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[^{18}F]Fluorination of an arylboronic ester using [^{18}F]selectfluor bis(triflate): application to 6-[^{18}F]fluoro-L-DOPA†

Ida S. R. Stenhagen,‡[a] Anna K. Kirjavainen,‡[b] Sarita J. Forsback,[b] Charlotte G. Jørgensen,[a] Edward G. Robins,[c] Sajinder K. Luthra,[c] Olof Solin[b] and Véronique Gouverneur*[a]

The Ag-mediated electrophilic [^{18}F]fluorination of an arylboronic ester is reported. This new radiochemical transformation uses [^{18}F]selectfluor bis(triflate) in acetone. The process gave 6-[^{18}F]-fluoro-L-DOPA with a RCY of 19 ± 12% and a specific activity of 2.6 ± 0.3 GBq μmol^{-1}.

Positron Emission Tomography (PET) is a diagnostic imaging modality used regularly to acquire essential clinical information.[1] At the present time, the field relies on innovative radiochemistry to access high performance PET radiotracers that can advance medicine.[2] The use of [^{18}F]fluorodeoxyglucose (FDG) and other [^{18}F]labeled radiotracers in oncology, brain diseases and cardiology has established the value of ^{18}F as a positron emitter for PET and encouraged new developments for late stage fluorination.[3] PET radiotracers difficult to access directly with [^{18}F]fluoride serve as a platform for reaction discovery with much effort currently focused on the [^{18}F]labeling of arenes not amenable to S_NAr. More recently, transition metals have been exploited for the [^{18}F]fluorination of allyl[4] and aryl[5] motifs using various [^{18}F]fluoride sources; for arenes, this radiochemistry requires the preparation of discrete organometallic Pd(II)–aryl[5a] or Ni(II)–aryl[5b] complexes prepared from arylboronic acids or aryl bromides respectively. A metal free approach was also developed featuring a reactivity switch of electron rich aromatics from nucleophilic to electrophilic entities in the presence of an external oxidant.[6]

The most logical approach for the labeling of electron rich substrates remains the direct electrophilic fluorination of precursors that are ideally either commercially available or easily accessible. This approach requires the production of [^{18}F]F_2,[7] a reagent for which appropriate taming may be necessary for late stage fluorination. The well-documented value of N–F reagents in fluorine chemistry encouraged us to use [^{18}F]F_2 to access [^{18}F]*N*-fluorobenzenesulfonimide[8] and [^{18}F]selectfluor bis(triflate),[9] two reagents offering unique opportunities in [^{18}F]radiochemistry for the synthesis of [^{18}F]arenes and more generally electron rich substrates. In our initial report,[9] [^{18}F]selectfluor bis(triflate) was successfully used for the silver(I)-mediated fluorination of model electron-rich arylstannanes. Following these precedents, our next objective was to illustrate the value of [^{18}F]selectfluor bis(triflate) with the preparation of 6-[^{18}F]fluoro-L-DOPA.[10] This important PET radiotracer traditionally employed in studies of the dopaminergic system has found use in the diagnosis and post-treatment monitoring of Parkinson's disease.[11] Its utility has expanded to oncology, particularly in the study of neuroendocrine tumors[12] and congenital hyperinsulinism.[13] To access 6-[^{18}F]fluoro-L-DOPA, we opted to explore the [^{18}F]fluorination of a novel arylboronic ester with [^{18}F]selectfluor bis(triflate), along with a comparative study investigating the reactivity of commonly used arylstannane precursors. To the best of our knowledge, there is no literature precedent on the direct [^{18}F]fluorination of arylboronic acid derivatives using either [^{18}F]F_2 or any other electrophilic [^{18}F]labeled reagents (Fig. 1).[14]

Prior to undertaking the labeling work, we interrogated the reactivity of three 6-fluoro-L-DOPA precursors towards 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octanebis(tetra-fluoroborate) (selectfluor). We selected the arylstannanes (*S*)-**1a** and (*S*)-**1b** as well as the novel arylboronic ester (*S*)-**2a** (Table 1). As anticipated, the protected *N*-Boc arylstannane precursor (*S*)-**1a** underwent fluorination using 1.2 equivalents (equiv.) of selectfluor and 2 equiv. of AgOTf in acetonitrile at room temperature (entry 1). The reaction, which can also be performed successfully in acetone (entry 2), produced the desired fluorinated product (*S*)-**3a** and the side-product (*S*)-**4a** resulting from competitive protodestannylation with an overall yield of ~65%. The addition of $NaHCO_3$ or the addition of molecular sieves (3 Å) did not encourage fluorination over protonation (entries 3 and 4).

[a] *Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK. E-mail: veronique.gouverneur@chem.ox.ac.uk; Fax: +44 (0)1865 285002; Tel: +44 (0)1865 276544*

[b] *Turku PET Centre, Radiopharmaceutical Chemistry Laboratory, Kiinamyllynkatu 4-8, FIN-20520 Turku, Finland*

[c] *The Grove Centre, White Lion Road, Amersham, HP7 9LL, UK*

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‡ The authors contributed equally to this work.

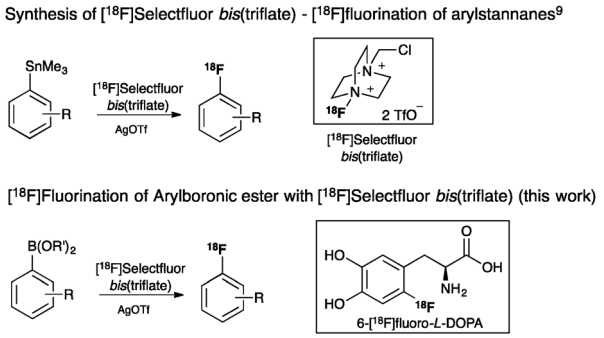
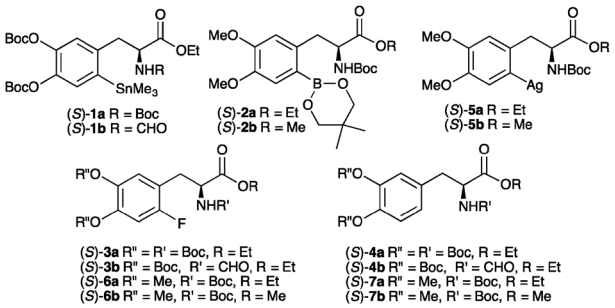


Fig. 1 Reactivity of arylboronic esters with [^{18}F]selectfluor.

Table 1 Fluorination of (*S*)-**1** and (*S*)-**2** with selectfluor



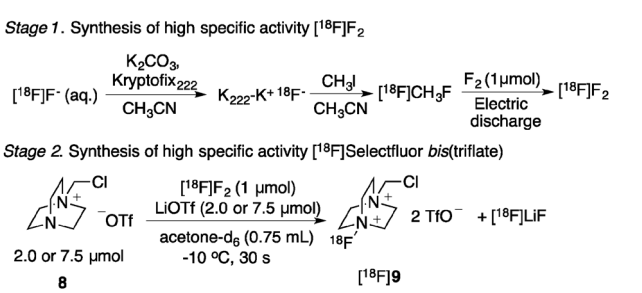
Entry	Precursor	Cond.[a]	Solvent	Ratio[f]	Yield[j] (%)
1	(*S*)-**1a**	I	Acetonitrile	1 : 0.57[g]	69
2	(*S*)-**1a**	I	Acetone	1 : 0.23[g]	67
3	(*S*)-**1a**	I[b]	Acetone	1 : 0.37[g]	66
4	(*S*)-**1a**	I[c]	Acetone	1 : 0.40[g]	56
5	(*S*)-**1b**	I	Acetone	1 : 0.54[h]	65
6	(*S*)-**1b**	I[d]	Acetone	1 : 0.41[h]	59
7	(*S*)-**2a**	II	Acetone	1 : 0.23[i]	35
8	(*S*)-**2a**	II[e]	Acetone	1 : 0.09[i]	50

[a] I: selectfluor (1.2 equiv.), AgOTf (2.0 equiv.), RT, 30 min; II: (i) NaOH (1.2 equiv.), MeOH (0.2 M), RT, 3 h, (ii) AgOTf (3.0 equiv.), 0 °C, 30 min, (iii) selectfluor (1.05 equiv.), acetone, 3 Å molecular sieves, RT, 30 min. [b] 3 Å molecular sieves. [c] $NaHCO_3$ (1.2 equiv.). [d] Selectfluor bis(triflate) (1.2 equiv.), $NaHCO_3$ (1.2 equiv.), 60 °C. [e] Selectfluor bis(triflate) (1.2 equiv.). [f] Ratio determined by ^{1}H NMR. [g] Ratio (*S*)-**3a** : (*S*)-**4a**. [h] Ratio (*S*)-**3b** : (*S*)-**4b**. [i] Ratio (*S*)-**6a** : (*S*)-**7a**. [j] Isolated yield of the mixture of products.

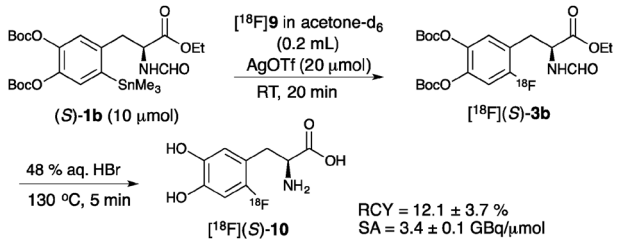
Similar results were obtained using the *N*-formyl protected precursors (*S*)-**1b** (entries 5 and 6). The fluorination of arylboronic acids mediated by silver(I)triflate with selectfluor was reported by Ritter and co-workers in 2009.[15] Based on this precedent, the new *N*-Boc protected arylboronate esters (*S*)-**2a** and (*S*)-**2b** were prepared by coupling the corresponding iodinated aryl precursor with bis(neopentylglycolato)diboron under Pd catalysis.[16] Optimization studies in cold mode were carried out on (*S*)-**2a**. The fluorination of (*S*)-**2a** proceeded in three stages: (i) treatment with 1.2 equiv. of NaOH in MeOH (0.2 M), (ii) transmetalation of the resulting boronic acid with 3.0 equiv. of AgOTf, a process leading to the aryl Ag(I) complex (*S*)-**5a**, and (iii) fluorination of (*S*)-**5a** with 1.05 equiv. of selectfluor after solvent exchange from methanol to acetone. In addition to the fluorinated product (*S*)-**6a**, undesired C–H bond formation leading to (*S*)-**7a** was observed but this competing pathway was less pronounced for the arylboronic ester (*S*)-**2a** than for the arylstannanes (*S*)-**1a** and (*S*)-**1b**. Using selectfluor, (*S*)-**2a** delivered the protected 6-fluoro-L-DOPA derivative (*S*)-**6a** and the side-product (*S*)-**7a** (ratio 5 : 1) in 35% overall yield (entry 7). The counter-ion of selectfluor influenced the efficiency of this process. The yield of the reaction was improved to 50% and the formation of (*S*)-**7a** (ratio (*S*)-**6a** : (*S*)-**7a** = ~10 : 1) minimized using triflate instead of tetra-fluoroborate (entry 8). Based on these observations, selectfluor bis(triflate) was chosen as most suitable for [^{18}F]radiolabeling.

A solution of [^{18}F]selectfluor bis(triflate) [^{18}F]**9** in acetone-d_6 was therefore preferentially required for the radiosynthesis of [^{18}F]6-fluoro-L-DOPA. The protocol applied for the preparation of [^{18}F]**9** was similar to that reported in the literature except for the solvent since the original protocol used acetonitrile. [^{18}F]**9** was prepared from high specific [^{18}F]F_2 generated following the post-target synthesis described by Bergman and Solin.[7b] The [^{18}F]F_2 gas was bubbled into a vial containing a mixture of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane triflate **8** (2.0 or 7.5 μmol) and lithium triflate (1 equiv.) in dry acetone-d_6 (0.75 mL) at −10 °C for approximately 30 seconds. [^{18}F]selectfluor bis(triflate) [^{18}F]**9** formed instantaneously. The activity of the crude stock solution in acetone-d_6 ranged from 5 to 10 GBq, depending on the cyclotron irradiation time. Aliquots (0.2 mL) of this crude stock solution were used directly in subsequent reactions. [^{18}F]selectfluor bis(triflate) was therefore prepared in acetone as efficiently as in acetonitrile. This could be advantageous for some applications as acetone is more volatile and has a different solubilisation profile (Scheme 1).

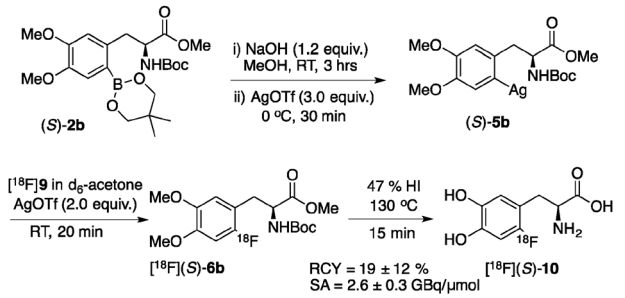
The [^{18}F]radiolabeling of the arylstannane precursor (*S*)-**1b** was considered first (Scheme 2). A solution of [^{18}F]**9** in acetone-d_6 (0.2 mL) was added to a reaction vial containing (*S*)-**1b** (10 μmol). Silver(I) triflate (20 μmol) was added and the solution stirred at room temperature for 20 minutes. The solvent was evaporated under a stream of helium. The deprotection of (*S*)-**3b** was carried out with 48% aqueous HBr (0.3 mL) at 130 °C for 5 minutes to release [^{18}F]-6-fluoro-L-DOPA [^{18}F](*S*)-**10**. The identity of both [^{18}F](*S*)-**3b** and [^{18}F](*S*)-**10** was confirmed by HPLC analysis. Optimization studies revealed that there was significant difference in the RCYs of the protected intermediate [^{18}F](*S*)-**3b** when using different amounts of precursor **8** in the preparation of selectfluor bis(triflate) [^{18}F]**9**. The average decay corrected radiochemical yield (RCY) of [^{18}F](*S*)-**10** was 12.1 ± 3.7% when using 2 μmol of 1-chloromethyl-4-aza-1-azoniabicyclo[2.2.2]-octane triflate **8** in 0.75 mL acetone-d_6 for the



Scheme 1 Synthesis of [^{18}F]selectfluor bis(triflate) in acetone-d_6.



Scheme 2 Synthesis of [^{18}F]-6-fluoro-L-DOPA from (*S*)-**1b**.



Scheme 3 Synthesis of [^{18}F]-6-fluoro-L-DOPA from (*S*)-**2b**.

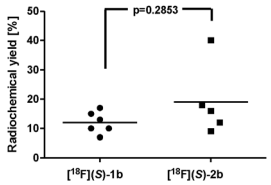


Fig. 2 Statistical analysis of the RCYs of [^{18}F]**10** from (*S*)-**1b** or (*S*)-**2b**.

preparation of selectfluor bis(triflate) [^{18}F]**9**. When 7.5 μmol of precursor **8** was used to access [^{18}F]**9**, the RCY was significantly lower (6.8 ± 1.8%). The specific activity (SA) of the final product was consistently in the range of 3.4 ± 0.1 GBq μmol^{-1}.

The radiolabeling of (*S*)-**2b** was examined next (Scheme 3). Unlike arylstannanes (*S*)-**1a** and (*S*)-**1b**, the transmetalation of the arylboronic ester (*S*)-**2b** was performed prior to [^{18}F]labeling. Practically, the arylboronic ester (*S*)-**2b** was therefore converted to the corresponding aryl Ag(I) complex (*S*)-**5b** prior to [^{18}F]fluorination. The complex (*S*)-**5b** freshly prepared was labeled successfully within 20 minutes at room temperature using selectfluor bis(triflate) [^{18}F]**9**. Deprotection of [^{18}F](S)-**6b** led to [^{18}F]-6-fluoro-L-DOPA [^{18}F]**10** with a RCY of 19 ± 12% and SA of 2.6 ± 0.3 GBq μmol^{-1}. The efficiency of this process is comparable to that of the best known protocol using [^{18}F]F_2.[10]

In a statistical analysis, the yield of 6-fluoro-L-DOPA [^{18}F](*S*)-**10** from (*S*)-**1b** did not differ significantly from the yield obtained when using (*S*)-**2b** (Fig. 2).

In conclusion, we have extended the scope of [^{18}F]selectfluor bis(triflate) for [^{18}F]radiochemistry. The demonstration that the arylboronic ester (*S*)-**2b** is a competent substrate for [^{18}F]fluorination suggests that a plethora of arylboronic acid derivatives can be radiolabeled using this new protocol. This study demonstrates that [^{18}F]selectfluor bis(triflate) is a suitable alternative to [^{18}F]F_2 to access [^{18}F]6-fluoro-L-DOPA from either the arylstannane (*S*)-**1b** or the protected arylboronic ester (*S*)-**2b**. These new developments suggest that fluorination using unlabeled selectfluor could be favorably considered, after adequate optimization, for the production of [^{18}F]material.

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