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Chemistry with [^{18}F]Fluoride Ion

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The success of molecular imaging with positron-emission tomography (PET) depends on the availability of selective molecular probes labeled with positron-emitters, such as fluorine-18 ($t_{1/2}$ = 109.7 min). No-carrier-added (NCA) [^{18}F]fluoride ion ($^{18}F^-$) is the primary reagent for the preparation of ^{18}F-labeled tracers in high specific activity. In this microreview, we survey current and advancing radiochemical methods and technologies for the use of NCA [^{18}F]-fluoride ion in the preparation of ^{18}F-labeled radiotracers for applications with PET.

1. Introduction

Fluorine-18 is a short-lived ($t_{1/2}$ = 109.7 min) positron-emitting isotope which now finds immense importance as a label for radiotracers used with the molecular imaging technique of positron-emission tomography (PET).[1–3] PET has advanced to become an important clinical diagnostic and research modality,[4] and also a valuable enabling technology in drug discovery and development.[5,6] The incorporation of fluorine-18 into a radiotracer couples the biochemical specificity of the tracer molecule with high sensitivity for radioactivity detection; this enables the imaging and quantification of a biochemical process or of a specific

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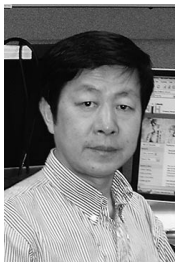
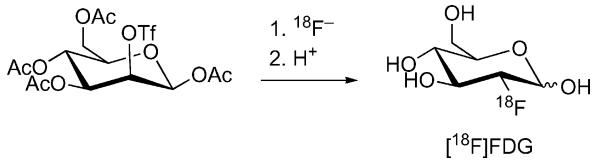


Dr. Shuiyu Lu received his BSc in Organic Chemistry in 1983 from Nanjing University and his PhD in Organic Polymer Chemistry in 1991 from the University of Manchester. After a two-year Fellowship at the University of Edinburgh, he became a Research Fellow at the University of Surrey (1994–2002) where he worked with the late Professor John R. Jones on the preparation and application of deuterium- or tritium-labeled compounds. In 2002 he joined NIMH as a Staff Scientist. His current research centers on the development of rapid, reliable and safe PET radiochemistry methodologies through the application of new reagents and innovative technologies (such as radiolabeling under microwave conditions and the application of micro-reactors to PET radiosynthesis), as well as the development of PET radioligands for brain imaging.

Dr. Victor W. Pike received his BSc in Chemistry from the University of Birmingham in 1972 and his PhD in Organic Chemistry from the same university in 1976. Following a Research Fellowship at Birmingham University he joined the MRC Cyclotron Unit (Hammersmith Hospital, Imperial College) in 1978 and in 1994 became Head of Chemistry and Engineering. In 2001 he joined the newly created Molecular Imaging Branch of NIMH (Bethesda) as the Chief of the PET Radiopharmaceutical Sciences Section. Dr. Pike has co-authored almost 200 papers in his main area of interests, namely PET radiotracer discovery and development and associated radiochemistry methodology development. His research groups have generated several successful radiotracers for application in human subjects and he has received a number of awards.

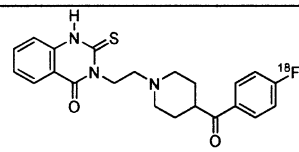
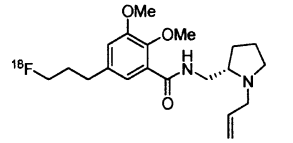
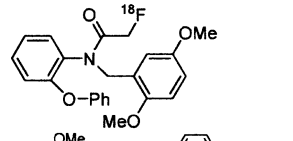
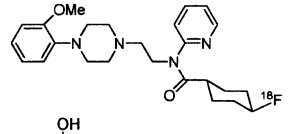
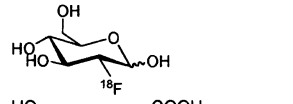
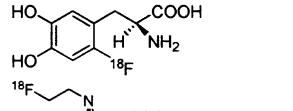
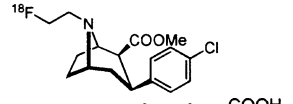
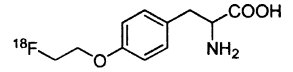
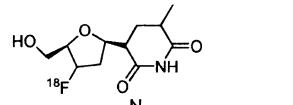
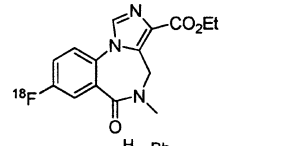
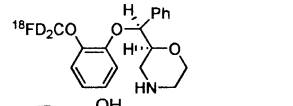
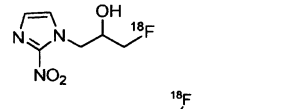
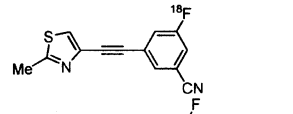
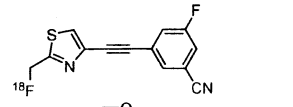
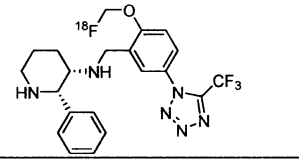
low-density protein target in vivo (Table 1). An example of the former is the incorporation of fluorine-18 into 2-deoxy-D-glucose to give [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]-FDG, Table 1) as a radiotracer of glucose utilization.[7] [^{18}F]FDG, originally developed in the late 1970s,[8] is now very widely used as a clinical research tool and as a diagnostic agent in oncology and neurology. This utility only became possible because a method[9,10] was later developed to prepare [^{18}F]FDG efficiently from high activities of [^{18}F]fluoride ion (Scheme 1), thereby making [^{18}F]FDG available to imaging centers within a few half-lives of transport time. An example of the high sensitivity that may be achieved with a PET radiotracer is provided by [^{18}F]-fallypride[11] (Table 1), which is used to measure dopamine subtype-2 (D_2) receptors in brain, including those in extrastriatal regions of very low receptor density (0.3–1.7 nM).[12] [^{18}F]Fallypride is also produced efficiently and directly from [^{18}F]fluoride ion. Considerable commercial and clinical interest exists to disseminate the application of useful and efficiently prepared ^{18}F-labeled tracers, as now occurs for [^{18}F]FDG.



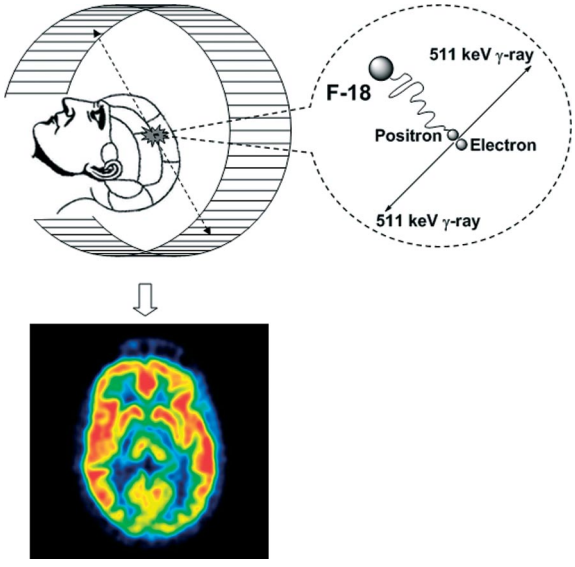
Scheme 1. The radiosynthesis of [^{18}F]FDG from [^{18}F]fluoride ion, according to Hamacher et al.[9]

Fluorine-18 may be produced by several methods[27] but by far the most useful is from a cyclotron through the proton irradiation of ^{18}O-enriched water.[28] This nuclear reaction, ^{18}O(p,n)^{18}F, is intrinsically high yielding at the low proton energies (< 16 MeV) that are now available from small compact cyclotrons. Several Curies may be produced from a single irradiation whereas only 5–15 mCi of radiotracer need be injected into a human subject for a single PET examination. The fluorine-18 is obtained as a solution of [^{18}F]fluoride ion in the irradiated target water. Another attractive feature of this method of production is that the fluorine-18 is obtained "no-carrier-added" (NCA). This means the [^{18}F]fluoride ion has a very high specific radioactivity (i.e., ratio of [^{18}F]fluoride ion radioactivity to its mass of carrier or total fluoride ion). Typically, the specific radioactivity exceeds 5 Ci/μmol. High specific radioactivity is mandatory for radiotracers, such as [^{18}F]fallypride, that are targeted at low density proteins, because low specific radioactivity (high carrier) would saturate the target proteins with non-radioactive ligand and so annul any signal from radiotracer binding. High specific radioactivity also enables radiotracers to be administered to human subjects in low mass doses (typically less than 1–10 nmol), without toxic or pharmacological effects. Moreover, the mode of decay of fluorine-18 is attractive for PET imaging, because fluorine-18 emits a quite low energy positron (maximally 0.635 MeV), which on average has a short path in vivo before its annihilation with an electron to give two opposed

Table 1. Some significant PET radiotracers produced from [^{18}F]-fluoride ion.

Radiotracer	Structure	Application to measurement of:
[^{18}F]Altanserin[13]		Brain 5-HT$_2$ receptors
[^{18}F]Fallypride[11]		Brain D_2 receptors
[^{18}F]FBR[14]		Brain 'peripheral' benzodiazepine receptors
[^{18}F]FCWAY[15]		Brain 5-HT$_{1A}$ receptors
[^{18}F]FDG[7]		Glucose utilization
[^{18}F]FDOPA[16]		Brain dopamine metabolism
[^{18}F]FECNT[17]		Brain dopamine transporters
[^{18}F]FET[18]		Tumor location
[^{18}F]FLT[19]		Cellular proliferation
[^{18}F]Flumazenil[20]		Brain benzodiazepine receptors
[^{18}F]FMeNER-d_2[21]		Noradrenaline transport
[^{18}F]FMISO[22,23]		Hypoxia
[^{18}F]FMTEB[24]		Brain mGluR5 receptors
[^{18}F]SP203[25]		Brain mGluR5 receptors
[^{18}F]SPA-RQ[26]		Brain neurokinin type-1 receptors

and externally detectable γ-rays, each 511 keV. This mode of decay of positron-emitters constitutes the physical basis of PET imaging (Scheme 2). The positron path (≤ 2 mm in water) is similar to the highest spatial resolution achievable with modern PET cameras (~ 2 mm), but is shorter than those of other useful positron-emitters, such as carbon-11. PET image quality is therefore optimal with fluorine-18. The decay of fluorine-18 gives innocuous ^{18}O as product atom. The half-life of fluorine-18, as well as permitting transport of radiotracers over considerable distances, allows PET scans to be acquired over a few hours. Hence, biological processes with quite slow kinetics can be followed.



Scheme 2. The physical basis of PET and an example of PET imaging of mGluR5 receptors in human brain with [18F]SP203 (Table 1). The ^{18}F-labeled tracer (e.g., [18F]SP203) distributes to brain after intravenous administration. Decay of the fluorine-18 atom emits a positron, which loses momentum and collides with an electron to form positronium; the latter promptly annihilates, giving rise to two opposed 511 keV γ-rays. The PET camera detects and records the coincident arrival of all γ-ray pairs as the basis for reconstruction of dynamic PET scans (scan by courtesy of Dr. A. K. Brown et al., NIMH).

Although, a fluorine atom may often replace a hydrogen atom at a carbon atom, this change is not closely isosteric (Table 2). A fluorine atom is, however, sterically similar to oxygen, and has a similar bond length to carbon; it may substitute for a hydroxy group with regard to isoelectronicity and ability to hydrogen bond. The fluorine atom is the most electronegative and its introduction into a molecule often perturbs one or more aspects of biological behavior (e.g., distribution, metabolism, protein binding). These perturbations may be deleterious or advantageous in a drug[29] or radiotracer design. The carbon–fluorine bond is intrinsically strong, but, even so, for aliphatic carbon is often prone to enzymatic cleavage in vivo. Such defluorination may sometimes be prevented by pharmacological intervention.[30,31] Aryl carbon–fluorine bonds are generally stable in vivo but pose a greater challenge for creation from [18F]fluoride ion, especially in electron-rich arenes (see Sections 2.2–2.4).

Table 2. Van der Waals radii, electronegativity and bond lengths to carbon of various atoms.

Element (X)	van der Waals radius [Å]	Electronegativity (Pauling scale)	Bond length of C–X [Å]
H	1.20	2.20	1.09
O	1.52	3.44	1.43
F	1.47	3.98	1.35

The production of ^{18}F-labeled tracers from cyclotron-produced [18F]fluoride ion poses several challenges to radiochemists. First, the [18F]fluoride ion is obtained in [18O]-water which renders the ion poorly reactive due to its high degree and strength of hydration. In general, the bulk water must be removed to generate [18F]fluoride ion of adequate nucleophilicity.[32] Usually, this ion must be solubilized in an organic solvent to perform chemical reactions. These reactions must be achievable over short time-scales (min) due to the short physical half-life of the fluorine-18. Finally, the low mass of fluoride ion may pose problems, through for example wasteful adsorption effects.

Chemistry with [18F]fluoride ion is frequently performed with very high levels of radioactivity (sometimes at Ci levels). This mandates that the radiochemistry is performed within an apparatus shielded from the operator for radiation safety. Lead-shielded "hot-cells" are used for this purpose. This in turn imposes a requirement that the radiochemistry be remotely controlled and preferably automated. Automated radiochemistry apparatus is available commercially and some academic centers have developed their own apparatus, adopting various idiosyncratic approaches (e.g., robotics, PC control, etc.) to meet the automation challenge. Such devices have recently been reviewed by Krasikova[33] and are not discussed here. Mainly, these devices are used to perform simple radiochemistry with [18F]fluoride ion on a "macro-scale" i.e., typically employing quite large amounts of precursor (mg quantities) in significant volumes (up to 1 mL).

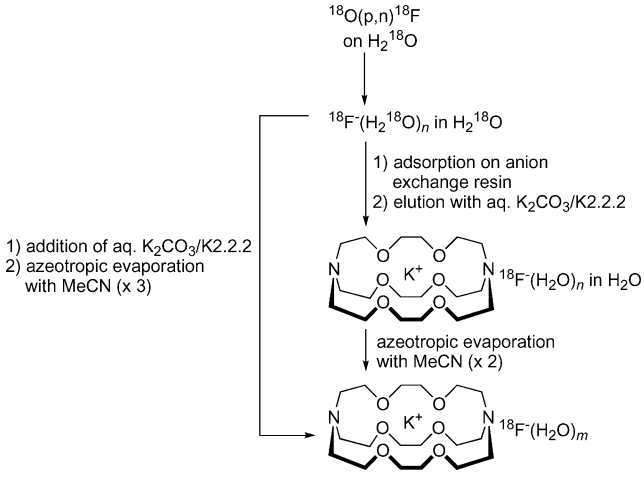
Traditional methods for the preparation of mono-fluoroorganics are preponderantly based on the use of electrophilic reagents (e.g., fluorine gas, xenon difluoride, or Selectfluor). By contrast the field of fluorine-18 chemistry is highly motivated to extend the range of new synthesis achievable with [18F]fluoride ion ($^{18}F^-$) as reagent rather than with cyclotron-produced [18F]fluorine (^{18}F–F) and its derivatives, which have intrinsic disadvantages of low specific activity and low radiochemical yields. (Henceforth, in this microreview we denote decay-corrected radiochemical yield as RCY.)

This microreview surveys current and advancing radiochemical methods and technologies for the use of [18F]-fluoride ion in the production of PET radiotracers, as seen from the authors' perspectives. As background, the reader is referred to several earlier reviews of fluorine-18 radiochemistry.[34–40] These often extend to discuss the many generated radiotracers, but here the emphasis is placed firmly on the essential chemistry of the [18F]fluoride ion.

2. Labeling with [^{18}F]Fluoride Ion

2.1. General Considerations

The first steps in radiochemistry with [^{18}F]fluoride ion are almost invariably removal of bulk [^{18}O]water and solubilization in an organic solvent. This is commonly achieved by adsorption of [^{18}F]fluoride ion onto an ion exchange resin,[41] to allow recovery of the expensive [^{18}O]water, followed by elution of the [^{18}F]fluoride ion in a small volume of an aqueous weak base (usually potassium carbonate). Water is then removed by (two or three) successive cycles of azeotropic evaporation with acetonitrile. Addition of a kryptand, such as aminopolyether 2.2.2 (K2.2.2), during this process enables the [^{18}F]fluoride ion to be solubilized subsequently in a polar aprotic solvent, such as acetonitrile (Scheme 3). The drying process is commonly performed in small (ca. 1 mL) volume open or closed vessels under nitrogen. The vessel material is an important consideration,[42] because a considerable proportion of the [^{18}F]fluoride ion may become stubbornly adhered to the vessel wall. Adsorption is generally decreased for vessel materials in the order of Pyrex > glassy carbon > platinum.



Scheme 3. Flow chart showing the structure of [^{18}F]fluoride ion–K2.2.2-K^+ complex and its preparation from cyclotron-irradiated [^{18}O]water by two alternative processes; *n* may be as great as 15 in fully hydrated fluoride ion;[43] *m* is expected to be < *n*.

The degree to which [^{18}F]fluoride ion is dried or dehydrated in this kind of process is unknown, but it is virtually certain that truly "naked" fluoride ion is never obtained. The removal of each water molecule of hydration is successively more difficult, and hence trace [^{18}F]fluoride ion will be hydrated to at least some extent by even very small traces of residual water. Step-wise reduction in the degree of hydration will correspondingly increase nucleophilicity. In general, our experience is that a high degree of dryness is required to endow [^{18}F]fluoride ion with adequate nucleophilicity for difficult reactions (e.g., aromatic nucleophilic substitution reactions), whereas less scrupulous drying is required for less demanding reactions (e.g., aliphatic nucleophilic substitution reactions). In some cases the addition of water may even be tolerated, and may assist in preventing adsorption of [^{18}F]fluoride ion to vessel walls.

Several variations in the above procedure for producing dry reactive [^{18}F]fluoride ion are practised, including variation in base (hydrogen carbonate, oxalate), kryptand (18-crown-6) or counterion (Rb^+, Cs^+, tBu_4N^+). A kryptand serves to capture the metal cation (usually K^+) and to separate it from the [^{18}F]fluoride ion, thereby enhancing its nucleophilicity. A large cation without kryptand (Cs^+, Et_4N^+, tBu_4N^+) serves the same purpose of charge separation.[44] The fluoride ion is easily rendered non-nucleophilic by protonation. Hence, most reactions with [^{18}F]fluoride ion are conducted under weakly basic conditions. Preferred bases are poorly nucleophilic such as CO_3^{2-}, HCO_3^- or $C_2O_4^{2-}$. Precursors for labeling should not themselves be sources of protons.

Other methods for isolating [^{18}F]fluoride ion may be used. For example, an electrochemical procedure is used in a few laboratories.[45,46]

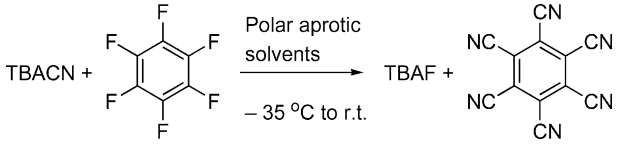
It is important to appreciate that much of the work so far reported on chemistry with [^{18}F]fluoride ion has been with "unpurified" cyclotron sources. Levels of contaminants and their effects will be variable. The proton-irradiated water itself will contain free radicals due to the irradiation and also to subsequent radiolysis. Removal of the irradiated water by evaporation may concentrate non-volatile contaminants (e.g., metal ions and anions) that arise from the cyclotron target during irradiation.[47] These contaminants may subsequently hinder reactions of [^{18}F]fluoride ion – the cations by binding [^{18}F]fluoride ion into refractory species and the anions by competing as nucleophiles. Recovery of [^{18}F]fluoride ion from irradiated [^{18}O]water by adsorption onto an ion-exchange resin, as commonly practised, may remove some impurities (e.g., metal ions), but may introduce others during elution. Specific radioactivity has generally been assumed to be high, but has not been measured in all reported studies. In this regard, dilution of [^{18}F]fluoride ion with extra carrier (fluoride ion) is known to increase radiochemical yields in some reactions,[48] but conversely to decrease yields in some others.[49] It should be borne in mind that 1 Ci of [^{18}F]fluoride ion delivered in, for example, 1 mL of irradiated [^{18}O]water at a specific radioactivity of 10 Ci/μmol (as might be typical but still much lower than the theoretical value for carrier-free fluorine-18, namely 1710 Ci/μmol) contains only 0.1 μmol (1.9 μg) of non-radioactive fluoride ion; this amount of reagent may easily be swamped by low (ppm) levels of impurities. Frequently, precursors for reaction with [^{18}F]fluoride ion are used in mg amounts and they must therefore be of very high purity to achieve optimal radiochemical yields. Unsurprisingly, because of differences in the quality (purity and specific activity) of [^{18}F]fluoride ion from different sources, results from its use in radiochemistry are not always strictly comparable.[50]

Some attempts have been made to purify cyclotron-produced [^{18}F]fluoride ion, for example by conversion into [^{18}F]fluorotrimethylsilane, which may then be distilled out and hydrolyzed back to [^{18}F]fluoride ion[51,52] (Scheme 4).

Such [18F]fluoride ion has been reported to give reproducible reaction rates in nucleophilic substitution reactions.[50,53] This or other methods of purification have however seldom been implemented, and for the most part cyclotron-produced [18F]fluoride ions might be considered a "dirty" reagent.

Scheme 4. Purification of the [18F]fluoride ion via conversion into distilled [18F]fluorotrimethylsilane.

In theory, truly anhydrous or "naked" [18F]fluoride ion could be very useful for implementing difficult reactions. Recently, it was claimed that truly anhydrous tetra-*n*-butylammonium fluoride (TBAF) has been produced through a chemical reaction between tetra-*n*-butylammonium cyanide (TBACN) and hexafluorobenzene (Scheme 5).[54] The naked fluoride ion showed remarkable reactivity towards a variety of substrates.[55] Aryl and aliphatic nucleophilic substitution reactions proceeded under mild conditions and in high yield. Sun and DiMagno[56] have therefore proposed a "fluoride relay" to obtain naked [18F]fluoride ion. Aqueous [18F]fluoride ion would first be incorporated efficiently into a fluoroarene shuttle, which would then be purified before being treated with TBACN to release naked [18F]-fluoride ion as TBA18F. Detailed studies are however needed to test whether "[18F]fluoride relay" is indeed feasible and practically advantageous, especially at a no-carrier-added level of specific radioactivity.

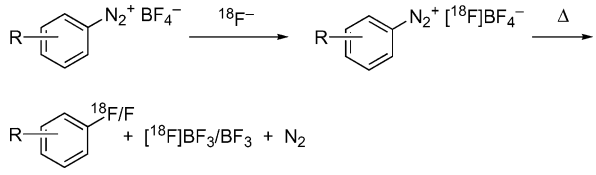


Scheme 5. Generation of anhydrous tetra-*n*-butylammonium fluoride in aprotic solvents.

2.2. Balz–Schiemann and Wallach Reactions with [18F]Fluoride Ion

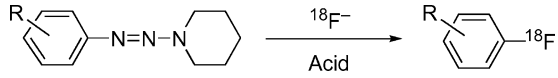
Incorporation of fluoride ion into the position originally occupied by an aryl amino group is a long known transformation and may be achieved through either the Balz–Schiemann[57] or Wallach[58] reaction.

The Balz–Schiemann reaction requires the preparation of an aryl diazonium salt followed by its thermal decomposition in the presence of a fluoride ion source to afford the corresponding fluoroarene (Scheme 6). This reaction has been adapted to prepare many [18F]fluoroarenes, including electron-rich arenes, such as 18F-labeled amino acids[59–63] (e.g., the 5-fluoro isomer of [18F]FDOPA in Table 1). Generally, the incorporation of 18F is low (2–15%). Low specific radioactivity is unavoidable if BF_4^- or other labile fluoride anions are used. In addition, the use of BF_4^- would theoretically limit the radiochemical yield to a maximum of 25%. Counterions without a labile fluoride source, such as BCl_4^-, have been tried in order to avoid dilution of specific radioactivity, but have had only limited success.[64] Side reactions of the diazonium salt with residual water or other trace adventitious species also limit the utility of the Balz–Schiemann reaction.



Scheme 6. The Balz–Schiemann reaction for the preparation of carrier-added [18F]fluoroarenes.

The Wallach reaction yields [18F]fluoroarene by acidic decomposition of a triazene precursor in the presence of [18F]fluoride ion (Scheme 7). The reaction is considered to go through a diazonium salt, which may be obtained, for example, through protonation of the triazene with triflic acid. Both diazonium salt and aryl triflate are formed, but high acid concentration favors the latter.[65] A variety of factors, including acid, solvent and reaction stoichiometry, have been examined to optimize the production of [18F]-fluoroarene. Even so, only modest yields of fluoroarenes have been achieved.[66,67] A synthesis of [18F]haloperidol[68] provides a scarce example of the application of the Wallach reaction to the preparation of a target radiotracer.



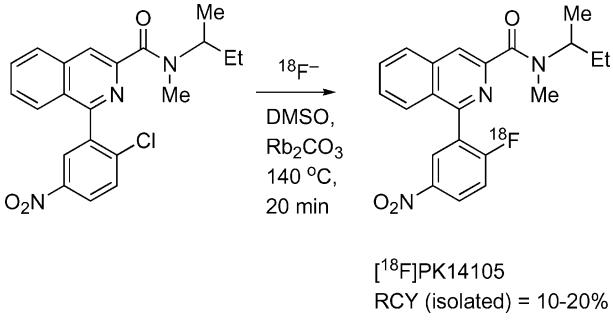
Scheme 7. The Wallach reaction for the preparation of [18F]fluoroarenes.

The Balz–Schiemann and Wallach reactions, mainly because of their low RCYs and emerging alternatives, are now rarely used to prepare 18F-labeled tracers.

2.3. Aromatic Nucleophilic Substitution with [18F]Fluoride Ion

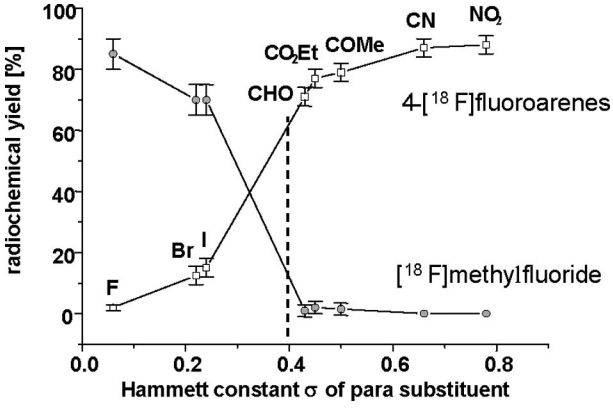
The most successful approach for introducing fluorine-18 at aryl carbons is direct nucleophilic substitution. This reaction however requires that the aryl ring possess a good leaving group, usually at an *o*- or *p*-position to at least one electron-withdrawing substituent.[34,69] Typical leaving groups, in approximate order of increasing ability, are: I < Br < Cl < F < NO_2 ≈ N^+Me_3. Note that the order of leaving group ability among the halogens is reversed to that in aliphatic nucleophilic substitution reactions (see Section 2.5). Typical electron-withdrawing groups, in approximate order of increasing ability, are: 3-NO_2 < 4-Ac < 4-CHO < 4-CN ≈ 4-CF_3 < 4-NO_2. Normally, the reaction conditions need to be quite harsh, for example, 120–180 °C in DMSO, in the presence of a kryptand (e.g., K2.2.2) plus base (e.g., K_2CO_3 or $K_2C_2O_4$). Interestingly, although the nitro group is much more nucleofugic than a halo group, the latter is substituted by [18F]fluoride ion from *p*-nitrohaloarenes as in the radiosynthesis of [18F]PK 14105 (Scheme 8).[70] In

this example, the precursor and labeled product, because of their close structural similarity, proved quite difficult to separate.



Scheme 8. The synthesis of [^{18}F]PK 14105.

In general, the use of Me_3N^+ as a good leaving group,[71,72] with chloride, perchlorate or triflate as counterion, also has the advantage of permitting easy separation of labeled product from precursor (because of charge difference), but sometimes has the disadvantage of competing formation of [^{18}F]fluoromethane. A detailed mechanistic study[36] has shown that *p*-substituents with high Hammet σ constant (e.g., NO_2) favor formation of the [^{18}F]fluoroarene over [^{18}F]fluoromethane, and vice versa for low σ (Scheme 9).

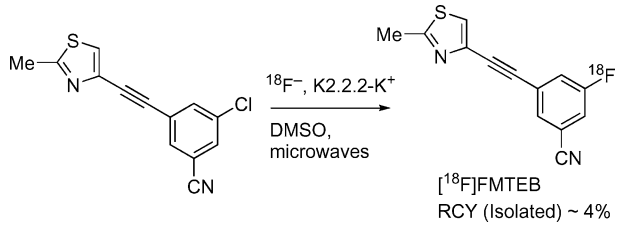


Scheme 9. Influence of *p*-substituents on competition between nucleophilic aromatic and aliphatic [^{18}F]fluorination with trimethylammonium as a leaving group. Reproduced from[36] with permission (by courtesy of Prof. H. H. Coenen, Jülich, Germany).

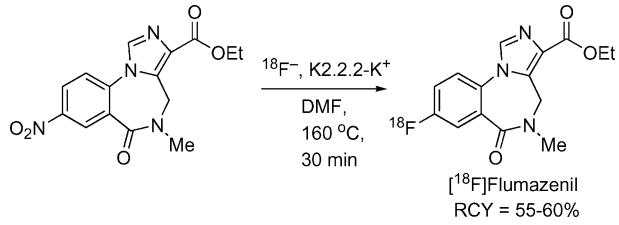
Only a few examples exist for efficient reactions with an electron-withdrawing group in *m*-position.[73,74] The mGluR5 radioligand, [^{18}F]FMTEB (Table 1), has been prepared from [^{18}F]fluoride ion by such a process, but only in low radiochemical yield (Scheme 10).

A recent synthesis of [^{18}F]flumazenil (Table 1) demonstrates that with judicious choice of reaction conditions it is sometimes possible to incorporate the [^{18}F]fluoride ion into a weakly activated aryl position (Scheme 11).

Recently, a stable molten salt, such as tetra-*n*-butylammonium mesylate (TBAOMs, m.p. 78 °C) or triflate (TBAOTf, m.p. 112 °C), has been used in place of aprotic



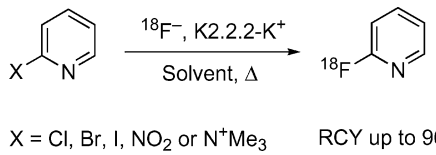
Scheme 10. The synthesis of [^{18}F]FMTEB.



Scheme 11. The radiosynthesis of [^{18}F]flumazenil.

solvent for aromatic nucleophilic substitution with [^{18}F]-fluoride ion.[75] Reaction of *p*-substituted nitrobenzenes or trimethylanilinium triflates with [^{18}F]fluoride ion in these molten salts gave the corresponding [^{18}F]fluorobenzenes in RCYs up to 82%, appreciably higher than in typical fluorination solvents, such as MeCN, DMSO or DMF (up to 59%).

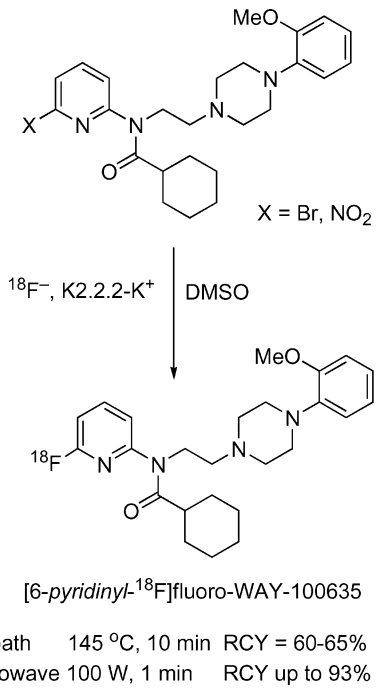
Nucleophilic substitution reactions with [^{18}F]fluoride ion have been expanded to heteroarenes, especially pyridines. This area has been extensively reviewed[76] and hence is only briefly discussed here. The most efficient method for the synthesis of [^{18}F]2-fluoropyridines is through nucleophilic substitution (Scheme 12). Almost quantitative yields can be achieved. Even so, quite harsh conditions, comparable to those needed for substitution in homoarenes, are still required. This points to the mechanistic similarity of nucleophilic substitution with [^{18}F]fluoride ion in homoarenes and heteroarenes. A variety of leaving groups have been used successfully for this reaction (Scheme 12).[77] Among the halo-pyridines, the iodo-derivatives are least reactive. Typical solvents for these reactions are DMSO and DMF.



Scheme 12. The syntheses of [^{18}F]2-fluoropyridines from [^{18}F]fluoride ion.

The ready labeling of the 2-position of a pyridinyl ring with [^{18}F]fluoride ion has been utilized in the production of a wide range of PET radiotracers, notably radioligands for nicotinic, 5-HT_{1A} and mGluR5 receptors,[78–81] as comprehensively reviewed by Dollé.[39,76] These syntheses show the

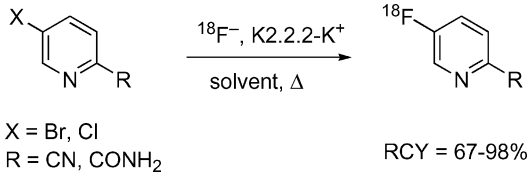
tolerance of the reaction for a second substituent on the pyridinyl ring, as exemplified in the synthesis of [6-*pyridinyl*-18F]fluoro-WAY-100635 (Scheme 13).[82]



Scheme 13. Synthesis of [6-*pyridinyl*-18F]fluoro-WAY-100635.

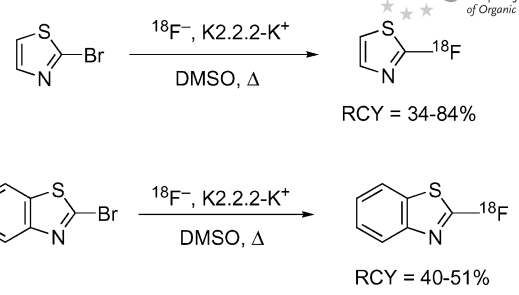
The synthesis of [18F]4-fluoropyridines from [18F]fluoride ion generally proceeds as efficiently as those of [18F]2-fluoropyridines. Nevertheless, the synthesis of 4-trimethylammonium salts, as desirable reactive substrates, has not been demonstrated. Curiously, no important radiotracer containing a [18F]4-fluoropyridinyl group has yet been reported.

For the introduction of [18F]fluoride ion into a pyridinyl 3-position, activation by an electron-withdrawing group is needed.[83] A cyano or amido group is sufficient. Either bromo or chloro can serve as the leaving group (Scheme 14).



Scheme 14. Syntheses of [18F]3-fluoropyridines from [18F]fluoride ion.

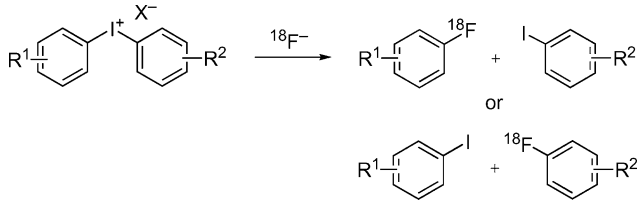
Further heteroarenes are also proving amenable to nucleophilic radiofluorination.[84,85] For example, aromatic nucleophilic substitution with [18F]fluoride ion has recently been demonstrated in 2-bromo-1,3-thiazoles (Scheme 15).[85]



Scheme 15. Nucleophilic substitution in 2-bromo-1,3-thiazoles with [18F]fluoride ion.

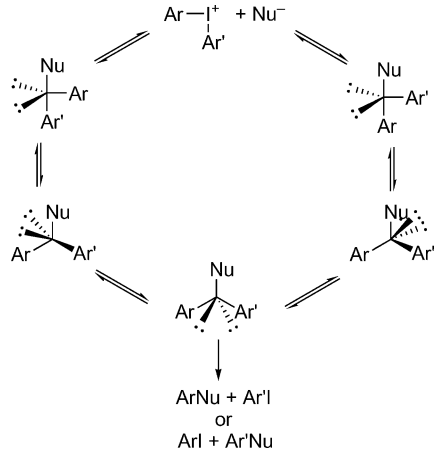
2.4. Reactions of Diaryliodonium Salts with [18F]Fluoride Ion

As noted above, a severe limitation of "classical" aromatic nucleophilic substitution reactions with [18F]fluoride ion is their lack of applicability to the labeling of electron-rich arenes whilst the Balz–Schiemann and Wallach reactions are poorly efficient. In 1995, a new method for introducing fluorine-18 into arenes was introduced, namely the reaction of diaryliodonium salts with [18F]fluoride ion (Scheme 16).[86] This method was found to be applicable to the 18F-fluorination of both electron-rich and electron-deficient arenes.[87] An interesting feature of this reaction is the "*ortho* effect"; an *o*-substituent on one of the aryl rings preferentially directs the radiofluorination to that ring. RCYs of the substituted [18F]fluoroarene increase as more substituents (e.g., Me) are added to the ring.[88] The existence of this effect and the ease of reaction of electron-rich rings in the salts suggest a mechanism other than direct aromatic nucleophilic substitition (i.e., other than direct attack of [18F]fluoride ion onto an aryl carbon). Originally, a "turnstile" mechanism was proposed[89] to account for the *ortho* effect in this type of reaction (Scheme 17). Subsequent theoretical studies suggest other possibilities, which may include the formation of bridged dimers[90] or trimers[91] of the diaryliodonium salts preceding their conversion into [18F]fluoroarene. Recently, others[92] have claimed that the mechanism is indeed aromatic nucleophilic substitution on the basis of a correlation of reaction rates with Hammett substituent constants. Not all reactions showing such a correlation involve reactions at aryl carbon sites and hence this conclusion may need to be treated with caution.



Scheme 16. Introduction of fluorine-18 into arenes through the reactions of diaryliodonium salts with [18F]fluoride ion.

Furthermore, radical scavengers, such as TEMPO, appear effective in promoting the yield and reliability of these

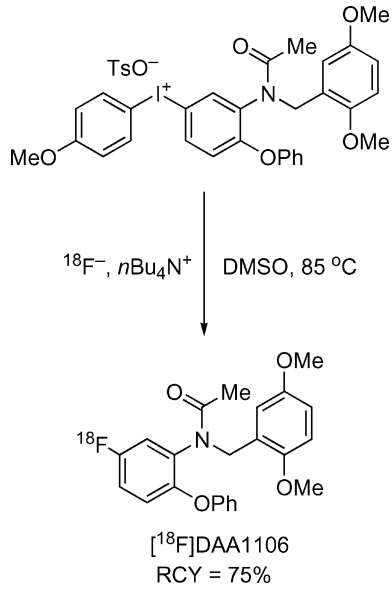


Scheme 17. Proposed "turnstile" mechanism for the polar reaction of a diaryliodonium salt with a nucleophile, such as fluoride ion. Nucleophilic attack upon the positive iodine atom in the iodonium cation forms a tricovalent intermediate which collapses in an S_N-like process to form products. The "*ortho*" effect is rationalised to result from the relief of steric strain in the transition state with the more bulky aryl substituent preferring to occupy an easily attacked equatorial position.

reactions, and especially in avoiding decomposition of salt before reaction with [^{18}F]fluoride ion is complete.[93,94] Generally, these reactions proceed under mild conditions compared to direct aromatic nucleophilic substitution (i.e., S_NAr) with [^{18}F]fluoride ion and hence low-boiling-point solvents (MeCN, DMF) may be utilized. Interestingly, it is also claimed that these reactions can be performed in the presence of large concentrations of water.[95]

For radiosynthetic utility, it is highly desirable to be able to direct the incorporation of fluorine-18 to the desired ring. In the absence of an *ortho* effect, the fluorine-18 is incorporated into the least electron-rich ring. Hence, an effective strategy for directing fluorine-18 to the desired ring is to make one of the aryl groups an electron-rich *p*-methoxyphenyl or 2-thienyl ring (Scheme 18).[96–98] The nature of the anion was noted to influence the rate and RCYs from the 2-thienyl compounds.

So far, this approach to ^{18}F-labeling has mainly been investigated for simple readily prepared diaryliodonium salts. Only a few applications to the preparation of specific radiotracers have emerged. One successful example is [^{18}F]-DAA1106, which was obtained in 75% RCY (Scheme 19).[99]

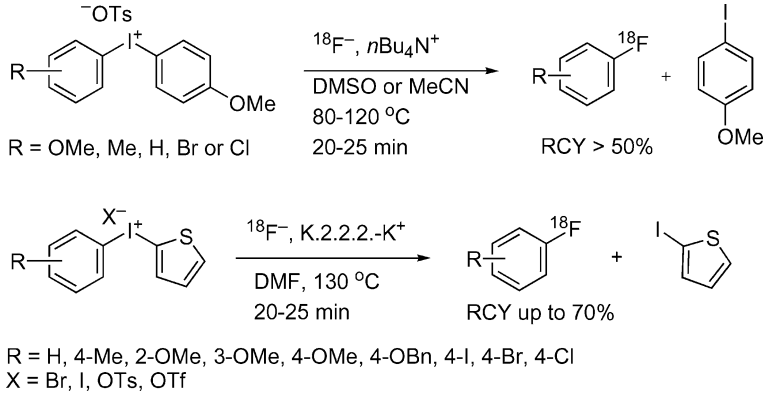


Scheme 19. Synthesis of [^{18}F]DAA1106 using DAA-I$^+$-anisole iodonium tosylate as precursor.

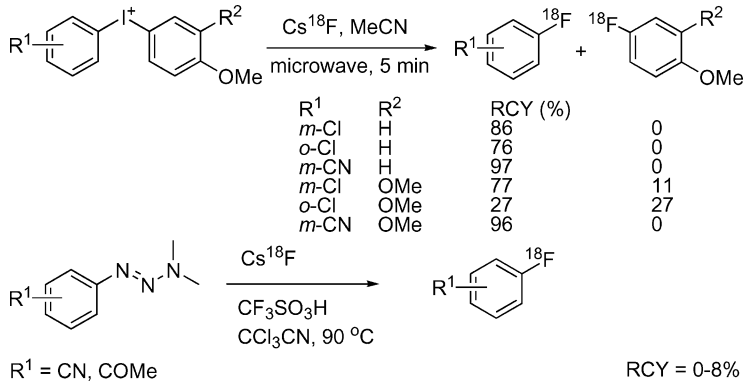
A comparison of the reactions of [^{18}F]fluoride ion with diaryliodonium salts or triazenes (the Wallach reaction) has shown that the former is indeed much superior to the latter (Scheme 20).[100,101]

The most efficient method to introduce fluorine-18 at a 3-pyridinyl position without assistance from an electron-withdrawing group is now through an appropriate diaryliodonium salt (Scheme 21).[102]

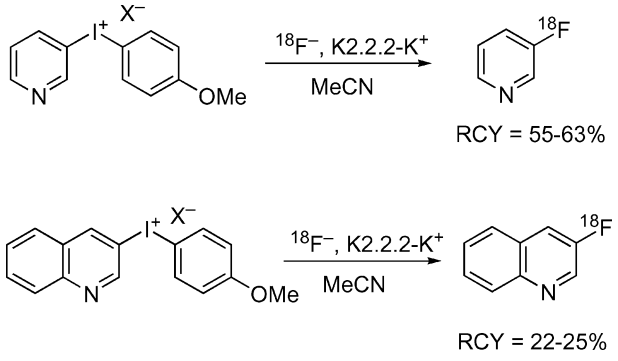
It should be noted that diaryliodonium salts may now be prepared by a variety of methods, of which the reactions of commercially available Koser's reagent with aryl boronic acids[103] and organostannanes[104] are particularly attractive. The purities with which diaryliodonium salts may be prepared will likely be critical to their wider application in preparing complex ^{18}F-labeled tracers.



Scheme 18. The electron-rich *p*-methoxyphenyl or 2-thienyl ring directs fluorine-18 to the desired arene.



Scheme 20. The reactions of [18F]fluoride ion with diaryliodonium salts compared to those with triazenes (the Wallach reaction).

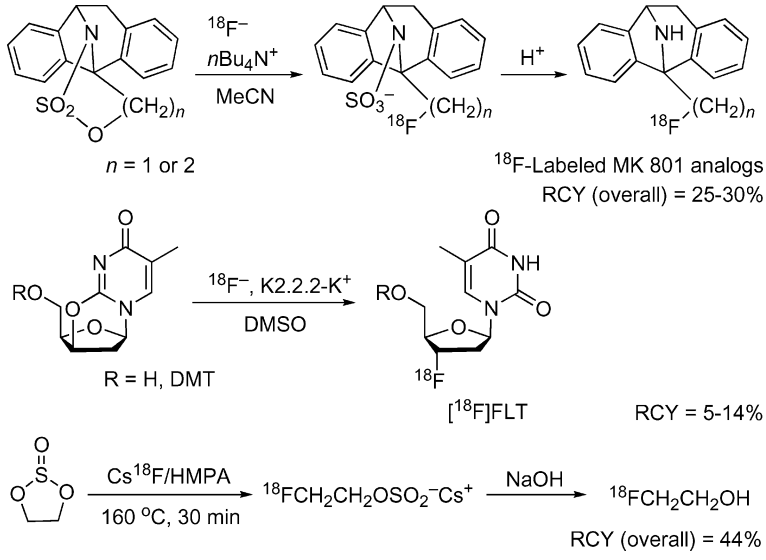


Scheme 21. Introduction of fluorine-18 at a 3-pyridinyl position through a diaryliodonium salt.

2.5. Aliphatic Nucleophilic Substitution with [18F]Fluoride Ion

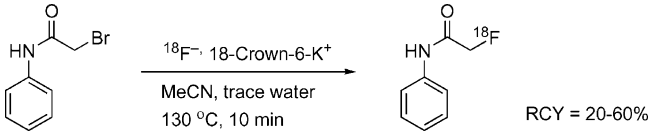
Aliphatic nucleophilic substitution with [18F]fluoride ion can be highly efficient; under favorable circumstances yields may be quantitative. Usually, the leaving groups are sulfonates (e.g., triflate, mesylate, tosylate or nosylate) or other halides (Cl, Br or I). Substrate reactivity closely follows the pattern of typical S_N2 type reactions, with substitution at primary carbon favored for high yield. Primary carbon sites may include benzylic and allylic carbons, α-positions of a carbonyl group (including ester, ketone and aldehyde) and the α-positions of cyanide and sulfonamide. Substitution at secondary carbon may be accompanied with heavy elimination from the precursor. Certain cyclic systems can be opened efficiently with [18F]fluoride ion, and this has been exploited, for example, in the syntheses of 18F-labeled MK 801 analogs,[105,106] [18F]FLT[107] and [18F]2-fluoroethanol[108] (Scheme 22). However, the opening of epoxides, requires acid catalysis, and is generally inefficient.[109,110]

Aliphatic nucleophilic substitution reactions with [18F]-fluoride ion are usually performed in a polar aprotic solvent such as acetonitrile, DMF, THF, DMSO, nitrobenzene, *o*-dichlorobenzene, dichloromethane or tetramethylsulfone (sulfolane). Acetonitrile is suitable and effective for many reactions and has the attraction of being easily removed. Perhaps counter-intuitively, protic solvents and even small amounts of water have proved beneficial for some reactions. Experimental studies show that the nucleophilicity of fluoride ion decreases with degree of solvation.[111] For example,



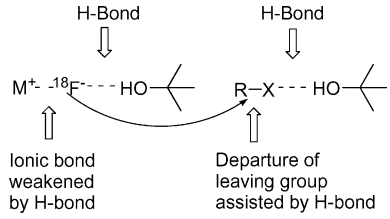
Scheme 22. Some ring-opening reactions of [18F]fluoride ion.

in a comparison of the hydrated nucleophiles, $F^-(H_2O)_n$ for reaction with *n*-octyl mesylate, the reaction rate with n = 1.5 is about 100-fold higher than with n = 8.5. Some nucleophilicity is however retained with even higher numbers of water of solvation, or even in the presence of bulk water.[112] A theoretical study[113] has rationalized how hydrated fluoride ion, despite its very high free solvation energy (439 kJ/mol),[114] can be a good nucleophile in certain reactions. In general, as the dryness and therefore nucleophilicity of the [^{18}F]fluoride ion increases, the tendency for adsorption onto reaction vessel walls also increases, so removing a proportion of the [^{18}F]fluoride ion from the reaction mixture and decreasing the overall radiochemical yield. This effect is particularly pronounced in Pyrex glass vessels.[42] For reactions involving reactive substrates, addition of known amounts of water may lead to optimal radiochemical yields, by reducing adsorption while also maintaining adequate nucleophilicity. The reactions of *N*-aryl-α-bromo acetamides with [^{18}F]fluoride ion in the presence of trace water,[115] which gave overall radiochemical yields up to 60%, exemplify this effect (Scheme 23).



Scheme 23. Reaction of *N*-aryl-α-bromo acetamides with [^{18}F]fluoride ion.

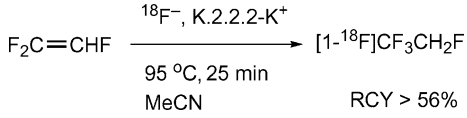
Recently, the use of polar protic solvents has been explored and applied successfully in several examples, including the syntheses of [^{18}F]Fp-CIT and [^{18}F]FLT[116] (Scheme 24). Sterically hindered alcohols, such as *tert*-butyl alcohol, gave optimal results. The polar *tert*-butyl alcohol medium actually increases the nucleophilicity of the fluoride ion, thereby increasing the rate of nucleophilic fluorination compared with conventional solvents and reducing competing formation of typical by-products, such as alkenes, alcohols, or ethers.[117] Quantum chemical analysis has suggested the reaction mechanism differs from classical S_N2.[118] Thus, *tert*-butyl alcohol may be acting both as a Lewis base to the bulky and polarizable counter cation (Cs^+) and as a Lewis acid to the leaving group (Scheme 25). Tertiary alcohols as a reaction medium for nucleophilic fluorination with [^{18}F]fluoride ion appear quite generally useful for aliphatic substrates.



Scheme 25. Aliphatic nucleophilic substitution using *tert*-butyl alcohol as solvent.

2.6. Nucleophilic Addition of [^{18}F]Fluoride Ion

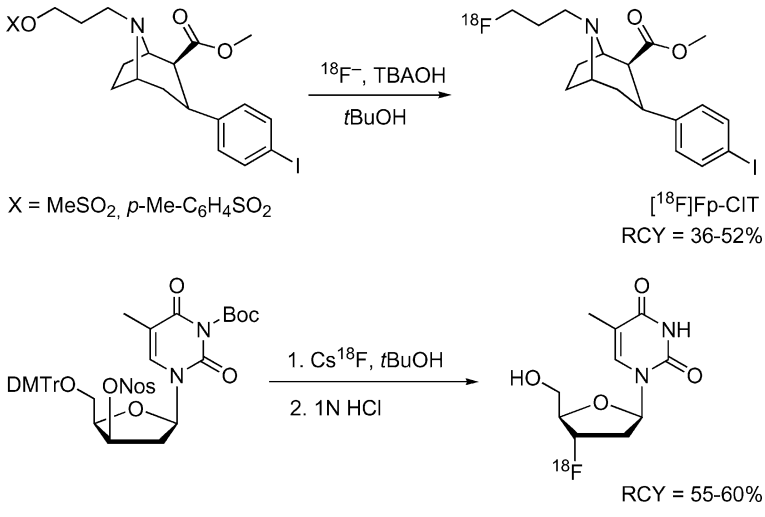
Reaction of [^{18}F]fluoride ion with trifluoroethylene has been used to label[119,120] eco-friendly 1,1,1,2-tetrafluoroethane (HFC 134a) selectively in the 1-position.[121] The proton required for product formation was found to come from the reaction solvent (MeCN) (Scheme 26). This is a rare example of the practical application of a nucleophilic addition of [^{18}F]fluoride ion.



Scheme 26. Preparation of [1-^{18}F]HFC 134a by nucleophilic addition.

2.7. Exchange Reactions of [^{18}F]Fluoride Ion

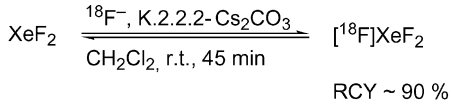
Exchange reactions of [^{18}F]fluoride ion always have the outcome of low specific radioactivity, which is usually un-



Scheme 24. Aliphatic nucleophilic substitution with [^{18}F]fluoride ion in polar protic solvents.

desirable, and they have rarely been used in radiotracer preparation. The possibility to produce radiotracers by exchange reactions of [18F]fluoride ion in fluoroarenes has gained some interest recently for producing radiotracers where high specific radioactivity is non-critical.[122] Although few details have been given, RCYs ranging between 29 and 95% have been reported.

[18F]Fluoride ion exchanges with xenon difluoride (Scheme 27).[123] This reaction is of interest as a means of producing an electrophilic radiofluorination agent from [18F]fluoride ion. Difficulties in reproducing this reaction[124] point to the capricious nature of [18F]fluoride ion chemistry, as alluded to in the introduction.

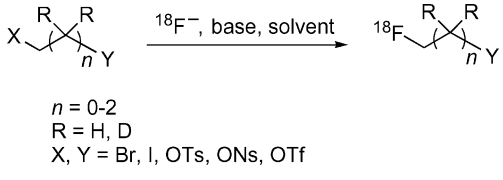


Scheme 27. Preparation of [18F]xenon difluoride from [18F]fluoride ion.

3. Labeling Agents Derived from [18F]Fluoride Ion

As may be appreciated from the preceding section, not all fluorine-containing target radiotracers are yet amenable to direct single-step labeling with [18F]fluoride ion; this is especially so for electron-rich arenes and macromolecules. A second useful strategy for obtaining 18F-labeled tracers is to prepare a reactive species (a labeling agent) from [18F]-fluoride ion, and to use this for the introduction of fluorine-18 into the target. Such labeling agents may be aliphatic or aromatic and the targets small molecules or macromolecules. This area has been reviewed[35–39,76] quite recently and in considerable depth, and hence only some of the most important aspects are discussed here.

An important range of labeling agents are the functionalized straight chain aliphatic [18F]fluorides,[125–135] prepared from the reaction of [18F]fluoride ion with α,ω-bifunctional agents (Scheme 28). The preparation of these agents has recently been reviewed at length.[136] The most widely used are the short chain [18F]ω-fluoroalkyl agents, especially [18F]fluoromethyl bromide[132,133] and [18F]2-fluoroethyl tosylate.[134,135]

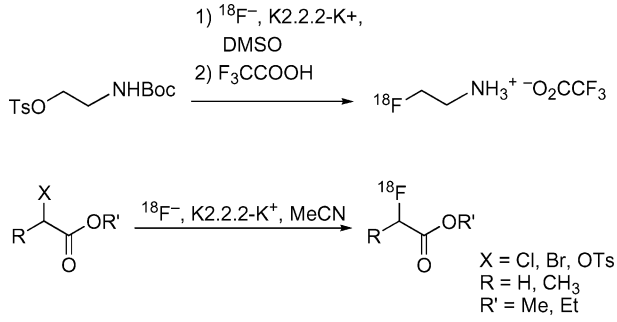


Scheme 28. The preparation of simple 18F-labeled fluoroalkylation agents.

[18F]Fluoromethyl bromide may be prepared from dibromomethane and purified by vapor phase transfer (in carrier nitrogen) through several Sep-Paks, before reaction with a precursor to obtain the target tracer by *O*- or *S*-alkylation (*N*-fluoromethyl compounds are generally unstable). Examples are the radiosyntheses of [18F]SPA-RQ (Table 1), [18F][D2]MeNER (Table 1), and [18F]fluoromethyl northionisoxetine.[137] The overall RCYs of these processes tend to be low. Moreover, the fluoromethyl group attached to the heteroatom may defluorinate to some extent in vivo. Inclusion of two deuterium atoms in the fluoromethyl group is claimed to counter this defluorination through an isotope effect.[138] [18F]Fluoromethyl bromide may be converted easily into a more reactive labeling agent, [18F]fluoromethyl triflate, by passage over heated silver triflate.[139]

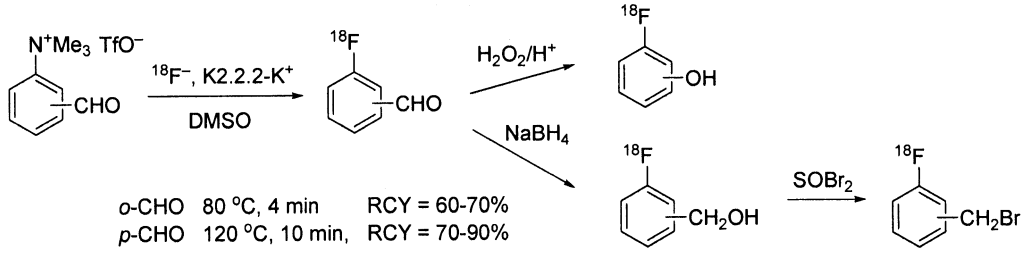
[18F]2-Fluoroethyl tosylate has been applied to the syntheses of several radiotracers, including [18F]FECNT (Table 1). This labeling agent is rather more reactive than the alternative [18F]fluoroethyl bromide and may be produced and used in situ.[140] [18F]Fluoroethyl aryl sulfonates of even higher reactivity may also be produced similarly, such as the nosylate.[141] Arylsulfonate-based nucleophile assisting leaving groups (NALGs) contain acyclic or cyclic polyether units in *o*-position at the arylsulfonyl ring. They display enhanced S_N2 type reactivity towards metal halides through the cation-chelating moiety that attracts nucleophilic metal salts to the site of attack and stabilizes the newly-forming leaving group through internal chelation.[142] Such advantages have also been realized in radiofluorination under microwave conditions.[143]

The [18F]fluoroalkylating agents are generally applied to the labeling of small molecules. By contrast labeling agents for 18F-fluoroamidation[144] and 18F-fluoroacylation[145] may be prepared similarly and are generally applied to the labeling of peptides and proteins under mild conditions (Scheme 29).



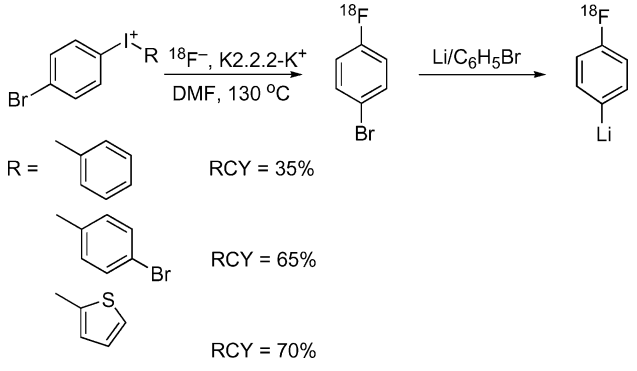
Scheme 29. The preparation of simple 18F-labeled fluoroacylation and fluoroamidation agents.

[18F]*o*- or *p*-fluorobenzaldehydes may be produced quite efficiently in one step by aromatic nucleophilic substitution in the corresponding benzaldehyde bearing a good leaving group, such as NO_2 or Me_3N^+.[146,147] These aldehydes are useful synthons in their own right, since they may be used in multi-step radiosyntheses of useful radiotracers, such as [18F]FDOPA (Table 1). They may also serve as entries into other useful labeling agents such as the corresponding [18F]-fluorobenzyl halides, through reduction and halogenation. An example is [18F]*p*-fluorobenzyl bromide (Scheme 30) for the synthesis of a brain CB_1 receptor ligand, [18F]Pip-ISB.[148]



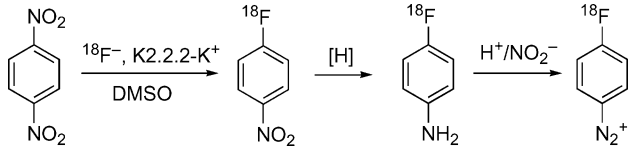
Scheme 30. Examples of the preparation of [^{18}F]*o*- or *p*-fluorobenzaldehydes and derivatives as labeling agents.

Other [^{18}F]fluoroarenes have also come to serve as synthons or labeling agents. An example is [^{18}F]*p*-fluorobromobenzene,[97,149] which is efficiently produced by the reaction of bis(*p*-bromophenyl)iodonium bromide or its 2-thienyl analog with [^{18}F]fluoride ion (Scheme 31). This may be further converted into the useful synthon [^{18}F]*p*-fluorophenyllithium.



Scheme 31. The radiosyntheses of [^{18}F]*p*-fluorobromobenzene and [^{18}F]*p*-fluorophenyllithium.

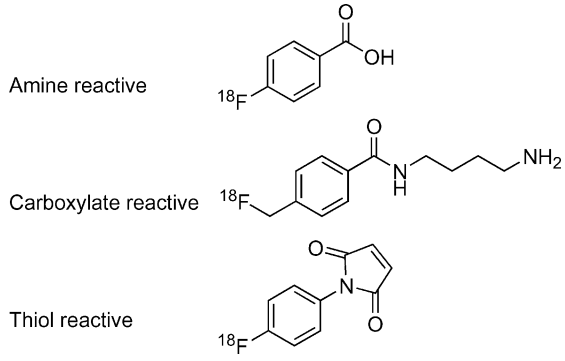
Further examples of aryl labeling agents include [^{18}F]*p*-fluoroaniline and [^{18}F]*p*-fluorophenyldiazonium ion, derived sequentially from dinitrobenzene and [^{18}F]*p*-fluoronitrobenzene (Scheme 32).[150]



Scheme 32. The radiosyntheses of [^{18}F]*p*-fluoroaniline and [^{18}F]*p*-fluorophenyldiazonium ion.

The application of such reactive [^{18}F]fluoroarenes is mainly limited to the preparation of small molecule radiotracers. This area has become very diverse and has recently been reviewed thoroughly by Wuest.[37]

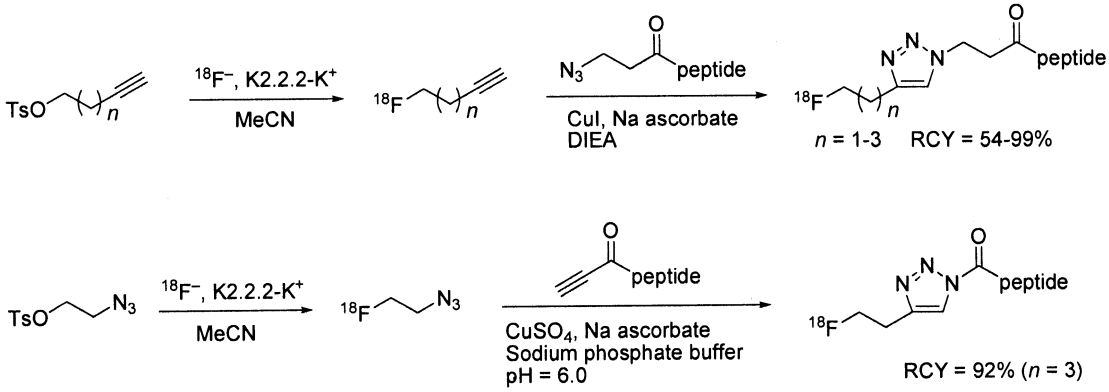
Interest in the ^{18}F-labeling of macromolecules, especially peptides and proteins, has been burgeoning. A wide range of labeling agents has been developed for this specific purpose. A comprehensive list of such agents for peptide and protein labeling with their reactivities and the important features of their production and utility has recently been compiled by Wester and Schotellius.[38] These reagents are often intended to react under mild conditions with nucleophiles in the macromolecule, such as amino, carboxylate or thiol groups. An example of each type of labeling agent is shown in Scheme 33.



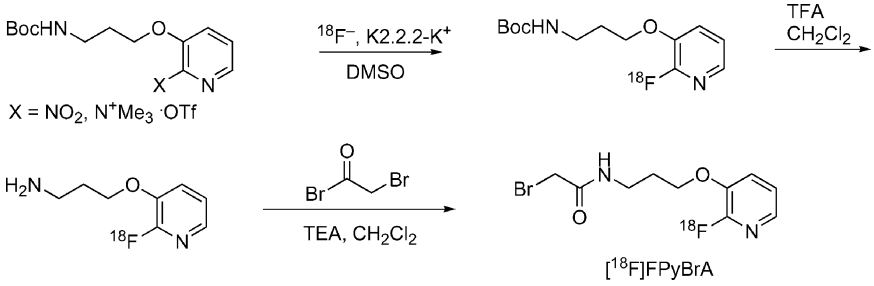
Scheme 33. Examples of labeling agents produced from [^{18}F]fluoride ion for the labeling of peptides at amino, carboxylate or thiol functions in peptides and proteins.

"Click" chemistry, which utilizes Huisgen 1,3-dipolar cycloaddition of terminal alkynes and azides to form 1,2,3-triazoles, has been adopted for the preparation of [^{18}F]fluoropeptides (Scheme 34).[151,152] The reaction requires Cu^{I} catalyst, proceeds under mild conditions in aqueous media and requires virtually no protection of other functional groups. Use of the non-radioactive component of the reaction in excess compensates for moderate reactivity. Thus, many labeling reactions can be completed within 20 min in moderate to high radiochemical yields. Depending on the availability of building blocks, the alkyne or azide group can be on either side of the triazole ring, thus providing more flexibility in choice of starting materials. The syntheses of many ^{18}F-labeled azides and alkynes are being investigated so that the repertoire of click chemistry can be expanded to include the synthesis of both peptide-like and small compounds for molecular imaging.[153,154]

The facile incorporation of [^{18}F]fluoride ion into the 2-position of the pyridinyl ring (see section 2.4) has been exploited to produce a useful labeling agent, [^{18}F]FPyBrA, for oligonucleotides containing a phosphorothioate monoester function (Scheme 35).[155]



Scheme 34. Two strategies for the labeling of peptides using Huisgen's 1,3-dipolar cycloaddition of terminal azides to alkynes, or "click chemistry".



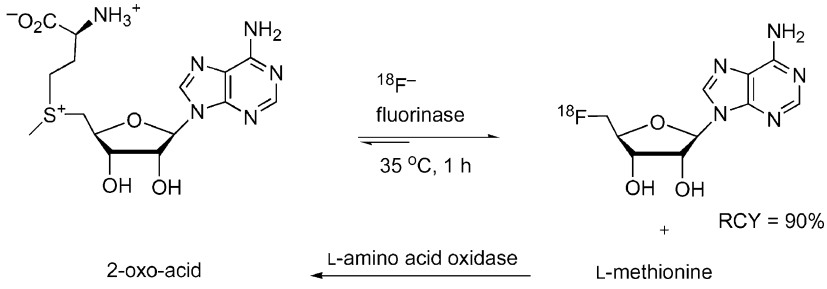
Scheme 35. The preparation of [18F]FPyBrA as a labeling agent for oligonucleotides containing a phosphorothioate group.

4. New Methods and Technologies for Chemistry with [18F]Fluoride Ion

4.1 Enzyme-Catalyzed [18F]Fluorination

Enzyme-catalyzed chemical transformations produce organic or bioorganic molecules in a stereo-, regio-, and chemo-selective manner.[156] The fact that most enzymes operate at near room temperature and in aqueous solution can be beneficial for application to the synthesis of ^{18}F-labeled tracers which are usually formulated in physiological media, such as saline. However, the rate of enzyme-catalyzed reactions must be within a range that gives product on a *nano*mol to *micro*mol scale within one or two half-lives of fluorine-18.

Enzymes have long been used to catalyze the transformation of functional groups, other than –F itself, to prepare ^{18}F-labeled compounds.[157] O'Hagan and co-workers reported the first example of the formation of a C–F bond by an enzyme, now called fluorinase (E.C. 2.5.1.63), which was isolated from the bacterium, *Streptomyces cattleya*.[158] Although radiofluorination of *S*-adenosyl-L-methionine was initially reported as inefficient with RCY at ca. 1%, they subsequently improved this procedure by introducing a second enzyme, L-amino acid oxidase, to shift the equilibrium to the formation of [18F]5′-fluoro-5′-deoxyadenosine

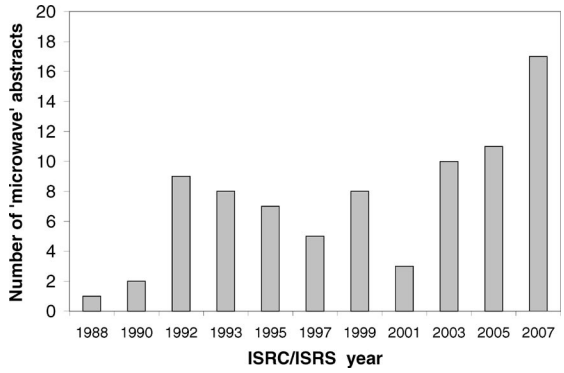


Scheme 36. The removal of L-methionine by L-amino acid oxidase shifts the equilibrium in favour of formation of [18F]5′-fluoro-5′-deoxyadenosine in *S. cattleya*.

(Scheme 36). RCY reached > 90% under optimal conditions.[159] The efficiency of these processes was enhanced by using a much higher concentration of enzyme (μM) than [^{18}F]fluoride ion (pM).

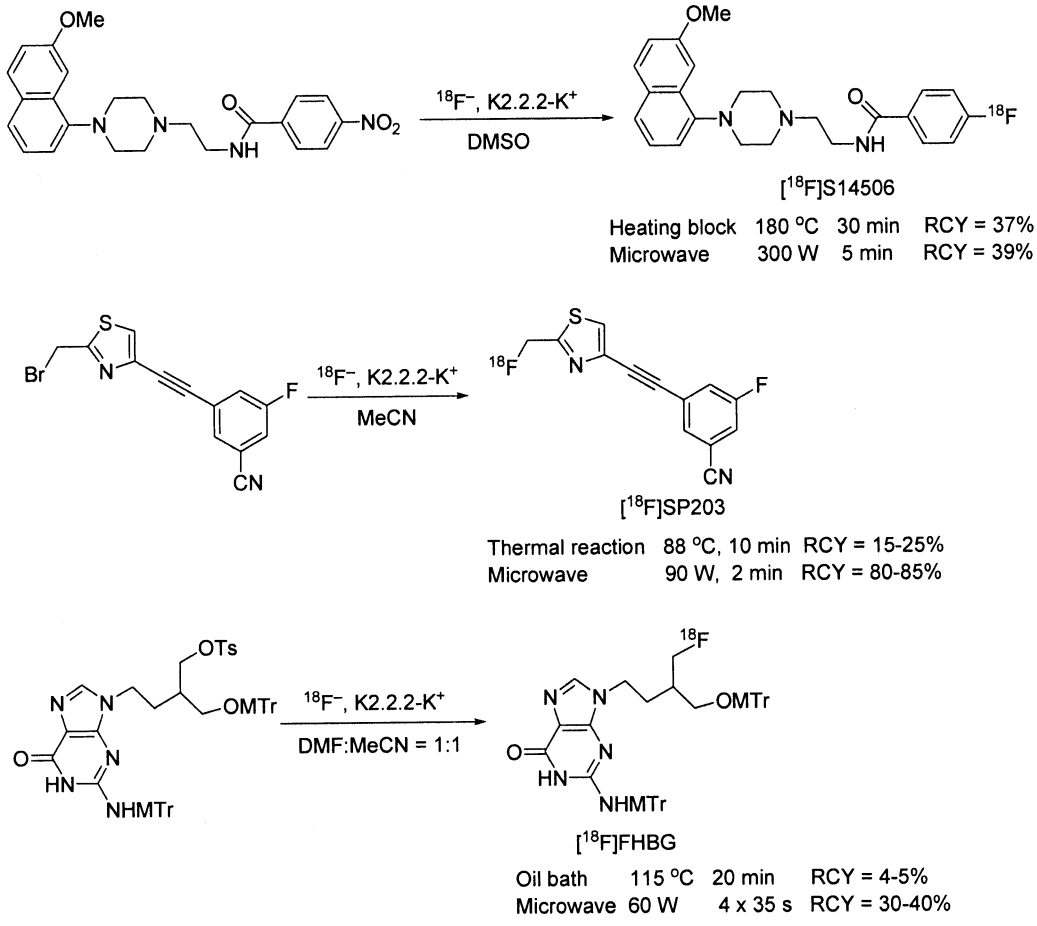
4.2 Microwave-Enhanced Reactions

The use of microwaves to enhance radiochemistry[160–162] has been gaining popularity because it offers speed, selectivity and efficiency. Earlier concerns on the safety of the technology have been addressed by the development of a new generation of microwave cavities that incorporate safety features such as pressure and temperature controls. Some instruments are now able to provide visual monitoring of the reaction.[163] The number of abstracts presented at the International Symposia on Radiopharmaceutical Sciences (ISRS, formerly the International Symposia on Radiopharmaceutical Chemistry, ISRC) serves as a good indication of the growth in this area (Scheme 37). The majority of these abstracts report applications of microwaves in [^{18}F]fluoride ion chemistry.



Scheme 37. Number of abstracts describing microwave-enhanced radiochemistry appearing in the last eleven International Symposia on Radiopharmaceutical Sciences (ISRS and formerly ISRC). The resurgence after 2001 corresponds to the advent of purpose-built safe instruments.

NCA [^{18}F]fluoride ion may be dried by microwave heating of the cyclotron-irradiated water with added K_2CO_3 and K2.2.2 followed by multiple steps of azeotropic evaporations, or by microwave drying of the eluent from an anion resin cartridge that pre-concentrates the [^{18}F]fluoride ion so



Scheme 38. Examples of microwave-enhanced aromatic and aliphatic nucleophilic substitutions used in the syntheses of ^{18}F-labeled tracers.

that fewer steps of azeotropic evaporations are required. In our laboratory, we developed a Synthia[164]-based microwave drying and reaction platform that regularly processes 200–400 mCi of [18F]fluoride ion in 400–800 μL [18O]water for radiotracer research or production.[165] This system is used for the production of radiotracers (e.g., [18F]SP203 and [18F]FBR, Table 1) for imaging in animals or human subjects. Other radiochemistry platforms with microwave components can process up to 3 Ci of [18F]fluoride ion.[166]

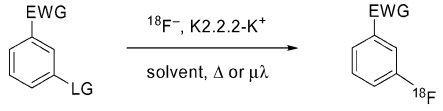
Examples of both aromatic and aliphatic radiofluorination under microwave conditions are shown in Scheme 38.[25,167,168] Decreases in reaction time and in the amount of required precursors, and improved RCYs are among the advantages that microwave-enhanced reactions can offer. The decreased precursor not only saves precious starting materials, but also reduces the product purification burden.

Introduction of fluorine-18 into *m*-aryl positions is difficult under thermal S_NAr conditions, because even strong electron-withdrawing groups, such as NO_2, have only a weak stabilizing effect ($m << o < p$) on the intermediate anion σ complex. Nevertheless, under microwaves, *m*-[18F]-fluoroarenes can be obtained *regio*-selectively in moderate to good radiochemical yields (Table 3).[165] Thus, difficult positions for labeling with fluorine-18 may become more accessible under the influence of microwaves.

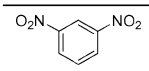
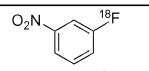
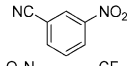
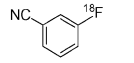
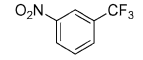
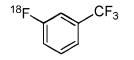
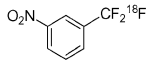
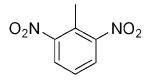
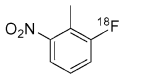
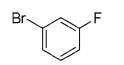
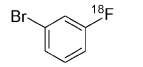
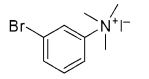
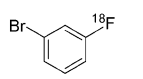
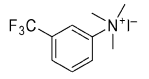
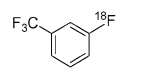
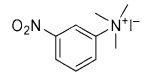
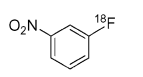
The decrease in reaction time and improvement in RCYs are also of great advantage in multi-step syntheses of radiotracers.[169,170] In certain cases, the synthesis of a secondary labeling agent has been accelerated under microwaves so that the saved time could be diverted to subsequent steps. In other cases, the first step has been performed as usual and the subsequent reaction enhanced by microwaves. Therefore, more choice of precursor and secondary labeling agent is available so that more rapid, selective and functional group-tolerating reactions can be developed.

The synthesis of [18F]*p*-fluoroiodobenzene and its application in Sonogashira cross-coupling reactions exemplifies the first strategy.[169] 4,4′-Diiododiphenyliodonium salts were used as precursors for the synthesis of [18F]*p*-fluoroiodobenzene, enabling convenient access to [18F]*p*-fluoroiodobenzene in up to 70% RCY (Scheme 39). High reaction temperatures (above 140 °C) were essential for efficient reaction of [18F]fluoride ion with diaryliodonium salt in a highly polar aprotic solvent to form *p*-[18F]fluoroiodobenzene. Microwave activation did not greatly improve the radiochemical yield of [18F]*p*-fluoroiodobenzene. However, because of the rapid access to high temperature under microwave conditions, the reaction time was reduced from 40 to 5 min, which was of great advantage in performing the subsequent reaction and in preserving activity and specific radioactivity.

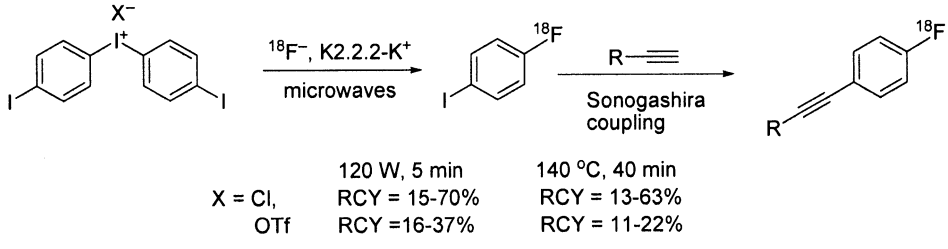
Table 3. *m*-Fluorination of substituted benzenes with [18F]fluoride ion under thermal and microwave-enhanced conditions.[a]



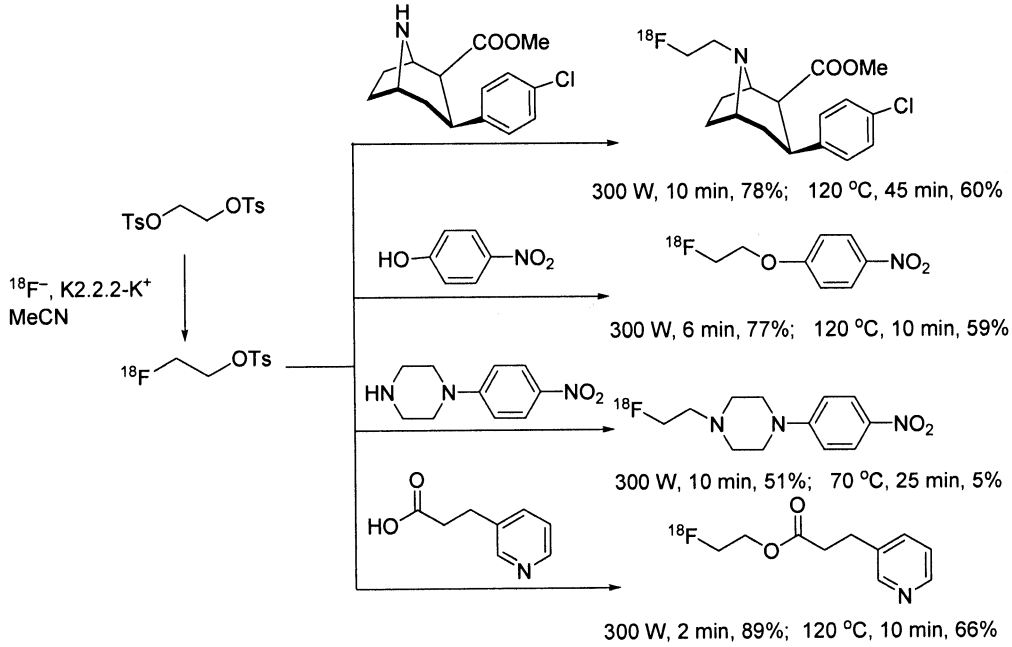
LG = NO_2, N^+Me_3, F EWG = NO_2, CN, Br, CF_3
solvent = *N*-methyl-2-pyrrolidinone (NMP), DMSO, DMSO+ionic liquid, CH_3CN

Precursor	Product	RCY (%, $n \geq 3$)	
		Thermal	Microwave
		21	47
		20	46
		8	13
		1	4
		11	41
		9	19
		3	17
		1	12
		4	8

[a] Optimal conditions. Solvent: NMP; microwave input: 90 W, 3 min; amount of precursor: 1.8–2.8 mg (11–19 μmol). Thermal heating: 150 °C, 10 min.



Scheme 39. Microwave-enhanced radiosynthesis of *p*-[18F]fluoro-iodobenzene and its subsequent application in Sonogashira cross-coupling.



Scheme 40. Examples of the preparation of [^{18}F]*N*-(β-fluoroethyl)amine, [^{18}F]β-fluoroethyl ether and [^{18}F]β-fluoroethyl ester using [^{18}F]β-fluoroethyl tosylate as labeling agent in a microwave-enhanced procedure.

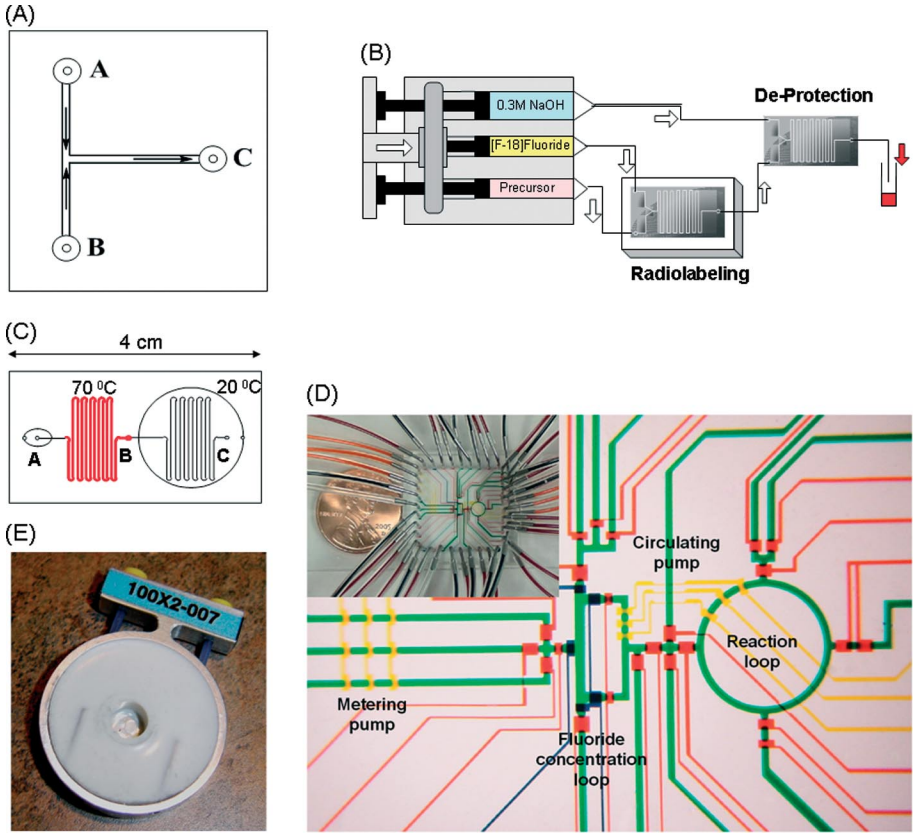
The reactions of [^{18}F]β-fluoroethyl tosylate with amine, phenol or carboxylic acid to form the corresponding [^{18}F]*N*-(β-fluoroethyl)amine, [^{18}F]β-fluoroethyl ether or [^{18}F]β-fluoroethyl ester exemplify the second strategy (Scheme 40).[170] The preparation of [^{18}F]β-fluoroethyl tosylate does not necessarily need microwaves. Nevertheless, microwaves allow the subsequent *O*- and *N*-alkylation reactions to be heated rapidly to 150 °C even in a low boiling point solvent, such as acetonitrile, and avoid the need to use high boiling point solvents, such as DMSO or DMF, to promote reaction. The microwave-enhanced reactions gave higher radiochemical yields than thermal reactions performed at similar temperatures and over similar reaction times.

4.3. Micro-Reactors

Micro-reactor devices or microfluidic chips, consisting of a network of micron-sized channels (typical dimensions in the range 10–300 μm), filters, separation columns, electrodes and reaction loops/chambers etched onto a solid substrate, are now emerging as an extremely useful technology for the intensification and miniaturization of chemical processes.[171–173] The ability to manipulate, process and analyze reagent concentrations and reaction interfaces in both space and time within the channel network of a micro-reactor provides the fine level of reaction control that is desirable in PET radiochemistry practice.[174,175] Benefits include the use of less materials, easier and faster purification with greater conservation of radioactive product and its specific radioactivity. Especially, precious or difficult to obtain precursors may be used in μg as opposed to mg quantities.

Early explorations of this technology in PET radiochemistry were performed with a simple T-shaped glass micro-reactor (Scheme 41, A).[176] Because of its wide utility and potential commercial value, [^{18}F]FDG radiosynthesis has been favored to test various devices. Initially, NCA [^{18}F]-fluoride ion/K2.2.2-K^+ solution was dried using the traditional azeotropic distillation method, then loaded into microfluidic devices driven by syringe pumps. For a two stage reaction, the reaction mixture from the first stage was infused into the second microfluidic chip (Scheme 41, B).[177,178] The two chips can be integrated, with one area heated and the other maintained at room temperature (Scheme 41, C).[178] A fully integrated chemical reaction circuit (CRC)[179] was incorporated into a polydimethylsiloxane (PDMS)-based chip (Scheme 41, D) that could produce [^{18}F]FDG in up to 1.5 mCi levels for micro-PET applications. Although this chip is easy to fabricate and control, solvent incompatibility prevented its wider application.

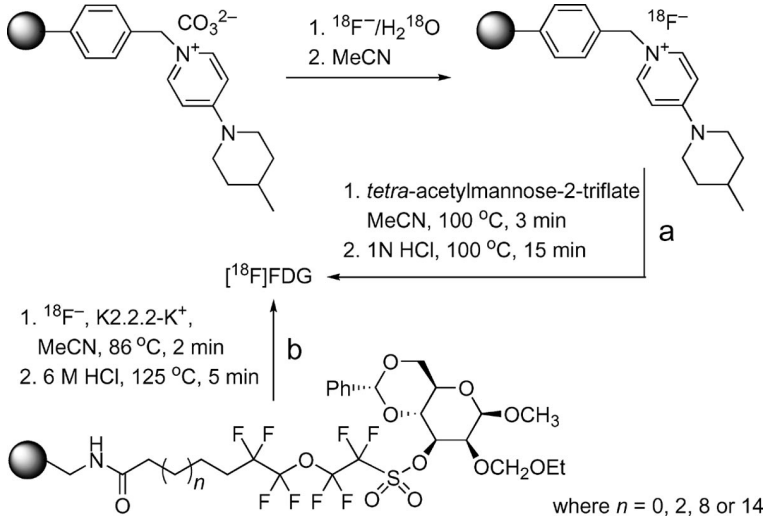
For convenient adaptation to various fluorine-18 research and development applications, micro-reactor systems based on silica glass are advantageous (Scheme 41, E).[180] These have better solvent compatibility and use the reagent reservoir to store radioactivity and precursor solution. Those solutions can then be used in many portions (typically 10 μL) to optimize reaction conditions, or in larger volumes to produce radiotracers in sufficient amount for imaging in monkey or even human subjects.[181,182] Such an approach has been used extensively in our laboratory for example for investigating the reaction of [^{18}F]fluoride ion with diaryliodonium salts and for [^{18}F]fallypride synthesis.



Scheme 41. Examples of micro-reactor or microfluidic apparatus for PET radiochemistry: (A) a simple T-micro-reactor; (B) two-stage [18F]FDG synthesis on two separate microfluidic chips; (C) two-stage [18F]FDG synthesis on a single two-stage microfluidic chip with localized heating, reproduced from[178] with permission (by courtesy of Dr. C. J. Steel, GE); (D) a fully integrated chemical reaction circuit (CRC), reproduced from[179] with permission (by courtesy of Dr. H. R. Tseng, UCLA) and (E) 2-m length silica glass reactor encased with high-temperature silicone in a brass support (by courtesy of Dr. A. M. Giamis, Advion).

4.4 Polymer-Supported Reagents in Radiofluorination

The attraction to use polymer-supported reagents in [18F]fluorination includes potentially (a) easy purification of final product and (b) convenient adaptation of radiosynthesis to automation. Two strategies – one is to trap [18F]fluoride ion on the polymer support with a weakly basic counterion and the other is to attach the precursor to the polymer-support – have been explored in fluorine-18 chemistry (Scheme 42). The former uses polymer-



Scheme 42. [18F]FDG synthesis with (a) polymer-supported [18F]fluoride ion or (b) polymer-supported precursor.

supported 4-aminopyridinium or tris(*n*-butyl)phosphonium salts.[183,184] The quaternary salts immobilize [^{18}F]fluoride ions and act as a phase-transfer catalyst, so removing the need for K2.2.2. The latter uses a perfluoroalkylsulfonate linker to immobilize a D-mannose derivative precursor.[185] Unreacted precursor remains on the resin and is separated from the product by a simple filtration. Both strategies have been tested as effective for the preparation of [^{18}F]FDG, but should equally well be applicable to the preparation of other ^{18}F-labeled tracers.[186]

Conclusions

The increasing importance of PET as a drug development tool and clinical research modality has driven the need for an increasing array of ^{18}F-labeled tracers. In turn, the cyclotron availability of [^{18}F]fluoride ion in high quantity and specific radioactivity has enabled and spurred the development of new more versatile and effective radiochemistry with this ion. Moreover, new technologies are clearly emerging to enable high activities of [^{18}F]fluoride ion to be handled safely, effectively and reliably in compact devices. These advances will likely underpin continued expansion in the use of ^{18}F-labeled tracers for clinical research and diagnosis and for drug discovery and development, with overall great benefit to society.

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