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Hypervalent aryliodine compounds as precursors for radiofluorination

Victor W. Pike

Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

Abstract

Over the last 2 decades or so, hypervalent iodine compounds, such as diaryliodonium salts and aryliodonium ylides, have emerged as useful precursors for labeling homoarenes and heteroarenes with no-carrier-added cyclotron-produced [^{18}F]fluoride ion ($t_{1/2}$ = 109.8 min). They permit rapid and effective radiofluorination at electron-rich as well as electron-deficient aryl rings, and often with unrestricted choice of ring position. Consequently, hypervalent aryliodine compounds have found special utility as precursors to various small-molecule ^{18}F-labeling synthons and to many radiotracers for biomedical imaging with positron emission tomography. This review summarizes this advance in radiofluorination chemistry, with emphasis on precursor synthesis, radiofluorination mechanism, method scope, and method application.

Keywords

aryliodonium ylide; diaryliodonium salt; fluorine 18; PET; radiofluorination; radiotracer

1 | INTRODUCTION

The molecular imaging modality of positron emission tomography (PET) relies on its use of radiotracers labeled with positron emitters for achieving biochemical specificity when they are applied in biomedical research programs or in drug development campaigns. For several reasons, ^{18}F is a favored radionuclide for labeling such radiotracers. First, this radionuclide is readily produced from cyclotrons in very high activities and high molar activities as [^{18}F] fluoride ion, according to the ^{18}O(p,n)^{18}F reaction on [^{18}O]water.[1] Moreover, the half-life of ^{18}F (109.8 min) is long enough to allow radiotracer kinetics to be followed in vivo over a few hours and also usefully permits transport of ^{18}F over considerable distances between radionuclide production and radiotracer imaging centers. The decay of ^{18}F is almost purely (97%) by emission of a relatively low-energy positron (β^+, 0.634 MeV), and this permits higher-resolution PET images to be obtained than with other useful

Correspondence Victor W Pike, Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Building 10, Room B3C346, 10 Center Drive, Bethesda, MD 20892-1003, USA. pikev@mail.nih.gov.

DISCLAIMER

Although V.W.P. is employed by the US Government, views expressed in this article do not represent those of the US government.

This review is dedicated to friend and colleague, Professor Heinz H. Coenen, in recognition of his productive scientific research, service and leadership over his career within the field of PET radiotracer development, including the area covered by this review.

positron emitters. Almost all PET radiotracers are metabolized in vivo.[2,3] Defluorination of many ^{18}F-labeled PET radiotracers gives [^{18}F]fluoride ion, which binds avidly to bone. This bone uptake can become problematic for measuring radioactivity in nearby tissue and thereby can compromise the value of PET scans. This is particularly so for brain scans when radioactivity is taken up in the skull.[2,3] Therefore, radiotracers need to be designed to avoid radiodefluorination in vivo. Labeling at an aryl or heteroaryl carbon is a favored strategy for this purpose. Consequently, the field of PET radiotracer development has sought to develop a battery of methods for unrestricted introduction of [^{18}F]fluoride ion at aryl and heteroaryl groups in late-stage radiosynthesis.[4-9] This review specifically covers the growing utility of hypervalent aryliodine compounds as precursors for use in such methods. The coverage is intended to be illustrative rather than exhaustive and builds on a previous review of this area.[10]

Historically, in the 1980s, classical aryl nucleophilic substitution reactions (S_NAr)[11] became the first useful methods for labeling arenes with [^{18}F]fluoride ion, quickly supplanting the use of the earlier but very much less useful Wallach[12] and Balz-Schiemann reactions[13] (Figure 1). The introduction of the aminopolyether, Kryptofix 2.2.2 (K 2.2.2; 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8] hexacosane), as a phase transfer agent for [^{18}F]fluoride ion by the Jülich group greatly facilitated this advance.[14] Although classical S_NAr reactions with [^{18}F]fluoride ion have led to the development of many successful PET radiotracers, and continue to do so, there are limitations in the substrate scope of this method.[4-10] Generally, homoarene precursors must contain a good leaving group that is activated by an electron-withdrawing group in the ortho or para position. Displacement of a leaving group from the meta position is only possible with nitro as the activating group, and then only under quite forcing conditions to give moderate yields.[15] For heteroarenes, such as substituted pyridines, an activating group may not be required, but low yields may be obtained even under forcing conditions.[16-18] Therefore, a need to expand the range of arenes that might be labeled with [^{18}F]fluoride ion was long apparent during the early unfolding of the PET radiochemistry field. This was especially so, because many important radiotracers, such as [^{18}F]L-6-fluoro-DOPA, have electron-rich rings, and traditionally they had been labeled with electrophilic agents such as cyclotron-produced [^{18}F]fluorine or the derivative [^{18}F]acetyl hypofluorite, each of which is difficult to produce and use, with yet further limitations of low yield, very low molar activity, and low reaction efficiency.[19] Importantly, use of [^{18}F]fluoride ion enables radiotracers to be labeled at high no-carrier-added (NCA) molar activity, as is essential for a potentially large range of radiotracers targeting low-density binding sites (eg, receptors and enzymes) in vivo.[3]

In 1995, a quite long-standing paper by Van der Puy[20] piqued my interest because this described the conversion of a class of hypervalent iodine compounds, namely, diaryliodonium salts ($ArI^+Ar^1X^-$), into fluoroarenes by decomposition (X = BF_4) or by treatment with KF (X = BF_4, CF_3COO, TsO, or Cl) in either the solid or solution phase. Moderate yields were reported from the thermal decomposition of symmetrical tetrafluoroborate salts (Ar = Ar^1) in the presence of KF, not only for p-fluorochlorobenzene (39%) but also for fluorobenzene (85%), *m*-fluoronitrobenzene (38%), and *p*-fluoroanisole (44%) (Figure 2). These results for fluorination at electron-rich rings or in the meta position indicated the operation of a nonclassical S_NAr mechanism with important

potential for expanding chemistry with [^{18}F]fluoride ion to the synthesis of electron-rich [^{18}F]fluoroarenes and for the introduction of [^{18}F]fluoride ion into meta positions. Trial reactions of [^{18}F]fluoride ion with simple diaryliodonium salts in aprotic solvents using K 2.2.2 as the cryptand for potassium ion from added potassium carbonate base quickly affirmed this potential (Figure 3).[21] Over the last 2 decades or so, this early report has been followed with extensive development of approaches to using diaryliodonium salts and other hypervalent iodine compounds for radiofluorination.[10] Important motivations in this research have been to expand and improve the repertoire of methods for the syntheses of diverse hypervalent aryliodine precursors, to control reaction chemoselectivity between possible radiofluorination products, to increase the understanding of mechanism, and to extend the methodology to prepare useful labeling synthons and useful PET radiotracers. This review now proceeds to summarize these developments.

2 | DISCUSSION

2.1 | Some structural features of hypervalent aryliodine compounds

As a basis for subsequent discussion on reactivity and mechanism, it is valuable to highlight important structural features of classes of hypervalent aryliodine compounds, such as the diaryliodonium salts and aryliodonium ylides that will be featuring prominently in this review. The term *hypervalent* is used to indicate a compound of a main group element that contains more than an octet of electrons in the valence shell. These compounds are commonly named following the *N-X-L* nomenclature, where *N* denotes the number of electrons formally assigned to the central atom, *X* its elemental symbol, and *L* the number of bonded ligands. Diaryliodonium salts (denoted $ArI^{+}Ar^{1}X^{-}$) are 10-*I*-3 compounds and belong to a broader class of iodine(III) compounds, commonly known as λ^{3}-iodanes. They show approximately T-shaped geometry with one aryl ring occupying an axial position and the other an equatorial position, but with fast and easy exchange of aryl ring position occurring through a process known as Berry pseudorotation (Figure 4). Highly electronegative ligands (eg, halide) tend to occupy an approximately apical position. Apical bonding through the central iodine atom is often referred to as “hypervalent” bonding, or as 3-center 4-electron (3c-4e) bonding.

The crystal structures of some diaryliodonium salts have been published, including those of some chlorides,[22-24] and recently those of 2 fluorides.[25] In the solid state, many of these compounds, such as diphenyliodonium chloride, exist as anion-bridged dimers held together by secondary iodine-halogen bonds (Figure 5). Tetrameric structures have also been observed, as exemplified by the 2 reported examples of diaryliodonium fluorides.[25] Whereas diaryliodonium salts appear to be fully ionized in polar protic solvents such as water, they may also exist as oligomers in organic solution. Such oligomers have been detected with mass spectrometry.[24]

Aryliodonium ylides are compounds in which the central iodine(III) atom carries a formal positive charge and is attached directly to an anionic site. In this review, aryliodonium ylides are denoted as $ArI^{+}—^{-}CX_2$ where X is an electron-withdrawing substituent, such as an acyl substituent. Iodonium ylides are also found to be T-shaped molecules with C—I—C angles close to 90°, indicating the ylidic C—I bond to be zwitterionic (Figure 5).[26] The CX_2 moiety

may be cyclic and if so may impart useful stability to the ylide. Cyclic ylides are of primary interest later in this review.

(Diacyloxyiodo)arenes ($ArI(RCO_2)_2$), such as the commercially available (diacetoxyiodo)arene [$PhI(OAc)_2$, DIB, PID, or PIDA], show a T-shaped geometry with the phenyl ring occupying an equatorial position and the 2 acetoxy groups the axial positions in a trigonal-bipyramidal arrangement of bonds and lone pairs around the central iodine atom.[27] The strong bonds between the central iodine atom to a carbon atom of the phenyl group and to one oxygen atom of each carboxylate group plus 2 secondary bonds to the 2 remaining oxygen atoms give an overall pentagonal-planar bonding arrangement (Figure 5). The simple trifluoroacetoxy analog [$PhI(CF_3CO_2)_2$; PIFA] exists as a bridged dimer in the solid state.[28]

2.2 | Synthesis of aryliodine(III) precursors for radiofluorination

For the development and expansion of the utility of any new radiofluorination methodology, precursors need to be readily accessible through effective and versatile synthetic methods. Ideally, these precursors should also be adequately stable for prolonged storage. Here, some of the main routes to aryliodine(III) precursors are surveyed.

2.2.1 | (Diacyloxyiodo)arenes—

(Diacyloxyiodo)arenes feature prominently as precursors or as nonisolated intermediates to other hypervalent iodine(III) compounds, particularly diaryliodonium salts[29] and aryliodonium ylides.[30] Recently, they have also been investigated as substrates for radiofluorination.[31] Some (diacyloxyiodo)arenes are commercially available, such as PIDA and PIFA. Numerous methods are available for the synthesis of (diacyloxyiodo)arenes.[32] These methods are of 2 main types: (1) oxidation of iodoarenes in the presence of the desired carboxylic acid or (2) ligand exchange in PIDA with the desired acid. So far, the oxidation route has been the most used for preparing (diacyloxyiodo)arenes as substrates for radiofluorination[31] or as intermediates for other radiofluorination precursors (Figure 6).[33] Peracetic acid,[31,34,35] sodium periodate,[36,37] or sodium perborate,[31,37,38] each in acetic acid, have been favored as oxidants, and they have given numerous diversely substituted (diacyloxyiodo)arenes, including (diacyloxyiodo)heteroarenes, as stable crystalline solids in moderate to high yields. In a few cases, where the substituent is strongly electron withdrawing, a better yield may be obtained by making the trifluoroacetate with Oxone ($KHSO_5 \cdot 0.5KHSO_4 \cdot 0.5K_2SO_4$) in trifluoroacetic acid as oxidant followed by ligand exchange with acetic acid to access the diacetate.[31]

Recently, a method has been developed for synthesizing (diacetoxyiodo)arenes in the absence of protic acids.[39] This method is based on treating a substituted iodoarene with Selectfluor (*N*-chloromethyl-*N*′-fluoro-triethylenediammonium bis(tetrafluoroborate); F-TEDA-BF_4) and TMSOAc (Figure 6). This method is applicable to electron-rich and electron-poor iodoarenes and tolerates both acid- and base-sensitive functional groups.

2.2.2 | Diaryliodonium salts—

Diaryliodonium salts are generally stable to air and moisture and may be prepared on a multigram scale.[39] Several diaryliodonium salts are now commercially available. Our laboratory's experience is that diaryliodonium salts can

be stored for months, even years, in the cold and dark without decomposition. Another laboratory has similarly reported a highly functionalized iodonium salt to be stable for 18 months at room temperature under argon,[38] and yet another reports a diaryliodonium salt precursor to be stable in a crimp-sealed amber vial at 5°C to 8°C under atmospheric conditions for at least 2 years.[40] Salts with paired electron-rich rings may however show some storage instability. For example, 4-anisyl(2-thienyl) iodonium bromide decomposes within 2 weeks under ambient conditions.[41]

Methods for synthesizing diaryliodonium salts abound and have been extensively reviewed.[29,42] Only some of the most popular and useful methods are mentioned here by way of illustration.

From the perspective of using diaryliodonium salts for radiotracer synthesis, unsymmetrical salts ($Ar \neq Ar^1$) are invariably preferred over symmetrical salts. One reason is that a simple cheap arene can serve as the source of one ring partner. Another reason is that the iodoarene that is extruded from a chemoselective radiofluorination reaction can usually be separated readily with high-performance liquid chromatography (HPLC) from the desired radiofluorination product. Unsymmetrical salts for radiofluorination are designed so that one aryl ring serves as the target for radiofluorination while the other ring serves as an electron-rich “spectator ring” that is relatively much less prone to radiofluorination (see below). As a formal anion, tosylate or another organic anion is often preferred over halide to confer good solubility of the salt in the organic solvent to be used for radiofluorination (eg, dimethylformamide [DMF] and acetonitrile [MeCN]). Simple metathesis reactions can be used to replace the anion with the one that is desired.[37,43-47] Nonetheless, halide anions have sometimes been found preferable for high radiofluorination yields.

Unsymmetrical diaryliodonium salts are now relatively easy to prepare along various pathways (Figure 7). A typical synthesis of an unsymmetrical salt involves oxidation of an iodoarene to a λ^3-iodane, either a (diacyloxyiodo)arene or a [hydroxy(tosyloxy)iodo]arene (HTIA), followed by ligand exchange with an electron-rich arene (eg, mesitylene,[35] 1,3,5-trimethoxybenzene,[33] anisole,[33] or thiophene),[33,48] or a more nucleophilic arylating agent (eg, arylsilane,[49,50] arylborate,[51] or arylstannane[52]). The simple λ^3-iodane, [hydroxy(tosyloxy)iodo]benzene (PhI(OH)OTs),[53] commonly known as Koser's reagent or HTIB, is stable and commercially available. HTIAs, including Koser's reagent, may be converted into congeners through ligand exchange with a substituted iodoarene, ie, $ArI(OH)OTs + Ar^1I \rightarrow Ar^1I(OH)OTs + ArI$.[45,53] Direct mild syntheses of HTIAs from iodine and a substituted arene or from an iodoarene have also been reported.[52-54] A (diacyloxyiodo)arene or an HTIA may be used as generated in situ, even in the presence of the Brønsted acid used for its synthesis.[33,35] If isolated, these hypervalent reagents may be used in either the presence[44] or absence of a Brønsted acid.[55,56] The absence of a Brønsted acid allows a diaryliodonium salt having 1 or more acid-labile protecting groups, such as a Boc or ester group, to be prepared.[55,56] Nevertheless, reactions of (diacyloxyiodo)arenes or HTIAs with electron-rich arenes, such as mesitylene, 1,3,5-trimethoxybenzene, anisole, or thiophene, do usually require acidic conditions. Clearly, regioselectivity cannot be an issue for reactions with the 1,3,5-tri-substituted arenes. The reactions with anisole and thiophene are found to be remarkably regioselective, for the 4-position in anisole and the

2-position in thiophene. The reactions with silanes, borates, and stannanes confer excellent regioselectivity under milder often acid-free conditions. Use of aryl borates is especially attractive because they are quite readily accessible, stable, and nontoxic. Arylstannanes are also often used as they may usually be prepared from the corresponding iodides. Yields of diaryliodonium salts from the metallated arenes are usually moderate but useful.

Methods have been developed recently for converting an arene-iodoarene pair into an unsymmetrical iodonium salt under mild conditions, where either aryl partner may be electron rich or electron deficient. These methods typically use *m*-chloroperoxybenzoic acid (*m*CPBA) as oxidant, in the presence of triflic acid,[57,58] toluenesulfonic acid,[59] or BF_3OEt_2.[60] A wide range of substituents in the aryl partners is tolerated. These substituents include Me,[57-60] 1,3,5-tri-Me,[58,59] F,[58,60] Cl,[57,58] Br,[58,60] I,[57,60] CF_3,[58,60] NO_2,[57,58] MeO,[57-60] CO_2H,[58] and CHO.[60] This method has also been adapted for the single-pot preparation of N-heteroaryliodonium salts.[61] The salts were isolated in protonated form but could then be deprotonated on basic alumina eluted with dichloromethane (DCM)/methanol. Recently, *m*CPBA in triflic acid has been found effective for the 1-pot synthesis of a wide range of substituted aryl(2,4,6-trimethoxyphenyl)iodonium triflates from iodoarenes.[62] Trifluoroacetates have been prepared similarly by use of trifluoroacetic acid instead of triflic acid.[63]

A recent method for the synthesis of acid-sensitive diaryliodonium salts uses a Lewis acid rather than a Brønsted acid (Figure 7).[39] In this method, a (diacetoxyiodo)arene is generated from an iodoarene with Selectfluor in the presence of TMSOAc and then treated with a metal aryltrifluoroborate plus TMSOTf. This method has provided several highly functionalized diaryliodonium triflates in moderate to high yields. Functionalities in these salts have included *N*-succinimidyl, carboxylate esters, protected amino acid side chains, or polyethylene glycol chains.

Of further note is an efficient 1-pot pathway developed for the preparation of aryl(substituted-isoquinolinyl) iodonium triflates based on treating mesoionic carbene silver complexes with the hypervalent iodine reagent, $PhI(Py')_2(OTf)_2$ where Py′ is a substituted pyridine (Figure 8).[64] The method displayed tolerance for a wide variety of substituents (eg, alkyl, aryl, halogen, OMe, and ester) and gave 40% to 94%.yields.

Symmetrical salts are occasionally useful precursors. An advantage conferred by a symmetrical salt precursor is that only 1 ^{18}F-labeled arene can be produced from the radiofluorination. This can be especially advantageous for the more difficult labeling of electron-rich arenes. For example [^{18}F]4-fluoroanisole can be prepared in good yield from bis(4-anisyl)iodonium trifluoroacetate,[21] and likewise [^{18}F]2-fluoroanisole from bis(2-anisyl)iodonium chloride.[65] Simple ^{18}F-labeling synthons may be prepared from protected symmetrical diaryliodonium salts, as exemplified by a synthesis of [^{18}F]4-fluorophenol.[47]

Symmetrical salts may be accessed by a variety of methods.[29,42] Very early methods typically used harsh acidic conditions,[43,66] such as treatment of an arene with $NaIO_4/I_2$ in concentrated sulfuric acid.[43] Most of the currently useful methods for preparing symmetrical salts are special cases of the methods for preparing unsymmetrical salts, as already

summarized. In addition, symmetrical diaryliodonium triflates have been prepared simply by treating arenes with iodine and *m*CPBA in triflic acid.[58]

2.2.3 | Aryliodonium ylides—Several methods exist for preparing iodonium ylides.[30] For the purpose of radiofluorination, stable crystalline spirocyclic aryliodonium ylides have been prepared readily from (diacetoxyiodo)arenes by treatment with spirocyclic derivatives of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) in 10% sodium bicarbonate ethanol (Figure 9).[65] This method is highly versatile with respect to both the aryl partner and the spirocyclic derivative. Open-ring analogs may also be prepared. A simple 1-pot 2-step procedure has been described for preparing aryliodonium ylides from the respective iodoarenes.[68] Iodoarenes are first oxidized with *m*CPBA in DCM and then treated with Meldrum's acid and KOH. This method has also been applied to prepare various spirocyclic ylides.[67] In general, low to moderate yields are obtained (Figure 9).

In summary, methods for the synthesis of hypervalent aryliodine compounds for radiofluorination are relatively cheap, numerous, and versatile for the incorporation of desired functionality. Therefore, the syntheses of these compounds are no longer a major impediment to their use in radiofluorination. Considering their high reactivities, most of these compounds show remarkably adequate storage stability.

2.3 | Practical approaches to radiofluorination

All approaches to radiofluorination begin with isolation of [^{18}F]fluoride ion from proton-irradiated [^{18}O]water (Figure 10). Typically, this is achieved by evaporation of the [^{18}O]water in the presence of base (eg, K_2CO_3-K 2.2.2) or by entrapment of the [^{18}F]fluoride ion on a quaternary ammonium ion exchange resin followed by elution with a solution of base or base containing a phase transfer agent (eg, K 2.2.2 or 18-crown-6). The [^{18}F]fluoride ion can then be taken to dryness with 2 or more cycles of MeCN addition and evaporation of the generated azeotrope.

Conventionally, the radiofluorination of a hypervalent aryliodine precursor is based on a batch reaction of $^{18}F^-$-K^+-K 2.2.2 complex with a small amount of precursor (often 1-15 mg) in a small volume (0.5-1.0 mL) of a polar aprotic solvent within a septum-sealed glass or glassy carbon vessel. In some instances, other bulky cations are used for solubilization of the [^{18}F]fluoride ion, such as K^+-18-crown-6, Cs^+, or R_4N^+ (R = Et or *n*Bu). Typically, the cation is introduced as a carbonate or bicarbonate salt. This approach is readily automated for radiotracer production and has been performed in custom-built or commercial radiosynthesis devices.[38,40,55,69-71]

Other approaches have also been explored for performing and studying the radiofluorination of diaryliodonium salts. One approach is described as “minimalist” as it uses neither the base nor other additives that are introduced in the conventional batch approach (Figure 10).[72] In this approach, the [^{18}F]fluoride ion is first trapped on an anion exchange resin, which is then flushed with methanol, followed by the precursor iodonium salt in methanol. The obtained solution of substrate and [^{18}F]fluoride ion is then evaporated, taken up in the reaction solvent, and heated. This type of procedure reduces the number of operational step, saves processing time, and is compatible with base-sensitive precursors and products.

The reactivity of diaryliodonium salts towards [^{18}F] fluoride ion is such that reactions proceed to useful yields in solvents with low water content.[56,65,73] Some salts are sufficiently reactive in solvent with high (28%) water content.[74] As in the minimalist approach, this can avoid the lengthy and tedious need to dry the aqueous [^{18}F]fluoride ion obtained from the cyclotron target.

Use of a commercial microfluidic apparatus (NanoTek, Advion), which incorporates a capillary silica tube as a microreactor, permits several radiofluorination reactions to be performed in sequence on a single day under highly controlled conditions of reagent concentration, time, and temperature (Figure 11). The microreactor is fed at constant rates from 2 reservoirs, one containing a precursor solution and the other containing the [^{18}F]fluoride ion reagent solution. As a result, the study of reaction kinetics and even the derivation of Arrhenius activation energies become feasible.[65] The microfluidic approach has more recently been extended to use hypervalent substrates for the synthesis of labeling synthons and for the routine production of a PET radiotracer, [^{18}F]FPEB.[75]

A pyrolytic approach has been developed specifically to the radiofluorination of diaryliodonium salts. The [^{18}F]fluoride salt is generated from a nonfluoride precursor in a solvent, such as MeCN, followed by drying and then thermolysis in a predominantly nonpolar aprotic solvent such as benzene, 10% MeCN in toluene, or toluene (Figure 12).[38,76] This approach has been incorporated successfully into commercially available automated radiosynthesis platforms such as the Synthera and TRACERlab modules.

The copper-mediated radiofluorination of aryl(mesityl)iodonium salts has recently been adapted to allow radiofluorination of C—H groups in electron-rich aryl and heteroarenes in situ.[77] The arene is treated directly with [hydroxy(tosyloxy)iodo]mesitylene and TMSOTf in DCM to form the aryl(mesityl)iodonium salt in situ over several hours, which is then subjected to Cu-mediated radiofluorination with [^{18}F]fluoride ion. This approach has allowed late-stage radiofluorination of toluenes, anisoles, anilines, pyrroles, and thiophenes in mostly good to high yields.

2.4 | Mechanisms of radiofluorination

2.4.1 | Diaryliodonium salts: “copper free”—The mechanism of the reactions of diaryliodonium salts with [^{18}F]fluoride ion matches that of many other nucleophiles.[78,79] Reactions proceed through ligand exchange with the nucleophile followed by “ligand coupling” and reductive elimination of iodoarene (Figure 13). For unsymmetrical iodonium salts, either iodoarene may be eliminated and either arylated nucleophile may be produced. The ratio of the arylated nucleophiles is termed the “chemoselectivity” of the process. For diaryliodonium salts that do not carry ortho alkyl substituents, radiofluorination of the most electron-deficient aryl ring is favored.[36,80,81] For unsymmetrical salts that carry 1 or more ortho alkyl substituents, the ortho-substituted ring may be radiofluorinated in preference to a more electron-deficient ring.[65,80] This reactivity behavior had been seen in analogous reactions of diaryliodonium salts with heavier halide ions and had been dubbed the “ortho effect.”[82,83] The ortho effect is one feature that distinguishes these reactions from classical S_NAr reactions. The abilities of ortho substitution patterns to impart an ortho effect in

radiofluorination reactions have been ranked as 2,6-di-Me > 2,4,6-tri-Me > Br > Me > Et ≈ *i*-Pr > H > OMe.[65]

Computational studies have been performed with the aim of understanding both chemoselectivity and the ortho effect in the radiofluorination of diaryliodonium salts.[25,80,84,85] An early computational and experimental study of the radiofluorination of heteroaryl(phenyl) iodonium salts came to the important conclusion that chemoselectivity was dictated by the difference in energy of the 2 possible transition states and not by the difference in the 2 ground state energies represented by axial-equatorial switching of the 2 aryl groups. Subsequent computational studies have reinforced this conclusion. Hill and Holland[85] performed extensive density functional theory computations on para-substituted phenyl(aryl)iodonium salts as precursors for radiofluorination and described the 2 possible transition states in terms of bond distances for the central iodine and fluorine to each other and to aryl carbons, plus the distribution of charge between these 4 atoms. Linear correlations with positive slope were found between Hammett constants ($\sigma_{m,p}$) and calculated transition state energy differences, indicating that electron-withdrawing substituents promote radiofluorination at the ipso aryl ring. Similar findings were found for meta-substituted salts and thus accord with experimental findings.[34] In this regard, Ross et al measured a linear correlation between the rate of radiofluorination of aryl(2-thienyl)iodonium bromides and Hammett constant (σ) with a positive slope.[36]

High-level computations have described geometries for the pair of transition states for the reaction of fluoride ion with a phenyl(2-tolyl)iodonium salt, each of which has [^{18}F]fluoride ion loosely bonded to the hypervalent iodine and to the ipso carbon of an equatorial ring (Figure 14).[25] The 2 transition states mainly differ by which aryl ring is in the equatorial position. A significant difference is that the fluorine-to-aryl carbon distance is slightly longer in the lower-energy transition state. The 2 transition states rapidly interconvert through a low-energy barrier.[25] Therefore, in accord with the Curtin-Hammett principle,[86] chemoselectivity is dictated by the size of this energy barrier and not by ground state or product state energy differences. In the phenyl(2-tolyl) iodonium salt example, the difference in transition state energies is computed to be 0.9 kcal/mol, which predicts an ortho effect and a chemoselectivity of about 2 in favor of the formation of 2-fluorotoluene over fluorobenzene. This agrees well with earlier experimental determination (0.63 kcal/mol).[65]

Experimentally, it is found that chemoselectivities are fixed and highly repeatable under any set of reaction conditions. Therefore, it is possible to design unsymmetrical diaryliodonium salts that are highly chemoselective for undergoing radiofluorination to the desired [^{18}F] fluoroarene. In these salts, one of the aryl rings is more electron rich and much less susceptible to radiofluorination than the other. As mentioned earlier, these aryl groups are termed *spectator groups*, and often in practice they are phenyl, 4-tolyl, 4-anisyl, 2,4,6-trimethoxyphenyl, or 2-thienyl, but not mesityl because of the ortho effect.

Various hypotheses have been put forward for the ortho effect, mostly based on steric and electronic considerations in ground state structures.[82,83] Recently, computational studies suggest that the ortho effect may be ascribed to differences in electrostatic interactions

between each of the 2 possible transition states.[25] Substituents other than alkyl, such as methoxy, may not impart the ortho effect.[25]

Yields from the radiofluorinations of some diaryliodonium salts have shown dependence on salt anion.[36,87] Such effects are not easily rationalized but may point to a role in the reaction pathway for oligomeric salts held together by anion bridges, where the anion must be displaced to allow radiofluorination to proceed.[25] Experimental[24,88] and computational studies[25] support the existence of diaryliodonium salts oligomers in organic solution. Other factors giving rise to anion dependence are also possible, such as perhaps small differences in salt purities.

Generally, the radiofluorinations of diaryliodonium salts have been assumed to be regiospecific. However, the thermal decompositions of 5-methoxy-substituted [2.2]paracyclophane(4-anisyl)iodonium fluoride was found to give some 3-fluoroanisole in addition to the expected 4-fluoroanisole (Figure 15).[89] The 7-methoxy analog also gave a mixture of 2 fluoro isomers. These results might be explained by the operation of an aryne mechanism due to electronic and steric effects.

A free radical scavenger, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl), has been found beneficial in many but not all radiofluorinations of diaryliodonium salts.[24,34,65,69,90] TEMPO may be acting to inhibit thermal or photochemical radical decomposition of diaryliodonium salt precursor, depending on salt structure.

2.4.2 | Diaryliodonium salts: copper-mediated—The inclusion of a copper salt in the fluorination of a diaryliodonium salt has a profound effect on reaction mechanism and outcome.[91,92] The ortho effect may be abolished, and the fluoride ion may tend to go to the more electron-deficient ring. In the radiofluorination of aryl(mesityl)iodonium salts ($ArI^+(Mes)X^-$), yield and chemoselectivity for [^{18}F]fluoroarene ($Ar^{18}F$) versus [^{18}F]mesityl fluoride ($Mes^{18}F$) have been found to depend strongly on the selected Cu precatalyst and solvent, under some conditions strongly favoring production of the [^{18}F]fluoroarene and under others [^{18}F] mesityl fluoride. The use of stable and commercially available $(MeCN)_4CuOTf$ in DMF at 85°C for 20 minutes gave high chemoselectivity for $Ar^{18}F$ versus $Mes^{18}F$ for a wide range of Ar groups, including electron-rich groups, such as 4-anisyl or 2,4,6-trimethoxyphenyl. Thus, under these conditions, a mesityl group serves as a very effective spectator group, giving generally very high chemoselectivity for $Ar^{18}F$. Yields vary from low to high depending on the substitution pattern in the aryl ring. Tetrafluoroborate was the favored salt anion for optimal yield.

Detailed theoretical and experimental investigations[41,92] suggest that the mechanism of these reactions involves a Cu(I/III) catalytic cycle (Figure 16). Experimental evidence suggests that where the catalyst is introduced as a Cu(II) species (eg, $Cu(OTf)_2$), this is first reduced to a Cu(I) species by DMF. Oxidation of a Cu(I) species by the $MesI^+Ar$ species is then considered to be the rate-limiting step on the path to producing the [^{18}F] fluoroarene.

2.4.3 | Aryliodonium ylides—The radiofluorination of aryliodonium ylides probably proceeds through a mechanism like that of the radiofluorination of diaryliodonium salts, except that the auxiliary ligand is not considered to be susceptible to radiofluorination (Figure 17).[85,93] Therefore, there is no chemoselectivity consideration. Labeling reactions have been performed with low amounts of ylide (eg, 2 mg) in DMF with Et_4NHCO_3 as base at 120°C for 10 minutes and have given generally low to moderate yields on a wide range of aryl and heteroaryliodonium ylides.[67] Simple arenes with electron-rich rings have been obtained with this method in moderate yield, such as [^{18}F] fluoromesitylene (45%). Labeling in the meta position was also moderately successful to produce, for example, [^{18}F]3-fluoropyridine (65%) and [^{18}F]3-fluorotrifluoromethyl benzene (71%).

One study has observed the formation of regioisomers in the radiofluorination of electron-rich ylides, such as ylides of 4-iodoanisole and 4-benzyloxyiodobenzene derived from Meldrum's acid.[92] The [^{18}F]4-fluoroarene and [^{18}F]3-fluoroarene products were obtained in a ratio of 3:1 from the 4-anisyliodonium ylide and 20:11 from the 4-benzyloxyphenyliodonium ylide. Lack of regioselectivity has also been observed for the radiofluorination of more elaborate but structurally related ylides designed as precursors to radiotracers.[94] These findings indicate involvement of an aryne mechanism for electron-rich aryliodonium ylides, as has already been alluded to for the radiofluorinations of highly electron-rich diaryliodonium salts.

2.4.4 | Other classes of hypervalent aryliodine compound—(Diacetoxyiodo)arenes undergo radiofluorination with [^{18}F]fluoride ion.[31] One mechanism for this reaction likely involves ligand exchange. Thus, quantum chemical calculations predict that formation of [(acetoxyfluoro) iodo]benzene from (diacetoxyiodo)benzene is thermodynamically favored with a low-energy barrier of 16.4 kcal/mol and that onward conversion of this intermediate into fluorobenzene has a free energy of activation (ΔG) of 33.8 kcal/mol.

Although iodylarenes ($ArIO_2$) are hypervalent aryliodine compounds, they only undergo radiofluorination with [^{18}F]fluoride ion in high yields when the aryl ring is strongly activated with an ortho- or para-electron-withdrawing group,[95] in a manner suggestive of a classical S_NAr mechanism.

2.5 | Radiosynthesis of labeling synthons

Tracer molecules that are not readily amenable to late-stage labeling with [^{18}F]fluoride ion may be amenable to labeling with synthons derived from [^{18}F]fluoride ion. Popular synthons are electrophilic agents, such as ^{18}F-labeled aryl halides, benzaldehydes, benzyl halides, benzyl azides, and aryl carboxylic acid esters.[96,97] Major applications of such synthons are in the labeling of peptides, proteins, and other macromolecules.[98] They may also be used for labeling small molecules. Many of these synthons may be accessed through classical S_NAr reactions with [^{18}F]fluoride ion, but improved methods are always sought, as well as access to all regioisomers.

2.5.1 | From diaryliodonium salts—Table 1 lists many of the labeling synthons that have been prepared from diaryliodonium salts. Overall, moderate to good yields of the listed

synthons have been obtained from rapid reactions (1-45 min) at low to moderately high temperatures (80°C-200°C). Not all the listed examples have been isolated for application.

[^{18}F]Fluorohalobenzenes have been accessed rapidly in moderate to good yields (Table 1, entries 1-10).[41,65,99-102] Notably, among these labeling synthons, [^{18}F]4-fluoroiodobenzene (entries 6-10)[100] can be prepared efficiently and has been applied to the radiosynthesis of several candidate radiotracers through efficient transition metal–mediated coupling reactions. These radiotracers include ^{18}F-labeled nucleosides,[103] a D_4 receptor ligand,[101] and a cyclooxygenase 2 inhibitor[104] (Figure 18).

[^{18}F]Fluorobenzaldehydes are well known to be useful labeling synthons, especially for multistep syntheses leading to labeled amino acids.[97] Only the 2- and 4-regioisomers are readily accessible through classical S_NAr reactions, whereas not only the 4-regioisomer but also the 3-regioisomer can be obtained through the radiofluorination of diaryliodonium salts in good yields (Table 1, entries 11-17).[46,72,105,106] It is notable that the formyl group resists possible oxidation during the syntheses of the salts and their radiofluorination reactions.

All regioisomers of the [^{18}F]fluorobenzyl chlorides,[46] bromides,[46] and azides[44] have been obtained in moderate yields from single-step radiofluorination reactions under microfluidic conditions using short residence times (≤4 min) at quite high temperatures (160°C-200°C) (Table 1, entries 18-26). In the syntheses of the [^{18}F] fluorobenzyl halides, potential competing displacement of the labile halogen was not a confounding issue. These single-step radiosyntheses are attractive compared with conventional multistep syntheses based on S_NAr. [^{18}F]3-Fluorobenzyl bromide has also been prepared from [^{18}F]3-fluorobenzaldehyde, itself prepared from a diaryliodonium salt, and applied to label an anticancer agent, lapatinib, with ^{18}F (Figure 18).[107] The [^{18}F] fluorobenzyl azides have utility for labeling macromolecules through “click reactions” with alkyne derivatives,[108] as exemplified by the labeling of proteins[109] and oligonucleotides[110] (Figure 18).

[^{18}F]Fluorophenoxy compounds are usually inaccessible through simple single-step S_NAr reactions because of unfavorable aryl ring electronics. [^{18}F]4-Fluorophenol is a useful labeling synthon for such compounds.[97] [^{18}F]4-Fluorophenol has been prepared in 2 steps in 34% to 36% overall yield through the radiofluorination of 4-benzyloxyphenyl(2-thienyl)iodonium bromide in DMF at 130°C for 5 minutes, followed by almost quantitative removal of the benzyl group with ammonium formate in methanol in the presence of palladium black (Table 1, entry 27).[37] Use of a bis(benzyloxyphenyl)iodonium tosylate precursor and microwave heating improved the yield of [^{18}F]4-fluorophenol to 52%. TEMPO did not improve the yield of this reaction (entry 28).[47]

[^{18}F]Fluorobenzoic acid esters can be useful labeling synthons, as exemplified by [^{18}F]*N*-succinimidyl 4-fluorobenzoate, which is widely used for labeling peptides and proteins.[97] The conventional method for synthesizing [^{18}F]*N*-succinimidyl 4-fluorobenzoate, based on initial S_NAr on the triflate salt of ethyl 4-(trimethylammonium) benzoate, is quite high yielding (38%) but takes 3 steps over about an hour.[111] [^{18}F]*N*-Succinimidyl 4-fluorobenzoate has been prepared in a single step from an aryl(2-thienyl)iodonium trifluoroacetate in 13% to 23% yields in shorter synthesis times (Table 1, entry 29).[112,113]

[^{18}F]Fluorohalopyridines are potentially useful labeling agents as they should, for example, participate in coupling chemistry like that of the [^{18}F]fluorohalobenzenes. Several [^{18}F]fluorohalopyridines have been synthesized in a microfluidic apparatus (NanoTek, Advion) from 4-anisyl(halopyridyl)iodonium tosylates in DMF at temperatures in the range of 100°C to 180°C with microreactor residence times of about 3 to 4 minutes.[112] Labeling yields ranged from 53% to 60% for [^{18}F]2-fluorohalopyridines (Table 1, entries 30-32) and from 28% to 36% for [^{18}F]3-fluorohalopyridines (entries 33-36).

2.5.2 | From aryliodonium ylides—The use of aryliodonium ylides to prepare labeling synthons is quite recent, and there are consequently relatively few examples. Nonetheless, the known examples generally show moderate to good yields from rapid reactions at quite low temperatures (Table 2).

Thus, [^{18}F]3-fluorobromobenzene has been prepared in 72% yield through radiofluorination of a spiroadamantyl aryliodonium ylide (Table 2, entry 1).[115] This labeling synthon, prepared in this manner, has been coupled to a cyclic amide in the presence of copper(I) iodide to give a candidate AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor radiotracer in 72% yield (Figure 18).[115] After work-up and purification, the final overall yield of the radiotracer was about 15%. [^{18}F]4-Fluoroiodobenzene has been obtained from the radiofluorination of an ylide prepared from Meldrum's acid, namely, (2,2-dimethyl-5,7-dioxo-1,3-dioxocan-6-yl) (4-iodophenyl)iodonium, in dimethyl sulfoxide (DMSO) at 110°C in the presence of *t*-butylammonium bicarbonate in 70% yield (entry 2). This yield is quite similar to that obtained from a symmetrical diaryliodonium salt (60%) (Table 1, entry 9)[99] and is appreciably higher than that from an unsymmetrical diaryliodonium salt (40%) (Table 1, entry 8).[101] [^{18}F]4-Fluoroiodobenzene prepared from the ylide precursor has been used in a multistep radiosynthesis of a candidate D_4 receptor radiotracer, known as [^{18}F]FAUC 316 (Figure 18).[101] This radiotracer was obtained for clinical use in 10% yield after 80 minutes of preparation time.

Spirocyclopentyl aryliodonium ylides have been used to prepare several useful labeling synthons. [^{18}F]3-Fluorobenzaldehyde has been prepared in variable yield (7%–52%) yield (Table 2, entry 3).[116] [^{18}F]3-Fluorobenzyl azide (entry 4)[117] and [^{18}F]4-fluorobenzyl azide[67,75,117] (entries 5-7) have been prepared in good nonisolated yields. Isolated yields for the 4-fluoro isomers ranged from low to moderate (entries 5-7). Other labeling synthons that carry reactive substituents at a benzyl position have also been prepared, including [^{18}F]3-fluorobenzoic acid methyl ester (77%) (entry 8).[67] [^{18}F]2-(3-Fluorophenyl) ethylamine has also been prepared in good yield (~70%) for labeling enzyme inhibitors (entry 9).[118]

Long-chain alkyl azido labeling synthons have been prepared through the radiofluorinations of “ortho-oxygen-stabilized iodonium derivatives” (Figure 19) in impressively high yields (Table 2, entries 10 and 11). In ortho-oxygen-stabilized iodonium derivatives, secondary bonding from the oxygen of a pendant ortho aliphatic substituent to the iodonium center provides extra thermal stability, which may account for the high radiofluorination yields. These labeling synthons were successfully applied to labeling single-stranded DNA aptamers (Figure 18).[117,119]

2.6 | Radiosynthesis of radiotracers

Although hypervalent aryliodine precursors have shown utility for preparing a wide variety of labeling synthons and these synthons have been used to meet challenging radiosynthesis requirements, the ideal is for radiotracers to be labeled at a late stage, preferably in a single step or a single labeling step followed by a single deprotection step. The utility of hypervalent aryliodine precursors for meeting this ideal is now summarized.

2.6.1 | From diaryliodonium salts (copper free)—Translocator protein (TSPO) 18 kDa is a recognized biomarker for neuroinflammation. Extensive efforts have been made to produce high-performing radiotracers for imaging TSPO 18 kDa. [^{18}F]FDAA1106, a candidate radiotracer for imaging this target, was the first radiotracer to be produced from a diaryliodonium salt.[120] Radiofluorination of crude 4-anisyl(aryl)iodonium tosylate in DMSO at 80°C for 20 minutes gave [^{18}F]FDAA1106 in moderate yield (46%) (Table 3, entry 1). In this early study, the iodonium salt was used in crude form because of concern about its stability. [^{18}F]4-Fluoroanisole was a significant by-product (19%). In this case, a classical S_NAr reaction would not have been feasible for the radiosynthesis of [^{18}F]FDAA1106 because there is no strong electron-withdrawing substituent in the ortho or para position to the fluoro substituent. The other radiotracer examples shown in Table 3 are also structures for which classical S_NAr would be either inapplicable or, at best, poorly applicable for ^{18}F labeling.

[^{18}F]MTEB and a diarylalkyne congener 3-fluoro-5-(2-(2-[^{18}F](fluoromethyl)-thiazol-4-yl)ethynyl)benzonitrile ([^{18}F]SP203) are high-performing radiotracers for imaging brain metabotropic glutamate receptor subtype 5 (mGlu5). [^{18}F]MTEB has been obtained in 20% yield through the radiofluorination of a 4-anisyl(aryl)iodonium tosylate precursor in DMF at 160°C under microwave irradiation for 4 minutes in the presence of TEMPO (Table 3, entry 2).[69] [^{18}F]SP203 has been obtained similarly from the corresponding 4-anisyl(aryl)iodonium tosylate in 33% yield (entry 3).[69] On the basis of experiments in a microfluidic apparatus, the chemoselectivities of the radiofluorination reactions for the desired radiotracers over [^{18}F]4-fluoroanisole are exceptionally high (>44), and much higher than from precursors having a phenyl spectator group. TEMPO was beneficial for improved yield in both microreactor syntheses and batch syntheses. The precursors were found to be stable for several months when stored in a refrigerator.

Synaptic vesicle glycoprotein 2A is a biomarker for synaptic loss in epilepsy and Alzheimer's disease. [^{18}F] UCB-H has been developed as the first radiotracer for imaging brain synaptic vesicle glycoprotein 2A in vivo.[40] The original production of this radiotracer had involved several steps performed over 2 hours, starting with [^{18}F]3-fluoroisonicotinaldehyde as labeling synthon, giving less than 15% yield.[40] Subsequently, a much improved single-step method has been devised for the preparation of [^{18}F]UCB-H based on radiofluorination of a 4-anisyl(3-pyridyl)iodonium tosylate in MeCN at 125°C for 10 minutes in the presence of TEMPO.[40] [^{18}F]UCB-H was produced regularly for clinical use according to this method in 34 ± 2% yield and with very high molar activity (815 GBq/μmol) (Table 3, entry 4). The difficulty of radiofluorinations in the 3-position of pyridyl compounds with classical S_NAr reactions is well known.[16] This radiosynthesis

exemplifies the utility of aryl(3-pyridyl) iodonium salts for introducing [^{18}F]fluoride ion into the 3-position of pyridyl substrates. In this work, the authors stressed the need to obtain the iodonium salt in fully deprotonated form (through the use of a basic alumina), as otherwise radiochemical yields were substantially decreased. Crystallization of the salt was important for purification and for ensuring good solubility.

The secondary arylamine, [^{18}F]4-(6-fluorobenzo[*d*] thiazol-2-yl)-*N*-methylaniline ([^{18}F]6-FBT), is a candidate radiotracer for imaging brain *β*-amyloid plaques in Alzheimer's disease. Two-step syntheses of [^{18}F]6-FBT from 5 *N*-Boc-protected diaryliodonium tosylates with different spectator groups have been compared.[56] Each salt was radiofluorinated in MeCN in the presence of TEMPO at 130°C for 10 minutes. [^{18}F]*N*-Boc-protected-6-FBT was produced from the salts with 2-Thi, 3-Thi, 4-Tol, Ph, or 4-An as spectator group in 34%, 60%, 27%, 24%, and 19% yield, respectively. Deprotection with 3M HCl in ethyl acetate gave [^{18}F]6-FBT in 30%, 41%, and 19% overall yield from radiosyntheses that started with the salts having 2-Thi, 3-Thi, and Ph spectator groups, respectively (Table 3, entry 5).

^{11}C-labeled flumazenil is a PET radiotracer long used for studying brain benzodiazepine receptors.[121] [^{18}F] Flumazenil has now been found to be an equally effective radiotracer.[122] The longer half-life of ^{18}F allows [^{18}F] flumazenil to be used at imaging sites remote from cyclotrons. The original method for producing [^{18}F]flumazenil, based on radiofluorination of a nitro precursor,[123] has a history of low and unreliable production yield.[124,125] [^{18}F] Flumazenil has since been obtained in over 67% yield from an aryl(4-tolyl)iodonium tosylate by radiofluorination in DMF in the presence of TEMPO at 150°C for 5 minutes (Table 3, entry 6).[70] In the development of this method, several key parameters were carefully evaluated and optimized, including spectator group (Ph, 2-Thi, 3-Thi, 3-An, 4-An, and 4-Tol), precursor amount (2, 4, and 8 mg), solvent (MeCN, DMF, and DMSO), base (*n*-Bu_4NHCO_3 and K 2.2.2-K_2CO_3), temperature (100°C, 125°C, and 150°C), time (5 and 15 min), presence or absence of TEMPO radical scavenger, and stability of salt during reaction.[126] The optimal conditions have been operated for the automated routine production of [^{18}F]flumazenil for imaging experiments over a 2.5-year period, and they have achieved impressive performance.[70] Thus, the average yield was 53% (n = 94), and the mean molar activity was 572 GBq/μmol (entry 6).

Another compound, resembling flumazenil in having a fluoro substituent in meta orientation to a carboxamido group, is fluoro-palonosetron. Radiofluorination of an anisyl(aryl)iodonium tosylate precursor under conditions similar to those used for the labeling of flumazenil gave [^{18}F]fluoropalonosetron in a nonoptimized yield of 14% (Table 3, entry 7).[125] By contrast, a matrix metalloproteinase radioligand having a carboxamido group in para orientation to fluorine was radiofluorinated in 2 steps from a protected precursor, in which the initial radiofluorination yield was 70% (Table 3, entry 8).[128]

In some cases, spectator groups other than 4-anisyl or 2-thienyl have been used successfully. Although the phenyl group is not the most effective spectator group for achieving high chemoselectivity in radiofluorination, aryl(phenyl)iodonium salts can still be quite attractive as precursors to radiotracers because of their relative ease of synthesis from commercially available Koser's reagent. Moreover, any [^{18}F]fluorobenzene

by-product from their radiofluorinations is easily separated off by evaporation or chromatography. An example of the use of phenyl as a spectator group, in addition to that already mentioned ([^{18}F]FDAA1106; Table 3, entry 1), is the radiosynthesis of the mGlu1 receptor radiotracer, [^{18}F]4-fluoro-*N*-methyl-*N*-(4-(6-(methylamino)pyrimidin-4-yl)thiazol-2-yl)benzamide ([^{18}F]FIMX), which contains a fluoro substituent in para orientation to a carboxamido group. Microwave-promoted (90-W) radiofluorination of an N-Boc-protected aryl(phenyl)iodonium tosylate in DMSO for 2.5 minutes gave [^{18}F]FIMX in 38% yield (entry 9).[55] Fortuitously, complete deprotection occurred during the radiofluorination reaction. The precursor showed excellent stability during cold storage in the dark. [^{18}F]FIMX could therefore be prepared regularly by this method for clinical use.[129] No [^{18}F]fluorobenzene was observed in this radiosynthesis. Prior attempts to prepare this radiotracer through S_NAr on a protected nitro precursor had failed.

The synthesis of [^{18}F]CB91, a CB_2 receptor radiotracer, provides an example of the effective use of a 2-thienyl spectator group. In this case, radiochemistry optimization and later high-activity radiotracer production were performed in a commercial microfluidic apparatus (NanoTek, Advion). [^{18}F]CB91 was obtained as a mixture of cis and trans isomers in 42% yield from reactions in DMSO at 190°C using about 25 seconds of microreactor residence time (Table 3, entry 10).[130] CB91 contains a fluorine substituent on a deactivated phenyl ring and therefore would have been a poor candidate for direct labeling through a classical S_NAr reaction.

A candidate 5-HT_{2C} receptor radioligand having a 4-(3-fluorophenethoxy)pyrimidyl substructure has been labeled in 7.8% isolated yield for imaging use in 2 steps from an *N*-Boc-protected aryl(4-tolyl)iodonium tosylate precursor in DMF in the presence of TEMPO.[131] The radiofluorination was conducted for 10 minutes at 130°C, followed by rapid removal of the Boc group with 2M hydrochloric acid (Table 3, entry 11).

[^{18}F]1-(3-Fluorobenzyl)guanidine ([^{18}F]MFBG) is a promising radiotracer for imaging neuroblastoma. Earlier syntheses of this radiotracer had required 3 steps from [^{18}F]fluoride ion that were overall inefficient.[132] An efficient 2-step synthesis of [^{18}F]MFBG has been developed from 4-anisyl(aryl)iodonium triflate having a fully protected guanidinyl group, based on generation of the [^{18}F]fluoride salt followed by thermolysis and acid deprotection (Table 3, entry 12).[71] The synthesis has been fully automated on a commercial radiosynthesis instrument (Synthera, IBA). This procedure gives [^{18}F]MFBG for clinical use in 56 minutes and in almost 3-fold higher yield (31%) than previous methods.

[^{18}F]4-Fluoro-3-hydroxyphenethylguanidine ([^{18}F] FMHPG) is a useful radiotracer for quantifying regional cardiac sympathetic nerve density. An attempt to produce this radiotracer through radiofluorination on an iodonium salt of a fully protected MHPG followed by single-step deprotection had proven unsuccessful.[133] Nevertheless, multistage synthesis starting with the radiofluorination of *O*-benzyl-*N*-Boc-protected aryl(2-thieny)iodonium bromide in the presence of TEMPO to give [^{18}F]*t*-butyl 3-(benzyloxy)-4-fluorophenethylcarbamate in 45% yield (Table 3, entry 13) followed by 2 more steps to install the guanadinyl group and deprotect gave [^{18}F]FMHPG for clinical use in 7% overall yield.[133]

[^{18}F]6-Fluorodopamine ([^{18}F]6-FDA) is an established radiotracer for imaging the cardiac norepinephrine transporter. Historically, [^{18}F]6-FDA has been produced through inefficient electrophilic methods starting from cyclotron-produced [^{18}F]fluorine gas. Although [^{18}F]6-FDA can be synthesized in 4 steps starting with radiofluorination on a nitro precursor, overall yield is low (9%).[134] More recently, a protected 4-anisyl(aryl) iodonium triflate has been developed as a precursor for [^{18}F]6-FDA.[38] Generation of the [^{18}F]fluoride salt from this triflate precursor in MeCN, followed by evaporation of solvent, thermolysis in toluene, and deprotection, gives [^{18}F]6-FDA. [^{18}F]6-Fluorodopamine for clinical use has been produced with this precursor on one automated radiochemistry platform (Synthera, IBA) in 36% yield after 65 minutes and on another automated platform (TRACERlab FX-FN, GE) in 72% yield after 130 minutes (Table 3, entry 14).

For several decades, [^{18}F]FDOPA has been a key PET radiotracer, mainly for studies of Parkinson disease. However, the widespread use of [^{18}F]FDOPA has been hampered because of the long-standing absence of a simple method for production in high yield from [^{18}F]fluoride ion.[135] Therefore, efforts have been made to synthesize [^{18}F]FDOPA through radiofluorination of a protected diaryliodonium salt followed by deprotection. According to a commercial report,[136] [^{18}F]FDOPA can be prepared in 30% to 40% yield by conversion of a 4-anisyl(aryl) iodonium triflate into the [^{18}F]fluoride salt in MeCN followed by solvent evaporation, thermolysis at 140°C for 5 minutes in diglyme, and then deprotection. The method has since been adapted to produce [^{18}F]FDOPA for clinical use in 14 ± 4% overall yield in a synthesis time of 117 minutes (Table 3, entry 15).[137] The protected precursor is commercially available.

General observations from Table 3 are that 4-anisyl has been selected most frequently as the spectator group, and weakly nucleophilic tosylate as the counterion. Functional group tolerance in the radiofluorinations is quite broad, but free amino, phenol, guanidinyl, and carboxyl groups have generally been protected. Amounts of precursor used in the radiosyntheses are generally low and very compatible with the use of a small volume of a polar aprotic solvent (eg, DMSO, DMF, and MeCN) in batch reactions. Different large cations have been used for solubilization of the [^{18}F] fluoride ion, including Cs^+, Et_4N^+, Bu_4N^+, and K^+-K 2.2.2, and these have not always given similar results in direct comparisons. The addition of the radical scavenger TEMPO has been found beneficial in many of these reactions. Reactions operate in a quite low temperature range (80°C-190°C) and are generally brief, proceeding to useful yields in just a few minutes. The radioactive fluoro derivatives of spectator groups have never been reported as being problematic in radiotracer separations. All the reactions may be regarded as NCA, and where reported, the molar activities are in the usual range for NCA radiofluorinations by other methods.

2.6.2 | From diaryliodonium salts (copper mediated)—The [$(MeCN)_4CuOTf$]-mediated radiofluorinations of protected aryl(mesityl)iodonium tetrafluoroborates for the radiosyntheses of [^{18}F]FDAA1106, protected [^{18}F]L-4-fluorophenylalanine ([^{18}F]4-FPhe), and protected [^{18}F]6-FDA, under minimalist conditions in DMF at 85°C for 20 minutes, have been reported to proceed in exceptionally high yields of 93%, 81% to 92%, and 71% to 94%, respectively (Table 4, entries 1-3).[105] A minimalist approach has since been used to produce [^{18}F]FDAA1106, [^{18}F]4-FPhe, and [^{18}F]6-FDA for clinical use in 60%, 53%

to 66%, and 46% overall yields, respectively.[105] Zischler et al have subsequently reported yields of 41% and 56% for the production of [^{18}F]FDAA1106 and [^{18}F]4-FPhe, respectively (entries 1 and 3).[136]

Copper-mediated radiofluorination of a fully protected aryl(mesityl)iodonium tosylate (6 μmol) with $^{18}F^{-}$-18-crown-6-K_2CO_3 in DMF (0.25 mL) for 20 minutes at 85°C provided a protected [^{18}F]FDOPA in 17% yield (Table 4, entry 4).[41] Radiofluorination yield almost doubled to 31% when an analogous tetrafluoroborate salt was used (entry 5). Exchange of [^{18}F]fluoride ion with the tetrafluoroborate anion occurred to some extent, and therefore, molar activity was only moderately high at 11 GBq/μmol. Radiofluorinations of appropriate aryl(mesityl)iodonium tetrafluoroborates under the same conditions gave protected [^{18}F]4-FPhe in 23% yield (entry 6).[41]

Overall, copper-mediated radiofluorinations of aryl(mesityl)iodonium salts are highly attractive because they share many of the beneficial features of the copper-free radiofluorinations of diaryliodonium salts, such as a need to use only small amounts of precursor and a requirement for only moderate reaction temperatures and short reaction times. The precursor salts are usefully stable for months in the dark. Moreover, radiofluorination reactions proceed cleanly to single desired products, which is attractive for reducing separation challenges. The moderate molar activities obtained from the use of high-yielding tetrafluoroborate salts are acceptable for some radiotracers, such as [^{18}F]FDOPA, [^{18}F]4-FPhe, and [^{18}F]6-FDA but unacceptable for radiotracers intended to bind to low-density protein targets, such as [^{18}F]FDAA1106. A further drawback is a need to test that final radiotracer products for human administration are not unacceptably contaminated with copper. Normally, however, only very low and acceptable levels of copper are found in chromatographically purified products.

2.6.3 | From aryliodonium ylides—Aryliodonium ylides having the auxiliary group derived from Meldrum's acid have been used to prepare [^{18}F]4-FPPMP and[^{18}F]3-FPPMP as candidate radiotracers for norepinephrine transporter and serotonin transporter, respectively (Table 5, entries 1 and 2).[94] Low but useful yields were obtained from *N*-Boc-protected precursors over 2 steps. These radiotracers have ^{18}F in highly electron-rich aryl rings. The radiofluorination of the precursor for [^{18}F]4-FPPMP in MeCN at 130°C for 20 minutes also gave the Boc-protected [^{18}F]3-fluoroisomer (~10%) in addition to the expected Boc-protected [^{18}F]4-fluoroisomer (20%), thereby implicating the operation of an aryne-type mechanism.

Stable spirocyclopentyl aryliodonium ylides are gaining considerable attention for PET radiotracer synthesis and production (Table 5, entries 3-11). [^{18}F]FPEB is a preferred radiotracer for imaging brain mGlu5 receptors. However, synthesis by radiofluorination through classical S_NAr is low yielding because of lack of activation by ring substituents. [^{18}F]FPEB has been synthesized through radiofluorination of a spirocyclopentyl aryliodonium ylide in DMF at 80°C for 5 minutes in 49% yield (Table 5, entry 3).[139] This reaction has been used to produce [^{18}F]FPEB for clinical use in moderately high yield (20%) in an automated microfluidic apparatus (entry 4).[139] Each production required less than 1 hour. The precursor was found to be stable for 2 months at room temperature. [^{18}F]FPEB

shares the same [^{18}F]fluoro-3-cyano,5-alkynylaryl structural motif as the earlier mentioned mGlu5 receptor radiotracers, [^{18}F]MTEB and [^{18}F]SP203. The yield of [^{18}F]FPEB from iodonium ylide precursor is quite comparable with those of [^{18}F]MTEB and [^{18}F]SP203 from 4-anisyl(aryl)iodonium tosylates (Table 3, entries 2 and 3).

A spirocyclopentyl aryliodonium ylide has been used in a 2-step synthesis of [^{18}F]LY2459989, a κ-opioid receptor radiotracer.[140] After the initial radiofluorination, the aryl nitrile group is oxidized to a carboxamido group with hydrogen peroxide. Optimal radiofluorination reactions in a microfluidic apparatus used DMF as solvent at 120°C for 1 minute and gave high incorporation of radioactivity (76%) into the nitrile intermediate (Table 5, entry 5). For high-activity production, the precursor was treated with [^{18}F]fluoride ion in a vial at 80°C for 5 minutes followed by nitrile hydrolysis to give [^{18}F]LY2459989 in 30% to 43% yield (entry 6). These yields were 30-fold higher than those obtained when starting with an S_NAr reaction in which [^{18}F]fluoride ion displaced an iodo or nitro group. In these SNAr reactions, the meta nitrile electron-withdrawing group provides only weak leaving group activation, and this activation is also countermanded by an ortho aryloxy group.

[^{18}F]*p*-Fluorohippurate ([^{18}F]PFH) shows promise for imaging renal function. The original radiosynthesis of [^{18}F]PFH consisted of a 2-pot 4-step procedure that provided the radiotracer in 95 minutes in an estimated yield of 60% to 65%.[141] By contrast, treatment of a protected spirocyclopentyl aryliodonium ylide with [^{18}F]fluoride ion in DMF for 10 minutes at 130°C followed by basic hydrolysis for 5 minutes at 130°C gave [^{18}F]PFH in 46% yield after 45 minutes (Table 5, entry 7).[142] A spirocyclopentyliodonium ylide has also been used under similar radiofluorination conditions to produce *N,O*-protected [^{18}F]4-FPhe (entry 8).[67]

Petersen et al prepared [^{18}F]CIMBI-198 in 2 steps from an *N*-Boc-protected spirocyclopentyl iodonium ylide (Table 5, entry 9).[143] The radiofluorination step proceeded in only low yield (12%), allowing the final product to be isolated in only 2% yield (entry 9). In [^{18}F]CIMBI-198, the ^{18}F is present in a highly substituted electron-rich aryl ring. A congeneric structure and candidate 5-HT_{2A} receptor radioligand was labeled in much higher isolated yield (10%-12%), with the radiofluorination step proceeding in high yield (76%-77%) (entry 10).[116]

A di-Boc-protected spirocyclopentyl aryliodonium ylide precursor was successfully radiofluorinated in DMF under quite mild conditions (80°C; 10 min) to give [^{18}F]lorlatinib, a candidate ROS1/ALK radiotracer, in useful isolated yield (14% non-decay-corrected) (Table 5, entry 11).[144] By comparison, classical S_NAr on a nitro precursor gave only 1% radiochemical yield.

A spiroadamantyl aryliodonium ylide has also been used to prepare another radiotracer for TSPO 18 kDa, namely, [^{18}F]FDPA.[145] The choice of base for use in the radiofluorination reaction was found to be critical. An experimental yield of 40% was obtained for reactions conducted in DMF (1.0 mL) at 120°C for 15 minutes with 2 mg of precursor in the presence of 12 mg of *t*-butyl ammonium mesylate (Table 5, entry 12). This method was modified to produce the radiotracer for clinical use in 45% yield (entry 13).

[^{18}F]Safinamide, [^{18}F]L-2-fluoro-meta-tyrosine ([^{18}F] FMT), and [^{18}F]MFBG have also been prepared from protected spiroadamantyl aryliodonium ylides.[93] [^{18}F] Safinamide was obtained in 15% yield through radiofluorination of precursor in DMF at 120°C for 10 minutes followed by deprotection (Table 5, entry 13). Treatment of the [^{18}F]FMT precursor gave 60% radioactivity incorporation after 20 minutes at 120°C in DMF. After deprotection and HPLC purification, [^{18}F]FMT was obtained in 12% non-decay-corrected yield (entry 14). The radiosynthesis time was about 1 hour. Treatment of the [^{18}F]MFBG precursor with [^{18}F]fluoride ion gave protected [^{18}F]MFBG intermediate in 70% yield with great reproducibility.[93] Deprotection and HPLC purification provided [^{18}F]MFBG for clinical use in 14% non-decay-corrected yield in less than 75 minutes (entry 16). This yield is somewhat lower than the production yield from an automated synthesis of [^{18}F]MFBG from a 4-anisyl(aryl)iodonium triflate (31%) (Table 3, entry 12).

3 | CONCLUSION

The radiofluorination of hypervalent aryliodine precursors is now established as a useful methodology for the radiosynthesis of [^{18}F]fluoroarenes as labeling synthons and PET radiotracers from NCA cyclotron-produced [^{18}F]fluoride ion. The methodology is broadly applicable to electron-rich arenes and heteroarenes in addition to electron-deficient arenes, and often without restriction on position of labeling. The hypervalent aryliodine precursors are synthetically accessible from inexpensive materials and are generally adequately stable for storage. Only small amounts are required in labeling procedures that are free of heavy transition metals and readily adaptable to automation under current good manufacturing practice conditions.

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Biography

Victor W. Pike is Chief of the PET Radiopharmaceutical Sciences Section of the Molecular Imaging Branch of the National Institute of Mental Health. His main research interest is in developing ^{11}C- or ^{18}F-labeled PET radiotracers for imaging specific proteins (enzymes, transporters, and receptors) that have relevance to the study and treatment of neuropsychiatric disorders. He has coauthored well over 300 peer-reviewed publications stemming from his research over nearly 4 decades.

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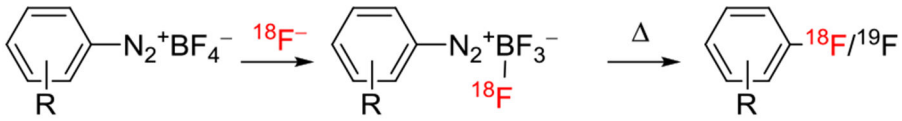
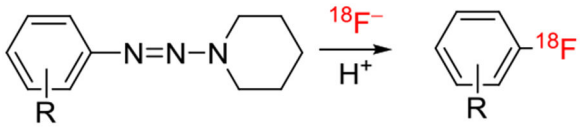
Balz-Schiemann reaction:



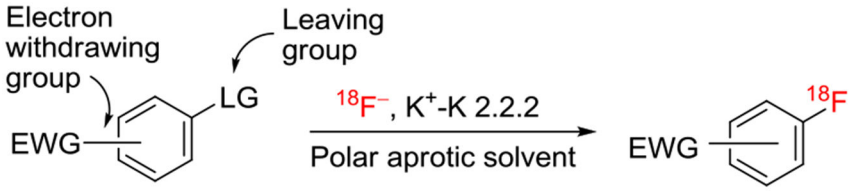
Low yields
Low molar activity

Wallach reaction:



Very low yields

Classical S_NAr reaction:



EWG = NO_2, CN, CHO, COR, COOR...
LG = Br, Cl, I, NO_2, Me_3N^+..

Moderate to high yields
but:
Requires *ortho* or *para* electron-withdrawing group(s)
Inapplicable to labeling of electron-rich arenes
Poorly applicable to preparing *m*-substituted [^{18}F]fluoroarenes

FIGURE 1.
Classical methods for the radiofluorination of arenes with [^{18}F]fluoride ion and some of their limitations

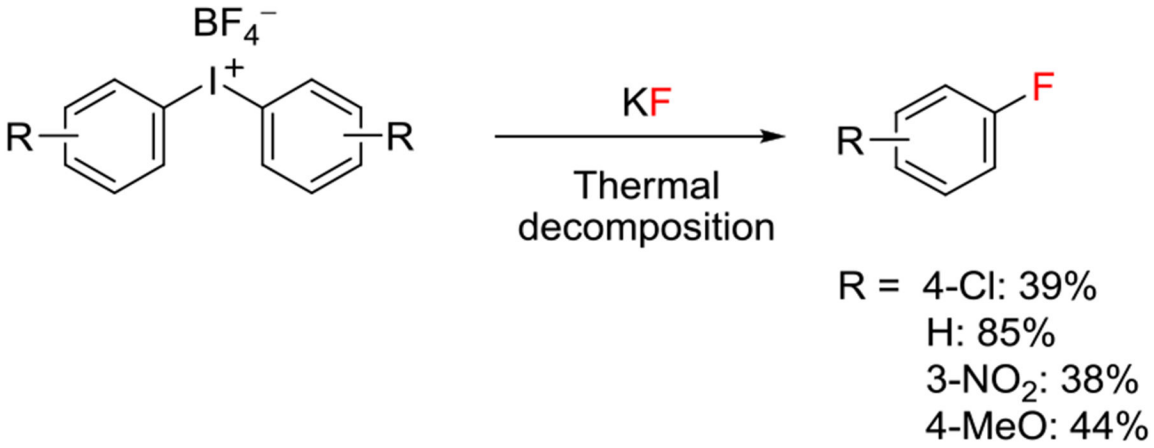


FIGURE 2.
Pyrolysis of diaryliodonium fluoroborates to give fluoroarenes[20]

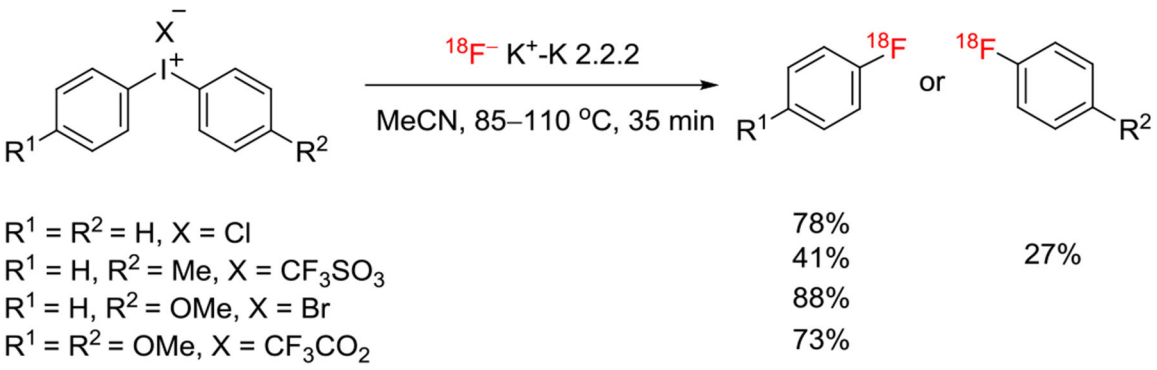


FIGURE 3.
Yields for [^{18}F]fluoroarenes from the radiofluorination of some simple diaryliodonium salts in acetonitrile[21]

FIGURE 4.
Exchange of axial and equatorial aryl ligands in diaryliodonium salts through pseudorotation

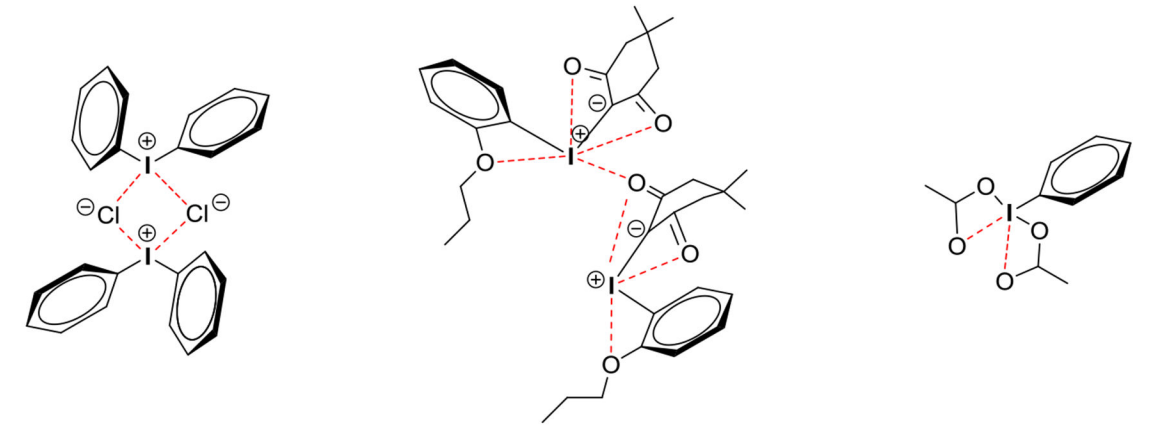


FIGURE 5.

Examples of primary (black) and secondary (red) bonding patterns in single crystals of some aryliodine(III) compounds

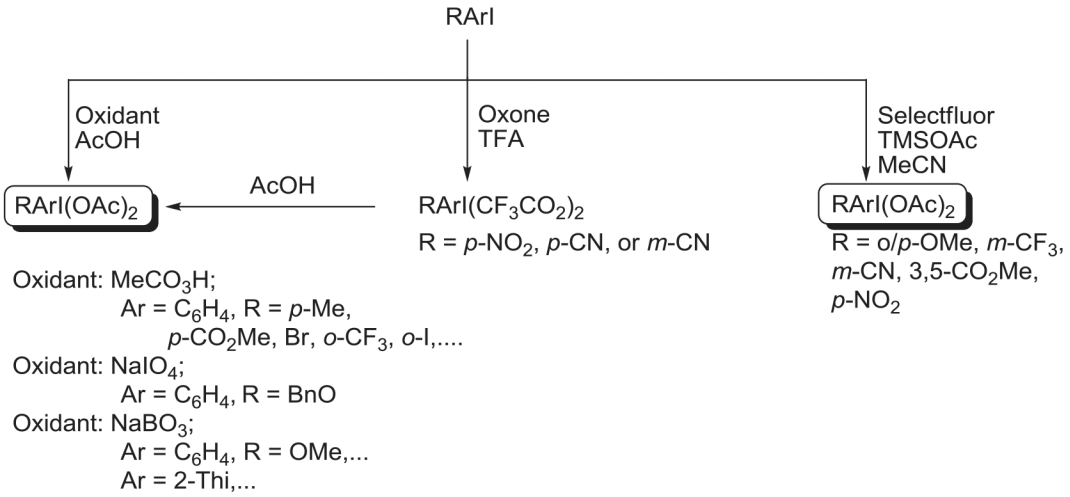


FIGURE 6.

Oxidative methods for preparing various substituted (diacetoxyiodo)arenes from iodoarenes

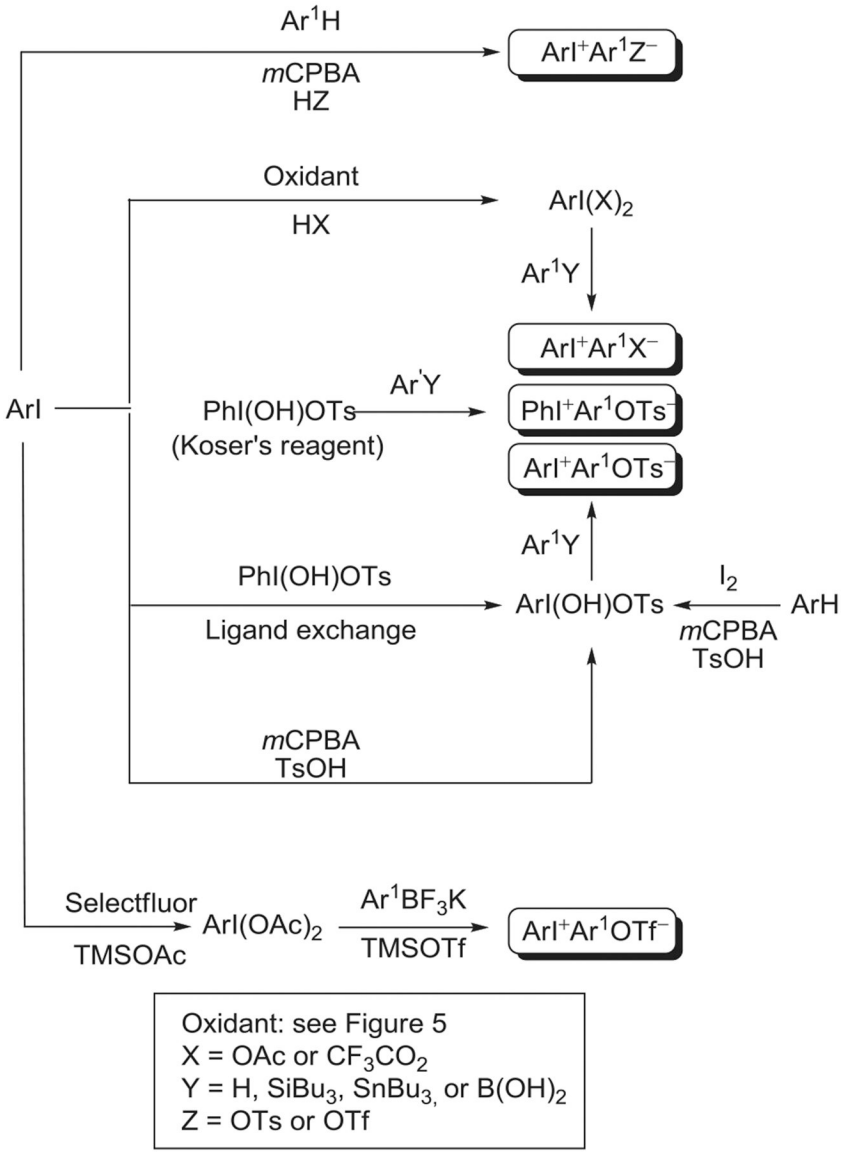


FIGURE 7.
Some pathways for the synthesis of unsymmetrical diaryliodonium salts

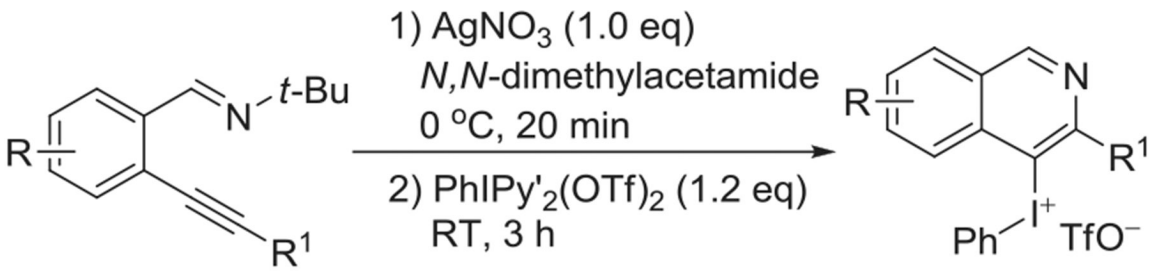


FIGURE 8.
Synthesis of phenyl(substituted-isoquinolinyl) iodonium triflates

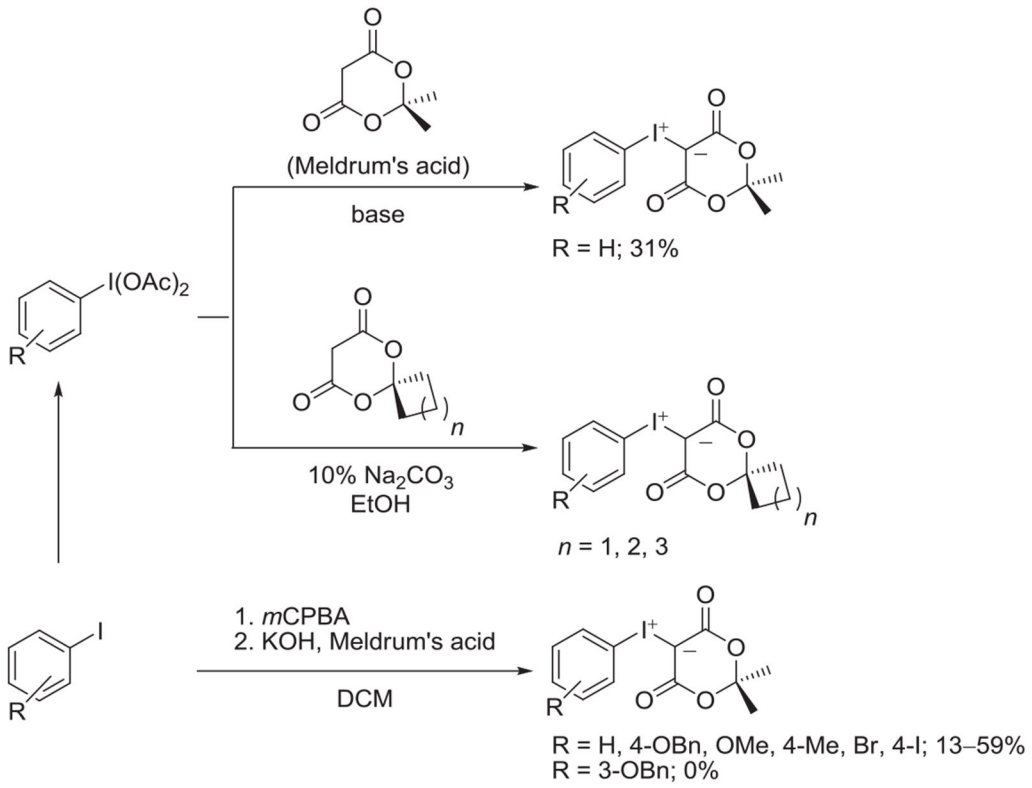


FIGURE 9.
Routes to aryliodonium ylide and spirocyclic iodonium ylides

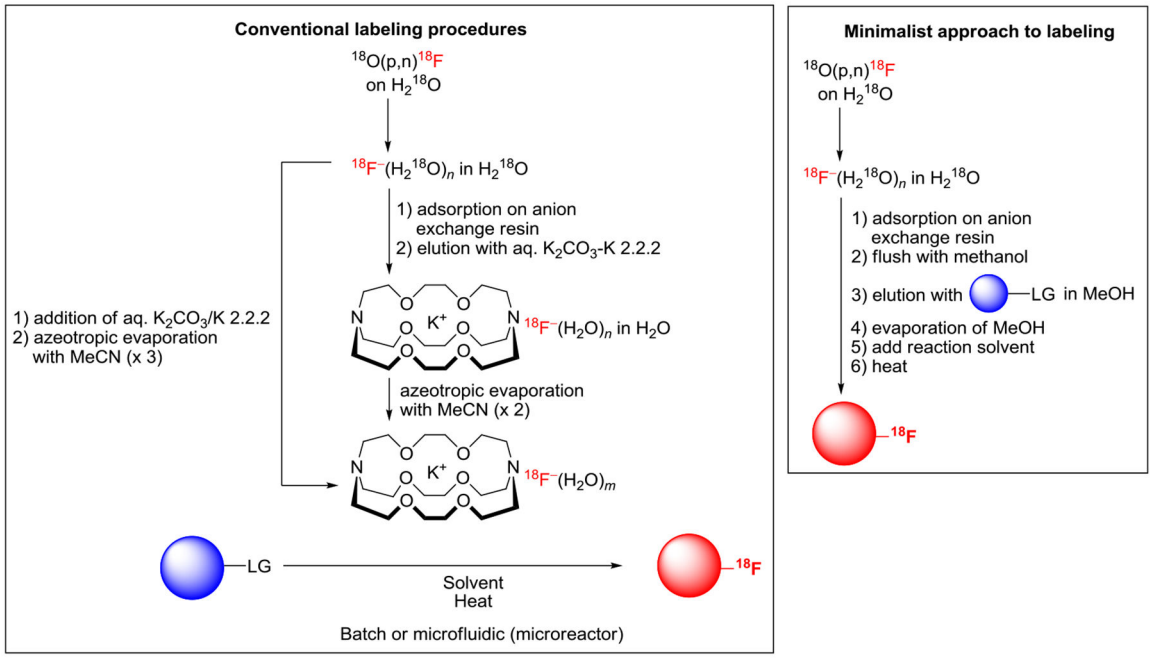


FIGURE 10.

Conventional and minimalist approaches to labeling substrates with [^{18}F]fluoride ion

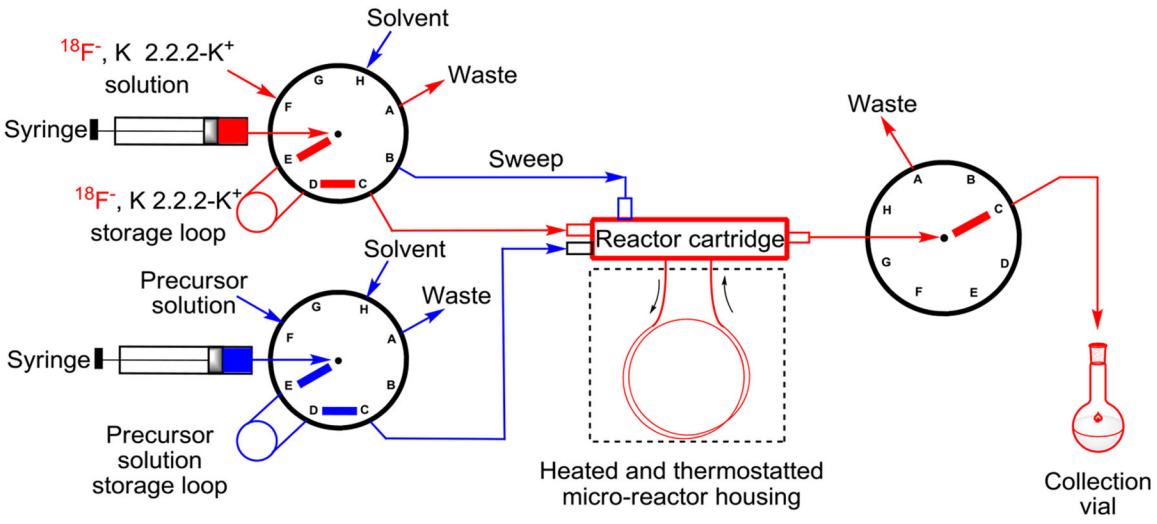


FIGURE 11.

Layout of a microfluidic apparatus for the investigation of the radiofluorination of hypervalent aryliodine precursors

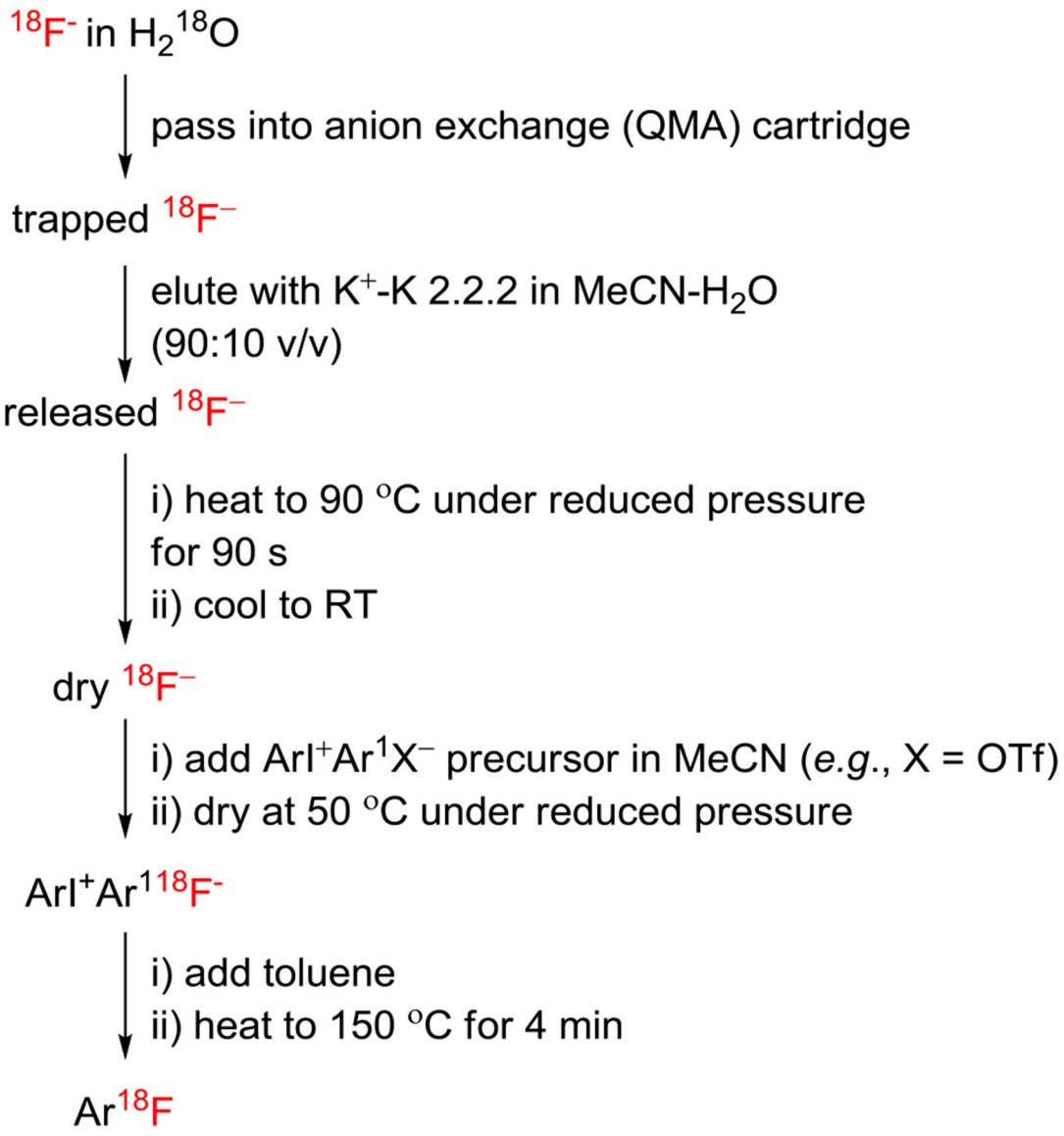


FIGURE 12.
A pyrolytic method for the radiofluorination of diaryliodonium salts

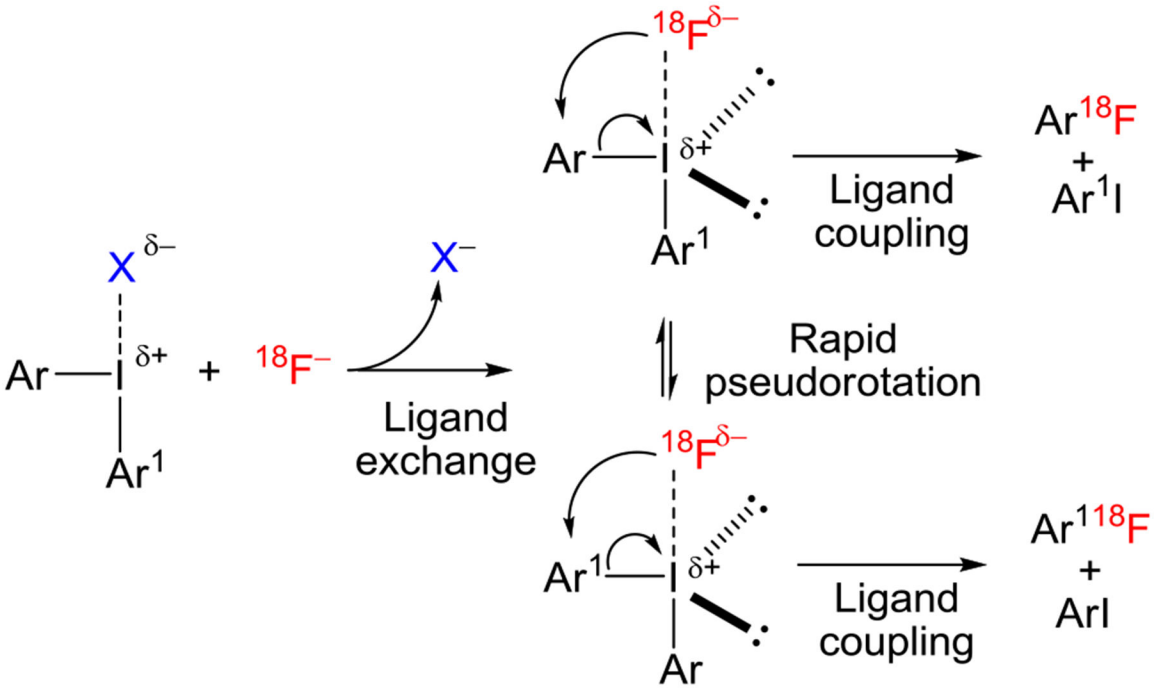


FIGURE 13.
Mechanism of the radiofluorination of unsymmetrical diaryliodonium salts

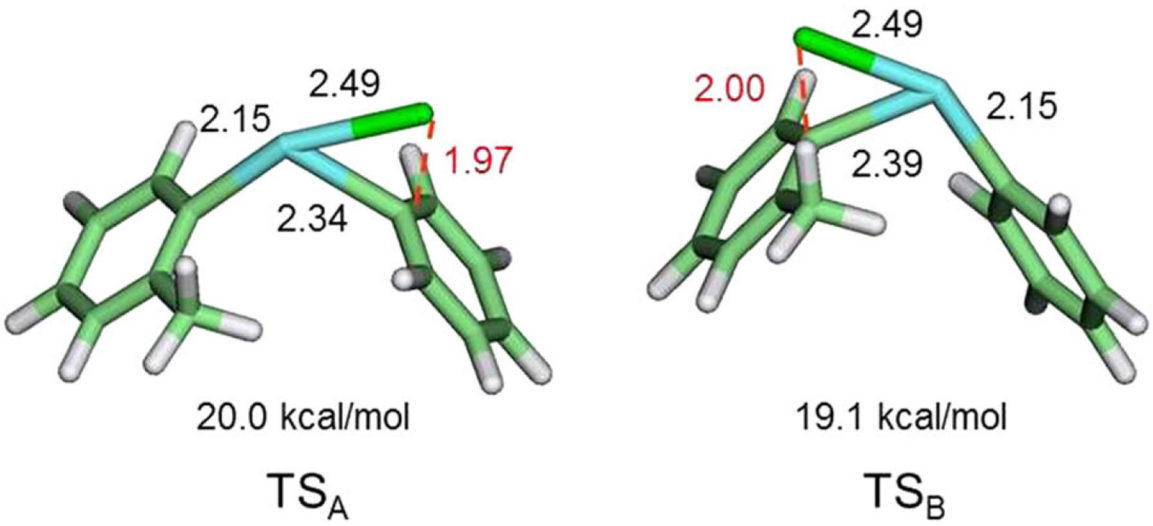


FIGURE 14.

Computed transition state geometries and energies (relative to ground state) for the fluorination of a phenyl(2-tolyl)iodonium salt.[25] TS_A leads to fluorobenzene and TS_B to 2-fluorotoluene. TS_B has somewhat lower energy (by 0.9 kcal/mol) such that 2-fluorotoluene is the preferred product. Bond distances are in Ångströms

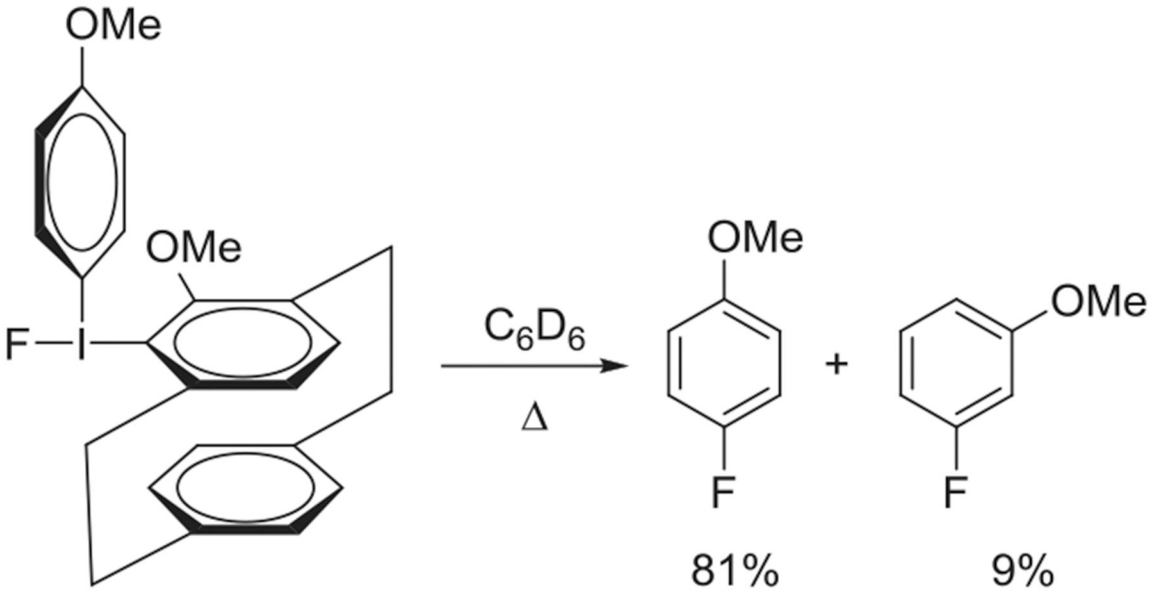


FIGURE 15.
Pyrolysis of 5-methoxy-[2.2]paracyclophane(4-anisyl)iodonium fluoride gives 3-fluoroanisole in addition to 4-fluoroanisole

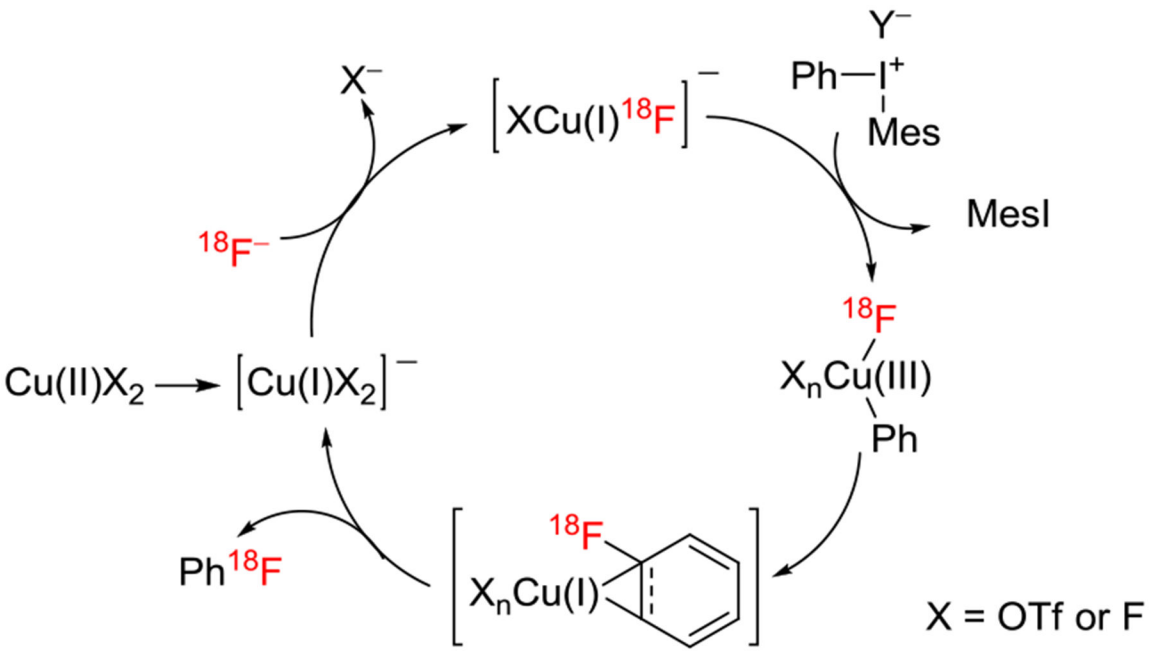


FIGURE 16.
Mechanism proposed for the radiofluorination of a phenyl(mesityl)iodonium salt in the presence of $(MeCN)_4CuOTf$ in dimethylformamide

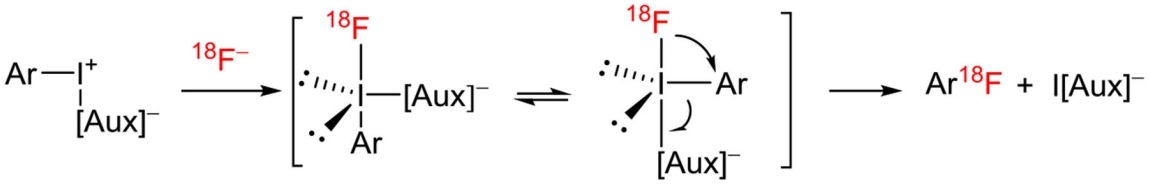


FIGURE 17.
Mechanism proposed for the radiofluorination of aryliodonium ylides

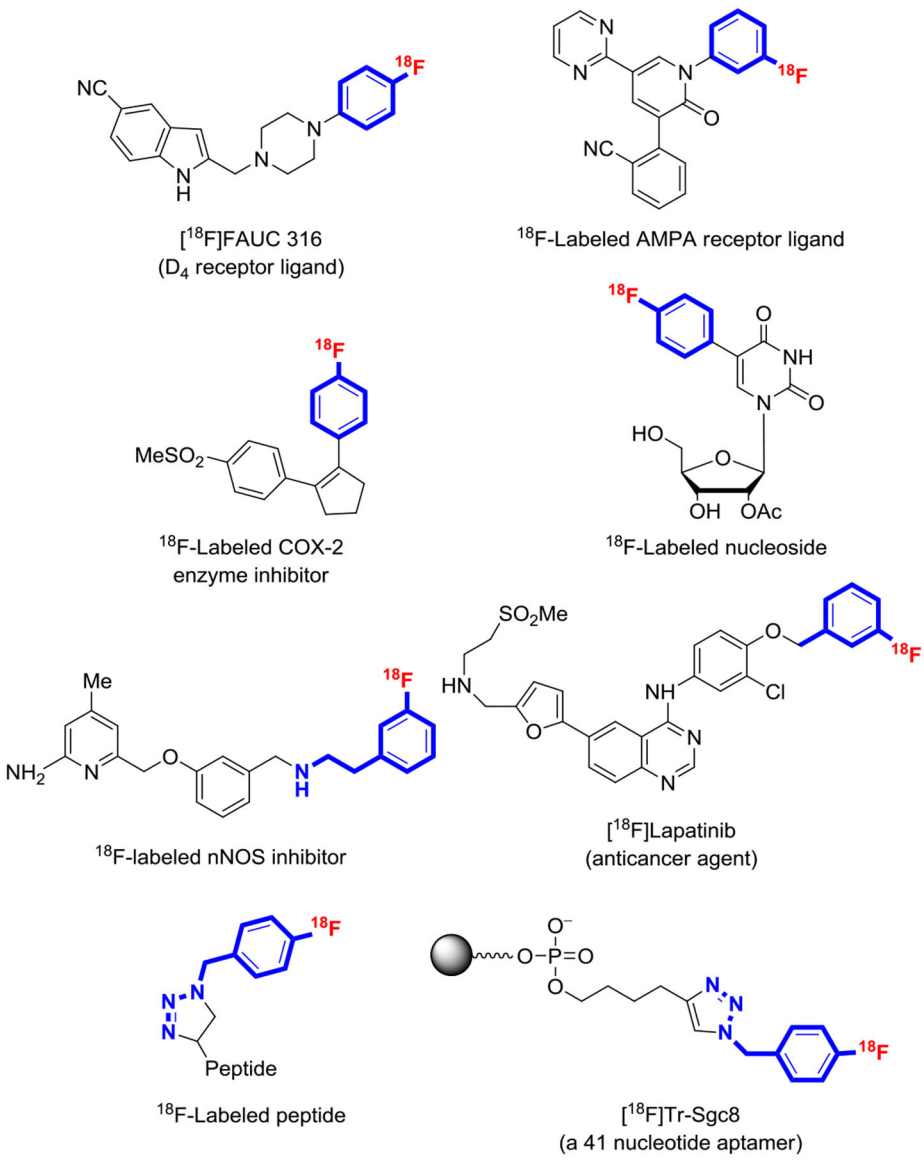


FIGURE 18.

Examples of compounds labeled with synthons prepared from hypervalent aryliodine precursors. Blue indicates the partial structure derived from the labeling synthon

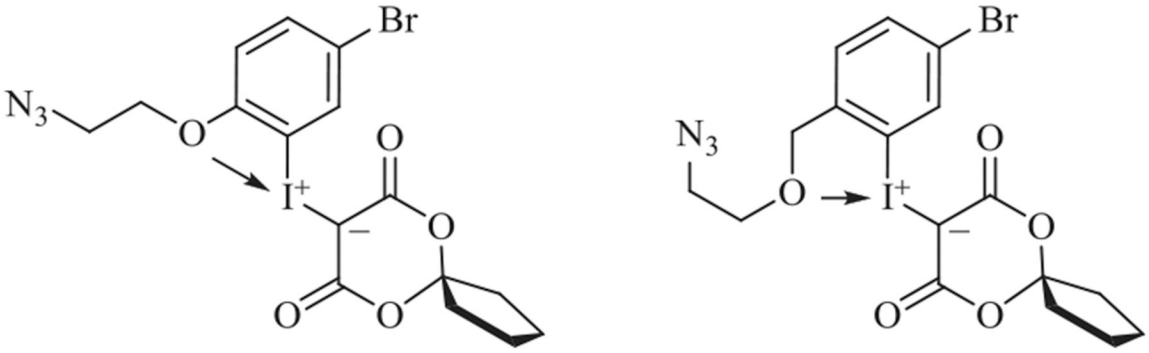
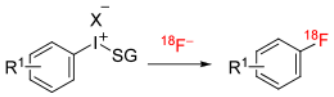


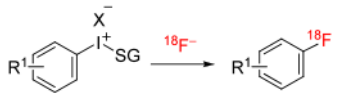
FIGURE 19.
Examples of ortho oxygen-stabilized aryliodonium ylides

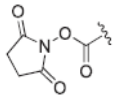
TABLE 1

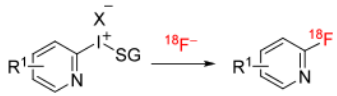
Labeling synthons prepared from diaryliodonium salts



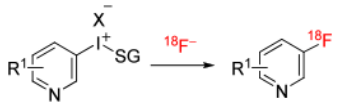
		Precursor			Labeling conditions					
Entry	**Labeling Synthon**	**R^1**	**SG**	**X^-**	Solvent	Mode	°C/W	min	**Yield,[a] %**	**Reference**
1	^{18}F]1-Chloro-4-fluorobenzene	4-Cl	4-An	TsO	DMSO	Batch	80	20	80	Way et al[99]
2	[^{18}F]1-Chloro-4-fluorobenzene	4-Cl	4-An	TsO	DMSO	MW	ns	5	70	Way et al[99]
3	[^{18}F]1-Bromo-2-fluorobenzene	2-Br	Ph	Cl^-	DMF	MR	190	4	68	Chun et al[65]
4	[^{18}F]1-Bromo-4-fluorobenzene	4-Br	2-Thi	Br^-	DMF	Batch	130	45	70	Way et al[99]
5	[^{18}F]1-Bromo-4-fluorobenzene	4-Br	4-BrC_6H_4	Br^-	DMF	Batch	130	10	65 ± 10	Ermert et al[102]
6	[^{18}F]1-Fluoro-4-iodobenzene	4-I	4-IC_6H_4	TsO^-	DMF	Batch	80-160	40	21-46	Wuest and Kniess[100]
7	[^{18}F]1-Fluoro-4-iodobenzene	4-I	4-IC_6H_4	Cl^-	DMF	MW	120	5	15-70	Wuest and Kniess[100]
8	[^{18}F]1-Fluoro-4-iodobenzene	4-I	4-An	TfO^-	DMF	Batch	130	10	40 ± 7	Kügler et al[101]
9	[^{18}F]1-Fluoro-4-iodobenzene	4-I	2-Thi	Br^-	DMF	Batch	130	45	60 ± 9	Way et al[99]
10	[^{18}F]1-Fluoro-4-iodobenzene	4-I	Mes	BF_4^-	DMF	Batch (Cu)	85	20	35 ± 8	Ichiishi et al[41]
11	[^{18}F]3-Fluorobenzaldehyde	3-CHO	Ph	Br^-	DMF	MW	110	5	80	Basuli et al[87]
12	[^{18}F]3-Fluorobenzaldehyde	3-CHO	Mes	BF_4^-	DMF	Batch (Cu)	85	20	35 ± 1	Ichiishi et al[41]
13	[^{18}F]3-Fluorobenzaldehyde	3-CHO	Mes	BF_4^-	DMF	Batch (Cu)	85	20	85	Zlatopolskiy et al[105]
14	[^{18}F]3-Fluorobenzaldehyde	3-CHO	4-An	I^-	DMSO	Batch	130	10	20-25	Richarz et al[72]
15	[^{18}F]3-Fluorobenzaldehyde	3-CHO	2-Thi	Cl^-	DMF	MR	180	~5	46	Chun and Pike[46]
16	[^{18}F]4-Fluorobenzaldehyde	4-CHO	4-An	Cl^-	DMF	MR	180	~5	73	Chun and Pike[46]
17	[^{18}F]4-Fluorobenzaldehyde	4-CHO	Ph	$CF_3CO_2^-$	DMF	MR	180	ns	83	Charlton and Carroll[106]
18	[^{18}F]2-Fluorobenzyl chloride	2-CH_2Cl	4-An	TsO^-	DMF	MR	180	~4	55	Chun and Pike[46]
19	[^{18}F]3-Fluorobenzyl chloride	3-CH_2Cl	5-Me-2-Thi	Cl^-	DMF	MR	200	~4	33	Chun and Pike[46]
20	[^{18}F]4-Fluorobenzyl chloride	4-CH_2Cl	TMP	TsO^-	DMF	MR	180	~3	52	Chun and Pike[46]
21	[^{18}F]2-Fluorobenzyl bromide	2-CH_2Br	TMP	TsO^-	DMF	MR	160	~3	50	Chun and Pike[46]
22	[^{18}F]3-Fluorobenzyl bromide	3-CH_2Br	2-Thi	Cl^-	DMF	MR	200	~4	31	Chun and Pike[46]



		Precursor			Labeling conditions					
Entry	**Labeling Synthon**	**R^1**	**SG**	**X^-**	Solvent	Mode	°C/W	min	**Yield,[a] %**	**Reference**
23	[^{18}F]4-Fluorobenzyl bromide	4-CH_2Br	TMP	TsO^-	DMF	MR	140	~4	20	Chun and Pike[46]
24	[^{18}F]2-Fluorobenzyl azide	2-CH_2N_3	4-An	TsO^-	DMF	MR	180	~3	41	Chun and Pike[44]
25	[^{18}F]3-Fluorobenzyl azide	3-CH_2N_3	4-An	TsO^-	DMF	MR	180	~3	39	Chun and Pike[44]
26	[^{18}F]4-Fluorobenzyl azide	4-CH_2N_3	4-An	Br^-	DMF	MR	200	~1.5	40	Chun and Pike[44]
27	[^{18}F]4-Fluorophenol[b]	4-OH	2-Thi	Br^-	DMF	Batch	130	15-20	**(34-36)**	Ross et al[37]
28	[^{18}F]4-Fluorophenol[b]	4-OH	4-BnO-C_6H_4	TsO^-	DMF	MW		1	52 ± 3	Heifer et al[47]
29	*N*-Succinimidyl 4-[^{18}F]fluorobenzoate		2-Thi	$CF_3CO_2^-$	DMF/TEMPO	Batch	130	5	4-23	Yan et al[112] Carrol and Yan[113]



30	[^{18}F]2-Fluoro-6-chloropyridine	6-Cl	4-An	TsO^-	DMF	MR	100	~4	60	Chun and Pike[114]
31	[^{18}F]2-Fluoro-5-bromopyridine	5-Br	4-An	TsO^-	DMF	MR	120	~4	64	Chun and Pike[114]
32	[^{18}F]2-Fluoro-6-bromopyridine	6-Br	4-An	TsO^-	DMF	MR	180	~4	53	Chun and Pike[114]



33	[^{18}F]3-Fluoro-2-chloropyridine	2-Cl	4-An	TsO^-	DMF	MR	180	~3	36	Chun and Pike[114]
34	[^{18}F]3-Fluoro-2-bromopyridine	2-Br	4-An	TsO^-	DMF	MR	160	~4	28	Chun and Pike[114]
35	[^{18}F]3-Fluoro-6-chloropyridine	6-Cl	4-An	TsO^-	DMF	MR	180	~4	28	Chun and Pike[114]
36	[^{18}F]3-Fluoro-6-bromopyridine	6-Br	4-An	TsO^-	DMF	MR	160	~4	30	Chun and Pike[114]

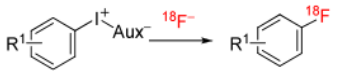
Abbreviations: (Cu), Cu-mediated reaction; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; MR, microreactor (microfluidic); ns, not specified; MW, microwave (batch); TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxyl.

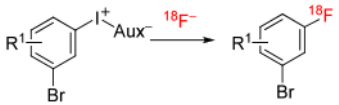
[a] Values in plain type are yields before isolation. Values in bold and parentheses are yields after isolation.

[b] Process is 2 steps from BnO-protected salt. Data are for the radiofluorination step.

TABLE 2

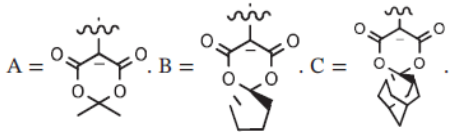
Some labeling synthons prepared from aryliodonium ylides



Entry	Labeling Synthon	Precursor		Labeling Conditions				Yield,[b] %	References
		R[1]	Aux−[a]	Mode	Solvent	°C	min		
1	[^{18}F]3-Fluorobromobenzene	3-Br	C	Batch	DMF	130	10	72 ± 3	Yuan et al[115]
2	[^{18}F]4-Fluoroiodobenzene	4-I	A	Batch	DMSO	110	15	70 ± 10	Kügler et al[101]
3	[^{18}F]3-Fluorobenzaldehyde	3-CHO	B	Batch	DMF	120	10	7-52	Petersen et al[116]
4	[^{18}F]3-Fluorobenzyl azide	3-CH_2N_3	B	Batch	DMF	120	ns	69 ± 8	Wang et al[117]
5	[^{18}F]4-Fluorobenzyl azide	4-CH_2N_3	B	Batch	DMF	120	10	70 ± 4 **(52 ± 2)**	
6	[^{18}F]4-Fluorobenzyl azide	4-CH_2N_3	B	Batch	DMF	120	10	**(25 ± 10)** [c]	Rotstein et al[67]
7	[^{18}F]4-Fluorobenzyl azide	4-CH_2N_3	B	MR	DMF	210	~1	68 ± 5 **(24 ± 0)**	Calderwood et al[75]
8	[^{18}F]3-Fluorobenzoic acid methyl ester	3-CO_2Me	B	Batch	DMF	120	10	77 ± 7	Rotstein et al[67]
9	[^{18}F]2-(3-Fluorophenyl)ethylamine[d]	3-$(CH_2)_2$NHBoc	A	Batch	DMF	110	10	~70	Drerup et al[118]
									
10	[^{18}F]1-(2-Azidoethoxy)-4-bromo-2-fluorobenzene	2-$(O(CH_2)_2N_3)$	B	Batch	DMF	120	10	69 ± 2	Wang et al[117]
11	[^{18}F]1-((2-Azidoethoxy)methyl)-4-bromo-2-fluorobenzene	2-$(CH_2\ O(CH_2)_2N_3)$	B	Batch	DMF	120	10	90 ± 2	Wang et al[117]

Abbreviations: DMF, dimethylformamide; DMSO, dimethyl sulfoxide; MR, microreactor (microfluidic); ns, not specified.

a



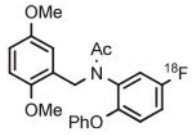
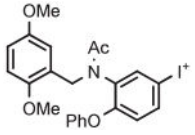
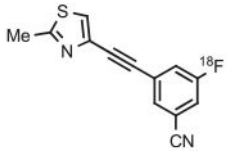
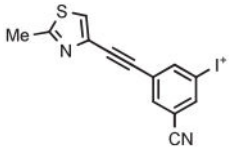
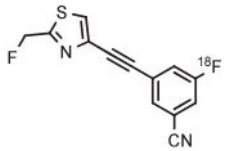
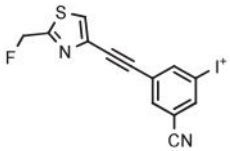
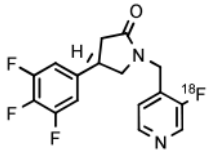
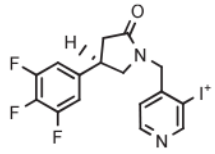
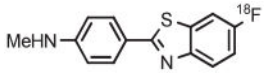
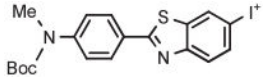
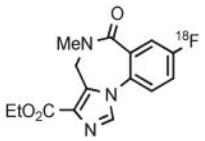
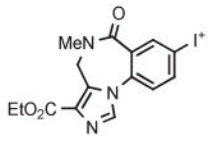
*b*Values in plain type are yields before isolation. Values in bold and parentheses are yields after isolation.

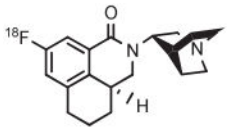
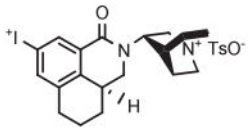
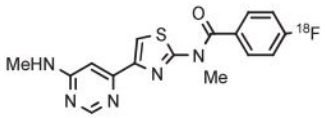
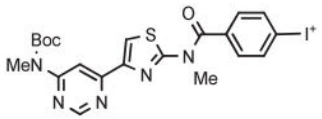
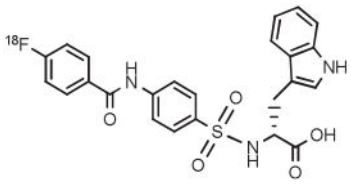
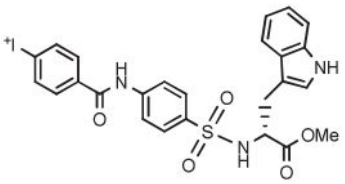
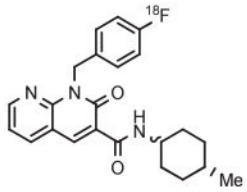
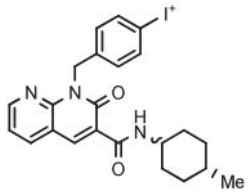
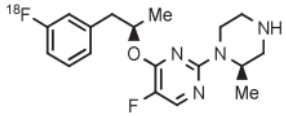
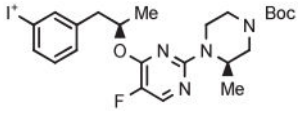
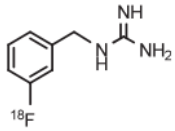
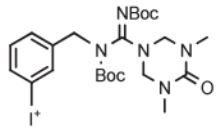
*c*Uncorrected for decay.

[d] Process is 2 steps. Data are for the radiofluorination step.

TABLE 3

Examples of radiotracers prepared from diaryliodonium salts under copper-free conditions

	Radiotracer		Precursor (ArI^+SGX^-)				Labeling Conditions				
Entry	Name	Structure	ArI^+	SG	X^-	Labeling Technique	Solvent	°C/W	min	Yield,[a] %	Reference
1	[^{18}F]FDAA1106			4-An	TsO^-	Batch (1 step)	DMSO	80	20	46	Zhang et al[120]
2	[^{18}F]MTEB			4-An	TsO^-	MW (1 step)	DMF with TEMPO	100	2 × 2	20 ± 1	Telu et al[69]
3	[^{18}F]SP203			4-An	TsO^-	MW (1 step)	DMF with TEMPO	100	2 × 2	33 ± 8	Telu et al[69]
4	[^{18}F]UCB-H			4-An	TfO^-	Batch (1 step)	MeCN with TEMPO	125	10	50 **(34 ± 2)**	Warnier et al[40]
5	[^{18}F]6-FBT			3-Thi	TsO^-	Batch (1 step)	MeCN with TEMPO	130	10	60 ± 6[a] **(19-40)**	Lee et al[56]
6	[^{18}F]Flumazenil			4-Tol	TsO^-	Batch (1 step)	DMF with TEMPO	150	5	67 ± 3 **(54 ± 9)**	Moon et al[70,126]

	Radiotracer		Precursor (ArI^+SGX^-)				Labeling Conditions					
Entry	Name	Structure	ArI^+	SG	X^-	Labeling Technique	Solvent	°C/W	min	Yield,[a] %	Reference
7	[^{18}F]Fluoro-palonosetron			4-An	TsO^-	Batch (1 step)	DMF with TEMPO	140	12	14 **(6)**	Mu et al[127]
8	[^{18}F]FIMX			Ph	TsO^-	MW (1 step)	DMSO with TEMPO	90	2.5	38 **(20)**	Xu et al[55]
9	Matrix metalloproteinase radioligand			4-An	ClO_4^-	Batch (2 steps)	DMF-trace H_2O	130	3	70 **(10-20)**	Selivanova et al[128]
10	[^{18}F]CB91			2-Thi	TFA^-	Microreactor (1 step)	DMSO	190	0.25	42 ± 7	Saccomanni et al[130]
11	5-HTc receptor radioligand			4-Tol	TsO^-	Batch with TEMPO (2 steps)	DMF	130	10	**(7.8 ± 2.7)**	Kim et al[131]
12	[^{18}F]MFBG			4-An	TfO^-	Pyrolysis of $^{18}F^-$ salt (2 steps)	Toluene-MeCN	120	8	**(31)**	Hu et al[71]

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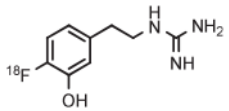
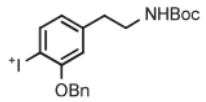
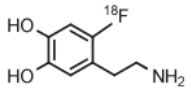
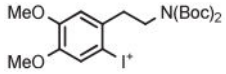
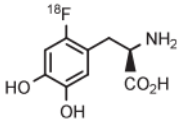
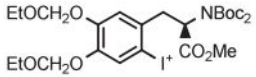
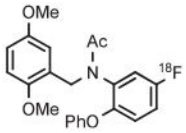
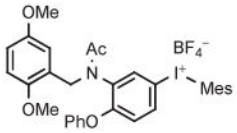
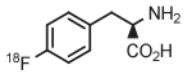
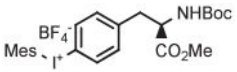
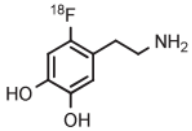
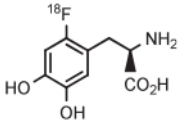
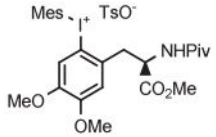
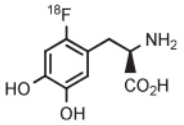
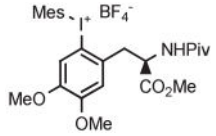
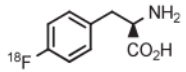
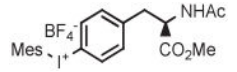
	Radiotracer		Precursor (ArI^+SGX^-)			Labeling Conditions					
Entry	Name	Structure	ArI^+	SG	X^-	Labeling Technique	Solvent	°C/W	min	Yield,[a] %	Reference
13	[^{18}F]FMHPG			2-Thi	Br^-	Batch with TEMPO (3 steps)	DMF-H_2O	150	25	45 (7)	Jang et al[133]
14	[^{18}F]6-FDA			4-An	TfO^-	Pyrolysis of $^{18}F^-$ salt (2 steps)	Toluene	150	4	46 ± 7 **(36 ± 4)** or **(72 ± 10)**	Neumann et al[38]
15	[^{18}F]FDOPA			4-An	TfO^-	Pyrolysis of $^{18}F^-$ salt (2 steps)	Diglyme	140	5	40 **(14 ± 4)**	Kuik et al[137]

Abbreviations: DMF, dimethylformamide; DMSO, dimethyl sulfoxide; [^{18}F]FIMX, [^{18}F]4-fluoro-*N*-methyl-*N*-(4-(6-(methylamino)pyrimidin-4-yl)thiazol-2-yl)benzamide; [^{18}F]FMHPG, [^{18}F]4-fluoro-3-hydroxyphenethylguanidine; [^{18}F]MFBG, [^{18}F]1-(3-fluorobenzyl)guanidine; [^{18}F]6-FBT, [^{18}F]4-(6-fluorobenzo[*d*]thiazol-2-yl)-*N*-methylaniline; [^{18}F]6-FDA, [^{18}F]6-fluorodopamine; [^{18}F]SP203, 3-fluoro-5-(2-(2-[^{18}F] (fluoromethyl)-thiazol-4-yl)ethynyl)benzonitrile; MW, microwave (batch); TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxyl.

[a]Values in plain type are yields before isolation. Values in bold and parentheses are yields after isolation.

TABLE 4

Radiotracers prepared from aryl(mesityl)iodonium salts: copper mediated

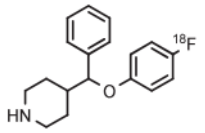
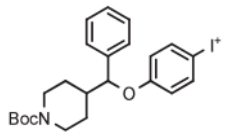
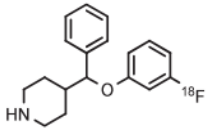
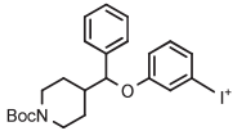
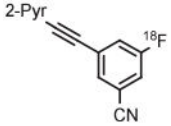
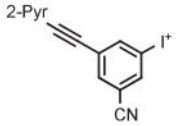
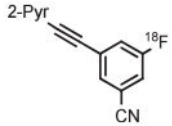
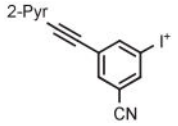
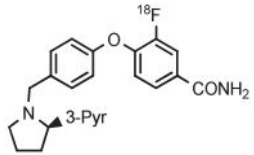
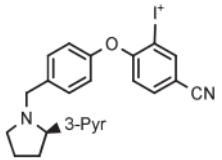
Entry	Target radiotracer Name	Target radiotracer Structure	Precursor Structure	Labeling Technique	Labeling Conditions Solvent	°C	min	Yield,[a] %	Reference
1	[^{18}F]FDAA1106			Minimalist (1 step)	dmf	85	20	93 **(60) (41 ± 3)**	Zlatopolskiy et al,[105] Zischler et al[138]
2	[^{18}F]4-FPhe			Minimalist (2 steps)	DMF	85	20	81-92 **(53-66) (56 ± 5)**	Zlatopolskiy et al,[105] Zischler et al[138]
3	[^{18}F]6-FDA			Minimalist (2 steps)	DMF	85	20	71-94 **(46)**	Zlatopolskiy et al[105]
4	[^{18}F]FDOPA			Batch	DMF	85	20	17 ± 5	Ichiishi et al[41]
5	[^{18}F]FDOPA			Batch	DMF	85	20	31 ± 3	Ichiishi et al[41]
6	[^{18}F]4-FPhe			Batch	DMF	85	20	23 ± 5	Ichiishi et al[41]

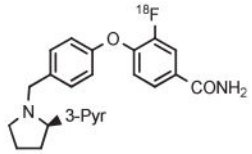
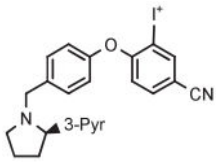
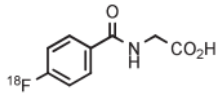
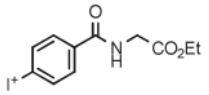
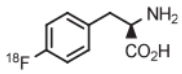
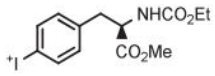
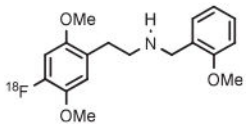
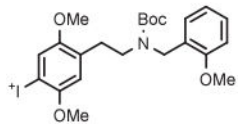
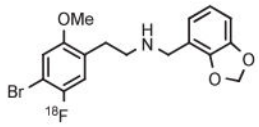
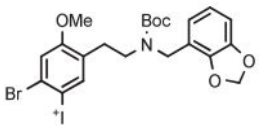
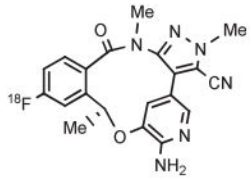
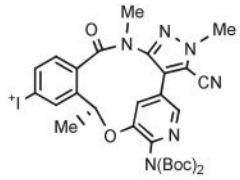
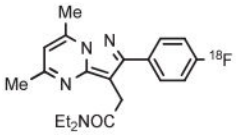
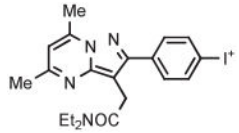
Abbreviations: DMF, dimethylformamide; [^{18}F]4-FPhe, [^{18}F]L-4-fluorophenylalanine; [^{18}F]6-FDA, [^{18}F]6-fluorodopamine.

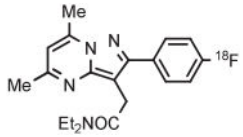
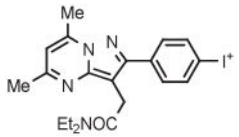
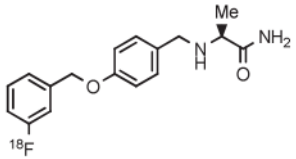
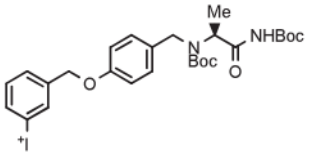
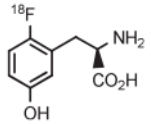
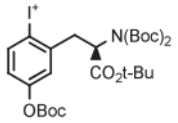
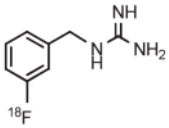
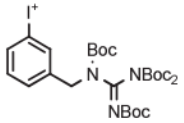
[a]Values in plain type are yields before isolation. Values in bold and parentheses are yields after isolation.

TABLE 5

Radiotracers prepared from aryliodonium ylides

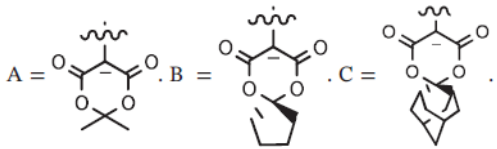
	Radiotracer Target		Precursor (ArI^+Aux^-)		Labeling conditions					
Entry	**Name**	**Structure**	**ArI^+**	**Aux^-**[a]	**Mode**	**Solvent**	**°C**	**min**	**Yield,**[b] **%**	**Reference**
1	[^{18}F]4-FPPMP			A	Batch (2 steps)	MeCN	130	20	20	Cardinale et al[94]
2	[^{18}F]3-FPPMP			A	Batch (2 steps)	MeCN	120	20	**(20 ± 5)**	Cardinale et al[94]
3	[^{18}F]FPEB			B	Batch (1 step)	DMF	80	5	49 ± 6	Stephenson et al[139]
4	[^{18}F]FPEB			B	MR (1 step)	DMF	200	~1	**(20 ± 5)**	Stephenson et al[139]
5	[^{18}F]LY2459989			B	MR (2 steps)	DMF	120	5	76	Cai et al[140]

	Radiotracer Target		Precursor (ArI^+Aux^-)		Labeling conditions					
Entry	**Name**	**Structure**	**ArI^+**	**Aux^-** [a]	**Mode**	**Solvent**	**°C**	**min**	**Yield,** [b] **%**	**Reference**
6	[^{18}F]LY2459989			B	Batch (2 steps)	DMF	80	5	49 **(30-43)**	Cai et al[140]
7	[^{18}F]PFH			B	Batch (2 steps)	DMF	130	10	**(46 ± 3)**	Nkepang et al[142]
8	[^{18}F]4-FPhe			B	Batch (2 steps)	DMF	120	10	55 ± 4	Rotstein et al[67]
9	[^{18}F]CIMBI-198			B	Batch with TEMPO (2 step)	DMF	135	20	12 ± 3 **(2)**	Petersen et al[143]
10	^{18}F-Labeled 5-HT_{2A} receptor radiotracer			B	Batch (2 steps) with TEMPO	DMF	135	20	76-77 **(10-12)**	Petersen et al[143]
11	[^{18}F]Lorlatinib analog			B	Batch (2 steps)	DMF	80	10	**(14)** [c]	Collier et al[144]
12	[^{18}F]FDPA			C	Batch (1 step)	DMF	120	15	40 ± 3	Wang et al[145]

	Radiotracer Target		Precursor (ArI^+Aux^-)		Labeling conditions					
Entry	**Name**	**Structure**	**ArI^+**	**Aux^{-a}**	**Mode**	**Solvent**	**°C**	**min**	**Yield,[b] %**	**Reference**
13	[^{18}F]FDPA			C	Batch (1 step)	MeCN	120	12	45 ± 8	Wang et al[145]
14	[^{18}F]Safinamide			C	Batch (2 steps)	DMF	120	10	15	Rotstein et al[93]
15	[^{18}F]FMT			C	Batch (2 steps)	DMF	120	20	60 **(12)**[cb]	Rotstein et al[93]
16	[^{18}F]MFBG			C	Batch (2 steps)	DMF	120	10	70 (**14**)[c]	Rotstein et al[93]

Abbreviations: DMF, dimethylformamide; [^{18}F]FMT, [^{18}F]L-2-fluoro-meta-tyrosine; MeCN, acetonitrile; [^{18}F]MFBG, [^{18}F]1-(3-Fluorobenzyl)guanidine; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxyl.

a



*b*Values in bold and parentheses are yields after isolation.

*c*Not decay corrected.