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ARTICLE

Triarylselenonium Triflates Provide Efficient Access to No-Carrier-Added *Ortho*-, *Meta*-, and *Para*- [^{18}F]Fluoroarenes

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Jake Sypniewski[1], Yong-Sok Lee[2], Phuc Tran[1], Sean Costner[1], Fabrice G. Siméon[1*], and Victor W. Pike[1*]

ABSTRACT: [^{18}F]Fluoroarenes feature prominently as radiotracers for biomedical imaging with positron emission tomography (PET). We report the syntheses of a wide range of triphenylselenonium triflates and demonstrate their reactivity towards cyclotron-produced [^{18}F]fluoride ($t_{1/2}$ = 109.8 min; β^+, 97%) for producing no-carrier-added (NCA) [^{18}F]fluoroarenes. Triphenylselenonium triflates having a single strong *p*-electron-withdrawing group gave substituted [^{18}F]fluoroarenes in high yields (72–90%). Salts having a *m*-nitro, chloro, or methyl substituent produced the substituted [^{18}F]fluoroarenes in lower but still useful yields (22–32%). A strong 'ortho effect' occurred in the radiofluorination of triphenylselenonium triflates with an *o*-substituent (Cl or Me), which induced moderately high yields (62 and 65%). In a head-to-head comparison, triarylselenonium triflates performed as well and in some cases better than the corresponding triarylsulfonium triflates, especially for producing ^{18}F-labeled electron-rich arenes. *p*-Anisyl groups proved to be effective spectator groups for the radiofluorination of triarylselenonium triflates. Thus, the radiofluorination of aryl(di-*p*-anisyl)selenonium triflates gave high yields (55–98%) of [^{18}F]fluoroarenes carrying an *o*-, *p*-, or *m*- halo, or alkyl substituent. Quantum computational analysis accords with a reductive elimination type mechanism. Finally, the utility of aryl(di-*p*-anisyl)phenylselenonium triflates for radiofluorination was demonstrated by producing known PET-like tracers, for example [^{18}F]FPEB and a [^{18}F]canagliflozin fragment; the yield of [^{18}F]FPEB from an aryl(di-*p*-anisyl)phenylselenonium triflate precursor was remarkably high (97%). In conclusion, substituted triarylselenonium triflates, and especially aryl(di-*p*-anisyl)selenonium triflates, are a useful addition to the range of precursors that can be considered for producing NCA *o*-, *m*-, and *p*- ^{18}F-labeled fluoroarenes as new PET tracers.

Keywords: fluorine-18; [^{18}F]fluoroarene; triarylselenonium; triarylsulfonium; radiofluorination; radiotracer

Introduction

Positron emission tomography (PET) is a sensitive molecular imaging technique that can provide quantitative information on the distribution of specific proteins in living animals or humans and on their physiological functions and interactions with experimental and clinically useful drugs.[1] Examples of such proteins include enzymes, receptors, transporters, and pathological plaques. The imaging of each protein requires a radiotracer that binds or interacts specifically with the protein of interest.[2] Fluorine-18 is widely incorporated into PET tracers because of its favorable physical and chemical properties. These include decay with a half-life of 109.8 minutes by 97% emission of a relatively low-energy positron (mean energy 250 keV) and an ability to make strong bonds to carbon in place of a hydrogen or a hydroxy substituent. Moreover, fluorine-18 can be prepared as [^{18}F]fluoride ion from biomedical cyclotrons in exceptionally high amounts and at high molar activities by the ^{18}O(p,n)^{18}F nuclear reaction on ^{18}O-enriched water.[3] This allows the [^{18}F]fluoride or derived tracers to be shipped to PET imaging centers lacking a

1. Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Rm B3 346A, Building 10, 10 Center Drive, Bethesda, Maryland 20892, USA.
2. Bioinformatics and Computational Biosciences Branch, National Institute of Allergy and Infectious Diseases, Rm 3B62, Building 31, 10 Center Drive, National Institutes of Health, Bethesda, Maryland 20892, USA.
* Corresponding authors

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cyclotron if they are within a few hours travel from a central cyclotron facility. The global market for ^{18}F-labeled tracers is very high and was set to exceed $3bn in 2023.[4] In the case of the most popular ^{18}F-labeled tracer, [^{18}F]2-fluoro-2-deoxy-D-glucose (commonly known as [^{18}F]FDG or FDG), this distribution model underpins a billion-dollar industry for biomedical diagnosis.

To further uncover the immense potential of PET for biomedical imaging, there is a growing need for the development of new methods for introducing fluorine-18 into bioactive molecules. Many experimental tracers that carry fluorine-18 at an alkyl carbon are prone to radiodefluorination *in vivo*, which can lead to [^{18}F]fluoride uptake in bone and to compromised PET imaging of nearby tissue.[5,6] By contrast, [^{18}F]fluoroarenes usually resist radiodefluorination.[2] Therefore, considerable effort has been made to devise methods for fast and efficient radiofluorination at aryl carbon, irrespective of aryl group electron density.[7,8,9] As recently comprehensively reviewed,[9] successful methods include the use of nitroarenes, diaryliodonium salts, aryliodonium ylides, arylboronic acids, arylboronic esters, arylstannanes, aryl sulfoxides, or triarylsulfonium salts as precursors. Radiofluorination yields from these precursors depend on many factors, including the nature, position, and accessibility of the leaving group on the aryl ring, and the nature and effect of proximal functional groups. Many of the methods require a metal mediator or catalyst, such as a palladium,[10] nickel,[11,12] ruthenium,[13,14,15] or copper[16,17,18,19] species, but catalyst-free methods are keenly sought for economy and simplicity and for easier regulatory compliance when producing PET tracers for clinical use. One such method is the radiofluorination of triarylsulfonium salt precursors.[20,21,22,23]

The utility of triarylsulfonium salts as precursors for ^{18}F-labeling has recently been exemplified in the syntheses of promising PET tracers, including: [^{18}F]FAMTO, a radiotracer for imaging CYP11B1 and CYP11B2 enzymes in adrenal glands[24]; [^{18}F]fluorobenzyl-candesartan, a radiotracer for the AT1 receptor[25]; and [^{18}F]Aldoview a tracer for imaging aldosterone synthase (hCYP11B2) in primary hyperaldosteronism (**Chart 1**) [26].

We considered that triarylselenonium salts might show similar or potentially improved reactivity over triarylsulfonium salts towards [^{18}F]fluoride ion because a selenium atom is larger and may show greater electrophilicity than a sulfur atom.[27,28] Many synthetic routes have been described for synthesizing alkyl(diaryl)selenonium salts, which now find diverse applications as reagents,[29,30,31] Lewis acids,[32] ionic liquids,[33] and corrosion inhibitors[34]. Triarylselenonium salts are less well studied than those of alkyl(diaryl)selenonium salts but have been gaining strong interest.[35,36,37,38,39,40,41,42] Methods for the syntheses of triarylselenonium salts have been reported using commercially available selenium dioxide,[36,40] potassium selenide[34] or selenourea[43]. This unlocks many possibilities for their future applications.

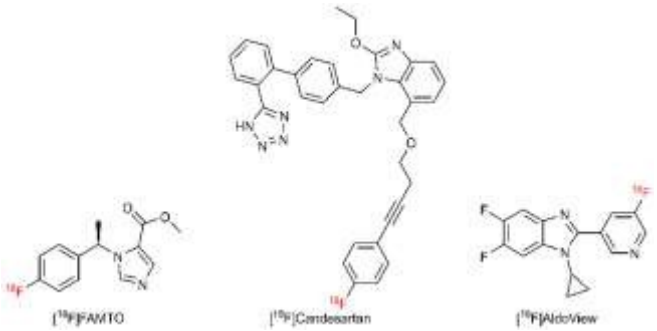

Chart 1. Some notable PET radiotracers produced by the radiofluorination of triarylsulfonium salts.

In 1929, Leicester and Bergstrom described the thermal decompositions of triphenylselenonium iodide and triphenylselenonium bromide to give iodobenzene and bromobenzene, respectively.[44] However, the utility of triarylselenonium salts as precursors for radiofluorination has not previously been reported. Here we show the unprecedented use of triarylselenonium salts as precursors for the radiofluorination of variously substituted arenes with no-carrier-added (NCA) cyclotron-produced [^{18}F]fluoride ion, including PET radiotracer-like products. We also report a direct comparison of the reactivities of *para*-substituted triphenylselenonium salts towards [^{18}F]fluoride ion with those of their corresponding sulfonium salts. Quantum chemical analysis is consistent with reductive elimination being the reaction mechanism for the radiofluorination. In addition, a triaryltelluronium salt was produced and found to be quite resistant to radiofluorination, as predicted from quantum chemical analysis. Notably, we discovered that *p*-anisyl groups can serve as effective spectators in the radiofluorination of aryl(di-*p*-anisyl)selenonium triflates to give high yields of the [^{18}F]fluoroarene, including those substituted in *o*-, *m*-, or *p*- position with alkyl or halo groups. This discovery was exploited to produce the well-known PET tracer, [^{18}F]FPEB, in an exceptionally high yield (97%).

Results and discussion

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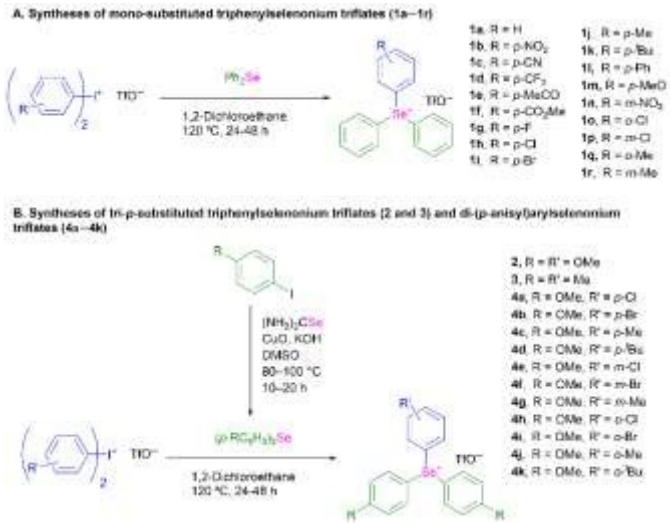
Syntheses of triarylchalcogenium salts

From the many available methods, we chose the method of Racicot et al.[38] for convenient access to a variety of mono-substituted triarylselenonium triflates. This method is based on treating diaryliodonium triflates with commercially available diphenyl selenide[37] (**Scheme 1A**). This method gave several mono-substituted triarylselenonium triflates in generally good yields (31–82%; see Supporting Information). Many of the required diaryliodonium triflates were not commercially available. Diaryliodonium triflates are now accessible from a wide range of synthetic methods.[45] We chose to prepare diaryliodonium triflates that could not be purchased through extensive use of the oxidation of iodoarenes with *meta*-chloroperbenzoic acid (*m*CPBA) in the presence of an arylboronic acid.[46] The synthesized triarylselenonium triflates were easily purified by flash chromatography to give mostly stable crystalline compounds; in fact, many examples required no special storage over several years.



Scheme 1. Syntheses of substituted triarylselenonium triflates. **A**) Mono-substituted triphenylselenonium triflates (**1a**–**1r**) by treatment of symmetrically substituted diphenyliodonium triflates with diphenyl selenide. **B**) Tri-*p*-substituted triphenylselenonium triflates (**2**, **3**, and **4a**–**4k**) by treatment of a symmetrical diaryliodonium triflate with either di-*p*-tolyl selenide or di-*p*-anisyl selenide, prepared from selenourea and *p*-iodotoluene or *p*-iodoanisole, respectively.

For triarylselenonium triflates in which more than one aryl ring carried a substituent, we treated a diaryliodonium salt with either di-(*p*-tolyl) selenide or di-(*p*-anisyl) selenide prepared from selenourea (**Scheme 1B**). The yields of these triarylselenonium triflates were generally good and in the range of 19 to 82% (see Supporting Information).

Triarylsulfonium triflates were either purchased or, if unavailable, synthesized by known procedures (see Supporting information). Triphenyltelluronium triflate was synthesized in 74% yield in 2 steps by treating benzene with aluminum chloride and tellurium(IV) tetrachloride[47], followed by metathesis of the triphenyltelluronium chloride product with silver(I) triflate (see Supporting Information).

Radiochemistry

Test radiofluorination on triphenylselenonium triflate (1a). We first tested the reactivity of a simple salt, triphenylselenonium triflate (**1a**), towards NCA [^{18}F]fluoride ion. Gratifyingly, when a solution of **1a** (10 μmol) in DMF (0.25 mL) was treated with azeotropically dried [^{18}F]fluoride and potassium carbonate-K 2.2.2 at 90 ^{o}C in a thermal oven for 20 minutes, the desired [^{18}F]fluorobenzene ([^{18}F]**5a**) was produced in high yield (58 ± 7%; n = 3). A much lower reaction temperature (50 ^{o}C) still gave a substantial yield (33%). Given these encouraging initial findings, we proceeded to test the radiofluorinations of a broad range of substituted triarylselenonium triflates.

Microwave-promoted radiofluorinations of mono-substituted triphenylselenonium triflates. Microwave irradiation is well-known to be useful for decreasing radiofluorination reaction times while improving reaction yields and product purities.[48] Because of the relatively short half-life of fluorine-18, we investigated the use of microwave irradiation to promote radiofluorination. We used a commercial microwave apparatus (Model 521, Resonance Instruments) for such reactions. Here, microwave irradiation of **1a** (R = H; 10 μmol) in DMF (0.25 mL) for 3 minutes (2 × 90 s, 80 W) at 150 ^{o}C provided [^{18}F]fluorobenzene ([^{18}F]**5a**) in 79% yield (**Table 1**). Thus, the microwave-promoted reaction gave a faster and slightly higher yield than the tested thermal reaction.

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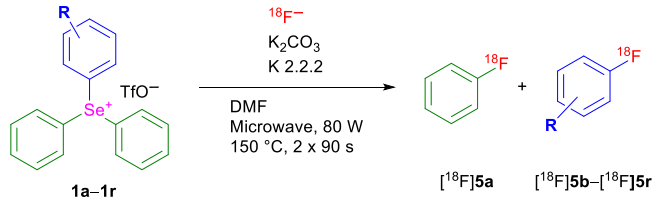
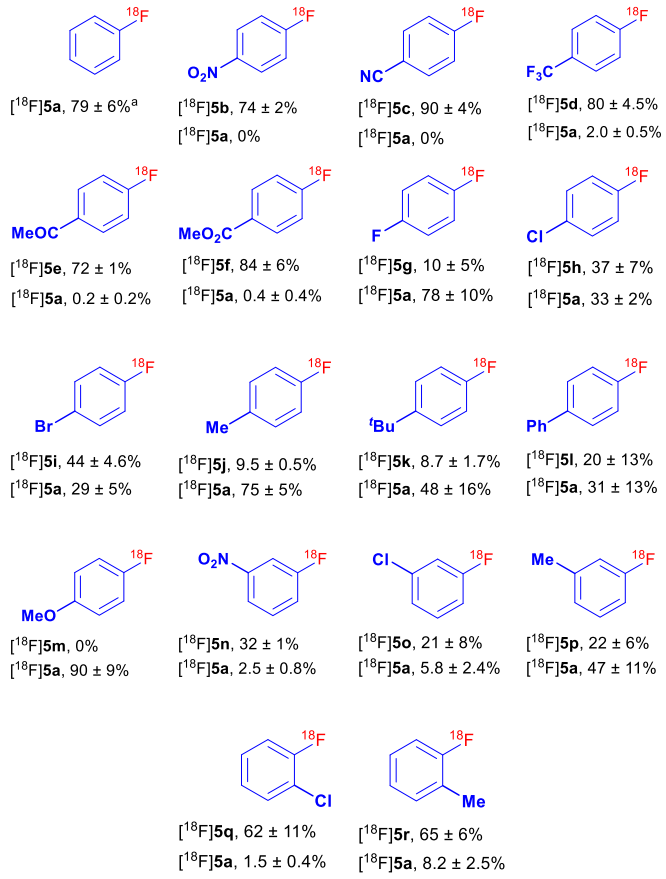
Table 1. Yields of [^{18}F]fluoroarenes from the microwave-promoted radiofluorinations of **1a** and mono-substituted triphenylselenonium triflates **1b**–**1r**.





[a] Decay-corrected radiochemical yield from HPLC. Data are mean ± SD for n = 3. The remainder of the activity was unreacted [^{18}F]fluoride ion.

Emboldened by these results, we used microwave irradiation for the radiofluorination of a variety of mono-substituted triphenylselenonium triflates (**Table 1**). Salts with a strong *p*-electron withdrawing group, such as nitro (**1b**), nitrile (**1c**), or trifluoromethyl (**1d**), gave the respective *p*-substituted [^{18}F]fluoroarenes, [^{18}F]**5b**, [^{18}F]**5c**, and [^{18}F]**5d**, in high yields with very little or no detectable [^{18}F]**5a** as byproduct (**Table 1**). Similarly, salts with an electron-withdrawing *p*-acetoxy (**1e**) or *p*-carboxymethyl **(1f**) substituent produced [^{18}F]*p*-fluoroacetophenone ([^{18}F]**5e**) and [^{18}F]*p*-fluorobenzoic acid methyl ester ([^{18}F]**5f**) in high yields of 72 and 84%, respectively, accompanied by only traces of the byproduct [^{18}F]**5a** (**Table 1**). In each case, [^{18}F]**5a** was removed easily by HPLC.

A strong trend was observed in the radiofluorination of triphenylselenonium salts carrying a *p*-halo substituent (**1g**–**1i**). As the size of the halo substituent increased from fluoro (**1g**) through to bromo (**1i**), the yield of the [^{18}F]*p*-halobenzene increased from 10 to 44%. Chemoselectivity also increased for producing the [^{18}F]*p*-halobenzene versus [^{18}F]**5a** (**Table 1**). Remarkably, however, [^{18}F]**5a** was the highly preferred product over the substituted [^{18}F]fluoroarene ([^{18}F]**5g**) when fluoro was the *p*-substituent (**Table 1**).

Because the radiofluorinations of mono-substituted diaryliodonium salts and aryliodonium ylides have in some instances resulted in mixtures of the expected *ipso*-substituted [^{18}F]fluoroarene with a regioisomer through a benzyne formed in situ,[49] we tested the regioselectivity of the radiofluorination of **1i**. We found that the reaction proceeded entirely by *ipso* substitution (see Supplementary Information).

When a weakly *p*-electron-donating group was present, such as methyl (**1j**), *t*-butyl (**1k**), or phenyl (**1l**), the corresponding substituted. [^{18}F]fluoroarenes ([^{18}F]**5j**–[^{18}F]**5l**) were obtained in modest 9–20% yields and with [^{18}F]**5a** as the major product (**Table 1**). The radiofluorination of *p*-anisyl(diphenyl)sulfonium triflate is known to give no [^{18}F]*p*-fluoroanisole.[20] Analogously, the presence of *p*-methoxy as a strong *p*-electron donating group in the selenonium salt, **1m**, abolished chemoselectivity in the radiofluorination reaction. Only [^{18}F]fluorobenzene ([^{18}F]**5a**) was produced in a remarkably high yield (90 ± 9%). [^{18}F]*p*-Fluoroanisole ([^{18}F]**5m**) was not produced under any reaction conditions applied to **1m**. The rank order of substituent effects on the radiochemical yields of *p*-substituted [^{18}F]fluoroarenes from the aryl(diphenyl)selenonium triflates (H > Br > Me > OMe) matches that reported for the radiofluorination of mono *p*-substituted triphenylsulfonium triflates.[20] Here, we observed a strong correlation (r^2 = 0.890; n = 12; P < 0.0001) of the yields of the *p*-substituted [^{18}F]fluoroarenes from mono *p*-substituted triphenylselenonium triflates with the Hammett σ_p substituent constants[50] (**Figure 1**).

The strong linearity of this plot was unexpected in that the plot is not a conventional Hammett plot of $\log(k_X/k_H)$, where k_X is the rate constant for the reaction of a substrate with a *p*-substituent X and k_H is that for a substrate without a substituent. Nonetheless, the plot clearly reveals the strong dependence of reaction yields on the

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electronic properties of the *p*-substituents. Notably, Gendron et al.[22] similarly observed a strong correlation (r^2 = 0.98; n = 5) between the

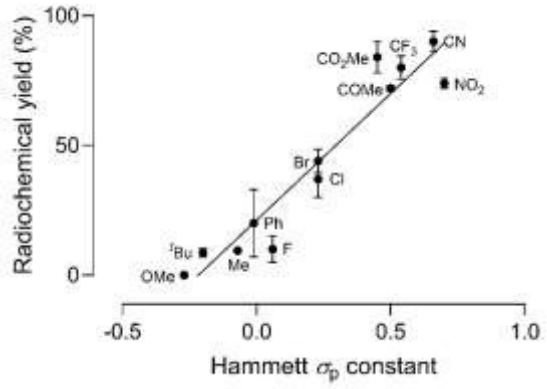


Figure 1. Radiochemical yields (from **Table 1**) correlate strongly with Hammett σ_p substituent constants for the microwave-promoted radiofluorination of *p*-substituted phenyl(diphenyl)selenonium triflates. Error bars (SD values) are within the symbol size, if not visible. Data-point labels identify the *p*-substituent in the fluoroarene.

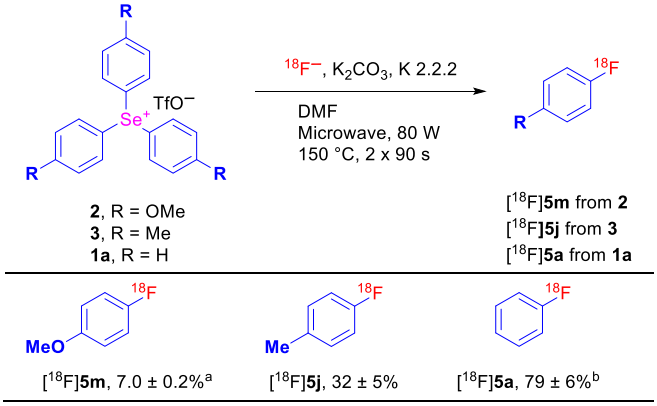
yields of [^{18}F]fluoroarenes and Hammett σ_p substituent constants for the radiofluorination of aryl(dibenzothiophene)sulfonium salts.

Installation of [^{18}F]fluoride into a *m*-position of an aryl ring is generally more challenging than at the *para* or *ortho* positions.[9] Gratifyingly, however, we obtained [^{18}F]*m*-fluoro-nitrobenzene ([^{18}F]**5n**) from *m*-nitrophenyl(diphenyl)selenonium triflate (**1n**) in 32% yield (**Table 1**). The radiofluorination of triarylselenonium triflates bearing an electron-neutral *m*-chloro or electron-donating *m*-methyl substituent also gave the corresponding *m*-substituted [^{18}F]fluoroarenes, [^{18}F]**5o** and [^{18}F]**5p**, in low but useful yields (21 and 22%, respectively). Thus, triarylselenonium triflates have very promising utility for the radiofluorination of radiotracers in *m*-positions.

Remarkably, [^{18}F]*o*-chloro-fluorobenzene ([^{18}F]**5q**) and [^{18}F]*o*-fluorotoluene ([^{18}F]**5r**) were obtained in higher yields and with higher chemoselectivities than their *p*- or *m*- regioisomers (**Table 1**). Yields from *o*-substituted compounds well exceeded those from salts comparably substituted in the *p*-position. We note a strong 'ortho effect' has likewise been reported for the radiofluorination of aryl(dibenzothiophenyl)sulfonium triflates having a bulky heterocyclic *o*-substituent.[51] These *ortho* effects are indicative of similar mechanistic influences. The radiofluorination of triarylselenonium salts appears especially promising for labeling PET tracers in *ortho* position, even for electron-rich aryl rings.

Radiofluorination of fully symmetrical triarylselenonium triflates. We postulated that difficultly accessible NCA [^{18}F]*p*-fluoroanisole ([^{18}F]**5m)** might be obtained from fully symmetrical (tri-*p*-anisyl)selenonium triflate (**2**). Under our standard microwave radiofluorination conditions, compound **2** gave NCA [^{18}F]**5m** in 7% yield (**Table 2**). Whereas this yield is still very low, this is the first synthesis of [^{18}F]**5m** from a triarylchalcogen salt precursor. Similarly, the (tri-*p*-tolyl)selenonium triflate **3** gave [^{18}F]*p*-fluorotoluene ([^{18}F]**5j**) in a useful yield of 32 ± 5% (**Table 2**), which is much higher than the 9.5% yield obtained from mono-substituted precursor **1j** (**Table 1**). In this regard, it may be noted that microwave-promoted radiofluorination of the fully symmetrical triphenylselenonium triflate **1a** gave a much higher yield of [^{18}F]fluorobenzene ([^{18}F]**5a**; 79 ± 6%; **Table 2**) than would be expected according to the low Hammett σ_p constant (zero) for hydrogen (**Figure 1**). These results show that fully symmetrical triarylselenonium salts can be useful for producing challenging [^{18}F]fluoroarene targets with electron-rich aryl rings. One notable downside of this approach, however, is its low atom efficiency.

Table 2. Yields of [^{18}F]fluoroarenes from the microwave-promoted radiofluorination of fully symmetrical *p*-substituted phenyl(diphenyl) selenonium triflates.



[a] As for footnote a in **Table 1**. [b] Data taken from **Table** 1 for ease of comparison.

Head-to-head comparison of the syntheses of [^{18}F]*p*-fluoroarenes from mono *p*-substituted triphenylsulfonium and triphenylselenonium triflates. The radiofluorinations of mono *p*-substituted triphenylselenonium triflates (**Table 1**) showed high similarity to those reported[20] for the corresponding sulfonium triflates with respect to substituent effects and yields. Exceptionally, yields obtained for the selenonium salts with electron-donating groups were moderately higher than those reported[20] from the corresponding sulfonium salts. To explore this observation further,

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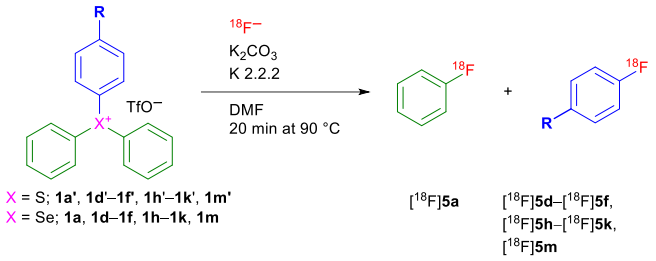
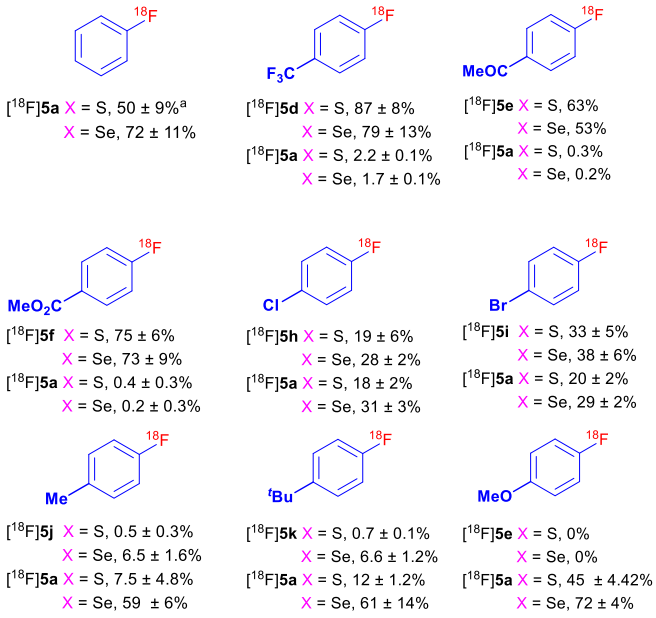
we devised a head-to-head comparison of radiofluorination between a series of nine selected mono *p*-substituted triphenylsulfonium triflates and the corresponding selenonium triflates. For a fair comparison, we also used the conditions previously described in the literature for the labeling of homologous sulfonium salts, namely, the use of a thermal oven at 90 °C, DMF as solvent, and a reaction time of 20 minutes.[20]

Overall, we found that triphenylsulfonium triflates having a *p*-electron-withdrawing group (**1d**–**1f**) reacted as well or slightly better than the corresponding triphenylselenonium triflates (**Table 3**).

Table 3. Head-to-head comparison of yields of [^{18}F]fluoroarenes from the thermal radiofluorination of mono *p*-substituted triphenylsulfonium and triphenylselenonium triflates.





[a] Decay-corrected radiochemical yield from HPLC. Data are mean ± SD for *n* = 3. The remainder of the activity was unreacted [^{18}F]fluoride ion.

However, selenonium salts having a neutral (**1a**) or electron-donating substituent (**1h**–**1k**) gave moderately higher or much higher yields than their sulfonium salt counterparts. For example, precursors with a *p*-methyl or *p*-*t*-butyl substituent ([^{18}F]**5j** and [^{18}F]**5k**, respectively) gave about 0.5% yield from their respective sulfonium triflates but over 6% yield from the corresponding selenonium triflates. Whereas this yield is still very low, it is 12-fold higher than that from the sulfonium triflate.

Finally, we observed that [^{18}F]fluoroarene yields and reaction chemoselectivities from mono *p*-substituted triphenylsulfonium triflates align very well with those observed by Mu et al. in their reported cases,[20] namely for no substituent (**1a'**) or with a bromo (**1i'**), methyl (**1j'**), or methoxy (**1t'**) substituent.

Strong linear relationships between the yields of [^{18}F]fluoroarenes and the Hammett σ_p substituent constants were also seen in this head-to-head comparison for both the mono *p*-substituted triphenylsulfonium and *p*-substituted ~~triph~~enylselenonium precursors (see Supporting Information, **Figure S2)**.

Thermal radiofluorinations of substituted aryl(di-(*p*-anisyl)selenonium triflates 6a–6k. In the head-to-head comparison, [^{18}F]*p*-fluoroanisole ([^{18}F]**5m**) was not produced from the radiofluorination of either *p*-anisyl(diphenyl)chalcogenium triflate (**1m'** or **1m**) (**Table 3**). This suggested that the *p*-anisyl group could serve as a useful spectator or directing group in the radiofluorination of triarylchalcogenium triflates. We first explored this possibility by synthesizing di-*p*-anisyl(*p*-chlorophenyl)selenonium triflate (**6a**) and testing its radiofluorination for yield and chemoselectivity. Under the usual microwave conditions (DMF, 80 W, 2 × 90 s, 150 °C), radiofluorination of **6a** produced [^{18}F]*1*-chloro-4-fluorobenzene ([^{18}F]**5h**) in high yield (59.7 ± 7.6%; *n* = 4), accompanied by only 1.17 ± 0.59% (*n* = 4) of [^{18}F]*p*-fluoroanisole ([^{18}F]**5m**). Both the yield of [^{18}F]**5h** and the reaction chemoselectivity far exceed those obtained from the radiofluorination of *p*-chlorophenyl(diphenyl)selenonium triflate (**1h**) (**Table 1**). In view of this result, we also assessed the radiofluorination of the corresponding di-*p*-anisyl(*p*-chlorophenyl)sulfonium triflate (**7a'**) under thermal conditions (DMF, 150 °C, 20 min) and obtained [^{18}F]**5h** in 7.48 ± 1.52% (*n* = 3) yield with no [^{18}F]**5m** byproduct. Thus, aryl(di-*p*-anisyl)selenonium triflates offer very appreciable radiofluorination yield advantage over the corresponding sulfonium triflates.

We proceeded to evaluate the yields of substituted [^{18}F]fluoroarenes and chemoselectivities for their formation from the thermal radiofluorination of a range of *para*-, *ortho*- and *meta*-substituted aryl(di-*p*-anisyl)selenonium triflates (**6a**–**6k**). under our

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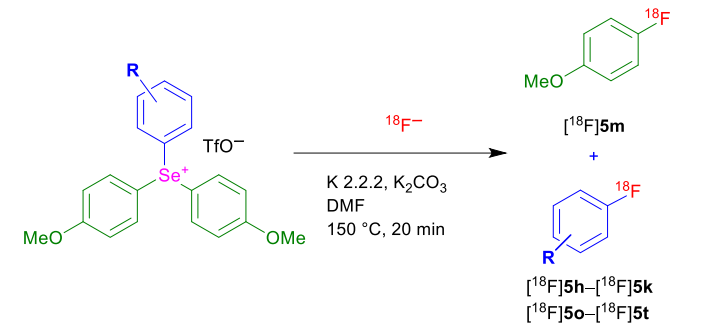
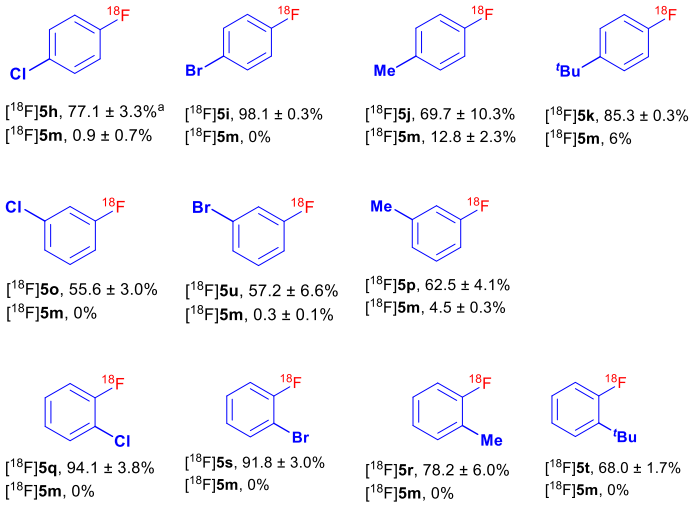
normal conditions (K 2.2.2/K_2CO_3, DMF, 150 °C, 20 min). Remarkably, these radiofluorinations proceeded with generally high chemoselectivity to high yields of the desired substituted [^{18}F]fluoroarenes. *p*-Substituted [^{18}F]fluoroarenes were produced in yields ranging from 69.7% (for Me substituent; [^{18}F]**5j**) to 98.1% (for Br substituent; [^{18}F]**5i**) (**Table 4**).

Table 4. Yields of substituted [^{18}F]fluoroarenes from the thermal radiofluorinations of substituted aryl(di-*p*-anisyl)selenonium triflates, **6a**–**6k**.

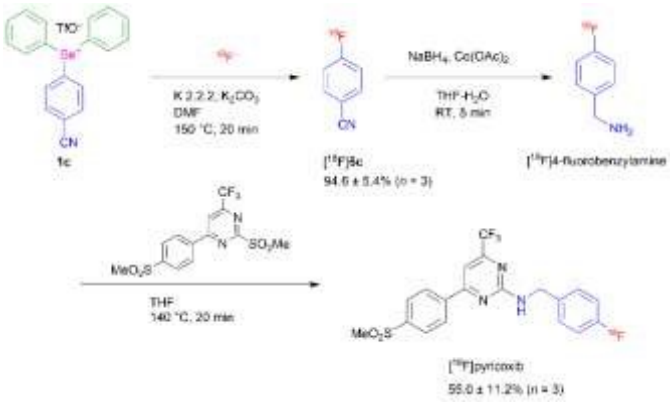




[a] Decay-corrected radiochemical yield from HPLC. Data are mean ± SD for *n* = 3. The remainder of the activity was unreacted [^{18}F]fluoride ion.

Chemoselectivity was very strong for reactions of the salts with *p*-halo substituents but weaker for salts with *p*-alkyl substituents. Three *m*-substituted [^{18}F]fluoroarenes, [^{18}F]**5u**, [^{18}F]**5o**, and [^{18}F]**5p**, were similarly obtained in high yields (55.6–62.5%) and with high chemoselectivities from the *m*-substituted aryl(di-*p*-anisyl)selenonium triflates, **6e**–**6g**. *o*-Substituted [^{18}F]fluoroarenes were obtained in remarkably high yields (68–94.1%) and with absolute chemoselectivities. The yields of [^{18}F]fluoroarenes from the radiofluorinations of substituted aryl(di-*p*-anisyl)selenonium triflates ([^{18}F]**Table 4**) far exceed those from the radiofluorinations of substituted aryl(di-phenyl)selenonium triflates (**Table 3**), not least because of the high chemoselectivities imparted by the two *p*-anisyl groups.

Syntheses of ^{18}F-labeled PET tracer-like compounds. An example of the utility of the radiofluorination of *p*-substituted



Scheme 2. Three-step radiosynthesis of [^{18}F]pyricoxib.

triphenylselenonium triflates is the three-step synthesis of [^{18}F]pyricoxib, a tracer for cyclooxygenase-2 (**Scheme 2**).[52]

Our new synthesis of [^{18}F]pyricoxib makes use of the very high yield of [^{18}F]*p*-fluorobenzonitrile ([^{18}F]**5c**) from precursor **1c** as the first step with completion of the radiosynthesis by efficient reduction of [^{18}F]**5c** to [^{18}F]*p*-fluorobenzylamine and coupling to the pyrazole ring of the tracer fragment by mesylate substitution in 2-(methylsulfonyl)-4-(4-(methylsulfonyl)phenyl)-6-(trifluoromethyl) pyrimidine, prepared according to the literature.[53] The yield of [^{18}F]pyricoxib over 3 steps was 55.0 ± 11.2% (*n* = 3). This is two-fold better than that reported by Tietz *et al.* (27 ± 11%, after HPLC purification), in which they made the starting [^{18}F]**5c** by nucleophilic substitution of [^{18}F]fluoride in *p*-trimethylammonium benzonitrile triflate.[53] The thermal synthesis of [^{18}F]**5c** proceeded in exceptionally high yield (94.6 ± 5.4%, *n* = 3), as for the microwave promoted synthesis (**Table 1**). The final [^{18}F]pyricoxib showed very high molar activity (107 GBq/μmol).

The utility of the radiofluorination of aryl(di-*p*-anisyl)selenonium salts for the syntheses of tracer-like compounds was further demonstrated with two examples, namely [^{18}F]FPEB, a radiotracer for brain mGluR5 receptors[54] and an ^{18}F-labeled fragment of canagliflozin[55], an antidiabetic drug. The synthesis of the requisite precursor (**8b**) for [^{18}F]FPEB was readily accomplished by treating commercially available 3-iodo-5-[(pyridin-3-yl)ethynyl]benzonitrile

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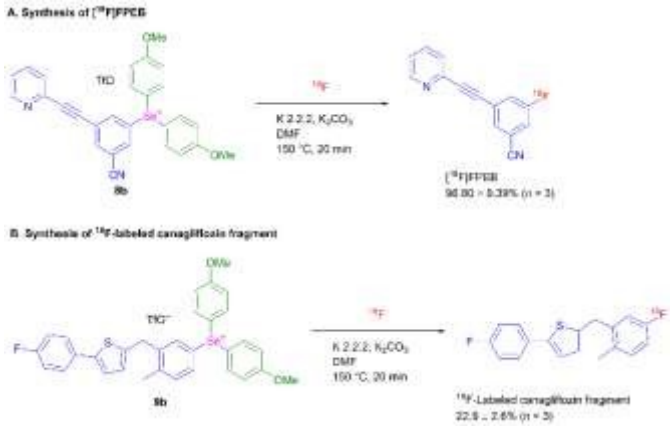
with *di-p*-anisyl diselenide to give 3-(4-methoxyphenylselanyl)-5-(pyridin-2-ylethynyl)benzonitrile (**8a**) followed by treatment of **8a** with di-*p*-anisyliodonium triflate (see Supporting Information). Radiofluorination of **8b** (1 μmol) under thermal conditions (0.25 mL DMF, 150 °C, 20 min) gave [^{18}F]FPEB in remarkably high yield of 96.80 ± 0.39% (*n* = 3), and with high molar activity (85 GBq/μmol) (**Scheme 3A**).

The precursor (**9b**) for the synthesis of a ^{18}F-labeled canagliflozin fragment was synthesized from commercially available 2-(4-fluorophenyl)-5-[(5-iodo-2-methylphenyl)methyl]thiophene by treatment with di-*p*-anisyl diselenide to give 2-(4-fluorophenyl)-5-(3-((4-methoxyphenyl)selanyl)benzyl)thiophene (**9a**), which was then treated with di-*p*-anisyliodonium triflate (see Supporting Information). Radiofluorination of **9b** (1 μmol) under thermal conditions (0.25 mL DMF, 150 °C, 20 min) gave the ^{18}F-labeled canagliflozin fragment in 22.9 ± 2.6% (*n* = 3) yield (**Scheme 3B**).



Scheme 3. The syntheses of ^{18}F-labeled PET tracer-like compounds from aryl(di-*p*-anisyl)selenonium triflates. **A**) [^{18}F]FPEB. **B**) ^{18}F-Labeled canagliflozin fragment.

General mechanistic considerations

Mu et al.[20] used density functional theory to explain the fluorination of *p*-iodophenyl(diphenyl)sulfonium salt with an S_NAr-type mechanism involving a separate transition state for each of the two [^{18}F]fluoroarene products. However, Gendron et al.[22] analyzed the fluorination of dibenzothiophene(phenyl)sulfonium salts with quantum chemistry and ruled out the stepwise S_NAr mechanism proceeding through a Meisenheimer complex. Instead, a mechanism based on a concerted process that may be described as either direct nucleophilic attack on sulfur or as reductive elimination from sulfur was identified. This mechanism involves a single low-energy transition state between the two rapidly interconverting conformers of the fluoride-dibenzothiophenene(phenyl) adduct. One conformer can pass through a transition state (***TS*$_A$**) to give a fluorobiphenyl product, and the other through a lower energy transition state (***TS*$_B$**)

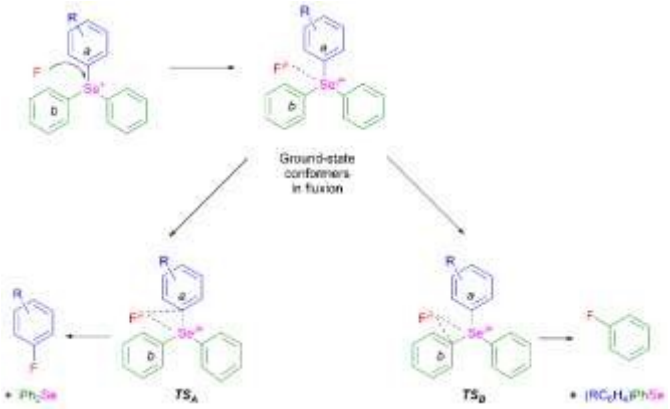


Figure 2. Depiction of a possible mechanism for the fluorination of triarylselenonium salts involving an initial attack of fluoride ion on the selenium cation through two rapidly interconverting transition states (***TS*$_A$** and ***TS*$_B$**) by analogy with that proposed by Gendron et al.[22] for the fluorination of aryl(dibenzothiophene)sulfonium salts.

to give fluorobenzene. This mechanism is analogous to that now established for the fluorination of diaryliodonium salts.[56] Clearly, this type of mechanism might be considered for the radiofluorination of triarylselenonium salts (**Figure 2**).

To further elucidate the fluorination mechanism for *p*- and *o*-substituted phenyl(diphenyl)selenonium salts, we resorted to density functional theory at the level of B3LYP/DGDZVP in the reaction field of acetonitrile. In the absence of an X-ray structure for triphenylselenonium fluoride, we optimized the structure of triphenylselenonium chloride both with and without an explicit water molecule and compared these to the reported X-ray structure of the monohydrate.[57] The geometry optimized *without* the water molecule shows good agreement with the experimental structure, exhibiting a root mean square deviation of 0.29 Å for the heavy atoms.

The calculated Se–Cl and the average Se–C distances (3.516 Å, 1.957 Å) are comparable with the experimental values of 3.530 Å and 1.932 Å, respectively. Inclusion of an explicit water molecule increases the Se–Cl distance to 3.710 Å, while the Se–C distances (1.955 Å) remain essentially unchanged. These results suggest that the water molecule has only a minor effect on the molecular structure. Accordingly, subsequent calculations on substituted phenyl(diphenyl)selenonium salts were all performed without explicit water at the B3LYP/DGDZVP level. This computational approach has been successfully utilized in the investigation of the fluorination mechanism of diaryliodonium salts.[56] **Table 5** lists the

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calculated activation free energies for the fluorination of *p*-substituted phenyl(diphenyl)selenonium salts through two pathways with respective transition states TS_A and TS_B, and the derived chemoselectivities for these reactions as $\exp(\Delta G^{\#}_{TS_B} - \Delta G^{\#}_{TS_A})$. These chemoselectivities are compared with those found experimentally from the microwave-promoted reactions (**Table 1**).

With a strong electron-withdrawing group, such as a *p*-nitro, *p*-nitrile, or *p*-trifluoromethyl group, the calculated energy differences between the two transition states are 7.9 kcal/mol, 5.7 kcal/mol, and 4.4 kcal/mol, respectively, thus favoring the formation of the *p*-substituted fluoroarene over fluorobenzene by 2,697-fold, 299-fold, and 81-fold respectively. These calculated values align well with those determined experimentally (**Table 1**), as shown in **Table 5**.

Predicted and observed chemoselectivities are also remarkably well aligned for the radiofluorinations of other *p*-substituted triphenylselenonium salts where the substituents are electronically neutral or electron-withdrawing (**Table 5**). Moreover, the yields of [^{18}F]fluoroarenes from the microwave promoted reactions (**Table 1**) are well correlated (r^2 = 0.915; P = < 0.0001; n = 8) with the computed activation energies ($\Delta G^{\#}_{TS_A}$) (**Table 5**) for TS_1 leading to these products (**Figure 3**). The strong linearity of this plot implies that the mechanism is similar, irrespective of the *p*-substituent in the triarylselenonium salt.

Further insight into the mechanism of these reactions comes from consideration of the chalcogen-fluorine and chalcogen-ipso carbon bond lengths. **Table 6** lists the calculated X–C_{ipso} and X–F bond distances (X = S, Se, or Te) of *p*-substituted triphenylchalcogen fluorides in their ground states. Where the substituent is *p*-methyl, the X–C_{ipso} bond distances increase in the order S–C_{ipso} (1.807 Å), Se–C_{ipso} (1.952 Å), and Te–C_{ipso} (2.151 Å), commensurate with the covalent radius of the central chalcogen, *i.e.*, S (1.03 Å), Se (1.17 Å), and Te (1.37 Å).

The same trend is seen for a *p*-trifluoromethyl substituent. However, these trends are unexpectedly reversed in the calculated X–F distances (**Table 6** and **Figure 4**). The calculated S–F distances for the 2 sulfonium compounds are longer than the covalent bond distance of 1.62 Å but shorter than the van der Waals distance of 3.27 Å, indicating that these bonds have a hybrid ionic and covalent nature

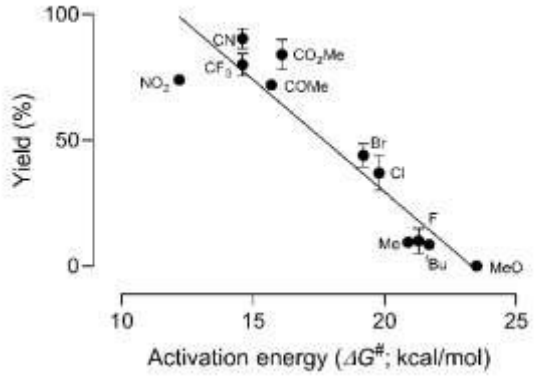

Figure 3. Yields of *p*-substituted fluoroarenes (from **Table 1**) versus the computed activation energies for reactions leading to these products. Datapoint labels identify the *p*-substituent in the fluoroarene. Error bars are SD, and within the symbol size if not visible.

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Table 5. Calculated free energies of activation ($\Delta G^{\#}$)[a] at the level of B3LYP/DGDZVP for the fluorination of mono-*p*-substituted triphenylselenonium salts, and comparison of predicted and experimentally determined radiofluorination chemoselectivities.

salt	*p*-substituent	$\Delta G^{\#}_{TS_A}$ (kcal/mol)	$\Delta G^{\#}_{TS_B}$ (kcal/mol)	$\Delta G^{\#}_{TS_B} - \Delta G^{\#}_{TS_A}$ (kcal/mol)	predicted selectivity for *p*-substituted product [b]	observed selectivity for *p*-substituted product [c]
1a	H	19.1	N/A	N/A	N/A	N/A
1b	NO_2	13.1	21.0	7.9	2,697	>100[d]
1c	CN	14.9	20.6	5.7	299	>100[d]
1d	CF_3	16.5	20.9	4.4	81	40 ± 7
1e	COMe	16.0	20.8	4.8	122	360 ± 211
1f	CO_2Me	16.4	21.4	5.0	148	210 ± 188
1g	F	21.6	21.1	– 0.5	0.61	0.13 ± 0.05
1h	Cl	20.2	21.0	0.8	2.23	1.13 ± 0.16
1i	Br	19.4	20.6	1.2	3.32	1.5 ± 0.2
1j	Me	20.5	19.4	– 1.1	0.33	0.13 ± 0.01
1k	^{t}Bu	22.0	21.1	– 0.9	0.41	0.18 ± 0.06
1m	MeO	23.7	20.8	–2.9	0.06	0.00

[a] Single-point energy calculations in the reaction field of DMF at 423.15 K on the optimized structures in the reaction field of acetonitrile. [b] Calculated as $\exp(\Delta G^{\#}_{TS_B} - \Delta G^{\#}_{TS_A})$, assuming reaction rates are proportional to $\exp^{\Delta G\#/RT}$, where R is the gas constant and T is absolute temperature. [c] Estimated as ratio of the yield of *p*-substituted [^{18}F]fluoroarene to that of [^{18}F]**5a** from **Table 1**. Errors are estimated by combining % standard errors from SDs in **Table 1** data. N/A = not applicable. [d] No byproduct ([^{18}F]**5a**) detected. The reported value assumes a detection limit of ≥ 1%.

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The progressive shortening of the X–F distance with atomic size of the chalcogen (X) indicates increasing covalency in their ground states.

Table 6. Calculated bond lengths in *p*-substituted triphenylchalcogenium fluorides (*p*-$YC_6H_4(Ph)_2XF$; X = S, Se, or Te).

Y	bond length (Å)					
	S–C	S–F	Se–C	Se–F	Te–C	Te–F
Me	1.807	2.417	1.952	2.280	2.151	2.223
CF_3	1.812	2.349	1.996	2.258	2.158	2.214
H	1.811	2.406	1.954	2.273	2.154	2.222

The calculated $\Delta G^{\ddagger}$ values for the fluorination of the salts with a *p*-methyl or *p*-trifluoromethyl substituent through TS_A further support the notion of increasing covalency from sulfur through to tellurium.

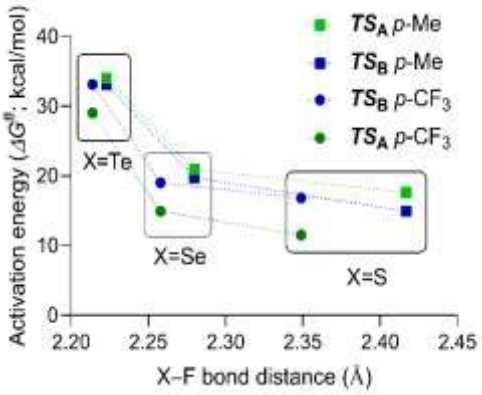

Figure 4. Dependence of calculated transition state activation energies for the fluorination of mono *p*-methyl and *p*-trifluoromethyl substituted triphenylchalcogen fluorides on calculated chalcogen (X) X–F distances.

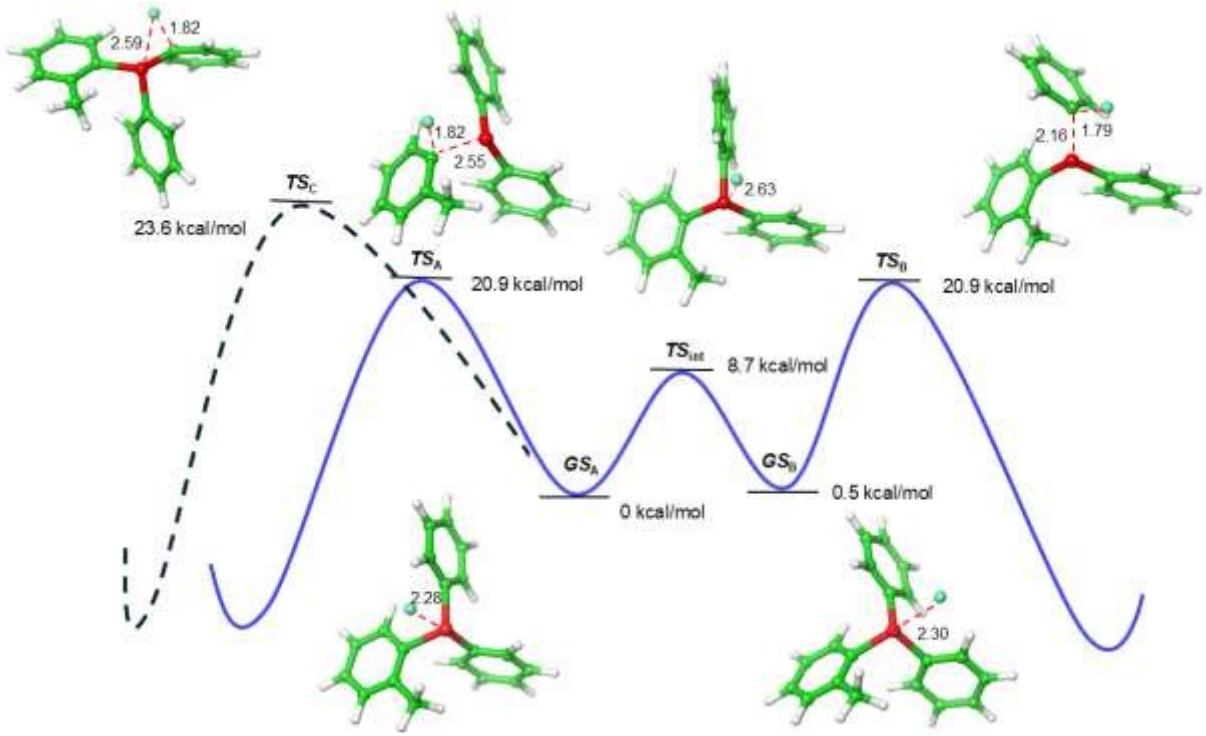

Figure 5. Structures calculated for the ground states (GS_A and GS_B) of diphenyl(*o*-tolyl)selenonium fluoride, the transition state for their pseudorotation,and for the three transition states (TS_A–TS_C) leading to fluoroarene products, either *o*-fluorotoluene (from TS_A) or fluorobenzene (from TS_B or TS_C). TS_{int} is the transition state for ground conformer interconversion. Free energy values are relative to the ground state, GS_A. Selenium is shown in red and fluoride as a light blue circle. Selenium fluoride and ipso aryl carbon-fluoride distances are in Ångströms.

With a *p*-methyl substituent, fluorobenzene would be the major product in all three chalcogen cases as indicated by lower $\Delta G^{\neq}$ for TS_B than for TS_A. Nonetheless, the $\Delta G^{\neq}$ for TS_B increases from 15.1 kcal/mol with X = S to 19.4 kcal/mol with X = Se and then appreciably to 33.3 kcal/mol with X = Te. This can be explained by the variation of the covalency in the X–F bond. Namely, the more covalency in the X–F bond, the less the bond becomes polarized in solvent, resulting in a higher energy barrier for fluorination. A similar trend is seen with the strong electron-withdrawing *p*-CF_3 group in terms of the X–F distance and transition state energy.

Trial radiofluorinations of triphenyltelluronium triflate under thermal conditions (DMF, 150 ºC, 20 min) gave extremely low (0.26 ± 0.14%, *n* = 3) or no yield of [^{18}F]fluorobenzene, in accord with the computed high free energy of activation for congeners of this class of compound (**Figure 4**).

Halogenations of *ortho*-substituted triarylchalcogenium salts pose special mechanistic considerations. In 1976, Lancer and Wiegand[58] observed that the pyrolysis of phenyl-*p*-tolyl-2,5-dimethylphenylsulfonium bromide at 25 °C gave bromobenzene, *p*-bromotoluene, and 2-bromo-*p*-xylene in the ratio of 1.9: 1.0: 11.8, along with dimethyl sulfide. This finding showed the strong effect of two *o*-methyl substituents for directing halogenation to its aryl ring. Because such a finding would not be expected from the operation of a classical S_NAr mechanism involving direct attack of the halide on aryl carbon, it was postulated that the halide has initial attack on the positively charged sulfur atom. The enhancing effect of *o*-methyl substituents on salt reactivity and ring directionality was thus dubbed the 'ortho effect'. A strong ortho effect has been observed in the radiofluorination of diaryliodonium salts.[56,59] Quantum chemical analysis of the mechanism for the fluorination of phenyl(*o*-tolyl)iodonium chloride indicated that the 'ortho effect' was due to a favorable electrostatic interaction between the incoming fluoride and the *o*-methyl group in the transition state.[59] A similar electrostatic effect may be involved in the ortho effect for the radiofluorination of *o*-methyl substituted triarylselenonium salts.

Mechanism of the fluorination of *ortho*-substituted triarylselenonium salts

Quantum chemical calculations indicate that diphenyl(*o*-tolyl)selenonium fluoride, can exist as two energetically comparable conformers in the ground state (**Figure 5**). The lower energy conformer (GS_A) is 0.5 kcal/mol more stable than the other (GS_B) in terms of free energy (ΔG) at 423.15 K. GS_A interconverts with GS_B by pseudo-rotation with a relatively low energy barrier of 8.7 kcal/mol. As a result, the fluorination can proceed through three transition states, TS_A, TS_B, and TS_C, with TS_A producing *o*-fluorotoluene and both TS_B, and TS_C producing fluorobenzene. According to the Curtin-Hammett principle, the chemoselectivity for the fluoro products should be dictated by the difference in activation energies of the transition states leading to their formation, if these are rapidly interconverting relative to the rates of reaction through to products. In this analysis, the two lowest energy pathways are through TS_A ($\Delta G^{\#}$ = 20.9 kcal/mol) and TS_B ($\Delta G^{\#}$ = 20.9 kcal/mol) to *o*-fluorotoluene and fluorobenzene, respectively. Therefore, fluorobenzene and *o*-fluorotoluene are predicted to be produced in equal amounts. However, *o*-fluorotoluene is the major product, seen experimentally by a factor of 7.9 (**Table 1**). This suggests that the energetics of the ground state conformer influence product selectivity when the transition state energetics are similar, as evidenced by the 0.5 kcal/mol stability of GS_A over GS_B. The greater stability of GS_A provides a greater population than that of GS_B for the reaction. We also evaluated the energetics in the reaction field of acetonitrile at 150 °C. The results show that GS_A is 0.5 kcal/mol more stable than GS_B. The transition states TS_A and TS_B both exhibit activation free energy of 20.9 kcal/mol, consistent with the values obtained in DMF. These findings suggest that the solvent has a negligible effect on the relative energetics at the B3LYP/DGDZVP level of theory.

Experimental

Materials

See Supporting Information for sources and syntheses of diaryliodonium triflates, diaryl selenides, triarylsulfonium salts, triarylselenonium salts, triaryltelluronium salt, and other materials.

General Methods and Equipment

See Supporting Information for those not described below.

General procedure for the syntheses of new triarylselenonium triflates. A diaryliodonium triflate (1.5 eq) and stirrer bar were loaded into a 10-mL heavy-walled pressure tube. The tube was loosely sealed with a gasketed Teflon screwcap, evacuated, and purged thrice with argon. Then, in an argon-gas glovebox, a diaryl selenide (1.0 eq.) was added to the tube. The tube contents were dissolved by adding 1,2-dichloroethane (2 mL) The tube was then tightly sealed, removed from the glovebox, immersed in a 110 °C oil-bath, and stirred for 24–48 h. Reaction progress was monitored by

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TLC until complete. The tube was removed from heat and cooled to room temperature. The product was separated from the crude reaction mixture with flash column chromatography (dichloromethane/methanol, gradient with methanol increased linearly from 0 to 5% over 20 minutes) The product fraction was concentrated under reduced pressure affording the targeted triarylselenonium triflate.

Radiofluorination procedures

Preparation of [^{18}F]fluoride-K$^+$-K 2.2.2 complex. [^{18}F]Fluoride ion was produced from the ^{18}O(p,n)^{18}F nuclear reaction by bombarding pure [^{18}O]water with protons (16.5 MeV, 35 or 45 μA) from a PETrace cyclotron (GE Healthcare). [^{18}F]Fluoride ion (~ 7.4 GBq) in [^{18}O]water (0.2–0.3 mL) was then added to a 1-mL glass vial containing an aliquot (80 μL) from a prepared standard solution of K 2.2.2 (5 mg, 0.79 μmol) and K_2CO_3 (0.5 mg, 0.22 μmol) in acetonitrile-water (100 μL; 9: 1 v/v).

Thermal radiofluorination reactions: The solution of [^{18}F]fluoride-K$^+$-K 2.2.2 complex was transferred to a Synthia apparatus[60,61] and dried azeotropically by three additions and evaporations of acetonitrile (each 0.3 mL). The dried [^{18}F]fluoride-K 2.2.2-K$^+$ complex was then taken into a 4-mL glass vial and dissolved in DMF (2 mL). For each experiment, an aliquot (200 μL) of [^{18}F]fluoride in DMF solution was added to a separate 2-mL borosilicate screwcap glass vial (Agilent) containing the triarylchalcogen precursor (~2–3 mg, 1 μmol). The glass vial was sealed, heated to 90 ºC for 20 min, and then cooled to RT before quenching the reaction mixture with acetonitrile-water (1: 1 v/v; 0.2 mL). An aliquot (50 μL) was analyzed with reversed phase HPLC for radiochemical yield determination (see below for method). The identity of the [^{18}F]fluoroarene product was confirmed by collecting the radioactive product fraction for co-injection with its corresponding reference compound onto analytical HPLC and checking for co-elution. In some cases, the radioactivity from injection to product collection was measured to determine an isolated radiochemical yield.

Microwave-promoted radiofluorination reactions. An aliquot (200 μL) of the dried [^{18}F]fluoride in DMF was charged to a 4-mL glass vial containing the triarylchalcogen triflate precursor (~4–5 mg, 10 μmol). The vial was sealed and heated to 150 ºC over 90 s under microwave irradiation (80–90 W) and then allowed to cool (to minimize solvent bumping) before repeating the heating to 150 °C with microwave irradiation (80–90 W) over 90 s. The vial was finally allowed to cool to RT. The contents were then quenched with acetonitrile-water (1: 1 v/v) and analyzed with reversed-phase HPLC (for method see below).

Radio-HPLC analysis

See Supporting Information for radio- HPLC methods.

Quantum chemistry

Quantum chemical calculations were carried out with the density functional theory at the level of B3LYP/DGDZVP as implemented in Gaussian G16-A03.[62] All geometry optimizations were performed in the reaction field of acetonitrile using the polarizable continuum model. To calculate the energy barriers for the fluorination, reaction paths were constructed by varying the distance between the fluoride and the respective *ipso* aryl carbon in the ***GS*** in increments of 0.1 Å while relaxing the rest of the structures. Transition states were obtained with the keywords of opt = (ts, calc, noeigentest). To incorporate the solvent effect of DMF in fluorination, single-point energy calculations were done in the reaction field of DMF at 423.15 K on the geometries optimized in the reaction field of acetonitrile. The coordinates of the compounds in **Table 4**, **Figure 3**, and **Figure 5** in both ground and transition states are listed in the Supporting Information.

Conclusions

Highly stable triarylselenonium triflates were readily prepared from diarylselenides and diaryliodonium triflates. Many of these salts are effective precursors for radiofluorination under thermal and microwave heating conditions to give high yields of NCA [^{18}F]fluoroarenes, depending on aryl substitution pattern. They compare well with triarylsulfonium salts for this purpose. [^{18}F]Fluoroarenes with electron-withdrawing substituents can be obtained in good to high yields from aryl(diphenyl)selenonium triflate precursors. [^{18}F]Fluoroarenes with electron-donating substituents are also accessible in moderate yields that are superior to those from the radiofluorination of corresponding triarylsulfonium triflates. Such electron-rich [^{18}F]fluoroarenes can be obtained in higher yields from symmetrically substituted triarylselenonium salts. A strong ortho effect enables useful radiofluorination in *o*-position, even for electron-rich aryl rings. Moreover, we found that *p*-anisyl groups can serve as useful spectator groups because of their strong resistance to radiofluorination in triarylselenonium triflates. Thus, the radiofluorination of aryl(di-*p*-anisyl)selenonium triflates gave high

yields of [^{18}F]fluoroarenes substituted with *o*- or *m*- alkyl or halo group with high chemoselectivity. This is an effective method for synthesizing PET-tracer like [^{18}F]fluoroarenes, such as NCA [^{18}F]FPEB which was obtained in almost quantitative radiochemical yield and with very high molar activity. Quantum computational analysis supports a common reductive elimination type mechanism for the radiofluorination of triarylselenonium triflates. Overall, substituted diarylselenonium triflates, and especially aryl(di-*p*-anisyl)selenonium triflates, are a useful addition to the range of precursors that can be considered for producing NCA ^{18}F-labeled fluoroarenes as new PET tracers.

Acknowledgments

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Associated content

Supporting information

Compound syntheses; NMR spectra; radiochemistry; HPLC methods; radiochromatograms; compound coordinates

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Author information

Corresponding authors

Fabrice G. Siméon – *Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, USA. ORCID: https://orcid.org/0000-0003-1337-5832.* Email: fabrice.simeon@nih.gov.

Victor W. Pike – *Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, USA. ORCID: https://orcid.org/0000-0001-9032-2553.* Email: pikev@mail.nih.gov.

Authors

Jake Sypniewski – *Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, USA. ORCID: https://orcid.org/0009-0000-8471-0218.* Email: jakesyp21@gmail.com.

Sean Costner – *Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, USA. ORCID: https://orcid.org/0009-0005-3856-6864.* Email: seancostner1@gmail.com.

Phuc Tran – *Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892, USA. ORCID: https://orcid.org/0009-0006-5085-5092:* Email: phuc.tran@nih.gov

Yong-Sok Lee – *Bioinformatics and Computational Biosciences Branch, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland 20892, USA. ORCID: https://orcid.org/0000-0002-6222-1197.* Email: leeys@mail.nih.gov.

Author Contributions

VWP: project conception, data analysis, and supervision. FGS: design, chemistry, and radiosynthesis; JS, PT, SC: synthesis, radiosynthesis and analysis; Y-SL computational chemistry. All authors contributed to the writing of this manuscript (overseen by FGS and VWP).

Conflict of interest Statement

The authors declare no competing financial interest.

Data availability

The data supporting this article has been included as part of the Supplementary Information (SI). Supplementary Information: all experimental setup and details, materials used, synthetic procedures, characterization of organic compounds including the ^{1}H, ^{13}C, ^{77}Se, and ^{19}F NMRs; HPLC radiochromatograms produced from the labeling of triarylselenonium and sulfonium triflates, calibration curves for molar activity measurements and mechanistic studies.

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DATA AVAILABILITY

The data supporting this article has been included as part of the supplementary information (SI). Supplementary information: all experimental setup and details, materials used, synthetic procedures, characterization of organic compounds including the ^{1}H, ^{13}C, ^{77}Se, and ^{19}F NMRs and copies of ^{1}H, ^{13}C, and ^{77}Se, HPLC radiochromatograms produced from the labeling of triarylselenonium and sulfonium triflates, calibration curves for molar activity measurements and mechanistic studies.