Radiochemistry

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Radiosynthesis and Evaluation of [^{18}F]Selectfluor bis(triflate)**

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Positron (β^+) emission tomography (PET) is a noninvasive molecular imaging technique that allows for the in vivo investigation of physiological processes.[1] As a radioisotope, fluorine-18 benefits from an advantageous half-life (109.7 min), a clean decay process (97 % β^+ emission), and a short β^+ trajectory, which is a property that enables the acquisition of high-resolution images. The global use of the radiotracer [^{18}F]-2-fluoro-2-deoxy-D-glucose has generated a vast amount of invaluable clinical data and has stimulated a worldwide interest in PET and ^{18}F radiochemistry. For applications other than radiolabeling, nucleophilic and electrophilic fluorination are complementary processes that are used indiscriminately; the method of choice depends on the reactivity profile of the precursor to be fluorinated.[2] A similar degree of synthetic flexibility would facilitate significantly the production and evaluation of new ^{18}F radiotracers but to date, this is far from the reality because the range of reactions suitable for ^{18}F labeling remains limited in comparison with the number of transformations available to access nonlabeled fluorinated material.[3] Electrophilic ^{18}F-fluorination suffers from well-recognized drawbacks. The carrier-added method employed for the production of [^{18}F]F_2 gas gives labeled products with low specific activity (SA). In addition, [^{18}F]F_2, a reagent that requires specialist equipment for its handling, can react unselectively and lead to a mixture of products. This complication lowers the radiochemical yield (RCY) and may lead to problematic and time-consuming purification processes. Despite these limitations, clinical doses of the radiotracers [F]-2-fluoro-L-tyrosine and [F]-6-fluoro-3,4-dihydroxy-L-phenylalanine are currently prepared relying on an electrophilic fluorodestannylation reaction using [^{18}F]F_2.[4]

Recently, our research group initiated a research programme aimed at advancing the utility of electrophilic ^{18}F-radiolabeling through the preparation of novel and more selective ^{18}F-labeled fluorinating N–F reagents.[5] We reported the synthesis of [^{18}F]-*N*-fluorobenzenesulfonimide (NFSi), a mild and selective reagent suitable for the radiolabeling of various silyl enol ethers and allylsilanes.[6] Selectfluor **1** (1-chloromethyl-4-fluorodiazonia-bicyclo[2.2.2]-octane bis-(tetrafluoroborate)) is a commercially available, easy to handle, and stable electrophilic fluorinating N–F reagent that has an exceptional synthetic scope, which has benefited many chemists since its appearance in 1992.[7] Although its reactivity is superior to *N*-fluorobenzenesulfonimide, it remains very selective. It is therefore not surprising that Selectfluor **1** is possibly the most commonly used reagent to perform the fluorination of electron-rich substrates. The availability of [^{18}F]-labeled Selectfluor could significantly advance electrophilic ^{18}F-radiochemistry, especially if this new reagent is prepared from high SA [^{18}F]F_2. To avoid unnecessary problems that arise from isotopic exchange, we chose to synthesize [^{18}F]Selectfluor bis(triflate) **2** in preference to [^{18}F]Selectfluor bis(tetrafluoroborate) **1**. The triflate salt **2** has a reactivity profile similar to **1** and, in some cases, it has been found to be a more suitable reagent, for example for the electrophilic fluorination of glycals.[8] Herein, we describe the synthesis of [^{18}F]Selectfluor bis(triflate) **2** from high SA [^{18}F]F_2.[9] We also demonstrate that this new [^{18}F]-**2** N–F reagent is suitable for radiolabeling processes (Scheme 1).

Typically, [^{18}F]F_2 is obtained from the nuclear reaction of ^{18}O(p,n)^{18}F through the addition of F_2 (0.2 %) to enriched [^{18}O]O_2. The specific activity for this "in-target" protocol is in the range of 1 GBq μmol^{-1} (Scheme 2, Protocol I), which is significantly lower than the specific activities reached using [^{18}F]fluoride (up to 5500 GBq μmol^{-1}).[10]

For most of the experiments described herein, we used high specific activity [^{18}F]F_2, a reagent prepared in an electrical discharge chamber by an ^{18}F/^{19}F exchange reaction involving [^{18}F]fluoromethane and a low amount of the F_2 carrier (Scheme 3, Protocol II or III). High specific activity [^{18}F]fluoromethane was produced by nucleophilic substitution of methyl iodide with [^{18}F]fluoride, which was obtained through the ^{18}O(p,n)^{18}F nuclear reaction upon irradiation of [^{18}O]-enriched water with a proton beam at 17 MeV. This "post-target" synthesis of high specific activity [^{18}F]F_2 (up to 55 GBq μmol^{-1}) was first reported by Bergman and Solin (Scheme 3).[9]

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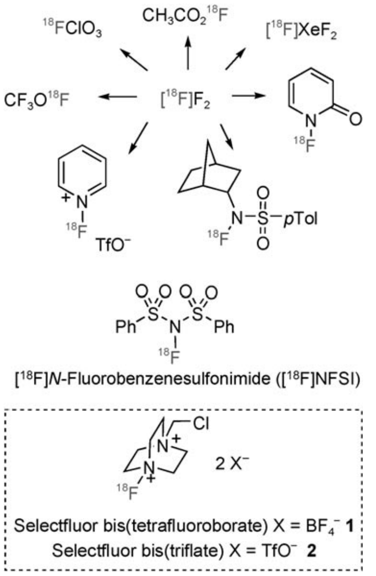
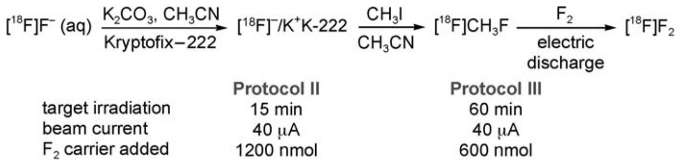


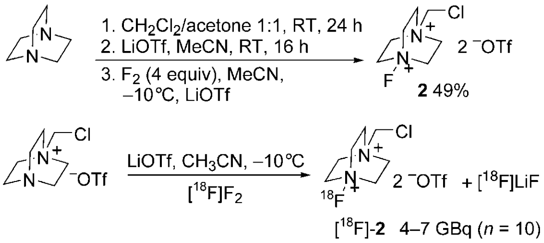
Scheme 1. ^{18}F-Labeled reagents for electrophilic fluorination. Tf = trifluoromethanesulfonyl, Tol = tolyl.

Scheme 2. Radiosynthesis of [^{18}F]F$_2$ from [^{18}O]O$_2$.



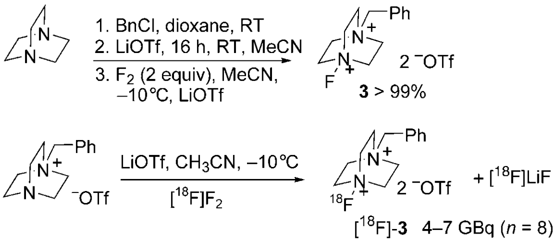
Scheme 3. Radiosynthesis of high specific activity [^{18}F]F$_2$ from [^{18}F]F$^-$. krytopfix-222 = 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo-[8.8.8]hexacosane.

To access Selectfluor bis(triflate) **2**, the original synthetic procedure was adapted.[10] Direct fluorination of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate (accessible in two steps from triethylenediamine (TEDA)) was performed in dry CH$_3$CN at −10 °C with fluorine (10 % F$_2$ in N$_2$) and in the presence of one equivalent of lithium triflate (Scheme 4). To prepare [^{18}F]-**2**, [^{18}F]F$_2$ was bubbled through a 0.02 M solution of the same precursor in anhydrous CH$_3$CN at −10 °C, which resulted in instantaneous fluorination. The crude stock solution (1–2 GBq, 3–7 GBq, or 17 GBq using Protocol I, II, or III, respectively for [^{18}F]F$_2$ production) was used without purification. For radiolabeling experiments to be carried out in acetone, the crude stock solution of [^{18}F]-**2** was concentrated by heating the reaction mixture at 80 °C under a stream of nitrogen and the residue was redissolved in acetone. The total preparation time from the end of bombardment to the delivery of [^{18}F]fluoride was less than 25 minutes. Starting material and [^{18}F]LiF were present in the stock solution used for further experimentation—these compounds do not interfere with the subsequent fluorination. Radio-HPLC analysis of the crude reaction mixture revealed the formation of a radioactive product ($t_r = 4.4$ min). The poor UV response of Selectfluor bis(triflate) did not allow us to conduct unambiguous identification studies by coelution of [^{18}F]-**2** with the cold reagent.



Scheme 4. Radiosynthesis of [^{18}F]-**2**. n = number of experiments.

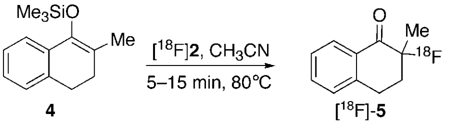
This limitation prompted us to consider simultaneously the synthesis of the structurally related benzyl-substituted N–F reagent [^{18}F]-**3** ([^{18}F]-1-benzyl-4-fluoro-1,4-diazoniabicyclo [2.2.2]octane bis(triflate); Scheme 5). The nonlabeled N–F reagent **3** was obtained with an overall yield of 74 % in three steps, which included the benzylation of TEDA with benzyl chloride, the counterion exchange of the chloride with lithium triflate, and the fluorination with elemental fluorine.[10] The radiosynthesis of [^{18}F]-**3** was performed following a protocol similar to the one applied for the preparation of [^{18}F]Selectfluor bis(triflate) **2** starting with 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]-octane triflate. When Protocol II was applied for the production of [^{18}F]F$_2$, 4–7 GBq of activity was routinely trapped in the stock solution of the reagent and was used in subsequent labeling reactions. The UV-HPLC trace of **3** revealed a peak at 4.3 min, the identity of which was confirmed by LCMS analysis. Radio-HPLC analysis of the crude material showed a product ($t_r = 4.6$ min) coeluting with the cold reference, thus suggesting the formation of [^{18}F]-**3**. Because both **3** and its precursor were detected throughout the baseline of the UV-HPLC trace, quantitative assessment of the efficiency of the synthesis of [^{18}F]-**3** was not deemed appropriate. To take advantage of the carrier-added protocol for the preparation of [^{18}F]F$_2$, further analysis was performed on decayed samples of [^{18}F]-**3**. Pleasingly, the ^{19}F NMR spectrum of decayed [^{18}F]-**3** showed signals at +52.6 ppm and −76.6 ppm, which are diagnostic of the presence of the N–F functionality and the triflate ion, respectively. High-resolution electron impact (EI) mass spectrometric analysis of



Scheme 5. Radiosynthesis of [^{18}F]-**3**. Bn = benzyl.

decayed [^{18}F]-**3** revealed a signal corresponding to the ion benzyl-Selectfluor mono(triflate) product ($C_{14}H_{19}F_4N_2O_3S^+$ *m*/*z* 371.1057, calcd 371.1047).

The successful radiosynthesis of [^{18}F]-**2** and [^{18}F]-**3** encouraged further radiolabeling work and [^{18}F]-**2** was selected for this investigation because this reagent is most commonly used for electrophilic fluorination.[7] To evaluate the usefulness of [^{18}F]-**2**, we first investigated the ^{18}F labeling of the silyl enol ether **4** derived from α-methyl tetralone (Scheme 6). After addition of the crude solution of [^{18}F]-**2** (2 mL, 50–300 MBq) to an excess amount of the substrate **4** (5 mgs) dissolved in CH_3CN, the reaction mixture was stirred at 80 °C. The crude reaction mixture was analyzed using HPLC by comparison with the trace of an authentic reference sample prepared independently using Selectfluor **1** or the bis(triflate) derivative **2**. As HPLC analysis did not allow for the fluorinating reagent [^{18}F]-**2** to be eluted as a single distinct peak uncontaminated from [^{18}F]LiF, purification of the radioactive reaction mixture by semipreparative HPLC was routinely performed to quantify how much of the measured radioactivity corresponded to the product and to determine the RCY, which could therefore not exceed 50 %.[11] The radiofluorination of the silyl enol ether **4** with [^{18}F]-**2** (Scheme 3, Protocol II) was completed within 15 minutes at 80 °C. Radio-HPLC analysis revealed the presence of the desired product [^{18}F]-**5** ($t_r = 4.4$ min) and a minor separable radioactive side product at $t_r = 6.1$ min. When Protocol I was applied for the production of [^{18}F]F_2, which led to [^{18}F]-**2**, the formation of this side product was eradicated. Purification by semipreparative HPLC allowed for the synthesis of radiochemically pure [^{18}F]-**5** in 50 % decay corrected RCY. This reaction was selected for the preparation of high specific activity [^{18}F]-2-fluoro-2-methyl tetralone **5**. Using high specific activity [^{18}F]F_2 (generated by applying Protocol III) for the synthesis of the N–F reagent [^{18}F]-**2**, [^{18}F]-**5** was obtained with a specific radioactivity of 16.4 ± 3.9 GBq µmol^{-1} ($n = 4$; Scheme 6).



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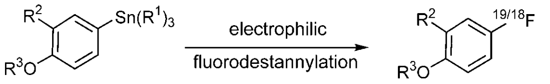
[^{18}F]-**5**

up to 50% RCY
SA = 16.4±3.9 GBq/µmol

Scheme 6. Radiosynthesis of [^{18}F]-**5** with [^{18}F]-**2**.

The electrophilic fluorodemetalation of electron-rich arylstannanes is an important transformation and a key step frequently used to access various PET radiotracers inclusive of [^{18}F]-2-fluoro-L-tyrosine and [^{18}F]-6-fluoro-3,4-dihydroxy-L-phenylalanine ([^{18}F]-6-fluoro-L-DOPA).[4] Our next goal was therefore to perform the electrophilic ^{18}F-fluorination of stannanes **6–8** using the novel N–F reagent [^{18}F]-**2**. The resulting fluorinated products **9–11** are unsuitable candidates for a radiosynthetic route that features a direct nucleophilic aromatic substitution (S_NAr) with the [^{18}F]fluoride ion.[12] The fluorination of **6–8** was investigated with the nonlabeled reagents [^{18}F]*N*-fluorobenzenesulfonimide ([^{18}F]NFSi), Selectfluor bis(tetrafluoroborate) **1**, or the bis(triflate) salt **2** prior to radiolabeling work. The results are summarized in Table 1.

Table 1: Electrophilic fluorodestannylation of **6**–**8**.



6 R^1 = Me, R^2 = OMe, R^3 = Me
7 R^1 = Me, R^2 = H, R^3 = Me
8 R^1 = Bu, R^2 = H, R^3 = H

9 R^2 = OMe, R^3 = Me
10 R^2 = H, R^3 = Me
11 R^2 = H, R^3 = H

Entry	Stannane	Product	Reaction conditions	Yield [%][a]	RCY [%][b, 11]
1	**6**	**9**	**A1**–**A3**[c]	0	–
2	**6**	**9**	**B**[d]	44	–
3	**6**	**9**	**C**[e]	68	–
4	**6**	**9**	**D**[f]	79	–
5	**7**	**10**	**C**[e]	62	–
6	**8**	**11**	**C**[e]	89	–
7	**6**	[^{18}F]-**9**	**E**[g]	–	2
8	**6**	[^{18}F]-**9**	**F**[h]	–	18 ($n = 3$)
9	**7**	[^{18}F]-**10**	**F**[h]	–	17 ($n = 3$)
10	**8**	[^{18}F]-**11**	**F**[h]	–	14 ($n = 3$)

[a] Yields of the isolated products. [b] Decay-corrected RCY (% of radioactivity after semipreparative HPLC). [c] **A1** NFSi (1 equiv), RT, 1.5 h, MeCN or **A2** NFSi (1 equiv), 80 °C, 1.5 h, MeCN or **A3** NFSi (1 equiv), AgOTf (2 equiv), RT, 1.5 h, acetone. [d] **B:** Selectfluor bis(triflate) **2** (1 equiv), MeCN, 80 °C, 30 min. [e] **C:** Selectfluor bis(triflate) **2** (1 equiv), AgOTf (2 equiv), acetone, RT, 20 min. [f] **D:** Selectfluor bis(tetrafluoroborate) **1** (1 equiv), AgOTf (2 equiv), acetone, RT, 20 min. [g] **E: 6** (5 mg), [^{18}F]-**2** (0.25 mL) in MeCN, 80 °C, 30 min. [h] **F: 6**, **7**, or **8** (0.01 mmol), AgOTf (0.02 mmol), [^{18}F]-**2** (0.2 mL) in acetone, RT, 20 min.

Preliminary investigation revealed that fluoroveratrole **9** was not accessible upon electrophilic fluorodestannylation of **6** using the mild N–F reagent NFSi under various reaction conditions (Table 1, entry 1). In contrast, use of Selectfluor bis(triflate) **2** led to the successful fluorodestannylation of **6** in acetonitrile at 80 °C and delivered, after 30 minutes, 4-fluoroveratrole **9** in 44 % yield (Table 1, entry 2). This reaction was much more effective using two equivalents of AgOTf as an additive and acetone as the reaction solvent;[13] **9** was obtained in 68 % yield after just 20 minutes at room temperature (Table 1, entry 3). This yield was increased to 79 % using Selectfluor bis(tetrafluoroborate) **1** (Table 1, entry 4). Under similar conditions, the fluorination of the stannylarenes **7** and **8** with **1** gave the fluoroaromatics **10** and **11** in 62 % and 89 % yield, respectively (Table 1, entries 5 and 6). The fluorodestannylation of **6–8** with the radiolabeled reagent [^{18}F]-**2** was examined next (Table 1, entries 7–10). In the absence of AgOTf, (4-trimethylstannyl)veratrole **6** barely responded to electrophilic fluorination upon exposure with the stock solution of [^{18}F]-**2** in acetonitrile at 80 °C for 30 minutes (Table 1, entry 7; RCY ≈2 %). Pleasingly, in the presence of AgOTf, the reaction proceeded successfully in acetone at room temperature within 20 minutes and gave [^{18}F]-**9** as the only radioactive product. After purification by semipreparative HPLC, [^{18}F]-**9** was obtained with a decay-corrected RCY of 18% (Table 1, entry 8; $n=3$).[11] The remaining radioactivity was observed at the solvent front and was attributed to unreacted [^{18}F]-**2** and [^{18}F]fluoride ion. The less electron-rich stannylated precursor **7** also reacted under similar conditions and gave [^{18}F]fluoroanisole ([^{18}F]-**10**) in a similar RCY (Table 1, entry 9). Most pleasingly, [^{18}F]fluorophenol **11** was accessible upon fluorodestannylation of **8** with a RCY of 14% (Table 1, entry 10; $n=3$).

In summary, [^{18}F]Selectfluor bis(triflate) **2** was prepared successfully and used for the synthesis of ^{18}F-labeled material. This labeled reagent has a unique reactivity profile in the sense that it is much milder and selective than elemental fluorine and suitable for the fluorination of electron-rich substrates that cannot be fluorinated using alternative N–F reagents. These characteristics are highly sought after, especially for the ^{18}F labeling of precursors that are not suitable for nucleophilic fluorination. The applicability of [^{18}F]Selectfluor bis(triflate) **2** was demonstrated with the radiolabeling of representative substrates. The silver-triflate-mediated ^{18}F fluorination of the electron-rich arylstannanes is of particular interest because this transformation can now be conducted selectively and rapidly under very mild conditions (room temperature; "shake and mix" type protocol). Significantly, the unprotected alcohol functionality of arylstannane **8** is well tolerated in this process. It was previously suggested that "the development of ^{18}F-labeled Selectfluor would revolutionize electrophilic fluorination in much the same way as the development of the unlabeled reagent".[7] This statement certainly stands true if the reagent allows for the preparation of high SA ^{18}F-labeled compounds. With the preparation of [^{18}F]-**2** from high SA [^{18}F]F_2, we have shown that the ^{18}F-labeled compound **5** was formed with SA in the range of 20 GBq µmol^{-1}. This work demonstrated that we are one significant step closer to the ultimate goal in the field, which is the availability of the electrophilic fluorinating reagent of tailored reactivity such as ^{18}F-labeled Selectfluor, suited for the preparation of radiotracers with SA matching the level currently attainable using [^{18}F]fluoride ion (in practice 8 Ci µmol^{-1} or $\approx$300 GBq µmol^{-1}). Ongoing work in our laboratories investigates further the applicability of [^{18}F]-**2** with the preparation of clinically useful radiotracers, including [^{18}F]-6-fluoro-L-DOPA.

Experimental Section

Typical procedure for the preparation of [^{18}F]-**9** from [^{18}F]Selectfluor bis(triflate) **2**: Compound **6** (0.01 mmol) was added to [^{18}F]-**2** (0.2 mL) in a solution of acetone and AgOTf (0.02 mmol). The reaction mixture was stirred at RT for 20 min. Analysis was performed by radio-HPLC of 0.1 mL of the reaction mixture diluted in 0.9 mL of CH_3CN/H_2O (1:1).

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