 18% RCY. Specific activities of up to 16 GBq μmol^{-1} were reported (Scheme 15).[71]



Scheme 15. ^{18}F Fluorodestannylation with [^{18}F]Selectfluor bis(triflate).

4. Conclusion

Since the advent of PET, much effort has been focused on facilitating the ^{18}F labeling of arenes. The methods available to date provide [^{18}F]fluoroaromatic compounds with a range of RCYs and specific activities. Direct comparison is difficult, since the methods used for the measurement of RCYs vary significantly. When possible, radiochemists will naturally opt for a nucleophilic aromatic substitution with [^{18}F]fluoride, as this reaction is familiar, well documented, and reproducible. For electron-neutral and electron-rich arenes, the ^{18}F fluorination of diaryliodonium salts has been extensively investigated because it offers a viable solution to a long-standing radiochemistry problem; the use of these salts for ^{18}F labeling has also been revitalized with the recent developments in hypervalent iodine chemistry emerging from the mainstream synthetic community. Although effective, this approach requires the preparation of the diaryliodonium precursors, which could be time-consuming and limiting, especially when targeting architecturally more complex functionalized molecules.

The need to diversify the range of ^{18}F-labeled probes has encouraged the identification of new transformations and new reactivities. Most recently, two innovative solutions have been offered for the coupling of electron-neutral and electron-rich aromatic compounds with [^{18}F]fluoride, a sought-after reaction that could accelerate PET imaging programs and benefit downstream applications. The first conceptual novelty is the development of a new [^{18}F]Pd^{IV}F complex which is prepared from [^{18}F]fluoride, but reacts as an electrophilic ^{18}F entity. This new complex allows access to [^{18}F]fluoroarenes not accessible by S_NAr reactions. Complementing this net fluoride umpolung strategy, recent studies has demonstrated that the labeling of electron-rich arenes with [^{18}F]fluoride is possible, thus imposing a reactivity switch through arene umpolung. In practice, this is implemented by reacting the arene (phenol) and fluoride source in the presence of an external oxidant. It still remains to be demonstrated that these umpolung-based approaches are generic and broad in scope or can facilitate the radiosynthesis of iconic biomarkers such as [^{18}F]-L-FDOPA or 6-[^{18}F]fluoro-*meta*-tyrosine ([^{18}F]FMT),[73] but these advances are opening the field to new perspectives. The problematic nature of nucleophilic fluorination with [^{18}F]fluoride can benefit from additional new advances. This includes, for example, the translation of recently developed palladium cross-coupling chemistry[74] to ^{18}F radiochemistry, as well as a better fundamental understanding of the parameters that modulate fluoride nucleophilicity.

Today, progress in electrophilic ^{19}F fluorination can not be translated to ^{18}F labeling without significant complications. The challenges are clearly defined, but this research problem is less popular, as it is fundamentally and logistically difficult. The collection of electrophilic ^{18}F sources has grown with the addition of ^{18}F-labeled NF reagents of tailored reactivity. All these reagents are prepared from [^{18}F]F_2, a limitation that restricts global use. The highest priority is the development of a no-carrier-added radiosynthesis of a larger collection of electrophilic ^{18}F sources for immediate applications in sites that routinely produce [^{18}F]fluoride.

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[1] a) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071 – 1081; b) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308 – 319; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330; d) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, Hoboken, **2009**.

[2] B. Beuthien-Baumann, K. Hamacher, F. Oberdorfer, J. Steinbach, *Carbohydr. Res.* **2000**, *327*, 107 – 118.

[3] a) P. M. Matthews, E. A. Rabiner, J. Passchier, R. N. Gunn, *Br. J. Clin. Pharmacol.* **2012**, *73*, 175 – 186; b) M. T. Klimas, *Mol. Imaging Biol.* **2002**, *4*, 311 – 337.

[4] a) *Fluorine in Pharmaceutical and Medicinal Chemistry, From Biophysical Aspects to Clinical Applications* (Eds.: V. Gouverneur, K. Müller), Imperial College Press, London, **2012**; b) R. Littich, P. J. H. Scott, *Angew. Chem.* **2012**, *124*, 1132 – 1135; *Angew. Chem. Int. Ed.* **2012**, *51*, 1106 – 1109; c) Z. Li, P. S. Conti, *Adv. Drug Delivery Rev.* **2010**, *62*, 1031 – 1051; d) M. R. Kilbourn, X. Shao in *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, Hoboken, **2009**, pp. 361 – 388; e) P. W. Miller, N. J. Long, R. Vilar, A. D. Gee, *Angew. Chem.* **2008**, *120*, 9136 – 9172; *Angew. Chem. Int. Ed.* **2008**, *47*, 8998 – 9033; f) L. Cai, S. Lu, V. W. Pike, *Eur. J. Org. Chem.* **2008**, 2853 – 2873; g) D. Le Bars, *J. Fluorine Chem.* **2006**, *127*, 1488 – 1493; h) M. S. Berridge, T. J. Tewson, *Appl. Radiat. Isot.* **1986**, *37*, 685 – 693.

[5] R. A. Ferrieri in *Handbook of Radiopharmaceuticals, Radiochemistry and Applications* (Eds.: M. J. Welch, C. S. Redvanly), Wiley-VCH, Weinheim, **2003**, pp. 229 – 282.

[6] M. R. C. Gerstenberger, A. Haas, *Angew. Chem.* **1981**, *93*, 659 – 680; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 647 – 667.

[7] D. J. Adams, J. H. Clark, *Chem. Soc. Rev.* **1999**, *28*, 225 – 231.

[8] a) F. Terrier, *Chem. Rev.* **1982**, *82*, 77 – 152; b) I. Fernández, G. Frenking, E. Uggerud, *J. Org. Chem.* **2010**, *75*, 2971 – 2980.

[9] L. Li, M. N. Hopkinson, R. L. Yona, R. Bejot, A. D. Gee, V. Gouverneur, *Chem. Sci.* **2011**, *2*, 123 – 131.

[10] a) M. Maeda, T. Fukumura, M. Kojima, *Appl. Radiat. Isot.* **1987**, *38*, 307 – 310; b) L. Mu, C. R. Fischer, J. P. Holland, J. Becaud, P. A. Schubiger, R. Schibli, S. M. Ametamey, K. Graham, T. Stellfeld, L. M. Dinkelborg, L. Lehmann, *Eur. J. Org. Chem.* **2012**, 889 – 892; c) M. S. Berridge, C. Crouzel, D. Comar, *J. Labelled Compd. Radiopharm.* **1985**, *22*, 687 – 694; d) M. Karramkam, F. Hinnen, Y. Bramoullé, S. Jubeau, F. Dollé, *J. Labelled Compd. Radiopharm.* **2002**, *45*, 1103 – 1113; e) J. Ermert, C. Hocke, T. Ludwig, R. Gail, H. H. Coenen, *J. Labelled Compd. Radiopharm.* **2004**, *47*, 429 – 441; f) B. Shen, D. Löffler, K.-P. Zeller, M. Übele, G. Reischl, H.-J. Machulla, *J. Fluorine Chem.* **2007**, *128*, 1461 – 1468; g) C.-Y. Shiue, M. Watanabe, A. P. Wolf, J. S. Fowler, P. Salvadori, *J. Labelled Compd. Radiopharm.* **1984**, *21*, 533 – 547.

[11] M. S. Haka, M. R. Kilbourn, G. L. Watkins, S. A. Toorongian, *J. Labelled Compd. Radiopharm.* **1989**, *27*, 823 – 833.

[12] a) H. Sun, S. G. DiMagno, *J. Fluorine Chem.* **2007**, *128*, 806 – 812; b) T. J. McCarthy, A. U. Sheriff, M. J. Graneto, J. J. Talley, M. J. Welch, *J. Nucl. Med.* **2002**, *43*, 117 – 124; c) W. R. Banks, M. R. Satter, D.-R. Hwang, *Appl. Radiat. Isot.* **1994**, *45*, 69 – 74.

[13] C. Lemaire, R. Cantineau, M. Guillaume, A. Plenevaux, L. Christiaens, *J. Nucl. Med.* **1991**, *32*, 2266 – 2272.

[14] M. R. Kilbourn, M. J. Welch, C. S. Dence, T. J. Tewson, H. Saji, M. Maeda, *Appl. Radiat. Isot.* **1984**, *35*, 591 – 598.

[15] G. Massaweh, E. Schirrmacher, C. la Fougere, M. Kovacevic, C. Wängler, D. Jolly, P. Gravel, A. J. Reader, A. Thiel, R. Schirrmacher, *Nucl. Med. Biol.* **2009**, *36*, 721 – 727.

[16] N. Lazarova, F. G. Siméon, J. L. Musachio, S. Lu, V. W. Pike, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 463 – 465.

[17] S. Telu, J.-H. Chun, F. G. Siméon, S. Lu, V. W. Pike, *Org. Biomol. Chem.* **2011**, *9*, 6629 – 6638.

[18] a) J. Becaud, L. Mu, M. Karramkam, P. A. Schubiger, S. M. Ametamey, K. Graham, T. Stellfeld, L. Lehmann, S. Borkowski, D. Berndorff, L. Dinkelborg, A. Srinivasan, R. Smits, B. Koksch, *Bioconjugate Chem.* **2009**, *20*, 2254 – 2261; b) S. M. Okarvi, *Eur. J. Nucl. Med.* **2001**, *28*, 929 – 938; c) D. S. Wilbur, *Bioconjugate Chem.* **1992**, *3*, 433 – 470.

[19] G. Vaidyanathan, M. R. Zalutsky, *Nucl. Med. Biol.* **1992**, *19*, 275 – 281.

[20] a) U. Ackermann, S. D. Yeoh, J. I. Sachinidis, S. S. Poniger, A. M. Scott, H. J. Tochon-Danguy, *J. Labelled Compd. Radiopharm.* **2011**, *54*, 671 – 673; b) R. Bejot, A. M. Elizarov, E. Ball, J. Zhang, R. Miraghaie, H. C. Kolb, V. Gouverneur, *J. Labelled Compd. Radiopharm.* **2011**, *54*, 117 – 122; c) M.-W. Wang, Y.-P. Zhang, Y.-J. Zhang, C. K.-F. Shen, *J. Radioanal. Nucl. Chem.* **2011**, *289*, 191 – 196; d) M. Glaser, E. Årstad, S. K. Luthra, E. G. Robins, *J. Labelled Compd. Radiopharm.* **2009**, *52*, 327 – 330; e) P. J. H. Scott, X. Shao, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 586 – 591; f) G. Tang, X. Tang, X. Wang, *J. Labelled Compd. Radiopharm.* **2010**, *53*, 543 – 547.

[21] a) L. Dolci, F. Dollé, S. Jubeau, F. Vaufrey, C. Crouzel, *J. Labelled Compd. Radiopharm.* **1999**, *42*, 975 – 985; b) M. Karramkam, F. Hinnen, F. Vaufrey, F. Dollé, *J. Labelled Compd. Radiopharm.* **2003**, *46*, 979 – 992.

[22] a) A. Abrahim, P. Angelberger, K. Kletter, M. Müller, C. Joukhader, T. Erker, O. Langer, *J. Labelled Compd. Radiopharm.* **2006**, *49*, 345 – 356; b) H. F. Beer, L. D. Frey, M. Häberli, P. A. Schubiger, *Nucl. Med. Biol.* **1995**, *22*, 999 – 1004.

[23] a) N. Malik, W. Voelter, H.-J. Machulla, C. Solbach, *J. Radioanal. Nucl. Chem.* **2011**, *287*, 287 – 292; b) N. Malik, C. Solbach, W. Voelter, H.-J. Machulla, *J. Radioanal. Nucl. Chem.* **2010**, *283*, 757 – 764.

[24] a) A. C. Valdivia, M. Estrada, T. Hadizad, D. J. Stewart, R. S. Beanlands, J. N. DaSilva, *J. Labelled Compd. Radiopharm.* **2012**, *55*, 57 – 60; b) B. de Bruin, B. Kuhnast, F. Hinnen, L. Yaouancq, M. Amessou, L. Johannes, A. Samson, R. Boisgard, B. Tavitian, F. Dollé, *Bioconjugate Chem.* **2005**, *16*, 406 – 420; c) B. Kuhnast, B. de Bruin, F. Hinnen, B. Tavitian, F. Dollé, *Bioconjugate Chem.* **2004**, *15*, 617 – 627; d) R. Schirrmacher, U. Mühlhausen, B. Wängler, E. Schirrmacher, J. Reinhard, G. Nagel, B. Kaina, M. Piel, M. Wießler, F. Rösch, *Tetrahedron Lett.* **2002**, *43*, 6301 – 6304.

[25] N. Vasdev, P. Cao, E. M. van Oosten, A. A. Wilson, S. Houle, G. Hao, X. Sun, N. Slavine, M. Alhasan, P. P. Antich, F. J. Bonte, P. Kulkarni, *Med. Chem. Commun.* **2012**, *3*, 1228 – 1230.

[26] a) T. Irie, K. Fukushi, T. Ido, *Appl. Radiat. Isot.* **1982**, *33*, 445 – 448; b) T. Irie, K. Fukushi, O. Inoue, T. Yamasaki, T. Ido, T. Nozaki, *Appl. Radiat. Isot.* **1982**, *33*, 633 – 636.

[27] H. Cai, D. Yin, L. Zhang, Y. Wang, *J. Labelled Compd. Radiopharm.* **2006**, *49*, 653 – 661.

[28] a) A. G. Horti, H. T. Ravert, W. B. Mathews, E. H. Abraham, R. L. Wahl, R. F. Dannals, *J. Labelled Compd. Radiopharm.* **2006**, *49*, 811 – 815; b) P. Marchand, C. Lorilleux, G. Gilbert, F. Gourand, F. Sobrio, D. Peyronnet, M. Dhilly, L. Barré, *ACS Med. Chem. Lett.* **2010**, *1*, 240 – 243.

[29] E. D. Hostetler, S. Sanabria-Bohórquez, H. Fan, Z. Zeng, L. Gammage, P. Miller, S. O'Malley, B. Connolly, J. Mulhearn, S. T. Harrison, S. E. Wolkenberg, J. C. Barrow, D. L. Williams, R. J. Hargreaves, C. Sur, J. J. Cook, *Nucl. Med. Biol.* **2011**, *38*, 1193 – 1203.

[30] a) F. G. Siméon, M. T. Wendahl, V. W. Pike, *J. Med. Chem.* **2011**, *54*, 901 – 908; b) F. G. Siméon, M. T. Wendahl, V. W. Pike, *Tetrahedron Lett.* **2010**, *51*, 6034 – 6036.

[31] A. D. Strouphauer, C. L. Liotta, R. W. Fink, *Appl. Radiat. Isot.* **1984**, *35*, 787 – 791.

[32] a) M. S. Yusubov, A. V. Maskaev, V. V. Zhdankin, *Arkivoc* **2011**, 370 – 409; b) E. A. Merritt, B. Olofsson, *Angew. Chem.* **2009**, *121*, 9214 – 9234; *Angew. Chem. Int. Ed.* **2009**, *48*, 9052 – 9070;

c) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299 – 5358; d) V. V. Grushin, *Chem. Soc. Rev.* **2000**, *29*, 315 – 324.

[33] a) V. W. Pike, F. I. Aigbirhio, *J. Chem. Soc. Chem. Commun.* **1995**, 2215 – 2216; b) A. Shah, V. W. Pike, D. A. Widdowson, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2043 – 2046.

[34] S. Martín-Santamaría, M. A. Carroll, C. M. Carroll, C. D. Carter, V. W. Pike, H. S. Rzepa, D. A. Widdowson, *Chem. Commun.* **2000**, 649 – 650.

[35] T. L. Ross, J. Ermert, C. Hocke, H. H. Coenen, *J. Am. Chem. Soc.* **2007**, *129*, 8018 – 8025.

[36] B. S. Moon, H. S. Kil, J. H. Park, J. S. Kim, J. Park, D. Y. Chi, B. C. Lee, S. E. Kim, *Org. Biomol. Chem.* **2011**, *9*, 8346 – 8355.

[37] J.-H. Chun, S. Lu, Y.-S. Lee, V. W. Pike, *J. Org. Chem.* **2010**, *75*, 3332 – 3338.

[38] a) V. V. Grushin, I. I. Demkina, T. P. Tolstaya, *J. Chem. Soc. Perkin Trans. 2* **1992**, 505 – 511; b) K. M. Lancer, G. H. Wiegand, *J. Org. Chem.* **1976**, *41*, 3360 – 3364.

[39] B. Wang, R. L. Cerny, S. Uppaluri, J. J. Kempinger, S. G. DiMagno, *J. Fluorine Chem.* **2010**, *131*, 1113 – 1121.

[40] a) S. Martín-Santamaría, M. A. Carroll, V. W. Pike, H. S. Rzepa, D. A. Widdowson, *J. Chem. Soc. Perkin Trans. 2* **2000**, 2158 – 2161; b) M. A. Carroll, S. Martín-Santamaría, V. W. Pike, H. S. Rzepa, D. A. Widdowson, *J. Chem. Soc. Perkin Trans. 2* **1999**, 2707 – 2714.

[41] Y.-S. Lee, M. Hodošček, J.-H. Chun, V. W. Pike, *Chem. Eur. J.* **2010**, *16*, 10418 – 10423.

[42] J.-H. Chun, S. Lu, V. W. Pike, *Eur. J. Org. Chem.* **2011**, 4439 – 4447.

[43] M. A. Carroll, J. Nairne, G. Smith, D. A. Widdowson, *J. Fluorine Chem.* **2007**, *128*, 127 – 132.

[44] M. A. Carroll, J. Nairne, J. L. Woodcraft, *J. Labelled Compd. Radiopharm.* **2007**, *50*, 452 – 454.

[45] A. J. Palmer, J. C. Clark, R. W. Goulding, *Appl. Radiat. Isot.* **1977**, *28*, 53 – 65.

[46] A. Knöchel, O. Zwernemann, *Appl. Radiat. Isot.* **1991**, *42*, 1077 – 1080.

[47] A. Knöchel, O. Zwernemann, *J. Labelled Compd. Radiopharm.* **1996**, *38*, 325 – 336.

[48] a) J. S. Ng, J. A. Katzenellenbogen, M. R. Kilbourn, *J. Org. Chem.* **1981**, *46*, 2520 – 2528; b) T. J. Tewson, M. J. Welch, *Chem. Commun.* **1979**, 1149 – 1150.

[49] N. Satyamurthy, J. R. Barrio, D. G. Schmidt, C. Kammerer, G. T. Bida, M. E. Phelps, *J. Org. Chem.* **1990**, *55*, 4560 – 4564.

[50] J. R. Barrio, N. Satyamurthy, H. Ku, M. E. Phelps, *J. Chem. Soc. Chem. Commun.* **1983**, 443 – 444.

[51] T. Pages, B. R. Langlois, *J. Fluorine Chem.* **2001**, *107*, 321 – 327.

[52] P. J. Riss, S. Kuschel, F. I. Aigbirhio, *Tetrahedron Lett.* **2012**, *53*, 1717 – 1719.

[53] E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker, T. Ritter, *Science* **2011**, *334*, 639 – 642.

[54] a) T. Furuya, D. Benitez, E. Tkatchouk, A. E. Strom, P. Tang, W. A. Goddard III, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 3793 – 3807; b) T. Furuya, T. Ritter, *J. Am. Chem. Soc.* **2008**, *130*, 10060 – 10061; c) T. Furuya, H. M. Kaiser, T. Ritter, *Angew. Chem.* **2008**, *120*, 6082 – 6085; *Angew. Chem. Int. Ed.* **2008**, *47*, 5993 – 5996.

[55] Z. Gao, Y. H. Lim, M. Tredwell, L. Li, S. Verhoog, M. Hopkinson, W. Kaluza, T. L. Collier, J. Passchier, M. Huiban, V. Gouverneur, *Angew. Chem.* **2012**, *124*, 6837 – 6841; *Angew. Chem. Int. Ed.* **2012**, *51*, 6733 – 6737.

[56] M. Noel, V. Suryanarayanan, S. Chellammal, *J. Fluorine Chem.* **1997**, *83*, 31 – 40.

[57] G. Reischl, G. J. Kienzle, H.-J. Machulla, *J. Radioanal. Nucl. Chem.* **2002**, *254*, 409 – 411.

[58] a) G. Reischl, G. J. Kienzle, H.-J. Machulla, *Appl. Radiat. Isot.* **2003**, *58*, 679 – 683; b) G. J. Kienzle, G. Reíschl, H.-J. Machulla, *J. Labelled Compd. Radiopharm.* **2005**, *48*, 259 – 273.

[59] a) S. Forsback, O. Eskola, J. Bergman, M. Haaparanta, O. Solin, *J. Labelled Compd. Radiopharm.* **2009**, *52*, 286 – 288; b) S. Forsback, O. Eskola, M. Haaparanta, J. Bergman, O. Solin, *Radiochim. Acta* **2008**, *96*, 845 – 848; for s solid-supported synthesis of [18F]FDOPA, see S. Luthra, F. Brady, H. J. Wadsworth, US 7,115, 249 B2, **2006**.

[60] a) R. E. Ehrenkaufer, R. R. MacGregor, *Appl. Radiat. Isot.* **1983**, *34*, 613 – 615; b) A. Hiller, C. Fischer, A. Jordanova, J. T. Patt, J. Steinbach, *Appl. Radiat. Isot.* **2008**, *66*, 152 – 157.

[61] R. Chirakal, G. Firnau, E. S. Garnett, *Appl. Radiat. Isot.* **1988**, *39*, 1099 – 1101.

[62] a) M. Ogawa, K. Hatano, S. Oishi, Y. Kawasumi, N. Fujii, M. Kawaguchi, R. Doi, M. Imamura, M. Yamamoto, K. Ajito, T. Mukai, H. Saji, K. Ito, *Nucl. Med. Biol.* **2003**, *30*, 1 – 9; b) H. H. Coenen, K. Franken, P. Kling, G. Stöcklin, *Appl. Radiat. Isot.* **1988**, *39*, 1243 – 1250; c) M. J. Adam, T. J. Ruth, J. R. Grierson, B. Abeysekera, B. D. Pate, *J. Nucl. Med.* **1986**, *27*, 1462 – 1466.

[63] a) F. Füchtner, P. Angelberger, H. Kvaternik, F. Hammerschmidt, B. P. Simove, J. Steinbach, *Nucl. Med. Biol.* **2002**, *29*, 477 – 481; b) E. F. J. de Vries, G. Luurtsema, M. Brüssermann, P. H. Elsinga, W. Vaalburg, *Appl. Radiat. Isot.* **1999**, *51*, 389 – 394; c) L. P. Szajek, M. A. Channing, W. C. Eckelman, *Appl. Radiat. Isot.* **1998**, *49*, 795 – 804; d) F. Dollé, S. Demphel, F. Hinnen, D. Fournier, F. Vaufrey, C. Crouzel, *J. Labelled Compd. Radiopharm.* **1998**, *41*, 105 – 114; e) M. Namavari, A. Bishop, N. Satyamurthy, G. Bida, J. R. Barrio, *Appl. Radiat. Isot.* **1992**, *43*, 989 – 996; f) A. Luxen, M. Perlmutter, G. T. Bida, G. van Moffaert, J. S. Cook, N. Satyamurthy, M. E. Phelps, J. R. Barrio, *Appl. Radiat. Isot.* **1990**, *41*, 275 – 281; g) H. H. Coenen, S. M. Moerlein, *J. Fluorine Chem.* **1987**, *36*, 63 – 75; h) M. Speranza, C.-Y. Shiue, A. P. Wolf, D. S. Wilbur, G. Angelini, *J. Fluorine Chem.* **1985**, *30*, 97 – 107; i) P. Di Raddo, M. Diksic, D. Jolly, *J. Chem. Soc. Chem. Commun.* **1984**, 159 – 160.

[64] E. Hess, S. Sichler, A. Kluge, H. H. Coenen, *Appl. Radiat. Isot.* **2002**, *57*, 185 – 191.

[65] O. Eskola, T. Grönroos, J. Bergman, M. Haaparanta, P. Marjamäki, P. Lehikoinen, S. Forsback, O. Langer, F. Hinnen, F. Dollé, C. Halldin, O. Solin, *Nucl. Med. Biol.* **2004**, *31*, 103 – 110.

[66] M. Namavari, J. R. Barrio, T. Toyokuni, S. C. Gambhir, S. R. Cherry, H. R. Herschman, M. E. Phelps, N. Satyamurthy, *Nucl. Med. Biol.* **2000**, *27*, 157 – 162.

[67] F. Oberdorfer, E. Hofmann, W. Maier-Borst, *J. Labelled Compd. Radiopharm.* **1988**, *25*, 999 – 1005.

[68] F. Oberdorfer, E. Hofmann, W. Maier-Borst, *Appl. Radiat. Isot.* **1988**, *39*, 685 – 688.

[69] N. Satyamurthy, G. T. Bida, M. E. Phelps, J. R. Barrio, *Appl. Radiat. Isot.* **1990**, *41*, 733 – 738.

[70] H. Teare, E. G. Robins, E. Årstad, S. K. Luthra, V. Gouverneur, *Chem. Commun.* **2007**, 2330 – 2332.

[71] H. Teare, E. G. Robins, A. Kirjavainen, S. Forsback, G. Sandford, O. Solin, S. K. Luthra, V. Gouverneur, *Angew. Chem.* **2010**, *122*, 6973 – 6976; *Angew. Chem. Int. Ed.* **2010**, *49*, 6821 – 6824.

[72] J. Bergman, O. Solin, *Nucl. Med. Biol.* **1997**, *24*, 677 – 683.

[73] O. T. DeJesus, C. J. Endres, S. E. Shelton, R. J. Nickles, J. E. Holden, *J. Nucl. Med.* **1997**, *38*, 630 – 636.

[74] D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. García-Fortanet, T. Kinzel, S. L. Buchwald, *Science* **2009**, *325*, 1661 – 1664.