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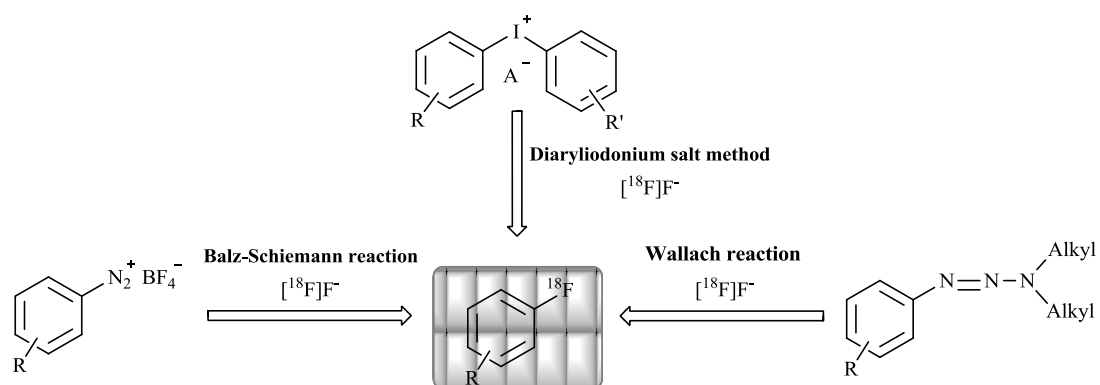


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Title: ^{18}F -Labeled Aryl-Tracers through Direct Introduction of $[^{18}\text{F}]$ Fluoride into Electron-Rich Arenes

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GRAPHICAL ABSTRACT



^{18}F -Labeled Aryl-Tracers through Direct Introduction of [^{18}F]fluoride into Electron-Rich Arenes

Mitja Kovač^{a,b}, Sylvie Mavel^a, Marko Anderluh^{b,*}

^a *Université François-Rabelais de Tours, INSERM U930, 37000 Tours, France*

^b *University of Ljubljana, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Aškerčeva 7, 1000 Ljubljana, Slovenia*

Correspondence should be sent to: Marko Anderluh, University of Ljubljana, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Aškerčeva 7, 1000 Ljubljana, Slovenia, Fax: +386-1-42-58-031, Tel: +386-1-47-69-639, E-mail: marko.anderluh@ffa.uni-lj.si.

ABSTRACT

Rapid and efficient methods using no-carrier-added [^{18}F]fluoride as the source of fluorine-18 for nucleophilic aromatic fluorination play an important role in the development of new radiopharmaceuticals for positron emission tomography (PET). Molecules that bear electron-rich aromatic moieties are especially difficult to label by direct single-step nucleophilic no-carrier-added radiofluorination. Classical Balz-Schiemann reaction with its modifications, Wallach reaction and diaryliodonium salts methodology are a few methods to enable this. The present review provides a critical overview of these chemical methods with the emphasis on diaryliodonium salt as precursors for the direct introduction of [^{18}F]fluoride into electron-rich arenes in synthesis of ^{18}F -labeled molecules for PET scanning.

Keywords: aromatic fluorination, arylfluoride, Balz-Schiemann reaction, diaryliodonium salts, ^{18}F -labeled molecules, PET, triazene.

1. INTRODUCTION

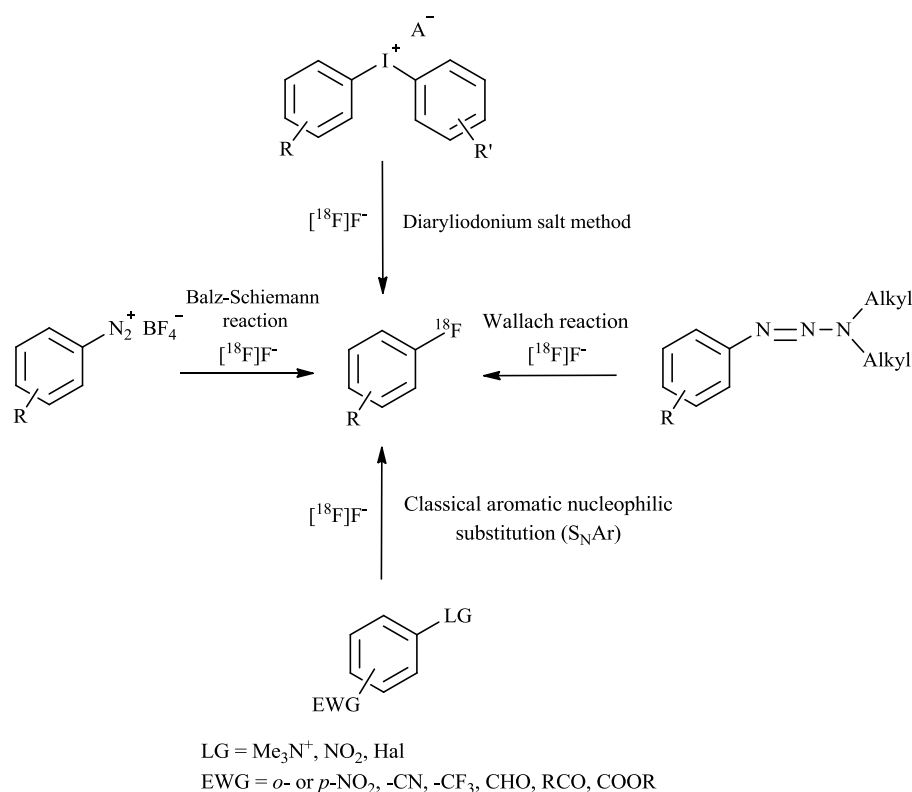
Positron emission tomography (PET) is a very powerful non-invasive *in vivo* molecular imaging technique that allows visualization, characterization, and quantification of biochemical target function and physiopathological processes at the cellular or molecular levels even before macroscopic anatomical and clinical signs of a disease are observed in animal and human subjects [1, 2, 3]. Thus, it is increasingly applied in clinical research and diagnosis, as well as in drug discovery, development, and therapy [1, 4–6]. Expansion of PET utility depends on the development and availability of selective and specific positron-emitting radionuclide-labeled molecular probes for particular biochemical targets or pathways that enable their non-invasive imaging and quantification *in vivo* [4, 7, 8]. The development of receptor-specific probes is far from trivial and represents an important challenge for synthetic and medicinal chemists. Fluorine-18 is the most attractive and favored radiolabel for *in vivo* imaging among the available PET radionuclides due to its characteristic physical and chemical properties [1-3, 9–15]. No-carrier-added (n.c.a.) [¹⁸F]fluoride ([¹⁸F]F⁻) is nowadays mostly produced via the proton irradiation of an [¹⁸O]-enriched cyclotron water target, and according to the ¹⁸O(p,n)¹⁸F reaction [9, 11, 12] which renders the anion, due to its high degree and strength of hydration in aqueous solution, poorly nucleophilic [16]. Still, a variety of rapid phase-transfer-type protocols have been developed based on trapping and subsequent elution of [¹⁸F]F⁻ from the anion-exchange resin [17], with the addition of either bulky counter-cations (e.g. of Bu₄N⁺ HCO₃⁻) or cryptands (e.g. diazacryptand Kryptofix 2.2.2., K₂₂₂) with alkali metal salts (e.g. K₂CO₃) in order to obtain (after azeotropic drying step(s)) a highly nucleophilic [¹⁸F]F⁻ system, such as Bu₄N⁺ [¹⁸F]F⁻ ([¹⁸F]TBAF) and [¹⁸F]KF/K₂₂₂ complex [9, 18]. Although completely anhydrous or “naked” [¹⁸F]F⁻ reagents are never obtained by these procedures, their degree of dryness are high enough to perform difficult reactions, such as aromatic nucleophilic substitution in polar aprotic anhydrous organic solvents (e.g. DMSO, CH₃CN, DMF).

A major challenge in PET radiotracer development is to find an efficient and rapid method for n.c.a. incorporation of cyclotron-produced [¹⁸F]F⁻ into an organic molecule. This may be achieved at aliphatic and aromatic sites by substitution reactions [9-12]. Labeling at aliphatic carbon atoms using sulfonate ester (mesylate, tosylate) or halide leaving groups can be accomplished very efficiently, even in the presence of trace water [19] or in sterically hindered alcohols such as *tert*-butyl alcohol (*t*-BuOH) as a protic reaction medium [9, 18, 20]. However, fluorine-18 bound to an aliphatic carbon atom is often prone to de-fluorination *in vivo*, giving rise to [¹⁸F]F⁻, which binds avidly to bone, including the skull, and compromises PET measurements with the failure to image specific target *in vivo* [21–23]. However, attachment of fluorine-18 to an aromatic carbon atom

through a stronger C-F bond compared to fluoroalkyl bond greatly reduces the tendency for radio-defluorination. Consequently, methods for the introduction of fluorine-18 into aromatic ring systems play an important role in the development of new radiopharmaceutical for PET.

There are principally two common strategies for the direct ^{18}F -labeling of the arenes: (1) electrophilic; and (2) nucleophilic ^{18}F -substitution, among which the latter dominates in importance of researches as will be discussed in the following sections. Several nucleophilic ^{18}F -substitution methods to obtain ^{18}F -labeled aryl fluorides have been established, evaluated, and applied [2, 3, 9, 11, 12]. As nucleophilic aromatic substitution is an energetically demanding reaction and not all biological molecules or drug candidates contain a suitably activated aryl ring for fluorination by the addition-elimination mechanism, the direct incorporation of ^{18}F into electron-rich arenes represents a significant challenge in the synthesis of PET tracers. In order to perform radiofluorination successfully, reproducibly, and in acceptable to high radiochemical yields (RCYs), radiotracers are usually designed so that the electron-withdrawing group (EWG), such as NO_2 , CN , CHO , COR , COOR , and CF_3 , is easily incorporated in the *para* and/or *ortho* position to the good leaving group (LG) (NO_2 , Halides, $\text{Me}_3\text{N}^+ \text{X}^-$; $\text{X}^- = \text{TfO}^-$, TsO^- , ClO_4^- , I^-) [9, 24–29]. In spite of the presence of EWG, quite high reaction temperatures are still required for n.c.a. ^{18}F -labeling. Synthesis of ^{18}F fluoropyridine derivatives proceeds in a similar fashion since these compounds are reactive toward nucleophilic substitution at the C(2) and C(4) positions [30]. In some cases, extra steps after labeling have to be performed occasionally to modify or completely eliminate the activating group on account of a certain loss of overall RCY and specific activity (SA) [31, 32]. Electron-rich aromatic rings can in principle be more conveniently directly radiolabeled by electrophilic ^{18}F -substitution using ^{18}F fluorine gas ($^{18}\text{F}\text{F}_2 = ^{18}\text{F}\text{-}^{19}\text{F}$) or less reactive but more selective electrophilic ^{18}F -fluorination reagents derived from it, such as acetyl ^{18}F hypofluorite ($\text{CH}_3\text{COO}[^{18}\text{F}]\text{F}$) [1, 2, 33, 34]. Fluoro-demetalation reactions using organomercuric or preferably less toxic organostannane precursors afford more regioselective aromatic ^{18}F -fluorination with $^{18}\text{F}\text{F}_2$ and $^{18}\text{F}\text{CH}_3\text{COOF}$ as electrophilic radiofluorinating agents. In this manner some important radiopharmaceuticals such as 6- ^{18}F fluoro-L-3,4-dihydroxyphenylalanine (6- ^{18}F fluoro-L-DOPA) [35–37], 2- ^{18}F fluoro-L-tyrosine [38] (1*R*,2*S*)-4- ^{18}F fluorometaraminol [39] have been prepared. Important consideration of using an organometallic approach is to ensure that there are no residual amounts of the metals in the final product which would complicate the quality control analysis. However, electrophilic radiofluorination of organic compounds has several significant shortcomings [1, 2, 11, 12]. Firstly, the theoretical maximum achievable RCY can be only 50% because only half the radioactivity of $^{18}\text{F}\text{F}_2$ can be utilized for mono-radiofluorination of an organic compound (only one of the fluorine atoms in molecular

$[^{18}\text{F}]$ fluorine carries the ^{18}F label, the other 50% of the input activity is lost in the form of fluoride) which has not been realized in practice. Secondly, electrophilic radiofluorination is not applicable to n.c.a. labeling, because $[^{18}\text{F}]\text{F}_2$ is produced along with non-radioactive fluorine gas ($^{19}\text{F}_2$) as a carrier in order to increase the recovering efficiency of $[^{18}\text{F}]\text{F}_2$ from the cyclotron target after its production. Thus, the addition of $^{19}\text{F}_2$ significantly lowers (100-1000x) the specific radioactivity (SA) of $[^{18}\text{F}]\text{F}_2$ compared to the SA of $[^{18}\text{F}]\text{F}^-$ even when $[^{18}\text{F}]\text{F}_2$ is generated via $^{18}\text{O}(p,n)^{18}\text{F}$ reaction [40]. Consequently, the SA of radiotracers prepared by the electrophilic approach are typically less than 0.4 GBq/ μmol (~ 0.011 Ci/ μmol) and usually too low for PET investigations of low density *in vivo* imaging. High SA also enables radiotracers to be administered to subjects in low mass doses (1-10 nmol or sub-microgram level) to avoid any toxic or pharmacological effects and perturbation of the biological target or process [9].



Scheme 1. Direct regioselective n.c.a. methods for the radiosyntheses of $[^{18}\text{F}]$ fluoroarenes using $[^{18}\text{F}]$ fluoride anion.

Given the above reasons, the ultimate goal is to perform direct regioselective n.c.a. $[^{18}\text{F}]\text{F}^-$ incorporation into complex electron-rich arenes as late as possible in the synthetic sequence to obtain a radiotracer of high SA. This is a particular challenge in arenes of high electron density, where an electrophilic aromatic carbon or intermediate should be generated. Only a limited number of available methods proceed via generation of

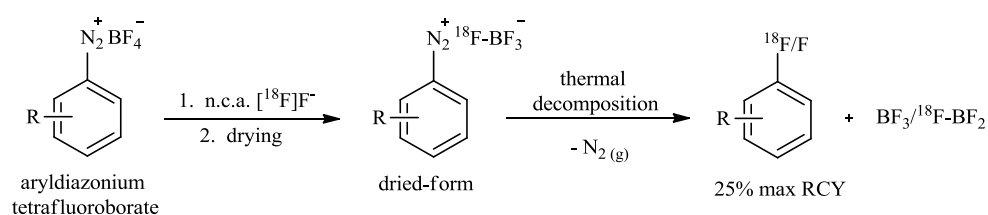
mentioned electrophilic species, namely, Balz-Schiemann reaction [41], Wallach reaction [42], and more recently with the use of diaryliodonium salt precursors (Scheme 1) [43, 44]. This review focuses on radiolabeling strategies applied in the synthesis of ^{18}F -labeled aryl-tracers from electron rich aryl precursors. Furthermore, pros and cons of each method are highlighted, and an overview of the successful and most recent examples with an emphasis on diaryliodonium salt precursors is provided.

2. RADIOFLUORINATION OF ELECTRON-RICH ARNES VIA A BALZ-SCHIEMANN REACTION

Although known for almost a century, the Balz-Schiemann reaction [41] is still the broadest substrate scope method for the regioselective nucleophilic introduction of fluorine into aromatic ring. This is a deaminative fluorination type of reaction composed of three sequential steps: (1) diazotiation of primary aromatic amine in aqueous medium with sodium nitrite (NaNO_2) and fluoroboric acid (HBF_4) at $0\text{--}5^\circ\text{C}$ to produce arenediazonium tetrafluoroborate ($\text{ArN}_2^+\text{BF}_4^-$); (2) isolation and drying of $\text{ArN}_2^+\text{BF}_4^-$ to avoid side formations of phenols and biaryl ethers [45]; and (3) thermal fluorinated decomposition of $\text{ArN}_2^+\text{BF}_4^-$ (fluoro-de-diazotiation) [46, 47]. However, this method suffers from yield reproducibility problems because isolation and complete drying can be tedious and unsafe, and controlled thermal decomposition of $\text{ArN}_2^+\text{BF}_4^-$ is problematic [45, 48]. To overcome reproducibility problems, simplify the procedure, broaden substrate tolerance, improve safety, and to increase the yields, alternative approaches based mostly on one-pot methodology (*in situ* fluoro-de-diazotiation) in non-aqueous solvents have been developed during the last few decades [48–56].

Decomposition of aryldiazonium cations can occur by an ionic (heterolytic) pathway via aryl cation intermediates or by a homolytic pathway that generates aryl radical intermediates which quickly react with fluoride or any other nucleophile due to their high reactivity and non-selectivity via a $\text{S}_{\text{N}}\text{Ar}1$ type of reaction mechanism [57–59]. The delicate decomposition pathway balance is crucially dependent on the substituents in the aromatic ring and reaction conditions. More precisely, substituents and their substitution pattern affect stability of the aryldiazonium ion, its redox potential, and consequently its decomposition temperature and pathway [47, 59, 60]. For successful fluoro-de-diazotiation, conditions should be carefully chosen to promote aryl cation formation. The solvent, pH of the medium, the nature of the counterion, and the presence of reducing agents and/or radical sources decisively influence arylfluoride yields. The choice of the solvent is one of the most important parameters [59, 60] and so to facilitate fluoro-de-diazotiation it should possess the following properties: (1) it should dissolve all the reagents with minimal solvation of fluoride anion; (2) it should be non-

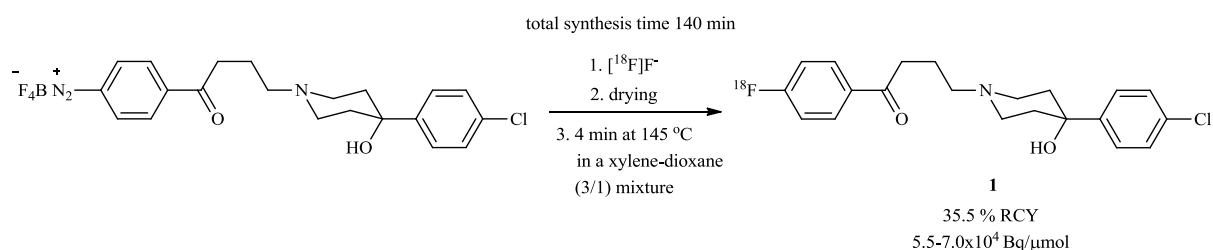
nucleophilic; (3) it should have suitably high redox potential to avoid reduction of the aryldiazonium ion and consequently suppress the homolytic decomposition pathway; (4) it should be aprotic; and (5) it should have a high enough boiling point as radical decomposition pathway is kinetically and thermodynamically favored to an ionic pathway. Chlorinated solvents (e.g. CCl_4) have been reported to have a beneficial effect on arylfluoride yields via probable enhancement of the ionic decomposition pathway [60]. Selection of the suitable counter-anion with non-nucleophilic and non-reducing properties is also an important consideration to avoid its interference with fluorination. Since only one of the four fluorine atoms is retained in the final product after thermal decomposition of diazonium tetrafluoroborate salt, the Balz-Schiemann reaction is from a radiochemical point very inefficient (Scheme 2). Therefore, the yield of $^{18}\text{F}^-$ labeling is theoretically limited to only 25%, and more importantly, the dilution of SA by the non-radioactive fluorine in the counterion $^{18}\text{F}^-/\text{BF}_3^-$ (carrier added $^{18}\text{F}^-$ in the form of ^{18}F -labeled tetrafluoroborate anion) is high with the consequential great possibility of failure to localize the biochemical target in the desired tissue(s) [61]. Namely, co-administered non-radioactive tracer would saturate targets by competitive displacement of radiotracer and thereby remove most of the localized signal from the radiotracer binding. In spite of the described limitations, the Balz-Schiemann reaction was the first method used in nucleophilic ^{18}F -labeling of arenes [62] and adapted to prepare some of the electron-rich ^{18}F -labeled amino acids, such as ^{18}F fluorophenylalanine isomers [63–65], 5- and 6- ^{18}F fluorotryptophan [66] as potential pancreas scanning agents, and 3,4-dihydroxy-5- ^{18}F fluorophenylalanine (5- ^{18}F fluoro-DOPA) as a potential brain capillaries scanner [67–71].



Scheme 2. The Balz-Schiemann reaction for the preparation of ^{18}F fluoroarenes; ^{18}F is introduced as ^{18}F -labeled tetrafluoroborate anion (carrier-added) via exchanged reaction.

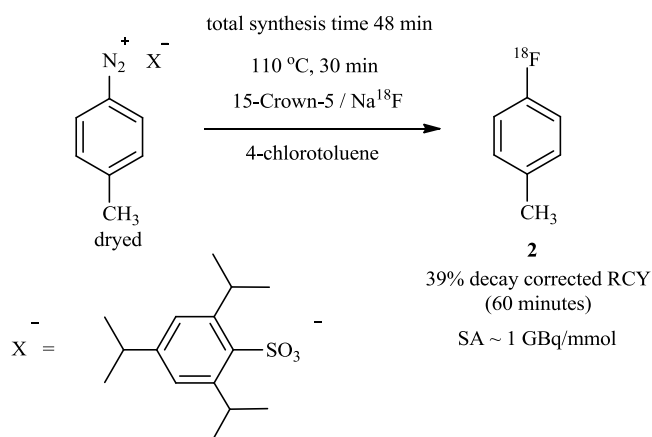
The syntheses of typical butyrophenone antipsychotic ^{18}F haloperidol (**1**) [70] and antifungal 4- ^{18}F fluconazole (1-2% decay non-corrected yield) [71] were performed by the modified Balz-Schiemann reaction. Also noteworthy, a 35.5% incorporation of ^{18}F into the ^{18}F haloperidol product from the corresponding diazonium fluoroborate precursor was reported (Scheme 3) [70]. A higher RCY than the maximal theoretical yield of 25% might be explained by the fact that ^{18}F introduced into the arene can come from $^{18}\text{F}^-$ which

exchanges into the fluoroborate salt (carrier-added) as well as coming from unexchanged [^{18}F]F $^-$ (non-carrier-added) [66]. Nevertheless, [^{18}F]haloperidol can be more conveniently prepared with higher SA using a single-step ^{18}F -for-LG exchange reaction [72] because the butyrophenone system is moderately activated toward a direct aromatic nucleophilic substitution.



Scheme 3. Synthesis of [^{18}F]haloperidol (**1**) by Balz-Schiemann reaction [70].

Knöchel and Zwernemann investigated several reaction parameters (solvents, reaction temperature and time, pH of the reaction medium, counter-anions, phase transfer catalysts, and the fluoride sources) influencing the [^{18}F]F $^-$ fluorination RCYs of *p*-tolylidiazonium ion used as a model precursor in a modified Balz-Schiemann reaction [73, 74]. The best result was obtained with *p*-tolylidiazonium 2,4,6-tri-isopropylbenzenesulfonate in *p*-chlorotoluene [74]. Under optimized conditions n.c.a. labeling with [^{18}F]fluoride gave a decay corrected (EOB) radiochemical yield of 39% (60 minutes) 4-[^{18}F]fluorotoluene (**2**) with a calculated specific radioactivity around 1GBq/μmol in a total synthesis time of 48 minutes (Scheme 4) [74]. In comparison, this method gave approximately 10⁴ times higher specific radioactivity of 4-[^{18}F]fluorotoluene than fluoro-de-diazonation using [^{18}F]-BF₃ as counter-anion in preparation of [^{18}F]haloperidol [70]. It should be noted that during optimization much lower or no fluorination yields of non-radioactive 4-fluorotoluene were obtained using K₂₂₂/KF and/or 18-Crown-6/KF complexes of the solubilized fluoride ion. The authors believe that the poor fluorination yields and slow reaction rates were related to ability of K₂₂₂ and 18-Crown-6 to complex the aryldiazonium ions [75–77]. In this regard solubilization of the fluoride was reduced, since parts of the cryptand reacted with aryldiazonium ion instead of mobilizing the potassium fluoride, thus enhancing the thermal stability of the complexed aryldiazonium ion and giving much lower fluorination yields.

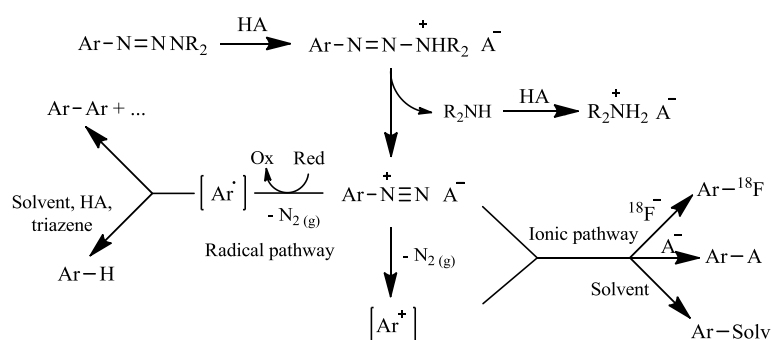


Scheme 4. No-carrier-added ¹⁸F-labeling of *p*-tolylidiazonium 2,4,6-triisopropylbenzenesulfonate by a modified Balz-Schiemann reaction [74].

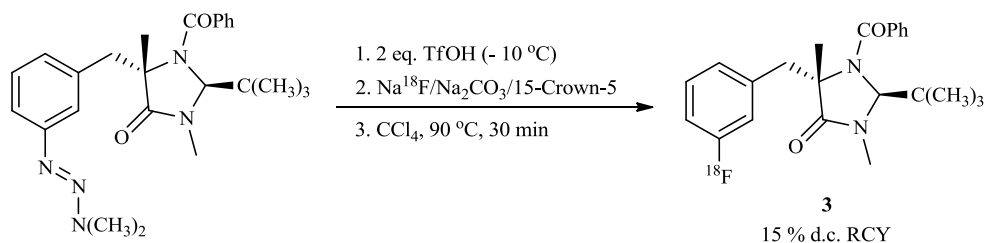
3. RADIOFLUORINATION OF ELECTRON-RICH ARENES BY WALLACH REACTION

1-Aryl-3,3-dialkyltriazenes (Ar-N=N-NR'R''), compounds having a diazoamino group are regarded as a protected form of anilines and stable surrogates of aryldiazonium ions [78]. Aryltriazenes are safely and mostly readily prepared by the coupling of diazotized aniline with amine, or by the action of Grignard reagents on aryl azides [79], and can be stored for a long period of time in cold temperatures protected from light. They are adaptable to numerous synthetic transformations with wide applicability in the chemical, medical, and technological fields [80, 81]. An essential advantage over aryldiazonium ions (Balz-Schiemann reaction) is their solubility in a number of (anhydrous) organic and ionic solvents that allows *in situ* generation of the corresponding aryldiazonium ion upon reacting with acids, and therefore enabling a one-pot fluoro-de-triazene reaction [60, 82]. In this respect laborious isolation, drying, and the accumulation of the potential hazardous and thermally unstable diazonium intermediates is avoided. Moreover, aryltriazenes can be easily isolated, chromatographically purified, introduced in the early stages of the synthesis, and functionalized and thermally decomposed in the presence of protic acid in the latest stages if the preceding reactions have been performed under non-acidic conditions [83, 84]. Thus, fluoro-de-triazene can be an attractive means of forming ¹⁸F-labeled fluoroarenes by direct nucleophilic substitution with [¹⁸F]F⁻ due to both the one-pot methodology and rapid nature of triazene transformation to fluoroarenes in order to obtain the tracers with good SA. Nevertheless, the decomposition of aryltriazenes proceeds via diazonium ions and consequently leads to the same yield and reproducibility problems as (modified) Balz-Schiemann method (Scheme 5).

Pages and Langlois [84] investigated the acidic decomposition of simple, non-activated 1-aryl-3,3-dialkyltriazenes in the presence of non-radioactive fluoride anions ($^{19}\text{F}^-$) by examining different parameters such as solvent, acid, fluoride source, stoichiometry, reaction temperature, time, and introduction order of the reaction components, in order to build a good model for radiofluorination so the radical decomposition pathway could be suppressed and the ionic pathway maximized. According to their findings, they have successfully radiofluorinated protected (*S*)-[^{18}F]-3-fluoro- α -methylphenylalanine (**1**) under optimized conditions through acidic decomposition of the corresponding 1-aryl-3,3-dimethyltriene precursor with 15 % RCY (decay corrected (d.c.) RCY, Scheme 6) [85].



Scheme 5. General competitive processes during n.c.a. [^{18}F]fluoro-de-triazonation and [^{18}F]fluoro-de-diazonation in the protic acid mediated decomposition of 1-aryl-3,3-dialkyltriazenes [84].

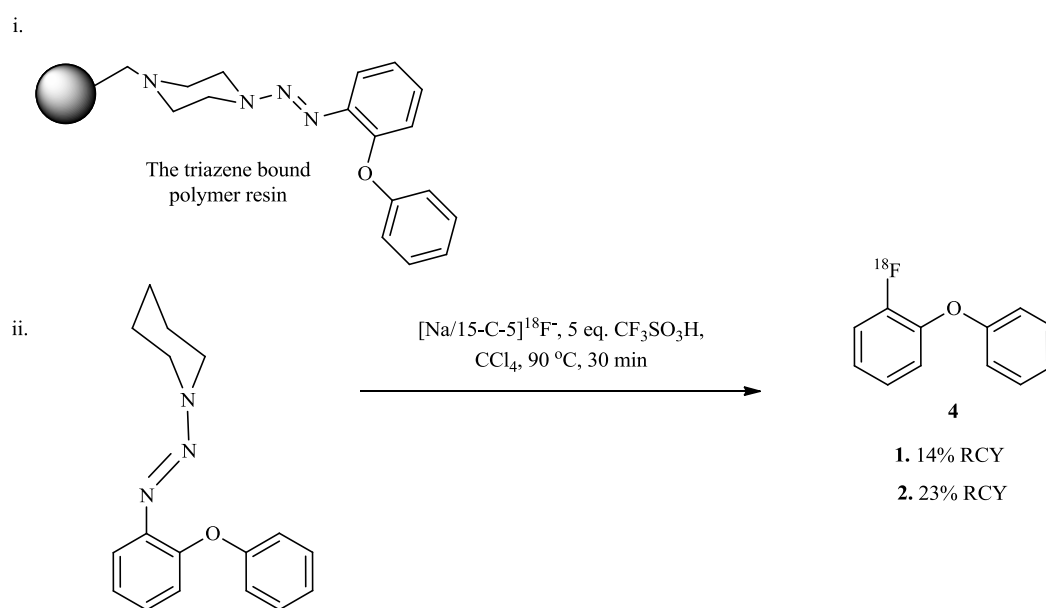


Scheme 6. Radiofluorination of protected form (*S*)-[^{18}F]-3-fluoro- α -methylphenylalanine (**3**) through acidic decomposition of the corresponding 1-aryl-3,3-dimethyltriene precursor [85].

The choice of the suitable protic acid is an important consideration to transform triazeno moiety via heterolytic decomposition into a diazonium group in order to obtain arylfluorides in reasonable yields. As the phenyl cation is highly reactive and a non-selective species, fluoro-de-triazonation is often accompanied by the formation of a substantial amount of the acid counterion-substituted byproduct (Ar-A). This is especially true when the protic acid is used in excess, even if its conjugate base (A^-) is considered non-nucleophilic (e.g. triflate anion) [84–87]. Since PET labeling reactions are performed with nanomolar amounts of [^{18}F]F $^-$, there is a vast

stoichiometric excess, typically about 10^3 - 10^4 -fold, of unlabeled precursor and acid [85]. Thus, the use of an acid constitutes a severe limitation to obtain considerable yields of Ar^{18}F by fluoro-de-triazonation. The competitive reactions during fluoro-de-triazonation are the main reason for very few examples of the successful application of the Wallach reaction in the preparation of complex ^{18}F fluoroarenes with RCYs not exceeding 2%: ^{18}F -1-methyl-4-(2-fluorophenyl)-1,2,3,6-tetrahydropyridine ($2\text{-}^{18}\text{F}$ -MPTP) [88], ^{18}F haloperidol, and ^{18}F spiroperidol [89].

Recently, Riss et al. [90] reported successful solid phase supported ^{18}F fluoro-de-triazonation of 2-phenoxy-1-(aryldiazenyl)piperazine to afford 1- ^{18}F fluoro-2-phenoxybenzene (**4**) in up to 14% RCYs using reaction conditions similar to that of Pages et al. (Scheme 7) [85]. It is however questionable whether the solid phase synthesis offers a significant advantage over the synthesis in solution, since the last method yielded the ^{18}F -labeled product under essentially the same conditions in a higher RCY of 23%.

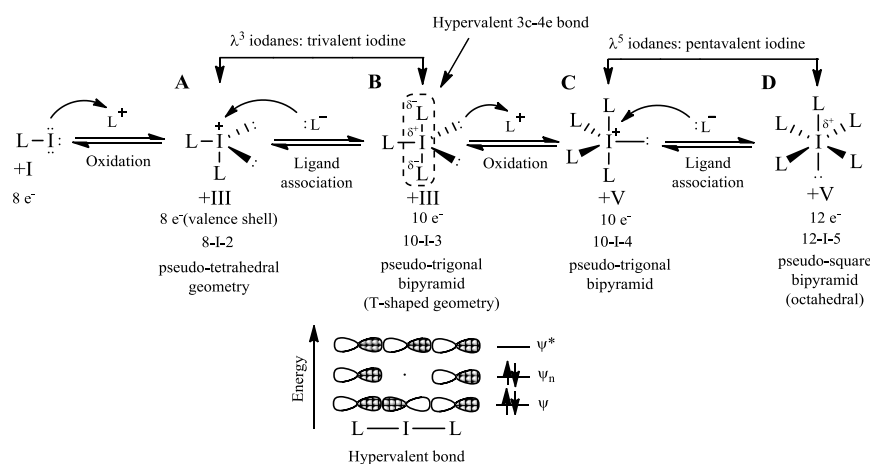


Scheme 7. (i.) N.c.a. ^{18}F fluoro-de-triazonation of solid phase supported 1-(aryldiazenyl)piperazine and (ii.) "soluble" n.c.a. ^{18}F fluoro-de-triazonation of 1-(aryldiazenyl)piperazine to obtain 1- ^{18}F fluoro-2-phenoxybenzene (**4**) [90].

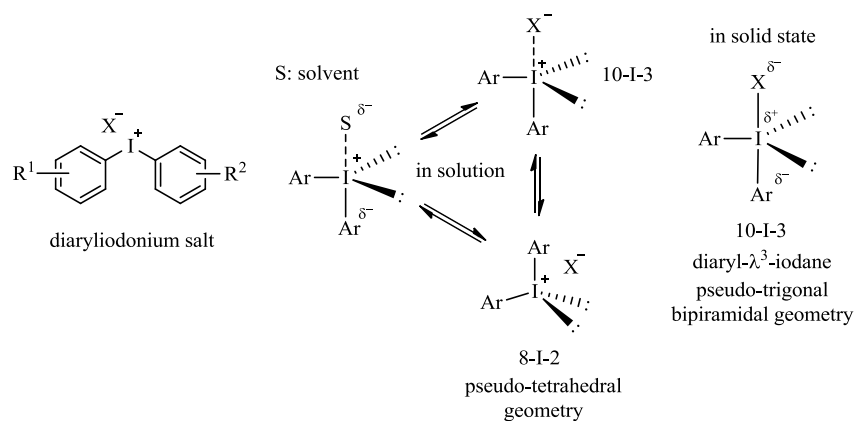
Because of limited RCYs, ^{18}F fluoro-de-triazonation is rarely applied for the production of ^{18}F -labeled tracers nowadays.

4. RADIOFLUORINATION OF ELECTRON-RICH ARENES BY DIARYLIODONIUM SALTS

Hypervalent iodine compounds have more than eight electrons in their valence shell [91]. The fundamental feature of these compounds is the highly polarized three-centered-four-electron (3c-4e) bond, in which the central iodine atom is electron-deficient or bears a positive charge, and monovalent ligands (L) share the corresponding negative charge. Thus, hypervalent iodine compounds react as electrophiles or/and oxidants at the iodine center. They belong to two general structural types: (1) iodine (III) compounds **A** and **B**, also named λ^3 -iodanes; and (2) iodine (V) compounds **C** and **D**, termed λ^5 -iodanes according to IUPAC nomenclature (Scheme 8) [91, 92]. In 10-I-3 species the interchange of axial and equatorial ligands via Berry pseudorotation as well as turnstile rotation is rapid, while such fluxional processes in 12-I-5 species is slower [93–95]. Hypervalent iodine compounds are used as mild, non-toxic (compare to heavy metals) and selective reagents due to exploitation of their electrophilic and excellent leaving-group character in a wide range of applications [91, 92, 96–99].



Scheme 8. General oxidation of iodine compounds. Polyvalent iodine compounds differ in the number of valence electrons surrounding the central iodine atom, the number of ligands and their chemical structure. In terms of the Martin-Arduengo N-X-L designation/notation [100], 8-I-2 (**A**) and 10-I-3 (**B**) species are derivatives of trivalent iodine and are termed according to IUPAC λ^3 -iodanes. 10-I-4 (**C**) and 12-I-5 (**D**) species are derivatives of pentavalent iodine and are termed λ^5 -iodanes (periodanes). According to the hypervalent model [101], the apical hypervalent 3c-4e bond in 10-I-3 species is close to linear, longer, and weaker compared to a regular covalent and equatorial bond and is responsible for high electrophilic reactivity of λ^3 -iodanes [96].

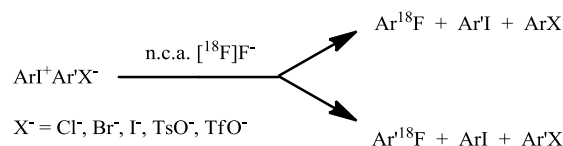


Scheme 9. Structure and configurations of diaryliodonium salts in solution and in the solid state.

The most common, stable, and well established class among polyvalent iodine compounds are diaryliodonium salts ($\text{ArI}^+\text{Ar}'\text{X}^-$). Their chemistry, preparative methods, and synthetic applications have been covered in previous reviews [43, 91, 92, 96]. According to conventional classification, they are defined as diaryl- λ^3 -iodanes or as positively charged 8-I-2 species with two aryl ligands and a closely associated negatively charged counterion. In a solid state, the overall X-ray experimentally determined geometry is pseudo-trigonal bipyramidal or approximately T-shaped with characteristic 3c-4e linear hypervalent bond (Schemes 8 and 9) [91, 92, 102, 103]. The least electronegative aromatic carbon or the most sterically demanding aryl group and both electron pairs reside in equatorial positions. On the other hand, the configuration of λ^3 -iodanes in solution is still debated, but a certain amount of dissociation is expected depending on the aryl substituents, anion of the salt, and the type of the solvent used [103]. Diaryliodonium salts are air- and moisture-stable, mild, nontoxic, and versatile, selective arylating agents delivering one of the aryl moieties to the nucleophile under polar, catalytic, or photo-chemical conditions. The salt is referred to as a symmetrical salt if $\text{R}^1 = \text{R}^2$, and as an unsymmetrical salt if $\text{R}^1 \neq \text{R}^2$ (Scheme 9).

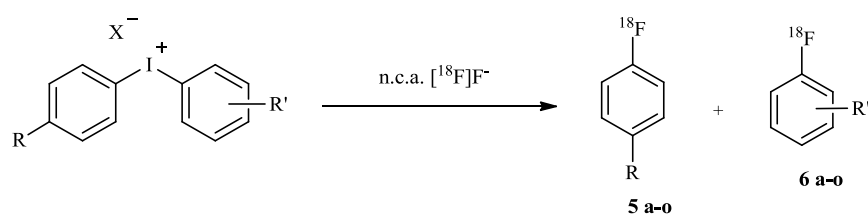
When utilizing diaryliodonium salts in reactions with nucleophiles, the nucleophile has a choice of displacing either of the two aryl groups due to the exceptional leaving group ability of the $-\text{IAr}$ fragment, which has been estimated to be roughly six orders of magnitude greater than that of triflate [104]. In this instance, one of the more recent application areas of diaryliodonium salts, firstly introduced in ^{18}F -radiochemistry by Pike and Aigbirhio in 1995 [105], is their use as suitable precursors for the preparation of n.c.a. ^{18}F -labeled arenes as potential radiotracers for PET imaging. Diaryliodonium salts allow direct introduction of ^{18}F fluoride ion in a single step into aromatic systems without the need for further activating groups and with little or no restriction on the nature of the functionality present [9]. Thus, they gain more and more interest for direct radiofluorination

of otherwise unfavorable electron-rich arenes. At this, symmetric diaryliodonium salts are generally preferred over unsymmetrical salts as no regioselectivity problems arise (Scheme 10). However, the use of unsymmetrical salts is in some situations desirable and necessary, such as when the starting materials are expensive or if one of the aryl substituent is very complex.



Scheme 10. Regioselectivity problems of direct n.c.a. [^{18}F]-fluorination of unsymmetrical diaryliodonium salts.

Table 1. Synthesis of simple n.c.a. [^{18}F]fluoroarenes via nucleophilic displacement of corresponding 4-substituted diaryliodonium salt by n.c.a. [^{18}F]fluoride. Selectivity for the product **6** increases with relative increase of electron density on the partner *para*-substituted phenyl ring.



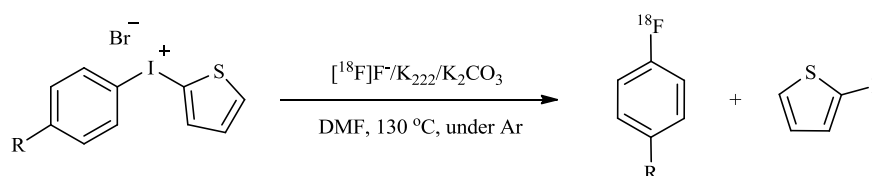
Compound	Ref.	R	R'	X ⁻	RCY 5 (%)	RCY 6 (%)	Selectivity for 6
5a/6a	[105]	CH ₃	H	TfO ⁻	~13 ^a	~26 ^a	2
5b/6b	[105]	OCH ₃	H	Br ⁻	^b	~62 ^a	> 62
5c/6c	[105]	OCH ₃	4-OCH ₃	CF ₃ CO ₂ ⁻	~55 ^a		
5d/6d	[107]	OCH ₃	H	TfO ⁻	0	96	> 96
5e/6e	[107]	<i>t</i> -BuO	H	TfO ⁻	0	95	> 95
5f/6f	[107]	OCH ₃	3-CH ₃	TfO ⁻	0	66	> 66
5g/6g	[28]	OCH ₃	3-Br	TfO ⁻	3±1	43±5	~ 14
5h/6h	[108]	CH ₃	H	TsO ⁻	10	43	~ 4
5i/6i	[108]	OCH ₃	H	TsO ⁻	~3 ^a	~77 ^a	~ 26
5j/6j	[108]	OCH ₃	4-CH ₃	TsO ⁻	9	36	4
5k/6k	[108]	OCH ₃	4-Cl	TsO ⁻	6	80	~ 13
5l/6l	[108]	OCH ₃	4-OCH ₃	TsO ⁻	90		
5m/6m	[109]	OCH ₃	3-CN	TsO ⁻	11	82	~ 7
5n/6n	[109]	OCH ₃	3-NO ₂	TsO ⁻	7	58	~ 8
5o/6o	[109]	OCH ₃	3-CF ₃	TsO ⁻	< 1	53	> 53

^a Average RCY, ^b Not detected

The outcome and regioselectivity of the fluorination has been shown to be strongly dependent on three parameters: (1) the electronic density (inductive and resonance effects of substituent groups on the aryl ring); (2) the substitution pattern; and (3) the steric structure of the diaryliodonium precursor [106]. Following the trend of $\text{S}_{\text{N}}\text{Ar}$, the n.c.a. [^{18}F]fluoride attack occurs preferably on the most electron-deficient arene in the absence of an *ortho* effect [9]. The strategy is therefore to make one of the aryl rings more electron-rich. Iodonium salts

containing *p*-methoxyphenyl (*p*-anisyl) (Table 1) [28, 105, 107–109] and 2-thienyl (Table 2) [106, 109–112] as highly electron rich arenes were found to lead to highly regioselective nucleophilic ^{18}F -fluorination of the partner aryl ring.

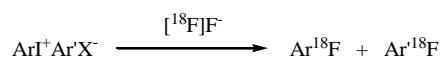
Table 2. Radiochemical yields of n.c.a. ^{18}F -fluorination of 4-phenyl(2-thienyl)iodonium bromides to obtain simple electron-rich and electron-poor 4-substituted ^{18}F -fluoroarenes [106].



R	H	CH ₃	OCH ₃	OBn	Cl	Br	I
RCY(%)	64 ± 4	32 ± 2	29 ± 3	36 ± 3	62 ± 4	70 ± 5	60 ± 8

Carroll et al. [113] have performed fluorination of simple 2-thienyliodonium salts and found that the process is not selective, and the 2-thienyl group, although highly electron-rich, may not be the ideal non-participating ring for production of fluoroarenes by the fluorination of diaryliodonium salts as had been described the same year by Ross et al. [106]. They concluded that it is the analysis, characterization, and isolation of 2-fluorothiophene that may be (extremely) problematic. Iodonium compounds with bulky aryl rings tend to undergo nucleophilic substitution on the bulky ring. However, the bulkiness alone is not an exclusive factor for stereoselective fluorination. The decisive factor is one (hydrophobic) group (e.g. methyl) at the *ortho*-position that shows a directing steric effect and induces an attack in the *ortho*-substituted aromatic ring [114–117], even though it is more electron-rich than the partner ring (Table 3, Entries 1, 3, 9-11, 15-16) [107, 118]. This preference increases further along with RCYs for doubly *ortho*- and/or more alkyl/methyl-substituted aryl rings in spite of increasing steric hindrance and electronic deactivation (Table 3, Entries 9-11, 15-17) [107, 118–120].

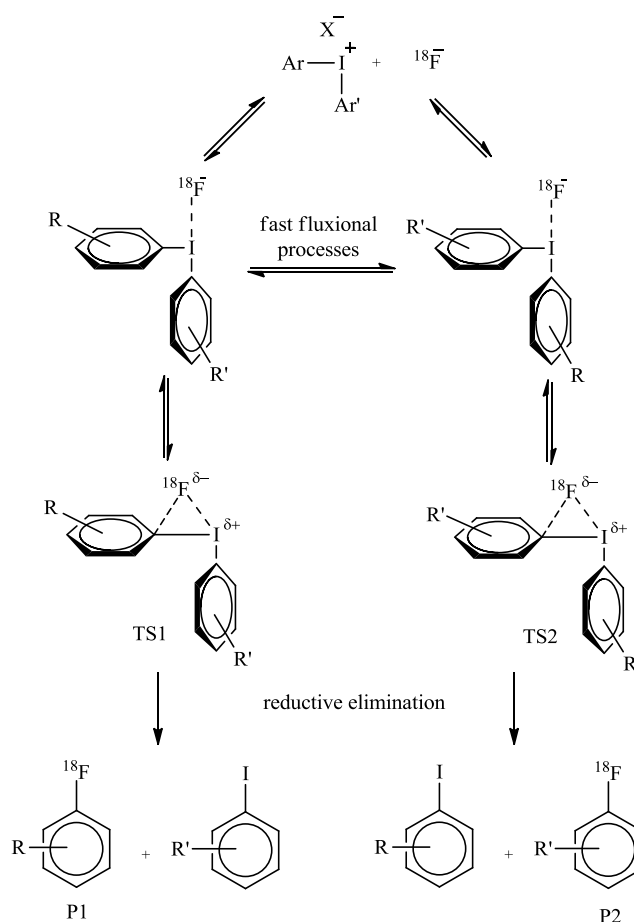
Table 3. Radiochemical yields and reaction selectivities of [¹⁸F]fluoroarenes obtained by radiofluorination of *ortho*-substituted diaryliodonium salts.



Entry	Ref.	Ar	Ar'	X ⁻	RCY of [¹⁸ F]fluoroarene (%)		Selectivity for Ar ¹⁸ F
					Ar ¹⁸ F	Ar' ¹⁸ F	
1	[118]	2-MeC ₆ H ₄	Ph	Cl ⁻	57	25	~2
2	[118]	2-MeC ₆ H ₄	2-MeC ₆ H ₄	Cl ⁻	83		
3	[118]	2-MeOC ₆ H ₄	Ph	Cl ⁻	6.5	60	~0.1
4	[118]	2-MeOC ₆ H ₄	2-MeOC ₆ H ₄	Cl ⁻	51		
5	[118]	2-BrC ₆ H ₄	Ph	Cl ⁻	68	25	~3
6	[118]	2-MeC ₆ H ₄	2-MeOC ₆ H ₄	Cl ⁻	75	4	~19
7	[118]	2-MeC ₆ H ₄	2-EtC ₆ H ₄	Cl ⁻	52	43	~1
8	[118]	2-MeC ₆ H ₄	2- <i>i</i> -PrC ₆ H ₄	Cl ⁻	48	40	~1
9	[118]	2,6-di-MeC ₆ H ₃	2-MeC ₆ H ₄	Cl ⁻	62	11	~6
10	[118]	2,4,6-tri-MeC ₆ H ₂	Ph	TsO ⁻	63	19	~3
11	[118]	2,4,6-tri-MeC ₆ H ₂	2-MeC ₆ H ₄	Cl ⁻	59	33	~2
12	[118]	2,4,6-tri-MeC ₆ H ₂	2,6-di-MeC ₆ H ₃	TsO ⁻	21	61	~0.3
13	[107]	2-MeC ₆ H ₄	4- <i>t</i> -BuC ₆ H ₄	TfO ⁻	48	12	4
14	[107]	2-MeC ₆ H ₄	4-MeOC ₆ H ₄	TfO ⁻	64	0	> 64
15	[107]	2,4,6-tri-MeC ₆ H ₂	Ph	TfO ⁻	96	0	> 96
16	[107]	2,4,6-tri-MeC ₆ H ₂	2-MeC ₆ H ₄	TfO ⁻	52	13	4
17	[107]	2,4,6-tri-MeC ₆ H ₂	4-MeOC ₆ H ₄	TfO ⁻	67	0	> 67
18	[106]	2-MeOC ₆ H ₄	2-thienyl	Br ⁻	61±5	^a	^a

^a Not detected.

The so-called ‘*ortho*-effect,’ first mentioned in 1967 by Le Count et al. [114], can be explained by examining the arrangement of the aryl groups around the iodine-centered pseudo trigonal bipyramidal intermediate; sterically more demanding *ortho*-substituted aromatic ring is preferentially in the equatorial position to decrease the steric strain to a greater extent, and is therefore more proximal (*syn*) for ¹⁸F-fluorination compared to other less bulky axial positioned arene (Scheme 11) [116, 117, 119–121].



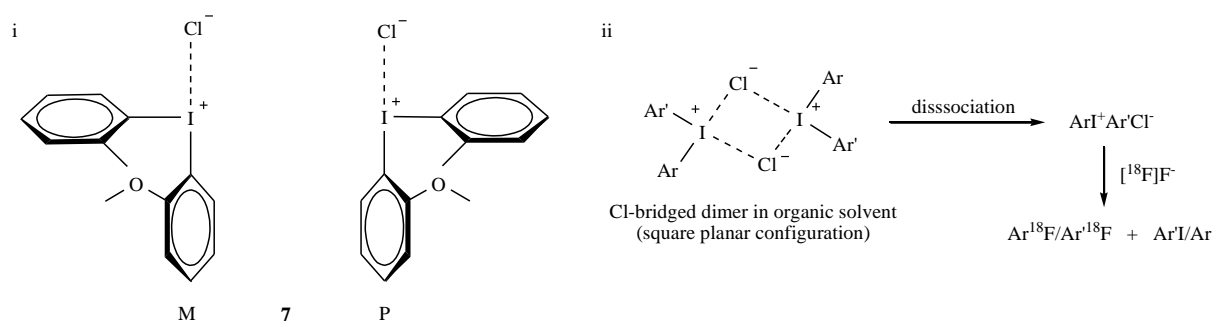
Scheme 11. Suggested outline mechanism for the radiofluorination of an unsymmetrical substituted diaryliodonium salt through transition states TS1 and TS2 to give ^{18}F -labeled products P1 and P2, respectively [118].

As studied and rationalized by Chun et al. [118] the electronic features of the *ortho*-substituent and transition state stabilities are important in determining product selectivity, because the *ortho*-effect is not purely related to substituent bulkiness (Table 3, Entries 3, 6-8). Opposing (Table 3, Entry 3) and reinforcing (Table 3, Entry 5) electronic properties of *ortho* substituent appeared to be important in determining product selectivity. Thus, when both of the *ortho* substituents are of similar effective bulkiness, $[^{18}\text{F}]$ fluoride together with the more electron-deficient ligand would eliminate in order to decrease the positive charge on the iodine atom (Table 3, Entries 6-8). They suggested that *ortho*-hydrophobic groups create lipophilic micro-environment in which the incoming $[^{18}\text{F}]$ fluoride can act as a powerful nucleophile (even in moderately hydrated state), by first loosely binding to the hypervalent iodine atom and then attacking the locally lipophilic *ortho*-substituted ring (Scheme 12). They also found evidence that the reactions of $[^{18}\text{F}]$ fluoride with unsymmetrical diaryliodonium salt (2-methylphenyl)(phenyl)iodonium chloride) comply with the Curtin-Hammett principle [118, 122]. Accordingly,

they proposed that radiofluorination of an unsymmetrical diaryliodonium salt involves an attack of [¹⁸F]fluoride onto either of the two rapidly interconverting conformers [94, 95] relative to the rate of product formation, yielding two transition states (TS1 and TS2) that each give a single radiofluorinated product (P1, P2), whereas the products do not undergo interconversion (Scheme 11). Consequently, the ratio of radiofluorinated products (P1/P2) was not in direct proportion to the relative concentrations of the conformational isomers in the substrate, but is dependent only on the difference in standard free energies of the respective transition states ($P1/P2=e^{-(G_{TS1}-G_{TS2})/RT}$), which is relatively small compared to the activation energies for the same reactions. In other words, P1/P2 will increase with increasing difference between free energies of the respective transition states. As depicted in the Scheme 11, generally higher Ar¹⁸F yields compared to Balz-Schiemann and Wallach reactions probably arise from a [¹⁸F]fluoride preferential attack on the proximal equatorial aryl ring, and subsequent decomposition of “trigonal” transition state which limits the formation of reactive intermediates, e.g. aryl cations or aryl radicals. This might explain why even the addition of water is not detrimental for successful radiofluorination [118, 123–125]. Other mechanisms for reactions of diaryliodonium salts with [¹⁸F]fluoride have also been proposed, such as ‘turnstile’ mechanism by Grushin [117] and S_NAr by Ross et al. [106] on the basis of a reasonable good linear fit between reaction rates of *para*-substituted aryl(2-thienyl)iodonium bromides and Hammett substituent constants. The application of the Hammett constants failed for the *ortho*-OMe substituted precursor, as claimed by Authors, due to the strong *ortho-effect* which could not be taken into account by that approach. *Meta*-derivatives are known to be electron-rich in comparison to corresponding *para*- and *ortho*-derivatives, and are therefore more problematic for nucleophilic fluorination. Unsymmetrical diaryliodonium salts have also been shown to be effective precursors to obtain simple 3-[¹⁸F]fluoroarenes bearing *meta* electron-withdrawing or *meta* electron-donating substituents [109, 112, 126] 3-[¹⁸F]fluoroheteroarenes [127] in moderate to high RCYs. Also noteworthy is that pyridyliodonium salts are the most appropriate precursors for the preparation of fluorine-18 labeled 3-fluoropyridine that is more stable *in vivo*, but less easily available via conventional S_NAr reaction than 2-fluoro and 4-fluoropyridines. The use of 4-methoxyphenyl moiety as a partner aromatic ring in 4-methoxyphenyl(3-pyridine) iodonium salt gave 3-[¹⁸F]fluoropyridine in radiochemical yields of about 60%. The same approach has been employed to yield 3-[¹⁸F]fluoroquinoline in about 25% RCY via a 4-methoxyphenyl(3-quinoline) iodonium salt precursor [127].

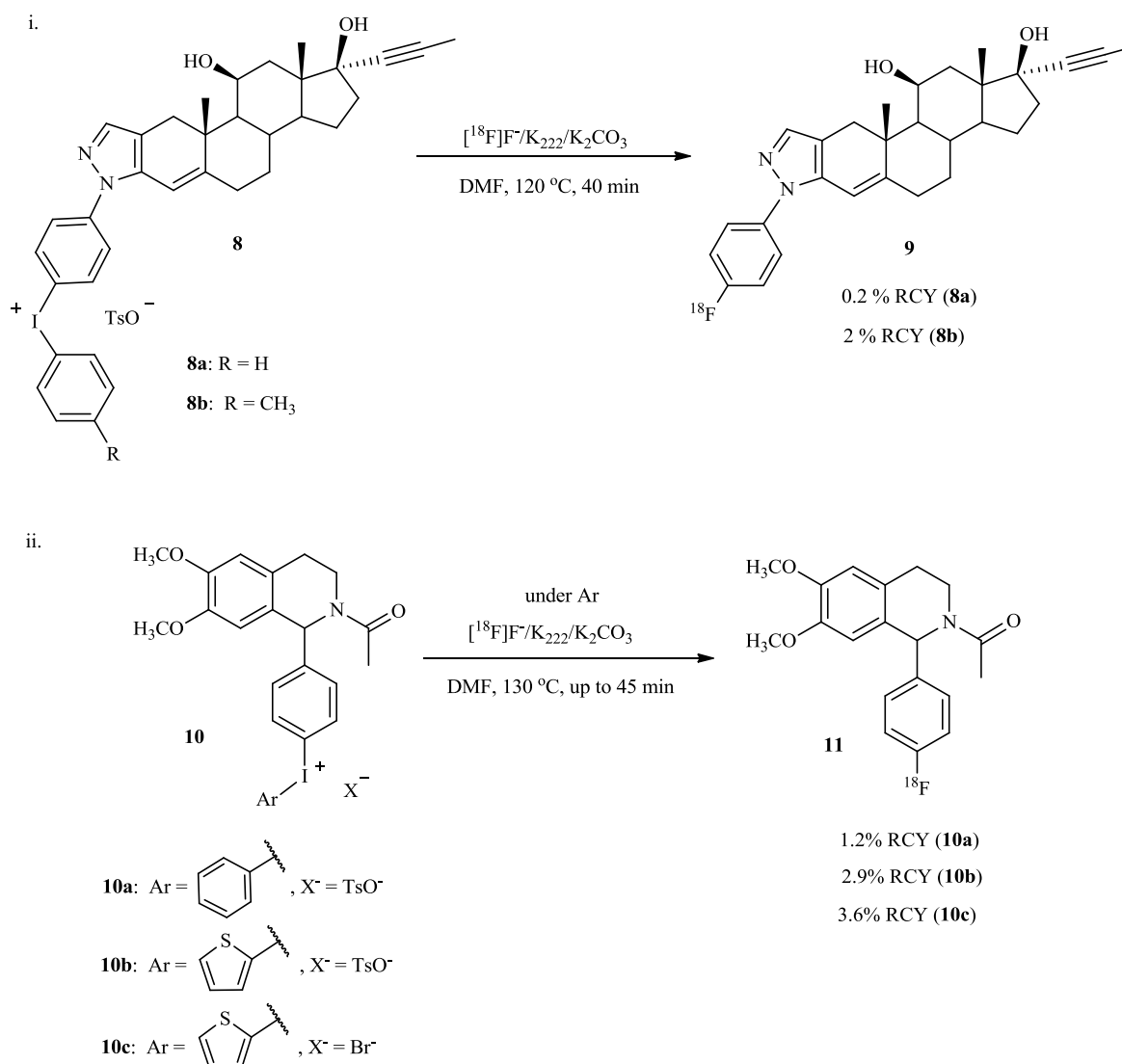
Besides the substitution pattern and electronic properties, parameters such as solvent, counter-anion(s), [¹⁸F]fluoride source, stoichiometry, reaction temperature, and time, strongly affect the outcome (product distribution) and RCYs of nucleophilic ¹⁸F-labeling reaction with diaryliodonium salts. An appropriate solvent

should be non-nucleophilic with weak power of cation and anion solvation, and with suitable redox potential to exclude or limit any redox processes between iodine (III) and solvent molecules [28, 106, 128]. Organic aprotic solvents like CH₃CN and DMF have appeared to be the most beneficial, according to the RCYs in contrast to DMSO which is very useful for direct S_NAr. To avoid the homolytic aryl-iodine bond fission [117], and consequently to improve RCYs and reproducibility, addition of radical scavengers (e.g. TEMPO) has been shown to be advantageous [125, 129–131]. According counter-anion's influence on RCYs, stability, reaction rates, and selectivity, inorganic and organic counter-anions such as bromide [105, 106], tosylate (TsO⁻) [108, 109, 124, 125, 131, 132], and triflate (TfO⁻) [105, 107] have appeared attractive considering their low nucleophilicity and good leaving group ability. Lee et al. determined X-ray structure of a representative unsymmetrical iodonium salt, 2-methylphenyl(2'-methoxy-phenyl)iodonium chloride (**7**), in order to achieve a deeper understanding of its structure, and to assist in understanding radiofluorination mechanism and similar reactions of diaryliodonium salts with nucleophiles in organic media [133]. Their X-ray study unveiled that the hypervalent iodine in **7** acts as a previously unrecognized stereogenic center within a dimeric structure as the unit cell in a centrosymmetric crystal, composed of conformational M and P enantiomers (Scheme 12). They investigated racemization process of **7** in CH₃CN solution with the *ab initio* replica path method, thereby revealing two additional pairs of conformational enantiomers. All identified six conformers of **7** were calculated to be comparable in energy and thus, all are likely to exist in CH₃CN at room temperature due to fast interconversion via two essentially isoenergetic transition states (calculate energy barrier of 9.1 kcal/mol in CH₃CN). In addition, their quantum chemical and dimerization energy calculations together with LC-MS observations of clusters of **7** suggested that it predominantly exists as dimers (dimeric anion-bridge clusters) in CH₃CN due to the secondary bonding interaction between I and the Cl atoms within an enantiomeric pair. The evidence of the existence of dimeric solution clusters of **7** further indicates that the reactions of diaryliodonium salts similar to **7** with nucleophiles (e.g. [¹⁸F]F⁻) in organic solvents may require dissociation of dimers or possibly even higher-ordered clusters (e.g. tetramers), preceding replacement of chloride ion with [¹⁸F]F⁻ and subsequent attack of the bound fluoride onto an aryl carbon atom to give either of the two possible [¹⁸F]fluorarene products (Scheme 12).



Scheme 12. (i.) M and P are conformational enantiomers of 2-methylphenyl(2'-methoxy-phenyl)iodonium chloride (**7**). (ii.) Favorable dimerization energy calculation and LC-MS observations of clusters suggest that dissociation of dimeric Cl-bridge cluster, held together by iodine-chloride ionic bonds, of diaryliodonium salt similar to **7** is preceding necessary step to allow formation of the two possible [¹⁸F]fluorarene products [133].

So far, diaryliodonium salts have mainly been proven to be useful precursors for the introduction of [¹⁸F]F⁻ onto simple aromatic rings via straightforwardly prepared precursors where comparison with the Wallach reaction has shown much greater efficiency for the former methodology [28, 134]. It was assumed that the ¹⁸F-labeling via iodonium precursors is somehow limited by the molecule size and complexity of the structure [120]. With further mechanistic, stability, permutational, and intramolecular interference studies, and also with an improvement of existent and development of new synthetic methods to obtain stable and highly pure complex diaryliodonium precursors, this approach will likely find wider application in preparing more complex ¹⁸F-labeled tracers for PET imaging. More complex ¹⁸F-labeled radiopharmaceuticals from corresponding diaryliodonium salts are represented in Schemes 13 and 14.

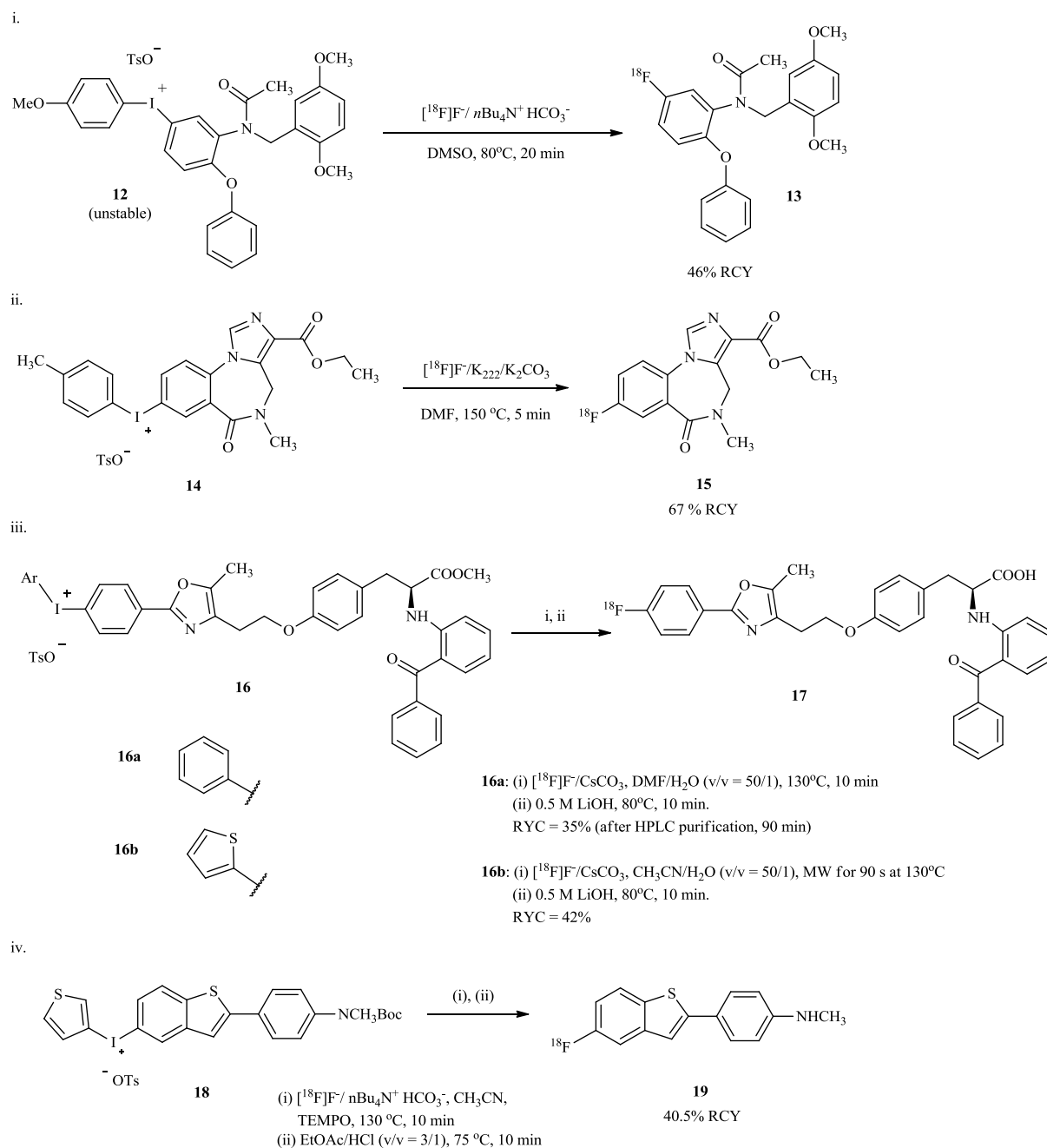


Scheme 13. Successful examples of ^{18}F -labeling using complex diaryliodonium precursors. (i.) Radiosynthesis of metabolically stable 4- ^{18}F fluorophenyl pyrazolo steroid (**9**) as high affinity ligand for brain glucocorticoid receptors [132]. (ii.) Radiosynthesis of **11** (^{18}F -ADTQ), classified as non-competitive AMPA receptor antagonist [120].

Radiosynthesis of metabolically stable 4- ^{18}F fluorophenyl pyrazolo steroid **9** as high affinity ligand for brain glucocorticoid receptors was accomplished by Wüst et al. [132]. Since the aromatic ring is not sufficiently activated by a strong electron-withdrawing group, diaryliodonium salts **8a** and **8b** were used as precursors for the incorporation of n.c.a. ^{18}F to obtain **9** in low decay-corrected radiochemical yields of 0.2 and 2.0%, respectively. The use of the more electron-donating tolyl-functionalized iodonium salt **8b** favored the formation of corticosteroid **9** which is in accordance of the *para*-substituted electronic effects of the counter rings. Authors also detected by radio-TLC analysis the formation of large amounts of ^{18}F fluorobenzene and ^{18}F fluorotoluene

as by-products. Ross reported radiosynthesis of **11** ($[^{18}\text{F}]\text{F-ADTQ}$), classified as a putative, non-competitive AMPA receptor antagonist, from iodonium precursors **10a**, **10b**, and **10c** [120]. Comparing the precursors **10a** and **10b**, the RCYs showed an increase from the phenyliodonium group (1.2 %) to the 2-thienyliodonium group (2.9 %), as expected for the electronic differences between the iodonium precursors and the corresponding aryl iodides as leaving groups. It should be noted that the synthesis starting from iodonium precursor **10c** with a bromide as a counter-anion showed the best RCY of about 3.6%, and was obtained in only 3% yield. Consequently, **11** was not isolated or prepared for pharmacological evaluation studies because of a very low RCY.

Preparation of **13** ($[^{18}\text{F}]\text{DAA1106}$) by Zhang et al., a PET ligand for imaging peripheral-type benzodiazepine receptor in the brain, was accomplished in much higher d.c. RCY of 46 % than in previous noted attempts and was therefore the first report of a complex and electron rich practical PET ligand synthesized by the reaction of diphenyliodonium salt with n.c.a. $[^{18}\text{F}]\text{F}^-$ in high RCY [108]. Based on consideration that the $[^{18}\text{F}]\text{fluoride}$ attacks the diphenyliodonium salt preferably at the electron-deficient benzene ring, *p*-iodoanisole as a leaving group was designed to increase the regioselectivity of ^{18}F into a desired ring. Since **12** was unstable, it was used for radiosynthesis after the respective coupling reaction without further purification. Another successful radiofluorination in high RCY via iodonium salts is the preparation of $[^{18}\text{F}]\text{flumazenil}$ (**15**) using 4-methylphenyl-mazenil iodonium tosylate precursor **14** without any structural modifications of the parent molecule [131]. Interestingly, **14** was superior to other precursors, in spite of the fact that 2-thienyl-, 3-thienyl-, and 4-methoxyphenyl-mazenil iodonium tosylate have relatively high electron densities. The authors observed that the more electron-rich diaryliodonium tosylate precursors have lower stability and selectivity for the desired product formation and that these correspond with the tendency of the $[^{18}\text{F}]\text{fluoride}$ incorporation yield. Thus, the best result was obtained for the reaction of **14** with n.c.a. $[^{18}\text{F}]\text{fluoride}$ and $\text{K}_{222}/\text{K}_2\text{CO}_3$ (0.6 equiv. of K_2CO_3 relative to the precursor) in the presence of TEMPO in DMF at 150 °C for 5 min. Under these conditions, d.c. RYC was 67 ± 2.7 % with more than 99% radiochemical purity after HPLC purification. The total synthesis time for **15** was about 55 min, including HPLC purification and the specific activity was in the range of 370-450 GBq/ μmol (10-12 Ci/ μmol). Further studies showed that the optimized reaction conditions were well adapted to the reproducible ($n = 26$ with no failure) high-scale automatic production of $[^{18}\text{F}]\text{flumazenil}$ (RCY 63.5 ± 3.2 % in total synthesis time 60 ± 1.1 min) in a commercial automated device (Scheme 14).



Scheme 14. Successful examples of ^{18}F -labeling using complex diaryliodonium precursors. (i.) Preparation of **13** ($[^{18}\text{F}]\text{DAA1106}$), a PET ligand for imaging peripheral-type benzodiazepine receptor in the brain [108]. (ii.) Preparation of **15** ($[^{18}\text{F}]\text{flumazenil}$), chemically indistinguishable from its non-radioactive counterpart, using 4-methylphenyl-mazenil iodonium tosylate precursor **14** [131]. (iii.) Radiochemical synthesis of benzophenone-tyrosine PPAR γ ligand **17** [124]. (iv.) Radiosynthesis of 6- $[^{18}\text{F}]\text{fluoro}$ -labeled benzothiazole analogue **19** as a promising PET probe for A β plaque imaging [125].

Lee et al. developed radiochemical synthesis of ^{18}F -labeled analog of the potent and selective PPAR γ agonist farglitazar (**17**), a tyrosine-benzophenone class of PPAR γ regulators) by radiofluorination of a diaryliodonium tosylate precursors **16a** and **16b** [124]. The radiosynthesis of **17** was accomplished in approximately 90 minutes with a good d.c. RCY of up to 42% and the SA after decay correction of approximately 37 GBq/ μmol (1 Ci/ μmol). Authors concluded that although the compound had high and selective PPAR γ binding affinities and also good metabolic stability, its nonselective target-tissue (brown and/or white fat) biodistribution uptake versus non-target tissues in rats indicated that it was likely to be unspecific for effective imaging of breast cancer or vascular disease in humans. It should be noted that the addition of some water significantly increased RCYs as suggested due to increased solubility of $\text{Cs}[^{18}\text{F}]\text{F}^-$ salt in the studied solvents (DMF and CH_3CN). It is also interesting to note that they were unable to obtain radiolabeled product **17** from the *p*-methoxyphenyl-based iodonium salt precursor, even though this precursor worked quite well to produce the unlabeled fluoroproduct [124, 135]. Similarly, the same authors (Lee et al.) have recently synthesized various diaryliodonium tosylate precursors (containing the more electron-rich *p*-methoxyphenyl, *p*-methylphenyl, 2- and 3-thienyl compare to phenyl ring on 6-position of benzothiazole ring) to allow aromatic ^{18}F -labeling at 6-position of benzothiazole ring [125]. The highest d.c. RYC 40.5% with SA 110 GBq/ μmol (2.97 Ci/ μmol) of one of the most promising AB plaque-specific PET imaging probes **19** was obtained via *one-pot* radiofluorination and deprotection of benzothiazole iodonium tosylate precursor **18** in the presence of TEMPO using $n\text{Bu}_4\text{N}[^{18}\text{F}]\text{fluoride}$ as the fluoride source.

5. CONCLUSIONS

A direct, one-step, no-carrier-added synthesis of inactivated or electron-rich ^{18}F fluoroaromatic compounds with high specific activity represent an important challenge for radiochemists. This is limited to only a few methods in preparative organic chemistry. The traditional Balz-Schiemann reaction with its modification and Wallach reaction are not particularly efficient due to the competing reactions of the highly reactive and non-selective intermediates leading to low radiochemical yields and specific activities of ^{18}F -labeled arenes. On the other hand, diaryliodonium salts have been shown to be the most suitable precursors for direct single-step nucleophilic ^{18}F fluorination of simple arenes with little or no restriction on the nature of the functionality present. The regioselectivity of this reaction has been found to be controlled electronically as well as by the steric bulkiness of the substituents. The so-called *ortho-effect* is the most prominent feature of this methodology and almost quantitatively radiochemical yields of small electron-rich arenes have been reported due to this effect.

Higher radiochemical yields compared to Balz-Schiemann and Wallach reactions have also been explained by the synchronous reductive elimination of the transition state which limits formation of reactive intermediates. The principal drawback of this method is that radiochemical yield is limited by the additional formation of undesirable counter [^{18}F]fluoroarene. Thus, to improve the radiochemical yield, symmetrically substituted diaryliodonium salts as precursors are preferred, which is not the case for complex arenes. So far, this approach has been limited for simple readily prepared diaryliodonium salts. However, very promising for future investigation are a few recent successful examples of direct aromatic nucleophilic ^{18}F -labeling of complex non-activated radiopharmaceuticals using corresponding diaryliodonium salts as precursors. With further mechanistic studies and with an improvement of existent synthetic methods and development of new to obtain stable and highly pure complex diaryliodonium precursors, this approach will likely find wider application in radiofluorination.

List of abbreviations: AMPA - 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid, EWG - electron-withdrawing group, LG - leaving group, N.C.A. - no-carrier-added, PET - positron emission tomography, PPAR - peroxisome proliferator-activated receptor, RCY - radiochemical yield, SA - specific activity, TEMPO - 2,2,6,6-tetramethylpiperidin-1-yl)oxyl.

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