Supporting Information

First radiosynthesis of 2-amino-5-[18F]fluoropyridines
via a “minimalist” radiofluorination/palladium-catalyzed amination sequence
from anisyl(2-bromopyridinyl)iodonium triflate

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1. Chemistry

1.1. General materials and methods

Chemicals, reagents and solvents were purchased commercially and used as received. Previously described starting anisylpyridinyliodonium salts (such as anisyl(2-chloropyridinyl)iodonium triflate 4, isomers and analogues bearing a cyano, methyl, methoxy, methylcarboxylate, N-methylcarboxamide) were prepared according to the literature procedures.\(^{1,2}\) \(^{1}\)H, \(^{13}\)C and \(^{19}\)F NMR spectra were recorded on a Brucker Avance 400 or 500 MHz spectrometer. Samples were dissolved in an appropriate deuterated solvent (CDCl\(_3\) or CD\(_3\)OD). Chemical shifts (\(\delta\)) are quoted in parts per million (ppm). Coupling constants (\(J\)) are given in Hz. Coupling patterns are abbreviated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), td (triplet of doublet). High resolution mass spectra (HRMS) were recorded using a Shimazu IT-TOF. Melting points were determined with an Electrothermal IA900 series of digital melting point instrument. They are uncorrected and given in °C. IR spectra were recorded on a FT-IR spectrometer and are given in cm\(^{-1}\).

1.2. Preparation and characterization of anisyl(2-bromopyridinyl)iodonium triflate 5

![Chemical structure of anisyl(2-bromopyridinyl)iodonium triflate 5](image)

To a solution of 2-bromo-5-iodopyridine (300 mg, 1.06 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (6 mL) was added dropwise TfOH (373 \(\mu\)L, 4.23 mmol, 4.0 equiv) under argon. The reaction mixture was stirred for 10 min at rt and \(m\)-CPBA (77%, 414.5 mg, 1.85 mmol, 1.75 equiv) was added. The reaction mixture was stirred for 1.5 h at rt then cooled to 0 °C. Water (38 \(\mu\)L, 2.11 mmol, 2.0 equiv) and anisole (138 \(\mu\)L, 1.27 mmol, 1.2 equiv) were added. The reaction mixture was stirred for 30 min at 0 °C then concentrated under vacuum. Et\(_2\)O (2 mL) was added to the crude residue, and the mixture was stirred for 30 min at 0 °C. The resulting precipitate was filtered through a glass sintered funnel, washed with additional Et\(_2\)O (50 mL) and lyophilized to give the title product 5 as a grey solid (295 mg, 52% yield). Mp (°C): 143; \(R_f\) (CH\(_2\)Cl\(_2\)/MeOH 90:10): 0.7; \(^{1}\)H NMR (600 MHz, CD\(_3\)OD) \(\delta\): 9.99 (d, \(J = 2.2\) Hz, 1H), 8.39 (dd, \(J = 2.5, 8.6\) Hz, 1H), 8.1 (d, \(J = 9.1\) Hz, 2H), 7.74 (d, \(J = 8.5\) Hz, 1H), 7.09 (d, \(J = 9.1\) Hz, 2H), 3.86 (s, 3H); \(^{13}\)C NMR (151 MHz, CD\(_3\)OD) \(\delta\): 164.8, 155.1, 146.8, 145.5, 138.8, 132.7, 121.8 (q, \(J = 316\) Hz), 119.1, 114.6, 104.5, 56.4; \(^{19}\)F NMR (376 MHz, CD\(_3\)OD) \(\delta\): -80.08; IR (cm\(^{-1}\)) \(\nu_{\text{max}}\): 3096, 1573, 1083, 514; HRMS (ESI): \(m/z\) calculated for C\(_{12}\)H\(_{10}\)BrINO ([M-OTf])\(^+\): 389.8985, found: 389.8975.
1.3. Preparation and characterization of 2-amino-5-fluoropyridines 1

1.3.1. General Procedure

To 2-bromo-5-fluoropyridine 9 (100 mg, 0.57 mmol, 1.0 equiv), Pd\textsubscript{2}(dba)\textsubscript{3} (10.4 mg, 0.011 mmol, 4 mol% Pd), Xphos (21.7 mg, 0.045 mmol, 8 mol%), NaO\textsubscript{t}Bu (163.8 mg, 1.70 mmol, 3.0 equiv) and amine (1.5 equiv) was added anhydrous toluene (2 mL) under argon. The reaction mixture was stirred at 100 °C for 24 h then cooled down to rt. The crude mixture was concentrated under vaccum. Purification by column chromatography on silica gel using CH\textsubscript{2}Cl\textsubscript{2} or a 9:1 mixture of CH\textsubscript{2}Cl\textsubscript{2}/MeOH as eluent gave the desired 2-amino-5-fluoropyridines 1.

1.3.2. 5-Fluoro-2-(piperidin-1-yl)pyridine 1a [1287218-71-6]

Fluoropyridine 1a was obtained according to General Procedure from 2-bromo-5-fluoropyridine 9 (100 mg, 0.57 mmol, 1.0 equiv) and piperidine (84 μL, 0.85 mmol, 1.5 equiv) as a slightly yellow oil (102 mg, quantitative yield). \( R_f \) (CH\textsubscript{2}Cl\textsubscript{2}): 0.7; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ: 8.02 (d, \( J = 3.1 \) Hz, 1H), 7.23-7.19 (m, 1H), 6.59 (dd, \( J = 3.4, 9.3 \) Hz, 1H), 3.43 (m, 4H), 1.65-1.60 (m, 6H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ: 157.0, 153.2 (d, \( J = 243.4 \) Hz), 134.6 (d, \( J = 24.1 \) Hz), 125.0 (d, \( J = 20.1 \) Hz), 107.9 (d, \( J = 3.6 \) Hz), 47.2, 25.5, 24.6; \textsuperscript{19}F NMR (471 MHz, CDCl\textsubscript{3}) δ: -144.01; IR (cm\textsuperscript{-1}) \( v_{\text{max}} \): 2933, 1225, 1128.

1.3.3. 5-Fluoro-2-(4-methylpiperazin-1-yl)-5-fluoropyridine 1b [1877101-49-9]

Fluoropyridine 1b was obtained according to General Procedure from 2-bromo-5-fluoropyridine 9 (100 mg, 0.57 mmol, 1.0 equiv) and 1-methylpiperazine (95 μL, 0.85 mmol, 1.5 equiv) as a brown oil (111 mg, quantitative yield). \( R_f \) (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 90:10): 0.6; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ: 8.04 (d, \( J = 3.0 \) Hz, 1H), 7.26-7.22 (m, 1H), 6.60 (dd, \( J = 3.3, 9.2 \) Hz, 1H), 3.48 (t, \( J = 5.1 \) Hz, 4H), 2.53 (t, \( J = 5.2 \) Hz, 4H), 2.34 (s, 3H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ: 156.7,
153.7 (d, $J = 244.3$ Hz), 134.8 (d, $J = 23.9$ Hz), 125.1 (d, $J = 20.2$ Hz), 107.8 (d, $J = 3.8$ Hz), 55.0, 46.3, 46.1; $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$: -142.84; IR (cm$^{-1}$) $\nu_{\text{max}}$: 2938, 1336, 1245; HRMS (ESI): $m/z$ calculated for C$_{10}$H$_{15}$FN$_3$ ([M+H]$^+$): 196.1250, found: 196.1249.

1.3.4. 2-(N,N-Dimethylamino)-5-fluoropyridine 1c [1420961-53-0]

Fluoropyridine 1c was obtained according to General Procedure from 2-bromo-5-fluoropyridine 9 (100 mg, 0.57 mmol, 1.0 equiv) and N,N-dimethyleamine (57 µL, 0.85 mmol, 1.5 equiv) as a yellow oil (59 mg, 74% yield). $R_f$ (CH$_2$Cl$_2$/MeOH 90:10): 0.5; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.03 (d, $J = 3.0$ Hz, 1H), 7.26-7.22 (m, 1H), 6.46 (dd, $J = 3.3$, 9.2 Hz, 1H), 3.06 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 155.2 (d, $J = 249.5$ Hz), 154.0, 135.4 (d, $J = 25.2$ Hz), 124.9 (d, $J = 20.2$ Hz), 115.3 (d, $J = 3.8$ Hz), 42.7; $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$: -145.88; IR (cm$^{-1}$) $\nu_{\text{max}}$: 2896, 1372, 1226.

1.3.5. 2-(n-Butylamino)-5-fluoropyridine 1d [1248193-14-7]

Fluoropyridine 1d was obtained according to General Procedure from 2-bromo-5-fluoropyridine 9 (100 mg, 0.57 mmol, 1.0 equiv) and n-butylamine (84 µL, 0.85 mmol, 1.5 equiv) as a yellow oil (95 mg, quantitative yield). $R_f$ (CH$_2$Cl$_2$): 0.4; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.17 (d, $J = 3.0$ Hz, 1H), 7.30-7.28 (m, 1H), 7.00 (dd, $J = 3.7$, 9.2 Hz, 1H), 4.07 (t, $J = 7.6$ Hz, 1H), 1.67-1.61 (m, 1H), 1.39-1.31 (m, 1H), 0.91 (t, $J = 7.4$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 155.3 (d, $J = 249.5$ Hz), 154.0, 135.4 (d, $J = 25.2$ Hz), 124.9 (d, $J = 20.2$ Hz), 115.3 (d, $J = 3.8$ Hz), 49.1, 30.4, 20.4, 14.1; $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$: -145.88; IR (cm$^{-1}$) $\nu_{\text{max}}$: 3031, 1392, 1226.

1.3.6. 2-Benzylamino-5-fluoropyridine 1e [1251026-62-6]

Fluoropyridine 1e was obtained according to General Procedure from 2-bromo-5-fluoropyridine 9 (100 mg, 0.57 mmol, 1.0 equiv) and benzylamine (93 µL, 0.85 mmol, 1.5 equiv) as a yellow oil (17.1 mg, 15% yield). $R_f$ (CH$_2$Cl$_2$): 0.6; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.97 (d, $J = 2.9$ Hz, 1H), 7.32-7.38 (m, 4H), 7.30-7.27 (m, 1H), 7.18 (m, 1H), 6.33 (dd, $J = 3.4$, 9.1 Hz, 1H), 4.87 (s, 1H) 4.47 (d, $J = 5.0$ Hz, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 155.5, 155.4, 152.6,
139.1, 134.8 (d, $J = 24.6$ Hz), 128.1, (d, $J = 160.7$ Hz), 127.4, 125.3 (d, $J = 20.6$ Hz), 107.1 (d, $J = 3.9$ Hz), 46.9; $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$: -143.45; IR (cm$^{-1}$) $\nu_{\text{max}}$: 3029, 1467, 1218.

1.3.7. 2-Anilino-5-fluoropyridine 1f [51269-88-6]

Fluoropyridine 1f was obtained according to General Procedure from 2-bromo-5-fluoropyridine 9 (100 mg, 0.57 mmol, 1.0 equiv) and aniline (78 µL, 0.85 mmol, 1.5 equiv) as a yellow solid (27 mg, 25% yield). Mp (°C): 87; $R_f$ (CH$_2$Cl$_2$): 0.6; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.99 (d, $J = 2.7$ Hz, 1H), 7.27-7.17 (m, 5H), 6.97 (t, $J = 7.2$ Hz, 1H), 6.77 (dd, $J = 3.4, 9.1$ Hz, 1H), 6.49 (s, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 155.4, 152.6, 140.8, 135.3 (d, $J = 25.2$ Hz), 129.5, 125.5 (d, $J = 21.4$ Hz), 123.0, 120.0, 109.1; $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$: -140.07; IR (cm$^{-1}$) $\nu_{\text{max}}$: 3031, 1392, 1226.

1.3.8. 2-(3-Anilinoamino)-5-fluoropyridine 1g

Fluoropyridine 1g was obtained according to General Procedure from 2-bromo-5-fluoropyridine 9 (100 mg, 0.57 mmol, 1.0 equiv) and 3-aminopyridine (80.2 mg, 0.85 mmol, 1.5 equiv) as a yellow solid (78 mg, 73% yield). Mp (°C): 146; $R_f$ (CH$_2$Cl$_2$/MeOH 90:10): 0.6; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.60 (s, 1H), 8.22 (d, $J = 4.4$ Hz, 1H), 8.08 (d, $J = 2.5$ Hz, 1H), 8.00 (d, $J = 7.9$ Hz, 1H), 7.32-7.30 (m, 1H), 7.26-7.23 (m, 1H), 6.94 (s, 1H), 6.80 (dd, $J = 3.1, 8.9$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 154.8 (d, $J = 246.9$ Hz), 151.7, 142.8, 140.8, 137.9, 135.0 (d, $J = 25.5$ Hz), 125.9 (d, $J = 20.4$ Hz), 125.6, 123.9, 110.5; $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$: -141.97; IR (cm$^{-1}$) $\nu_{\text{max}}$: 3036, 1486, 1227; HRMS (ESI): $m/z$ calculated for C$_{10}$H$_9$FN$_3$ ([M+H]$^+$): 190.0781, found: 190.0785.

2. Radiochemistry

2.1. General procedures, materials

All experiments were carried behind a lead-wall or in a lead-shielded hot-cell to minimize the radiation exposure to personnel. No-carrier-added (nca) [$^{18}$F]fluoride anion was obtained through the $^{18}$O(p, n)$^{18}$F nuclear reaction by irradiating $^{18}$O-enriched water (97%, Eurisotop; 1.8 mL) with a beam of protons (18 MeV; 20–25 µA for 10–20 min) generated from a biomedical Cyclone 18/9 (IBA) cyclotron. Radioactivity measurements were performed using a calibrated ionizing chamber (Capintec R15C) and were corrected from background. Analytical High Performance Liquid Chromatography (HPLC) was carried out on a Waters e2695 (Separations module) coupled with a Waters 2998 (Photodiode Array Detector) and a MIP10 radioactive
detector (Nardeux). Semi-preparative HPLC was carried out using a Waters 515 HPLC pump coupled with a Waters 2487 UV detector set up at $\lambda = 254$ nm and a MIP10 radioactive detector (Nardeux). Pre-conditioned Light QMA carbonate anionic cartridges (Waters) were obtained from ABX. Silica Sep Pack cartridges were purchased from Waters.

2.2. Testing “minimalist” radiofluorination reaction from anisyl(2-chloropyridinyl)iodonium salts

2.2.1. Protocol

Minimalist radiofluorination of iodonium salts was conducted according to protocol based on works reported by Richarz et al.\(^3\)

*Method in DMF*: [$^{18}$F]fluoride ion was fixed an a QMA carbonate anionic resin cartridge. The cartridge was washed with anhydrous MeOH (1 mL) and the radiofluoride was eluted with a solution of iodonium salt (0.02 mmol, 1 equiv) in anhydrous MeOH (500 µL). The elution yield was determined by comparing the radioactivity eluted into the reaction vial with the total radioactivity trapped on the anion exchange resin. MeOH was removed by heating at 70 °C for 3 min under nitrogen flow. TEMPO (1 equiv) in DMF (500 µL) was added to the residue, and the reaction mixture was stirred for 30 min at 130 °C then cooled to rt. After addition of mixture of ACN/H$_2$O (60:40 v/v; 500 µL), the mixture was injected onto a semi-preparative HPLC column (LUNA C18(2), 5 µm, 250 x 10 mm, flow rate at 3.5 mL/min, ACN/H$_2$O as eluent) for isolation of $^{18}$F-products. The unreacted [$^{18}$F]fluoride and the desired [$^{18}$F]fluoropyridine were collected and measured for radioactivity. Isolated radiochemical yield was calculated as the ratio of the radioactivity of the desired [$^{18}$F]fluoropyridine compared to the total radioactivity injected onto the semi-preparative HPLC column.

*Method in ACN*: [$^{18}$F]fluoride ion was fixed an a QMA carbonate anionic resin cartridge. The cartridge was washed with anhydrous MeOH (1 mL) and the radiofluoride was eluted with a solution of iodonium salt (0.02 mmol, 1 equiv) in anhydrous MeOH (500 µL). The elution yield was determined by comparing the radioactivity eluted into the reaction vial with the total radioactivity trapped on the anion exchange resin. MeOH was removed by heating at 70 °C for 3 min under nitrogen flow. TEMPO (1 equiv) in ACN (500 µL) was added to the residue, and the reaction mixture was stirred for 15 min at 90 °C then cooled to rt. After addition of mixture of ACN/H$_2$O (60:40 v/v; 500 µL), the mixture was injected onto a semi-preparative HPLC column (LUNA C18(2), 5 µm, 250 x 10 mm, flow rate at 3.5 mL/min, ACN/H$_2$O as eluent) for isolation of $^{18}$F-products. The unreacted [$^{18}$F]fluoride and the desired [$^{18}$F]fluoropyridine were collected and measured for radioactivity. Isolated radiochemical yield was calculated as the ratio of the radioactivity of the desired [$^{18}$F]fluoropyridine compared to the total radioactivity injected onto the semi-preparative HPLC column.

Results are presented in the following sections.
2.2.2. Table S1: Influence of additives (K₂CO₃, K₂2₂, TEMPO) and of purification process for iodonium triflate 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isolation process for 4</th>
<th>K₂CO₃ equiv</th>
<th>TEMPO equiv</th>
<th>RCC±SEM b (%)</th>
<th>Isolated RCY±SEM c (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Precipitation d</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>22±3</td>
</tr>
<tr>
<td>2</td>
<td>Precipitation d</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>3</td>
<td>Precipitation d</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>9.5</td>
</tr>
<tr>
<td>4</td>
<td>Precipitation d</td>
<td>0.2 f</td>
<td>0.28</td>
<td>3</td>
<td>9.5</td>
</tr>
<tr>
<td>5</td>
<td>Precipitation d</td>
<td>3.6 f</td>
<td>5</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>6</td>
<td>Al₂O₃ e</td>
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<td>0</td>
<td>1</td>
<td>3.2</td>
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<tr>
<td>7</td>
<td>Al₂O₃ e</td>
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<td>0</td>
<td>3</td>
<td>9.5</td>
</tr>
<tr>
<td>8</td>
<td>Al₂O₃ e</td>
<td>0.2 f</td>
<td>0.2</td>
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<td>9.5</td>
</tr>
<tr>
<td>9</td>
<td>Al₂O₃ e</td>
<td>3.6 f</td>
<td>5</td>
<td>1</td>
<td>3.2</td>
</tr>
</tbody>
</table>

a Iodonium triflate 4 (10 mg, 0.02 mmol, 1 equiv).
b Radiochemical conversion of [¹⁸F]fluoride ion, measured from HPLC chromatogram.
c Isolated decay corrected radiochemical yield calculated from [¹⁸F]fluoride.
d Precipitation of the crude product as previously reported.²
e Basic alumina column after precipitation, then recrystallization as previously reported.¹ ²
f K₂2₂ (0.4 equiv or 7.2 equiv) was added when K₂CO₃ (0.2 equiv or 3.6 equiv) was present.

1) Elution with 4 (1 equiv) in MeOH
2) Evaporation of MeOH
3) K₂CO₃, K₂2₂, TEMPO DMF, 130°C, 30 min
2.2.3. **Table S2.** Influence of the solvent in the minimalist radiofluorination of iodonium triflate 4 in the absence of K$_2$CO$_3$ and K$_{222}$$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>t (min)</th>
<th>RCC ± SEM$^b$ (%; n = 3)</th>
<th>Isolated RCY ± SEM$^c$ (%) (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>130</td>
<td>30</td>
<td>54±4</td>
<td>43±3</td>
</tr>
<tr>
<td>2</td>
<td>ACN</td>
<td>90</td>
<td>15</td>
<td>64±2</td>
<td>50±4</td>
</tr>
<tr>
<td>3</td>
<td>ACN</td>
<td>90</td>
<td>30</td>
<td>64±5</td>
<td>53±3</td>
</tr>
</tbody>
</table>

$^a$ Iodonium triflate 4 (10 mg, 0.02 mmol, 1 equiv) isolated by precipitation as previously reported,$^2$ TEMPO (3.2 mg, 0.02 mmol, 1 equiv).

$^b$ Radiochemical conversion of $[^{18}F]$fluoride ion, measured from HPLC chromatogram.

$^c$ Isolated decay corrected radiochemical yield calculated from $[^{18}F]$fluoride.

2.2.4. **Table S3.** Influence of the counter-ion of iodoniums 4 in its minimalist radiofluorination in the absence of K$_2$CO$_3$ and K$_{222}$$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodonium</th>
<th>X</th>
<th>RCC ± SEM$^b$ (%; n = 3)</th>
<th>Isolated RCY ± SEM$^c$ (%) (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4$^d$</td>
<td>OTf</td>
<td>54±4</td>
<td>43±3</td>
</tr>
<tr>
<td>2</td>
<td>4$'$</td>
<td>BF$_4$</td>
<td>39±2</td>
<td>44±2</td>
</tr>
<tr>
<td>3</td>
<td>4$''$</td>
<td>Br</td>
<td>2±2</td>
<td>2±1</td>
</tr>
<tr>
<td>4</td>
<td>4$'''$</td>
<td>OTs</td>
<td>40±3</td>
<td>32±1</td>
</tr>
</tbody>
</table>

$^a$ Iodonium salt 4-4$'''$ (0.02 mmol, 1 equiv), TEMPO (3.2 mg, 0.02 mmol, 1 equiv).

$^b$ Radiochemical conversion of $[^{18}F]$fluoride ion, measured from HPLC chromatogram.

$^c$ Isolated decay corrected radiochemical yield calculated from $[^{18}F]$fluoride.

$^d$ 4 isolated by precipitation as previously reported.$^2$
2.2. Scope of “minimalist” radiofluorination reaction from functionalized anisyl(pyrindinyl)iodonium triflates

\[
\begin{align*}
\text{1) Elution with diaryliodonium salt (1 equiv)} \\
\text{2) Evaporation of MeOH} \\
\text{3) TEMPO (1 equiv)}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>[\textsuperscript{18}F]Fluoropyridine</th>
<th>Isolated Yields ± SEM (%; n = 3)</th>
<th>DMF, 130 °C, 30 min</th>
<th>MeCN, 90°C, 15 min</th>
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<td>44±2</td>
<td>11±1</td>
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<td>36±3</td>
<td>49±2</td>
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\textsuperscript{a} Iodonium triflates isolated by precipitation as previously reported.\textsuperscript{2}
2.3 Radiosynthesis of 2-amino-5-[\(^{18}\)F]fluoropyridines [\(^{18}\)F]I

2.3.1 Route A (using classical radiofluorination procedure)

Aqueous cyclotron produced [\(^{18}\)F]fluoride was absorbed onto QMA carbonate anionic resin cartridge (from ABX) and then eluted in a V-vial with a solution of K\(_2\)CO\(_3\) (5 mg, 36 \(\mu\)mol) and K\(_{222}\) (28 mg, 74 \(\mu\)mol) in MeCN/H\(_2\)O (50:50 v/v; 800 \(\mu\)L). Three successive cycles of azeotropic addition and evaporation of anhydrous MeCN (1 mL for each addition) were performed at 110 °C for 5 min under a nitrogen stream. Iodonium triflate precursor 4 or 5 (20 \(\mu\)mol) and TEMPO (3.1 mg, 20 \(\mu\)mol) in ACN (500 \(\mu\)L) were added to dried [\(^{18}\)F]fluoride. The reaction mixture was stirred for 30 min at 130 °C and then cooled to rt. An aliquot was taken off and injected to analytical HPLC (LUNA C18(2), 5 \(\mu\)m, 100 Å, 250 x 4.6, elution at 0.7 mL/min with a solution of MeCN/H\(_2\)O). Chromatograms revealed the formation of 2-halo-[\(^{18}\)F]fluoropyridines [\(^{18}\)F]8 and [\(^{18}\)F]9 in around 80±6% and 92±6% yields respectively. The crude mixture resulting from radiofluorination reaction was then passed through a silica Sep Pack cartridge (preconditioned with 1 mL toluene), then elution of the total radioactivity was carried out with toluene (1 mL) or a 1:1 mixture of ACN/toluene (1 mL). To the resulting solution were added Pd\(_2\)(dba)\(_3\) (4.7 mg, 5 \(\mu\)mol), XPhos (4.6 mg, 10 \(\mu\)mol), NaO\(_t\)Bu (14.2 mg, 150 \(\mu\)mol) and piperidine (15 \(\mu\)L, 150 \(\mu\)mol). The mixture was stirred for 30 min at 100 °C, then cooled down to rt. Analytical HPLC (LUNA C18(2), 5 \(\mu\)m, 100 Å, 250 x 4.6 mm, elution at 0.7 mL/min with a solution of MeCN/H\(_2\)O) was performed for the identification of [\(^{18}\)F]-products. Results are given in Table 2 of the manuscript.

2.3.2 Route B (via minimalist radiofluorination)

[\(^{18}\)F]Fluoride ion was fixed an a QMA carbonate anionic resin cartridge. The cartridge was washed with anhydrous MeOH (1 mL) and the radiofluoride was eluted was eluted with a solution of iodonium salt (0.02 mmol, 1 equiv) in anhydrous MeOH (500 \(\mu\)L). The elution yield
was determined by comparing the radioactivity eluted into the reaction vial with the total radioactivity trapped on the anion exchange resin. MeOH was removed by heating at 70 °C for 3 min under nitrogen flow. TEMPO (2.9 mg, 0.02 mmol, 1 equiv) in ACN (500 µL) were added to the residue and the reaction mixture was stirred for 30 min at 110 °C then cooled to rt. Toluene (500 µL) was added. An aliquot was taken off and injected to analytical HPLC (LUNA C18(2), 5 µm, 100 Å, 250 x 4.6, elution at 0.7 mL/min with a solution of MeCN/H₂O). Chromatograms revealed the formation of 2-halo-[¹⁸F]fluoropyridines [¹⁸F]8 and [¹⁸F]9 in around 62±9% and 88±11% yields respectively. The crude mixture resulting from radiofluorination reaction was passed through a silica Sep Pack cartridge (preconditioned with 1 mL toluene) then elution of the total radioactivity was carried out with toluene (1 mL) or a 1:1 mixture of ACN/toluene (1 mL). To the resulting solution were added Pd₂(dba)₃ (4.7 mg, 5 µmol), XPhos (4.6 mg, 10 µmol), NaO'Bu (14.2 mg, 150 µmol) and piperidine (15 µL, 150 µmol). The mixture was stirred for 30 min at 100 °C, then cooled down to rt. Analytical HPLC (LUNA C18(2), 5 µm, 100 Å, 250 x 4.6 mm, elution at 0.7 mL/min with a solution of MeCN/H₂O) was performed for the identification of ¹⁸F-products. Results are given in Table 2 of the manuscript. Semi-preparative HPLC (LUNA C18(2), 5 µm, 100 Å, 250 x 10 mm, elution at 3.5 mL/min with a solution of MeCN/H₂O) was performed for the isolation of ¹⁸F-products.
3. $^1\text{H}$, $^{13}\text{C}$ and $^{19}\text{F}$ NMR Spectra

![NMR Spectrum](image)
4. HPLC chromatograms

4.1 [\(^{18}\text{F}\)]Fluoropyridines obtained by minimalist radiofluorination of iodonium precursors

LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H\(_2\)O (20:80 to 50:50 over 10 min); flow rate: 0.7 mL/min; UV detection at \(\lambda = 254\) nm.

*Radioactive channel*

*UV channel (crude product with added reference compound)*
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H₂O (40:60 to 90:10 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

*Radioactive channel*

![Radioactive channel graph](image1)

*UV channel (crude product with no reference compound)*

![UV channel graph](image2)
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H₂O (50:50 to 60:40 over 8 min); flow rate: 1 mL/min; UV detection at λ = 254 nm.

Radioactive channel

UV channel (crude product with added reference compound)
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H₂O (50:50 to 60:40 over 8 min); flow rate: 1 mL/min; UV detection at λ = 254 nm.

Radioactive channel

UV channel (crude product with added reference compound)
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H₂O (50:50 to 60:40 over 8 min); flow rate: 1 mL/min; UV detection at \( \lambda = 254 \) nm.

**Radioactive channel**

![Image of radioactive channel](image1)

**UV channel (crude product with added reference compound)**

![Image of UV channel](image2)
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H2O (20:80 to 50:50 over 10 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

UV channel (crude product with added reference compound)
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H$_2$O (5:95 to 50:50 over 10 min); flow rate: 0.5 mL/min; UV detection at $\lambda = 254$ nm.

Radioactive channel

UV channel (crude product with added reference compound)
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H₂O (50:50 to 60:40 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

UV channel (crude product with added reference compound)
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H$_2$O (50:50 to 60:40 over 8 min); flow rate: 0.7 mL/min; UV detection at $\lambda = 254$ nm.

*Radioactive channel*

*UV channel (crude product with added reference compound)*
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H₂O (50:50 to 60:40 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

**Radioactive channel**

**UV channel** (reference compound)
4.1 Amino-[¹⁸F]-fluoropyridines 1

LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H₂O (40:60 to 50:50 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

UV channel (reference aminofluoropyridine)
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H₂O (50:50 to 60:40 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

Radioactive channel

UV channel (reference aminofluoropyridine)
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H₂O (30:70 to 50:50 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

**Radioactive channel**

![Radioactive Channel](image1)

**UV channel (reference aminofluoropyridine)**

![UV Channel](image2)
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H₂O (30:70 to 50:50 over 8 min); flow rate: 0.7 mL/min; UV detection at λ = 254 nm.

**Radioactive channel**

![Radioactive channel](image)

**UV channel (reference aminofluoropyridine)**

![UV channel](image)
LUNA C18(2) 100Å, 250 x 4.6 mm, 5 µm; Eluent: MeCN/H$_2$O (30:70 to 50:50 over 8 min); flow rate: 0.7 mL/min; UV detection at $\lambda = 254$ nm.

**Radioactive channel**

**UV channel** (reference aminofluoropyridine)
5. References

