One-Pot Palladium-Catalyzed Synthesis of Sulfonyl Fluorides from Aryl Bromides

Alyn T. Davies,† John M. Curto,‡ Scott W. Bagley,*‡ and Michael C. Willis*†

† Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, United Kingdom
‡ CVMET Medicinal Chemistry, Pfizer, Inc., Eastern Point Road, Groton, Connecticut 06340, United States

E-mail: michael.willis@chem.ox.ac.uk
E-mail: scott.w.bagley@pfizer.com

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1 Experimental

1.1 General information

Chemicals were purchased from Sigma Aldrich, Alfa Aesar, Apollo Scientific or Acros Organics and used without further purification. Pd(AmPhos)$_2$Cl$_2$ precatalyst (dichlorobis(di-tert-butyl(4-dimethylaminophenyl)phosphine) palladium(II)) was purchased from Johnson-Matthey (CAS# 887919-35-9, cat # Pd-132).

Solvents were purchased from Sigma Aldrich, Fischer Scientific or Rathburn and unless otherwise mentioned, used without further purification. “Pet. ether” refers to the fraction of petroleum ether boiling in the range 40-60 °C. Anhydrous THF, CH$_2$Cl$_2$, CH$_3$CN, Et$_2$O, MeOH and toluene were obtained from an in-house solvent drying system having passed through dried alumina columns.

Reactions were performed with continuous magnetic stirring, under an atmosphere of nitrogen (passed through a Drierite® filled tube), unless otherwise stated, and all glassware was dried in an oven (>200 °C, overnight) and allowed to cool under vacuum prior to use. “Reaction tube” refers to a 10 mL CEM microwave reaction vial. Unless stated otherwise, reactions were carried out at room temperature (~23 °C). Cooling between −20 °C and −78 °C was achieved using a dry ice/acetone bath. Flash column chromatography was performed using Apollo Scientific silica gel 60 (particle size 0.040-0.063 mm) with the indicated eluents, or using an automated system with prepackaged columns and gradient elution. Thin layer chromatography (TLC) analysis was carried out on Merck Kieselgel 60 PF254 pre-coated aluminium backed sheets and visualized either by UV fluorescence (254 nm) and/or staining with potassium permanganate solution.

NMR spectra were recorded at ambient temperature on a 200 MHz, 400 MHz, 500 MHz or 600 MHz spectrometer. Chemical shifts (δ) reported are in parts per million (ppm) and referenced to the residual solvent peak(s). Coupling constants (J) are given in Hertz (Hz). Assignments were made on the basis of chemical shift, coupling constants and comparison with spectra of related compounds. Singlet multiplicities are denoted as: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; br, broad.

Melting points were measured on a Leica Gallen III hot-stage microscope. Low resolution mass spectra were recorded on a Fisons Platform spectrometer (ESI). High-resolution mass spectrometry (HRMS) was performed via atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) sources. m/z Ratios are reported in Daltons; high resolution values are calculated to four decimal places from the molecular formula. Infrared spectra were determined with an internal range of 600-4000 cm$^{-1}$. 


### 1.2 Optimisation of Palladium-Catalyzed Sulfinate Synthesis with DABSO

**Table S1**: Optimization of Palladium-Catalyzed Sulfinate Synthesis with DABSO

![Chemical Structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd]</th>
<th>Ligand</th>
<th>Consumption of 1a</th>
<th>Reduction to 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>PdAd$_3$-n-Bu</td>
<td>33%</td>
<td>2%</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>L1</td>
<td>37%</td>
<td>3%</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>L2</td>
<td>28%</td>
<td>2%</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>L3</td>
<td>33%</td>
<td>2%</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>L4</td>
<td>58%</td>
<td>2%</td>
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<tr>
<td>6</td>
<td>Pd(OAc)$_2$</td>
<td>L5</td>
<td>77%</td>
<td>10%</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$</td>
<td>L6</td>
<td>83%</td>
<td>3%</td>
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<tr>
<td>8</td>
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<td>11</td>
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<td>L10</td>
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<td>L12</td>
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<tr>
<td>14</td>
<td>PdCl$_2$(AmPhos)$_2$</td>
<td>N/A</td>
<td>91%</td>
<td>1%</td>
</tr>
</tbody>
</table>

**Notes**:
- L1: Ar = 2,6-(iPrO)$_2$C$_6$H$_3$
- L2: Ar = 2-Me$_2$NC$_6$H$_4$
- L3: Ar = 2,4,6-iPr$_3$C$_6$H$_2$
- L4: Ar = 2-MeC$_6$H$_4$
- L5: Ar = 2,6-(MeO)$_2$C$_6$H$_3$
- L9: Ar = Ph
- L12: Ar = 2,6-(Me$_2$N)$_2$C$_6$H$_3$
- L8: Ar = Ph
- L10: Ar = Ph
- L11: Ar = 2,4,6-iPr$_3$C$_6$H$_2$
- L6 (AmPhos)
- L7: Ar = 2,4,6-iPr$_3$C$_6$H$_2$
1.3 Optimisation of Palladium-Catalyzed Sulfinate Synthesis with K$_2$S$_2$O$_5$

Table S2: Optimization of Palladium-Catalyzed Sulfinate Synthesis with K$_2$S$_2$O$_5$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation</th>
<th>Consumption of 1a</th>
<th>Reduction to 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>98%</td>
<td>29%</td>
</tr>
<tr>
<td>2</td>
<td>IPA instead of MeCN, no NaCO$_2$H</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>3</td>
<td>No 1,10-phenanthroline</td>
<td>56%</td>
<td>56%</td>
</tr>
<tr>
<td>4</td>
<td>No TBAB</td>
<td>71%</td>
<td>23%</td>
</tr>
<tr>
<td>5</td>
<td>No PPh$_3$</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

1.4 Synthesis of Aryl Bromides

4-Bromo-N-methoxy-N-methylbenzamide (S1)

Triethylamine (0.64 mL, 4.6 mmol) was added dropwise to a suspension of $N,O$-dimethylhydroxylamine hydrochloride (215 mg, 2.2 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C. A solution of 4-bromobenzoyl chloride (439 mg, 2.0 mmol) in CH$_2$Cl$_2$ (5 mL) was added dropwise at 0 °C and the suspension warmed to room temperature and left stirring for 3 h. The reaction was quenched with sat. aq. NaHCO$_3$ (20 mL) and extracted with CH$_2$Cl$_2$. The organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo to leave the crude product, which was purified by column chromatography on silica (30% Et$_2$O in pet. ether) to leave 4-bromo-N-methoxy-N-methylbenzamide as a colourless oil (414 mg, 1.70 mmol, 85%) with spectroscopic data in accordance with the literature.$^{[1]}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H: 7.61 – 7.51 (m, 4H), 3.53 (s, 3H), 3.35 (s, 3H); $^{13}$C {$^1$H} NMR (101 MHz, CDCl$_3$) $\delta$H: 168.7, 132.8, 131.3, 130.0, 125.2, 61.2, 33.5; LRMS (ESI) $m/z$ 244 ([M($^{79}$Br)+H$^+$]), 246 ([M($^{81}$Br)+H$^+$]), 266 ([M($^{79}$Br)+Na$^+$]), 268 ([M($^{81}$Br)+Na$^+$]); HRMS (ESI) found $m/z$ 243.99701 [M+H$^+$], C$_9$H$_{11}$$^{79}$BrNO$_2$ requires $m/z$ 243.99677, found $m/z$ 245.99484 [M+H$^+$], C$_9$H$_{11}$$^{81}$BrNO$_2$ requires $m/z$ 145.99472.
1.5 Palladium-Catalyzed Synthesis of Sulfonyl Fluorides

General Procedure A: Synthesis of sulfonyl fluorides from aryl bromides, DABSO and NFSI as exemplified by the preparation of 4-phenylbenzenesulfonyl fluoride (4a)

\[
\text{PhBr} + \text{O}_2\text{S} = \text{N} \xrightarrow{\text{i} \text{ PdCl}_2(\text{AmPhos})_2 (5 \text{ mol\%}) \text{ Et}_3\text{N} (3 \text{ eq.}), \text{IPA, 75 }^\circ\text{C, 16 h}} \text{SO}_2\text{F}^-
\]

A glass reaction tube was charged with DABSO (58 mg, 0.24 mmol, 0.6 eq.), PdCl\(_2\)(AmPhos\()\_2\) (14.2 mg, 0.020 mmol, 0.05 eq.) and 4-bromobiphenyl (93 mg, 0.40 mmol, 1.0 eq.), sealed with a rubber septum and evacuated and filled with N\(_2\) four times. Anhydrous isopropanol (1.5 mL) and anhydrous triethylamine (167 μL, 1.2 mmol, 3.0 eq.) were added sequentially through the septum and the reaction mixture stirred under positive pressure of N\(_2\) in a preheated aluminium heating block at 75 °C for 24 h. After cooling to r.t., NFSI (189 mg, 0.6 mmol, 1.5 eq.) was added and the reaction mixture stirred for 3 h until completion. The reaction mixture was concentrated in vacuo, then dissolved in EtOAc and filtered through celite. The filtrate was washed with sat. aq. Na\(_2\)S\(_2\)O\(_3\) and brine, dried (MgSO\(_4\)), filtered and concentrated in vacuo to leave the crude product, which was purified by column chromatography on silica (20% CH\(_2\)Cl\(_2\) in pet. ether) to leave 4-phenylbenzenesulfonyl fluoride as a white crystalline solid (79.7 mg, 0.337 mmol, 84%); mp 81-82 °C; IR ν\(_{\text{max}}\) (neat)/cm\(^{-1}\) 1589, 1479, 1406, 1186, 1099, 1007; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ\(_H\): 8.12 – 8.04 (m, 2H), 7.86 – 7.80 (m, 2H), 7.67 – 7.58 (m, 2H), 7.44 – 7.55 (m, 3H); \(^19\)F NMR (377 MHz, CDCl\(_3\)) δ\(_F\): 66.5; \(^{13}\)C \{\(^1\)H\} NMR (101 MHz, CDCl\(_3\)) δ\(_C\): 148.7, 138.5, 131.4 (d, J 24.7 Hz), 129.3, 72.9, 129.0, 128.2, 127.5; HRMS (CI) found m/z 254.0645 [M+H]\(^+\), C\(_{12}\)H\(_9\)FO\(_2\)S requires m/z 254.0646.

Benzenesulfonyl fluoride (4b)

\[
\text{PhSO}_2\text{F}
\]

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl\(_2\)(AmPhos\()\_2\) (14.2 mg, 0.020 mmol), bromobenzene (43 μL, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (10% CH\(_2\)Cl\(_2\) in pet. ether) to leave benzenesulfonyl fluoride as a colourless oil (33.6 mg, 0.210 mmol, 53%) with spectroscopic data in accordance with the literature;

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ\(_H\): 8.05 – 8.00 (m, 2H), 7.84 – 7.74 (m, 1H), 7.64 (app tt, J 7.7, 1.1 Hz, 2H); \(^19\)F NMR (377 MHz, CDCl\(_3\)) δ\(_F\): 65.9; \(^{13}\)C \{\(^1\)H\} NMR (101 MHz, CDCl\(_3\)) δ\(_C\): 135.6, 133.1 (d, J 23.9 Hz), 129.7, 128.4; HRMS not available.
Naphthalene-1-sulfonyl fluoride (4c)

\[
\begin{array}{c}
\text{SO}_2F \\
\text{N}
\end{array}
\]

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl\(_2\)(AmPhos)\(_2\) (14.2 mg, 0.020 mmol), 1-bromonaphthalene (56 µL, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 µL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (10% CH\(_2\)Cl\(_2\) in pet. ether) to leave naphthalene-1-sulfonyl fluoride as a colourless oil (60.6 mg, 0.288 mmol, 72%); IR \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 1395, 1364, 1350, 1206, 1194; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta H\): 8.54 (dd, \(J=8.4, 2.3\) Hz, 1H), 8.36 (app dt, \(J=7.4, 0.9\) Hz, 1H), 8.22 (d, \(J=8.3\) Hz, 1H), 7.77 (ddd, \(J=8.5, 7.0, 1.4\) Hz, 1H), 7.68 (ddd, \(J=8.1, 6.9, 1.1\) Hz, 1H), 3.92 (s, 3H); \(^{19}\)F NMR (377 MHz, CDCl\(_3\)) \(\delta F\): 62.6; \(^{13}\)C \({}^1\)H NMR (101 MHz, CDCl\(_3\)) \(\delta C\): 137.0, 134.0, 131.10, 131.08, 129.5, 129.2, 128.3, 127.8, 124.2, 124.1; HRMS (CI) found \(m/z\) 228.0489 [M+NH\(_4\)]\(^+\), \(C_{10}H_{11}FNO_2S\) requires \(m/z\) 228.0489.

4-Methoxybenzenesulfonyl fluoride (4d)

\[
\begin{array}{c}
\text{MeO} \\
\text{SO}_2F \\
\text{N}
\end{array}
\]

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl\(_2\)(AmPhos)\(_2\) (14.2 mg, 0.020 mmol), 4-bromoanisole (50 µL, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 µL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol), with the first step being heated under microwave irradiation at 90 °C for 1 h. The crude product was purified by column chromatography on silica (20% CH\(_2\)Cl\(_2\) in pet. ether) to leave 4-methoxybenzenesulfonyl fluoride as a colourless oil (50.1 mg, 0.263 mmol, 66%) with spectroscopic data in accordance with the literature; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta H\): 7.99 – 7.89 (m, 2H), 7.11 – 7.01 (m, 2H), 3.92 (s, 3H); \(^{19}\)F NMR (377 MHz, CDCl\(_3\)) \(\delta F\): 67.3; \(^{13}\)C \({}^1\)H NMR (101 MHz, CDCl\(_3\)) \(\delta C\): 165.2, 130.9, 124.1 (d, \(J=24.8\) Hz), 114.9, 55.9; HRMS (CI) found \(m/z\) 228.0489 [M+NH\(_4\)]\(^+\), \(C_{10}H_{11}FO_2S\) requires \(m/z\) 228.0489.

4-(Methylthio)benzenesulfonyl fluoride (4e)

\[
\begin{array}{c}
\text{MeS} \\
\text{SO}_2F \\
\text{N}
\end{array}
\]

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl\(_2\)(AmPhos)\(_2\) (14.2 mg, 0.020 mmol), 4-bromothioanisole (93 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 µL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was
purified by column chromatography on silica (25% CH₂Cl₂ in pet. ether) to leave 4-(methylthio)benzenesulfonyl fluoride as a white crystalline solid (67.6 mg, 0.328 mmol, 82%); mp 62-63 °C; IR ν max (neat)/cm⁻¹ 2928, 1576, 1476, 1449, 1391, 1207, 1107, 1080; ¹H NMR (400 MHz, CDCl₃) δ: 7.91 – 7.83 (m, 2H), 7.33 – 7.42 (m, 2H), 2.55 (s, 3H); ¹⁹F NMR (377 MHz, CDCl₃) δ: 66.9; ¹³C {¹H} NMR (101 MHz, CDCl₃) δ: 150.3, 128.6, 128.0 (d, J 24.7), 125.4, 14.6; HRMS (CI) found m/z 224.0215 [M+NH₄]⁺, C₇H₁₁FNO₂S₂ requires m/z 224.0210.

4-Methylbenzenesulfonyl fluoride (4f)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl₂(AlPhos)₂ (14.2 mg, 0.020 mmol), 4-iodotoluene (87 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (10% CH₂Cl₂ in pet. ether) to leave 4-methylbenzenesulfonyl fluoride as a colourless oil (41.2 mg, 0.237 mmol, 58%) with spectroscopic data in accordance with the literature; ¹H NMR (400 MHz, CDCl₃) δ: 7.90 (d, J 8.4 Hz, 2H), 7.42 (d, J 8.5 Hz, 2H), 2.49 (s, 3H); ¹⁹F NMR (377 MHz, CDCl₃) δ: 66.3; ¹³C {¹H} NMR (101 MHz, CDCl₃) δ: 147.1, 130.3, 130.1 (d, J 24.5 Hz), 128.5, 21.9; HRMS (CI) found m/z 192.0485 [M+NH₄]⁺, C₇H₉FNO₂S requires m/z 192.0489.

Benzo[d][1,3]dioxole-5-sulfonyl fluoride (4g)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl₂(AlPhos)₂ (14.2 mg, 0.020 mmol), 5-bromobenzo[d][1,3]dioxole (48 μL, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (30% CH₂Cl₂ in hexane) to leave benzo[d][1,3]dioxole-5-sulfonyl fluoride as a white crystalline solid (48.7 mg, 0.237 mmol, 60%); mp 71-72 °C; IR ν max (neat)/cm⁻¹ 2922, 1501, 1483, 1433, 1396, 1246, 1202, 1167, 1116, 1060, 1032; ¹H NMR (400 MHz, CDCl₃) δ: 7.61 (ddd, J 8.3, 1.9, 0.8, 1H), 7.37 (d, J 1.9, 1H), 6.97 (dd, J 8.3, 0.9, 1H), 6.16 (s, 2H); ¹⁹F NMR (377 MHz, CDCl₃) δ: 66.9; ¹³C {¹H} NMR (101 MHz, CDCl₃) δ: 153.9, 148.7, 125.2, 108.8, 108.2, 103.0, 1 × ArC not observed; HRMS (CI) found m/z 222.0236 [M+NH₄]⁺; C₇H₆FNO₂S requires m/z 222.0231.
3-Methoxybenzenesulfonyl fluoride (4h)

![Structure](image)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PbCl₂(AmPhos)₂ (14.2 mg, 0.020 mmol), 3-bromoanisole (51 μL, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (20% CH₂Cl₂ in hexane) to leave 3-methoxybenzenesulfonyl fluoride as a colourless oil (47.5 mg, 0.250 mmol, 63%); IR νmax (neat)/cm⁻¹ 1601, 1487, 1404, 1327, 1292, 1248, 1206, 1032; ¹H NMR (400 MHz, CDCl₃) δH: 7.60 (ddd, J 7.8, 1.8, 0.8, 1H), 7.53 (app td, J 8.0, 1.1, 1H), 7.47 (dd, J 2.5, 1.7, 1H), 7.28 (app ddt, J 8.0, 2.4, 0.7, 1H), 3.89 (s, 3H); ¹⁹F NMR (377 MHz, CDCl₃) δF: 65.6; ¹³C {¹H} NMR (101 MHz, CDCl₃) δC: 160.2, 134.0 (d, J 25.9 Hz), 130.7, 122.2, 120.6, 112.6, 55.9; HRMS (CI) found m/z 191.0167 [M+H]+, C₇H₇FO₃S requires m/z 191.0173.

4-Chlorobenzenesulfonyl fluoride (4i)

![Structure](image)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PbCl₂(AmPhos)₂ (14.2 mg, 0.020 mmol), 1-bromo-4-chlorobenzene (77 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (10% CH₂Cl₂ in pet. ether) to leave 4-chlorobenzenesulfonyl fluoride as a white crystalline solid (52.4 mg, 0.268 mmol, 67%) with spectroscopic data in accordance with the literature;[⁴] mp 45-46 °C; ¹H NMR (400 MHz, CDCl₃) δH: 7.99 – 7.93 (m, 2H), 7.65 – 7.59 (m, 2H); ¹⁹F NMR (377 MHz, CDCl₃) δF: 66.5; ¹³C {¹H} NMR (101 MHz, CDCl₃) δC: 142.7, 131.4 (d, J 25.9 Hz), 130.1, 129.9; HRMS (CI) found m/z 211.9947 [M+NH₄]+, C₆H₈ClFNO₂S requires m/z 211.9943.

Methyl 4-(fluorosulfonyl)benzoate (4j)

![Structure](image)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PbCl₂(AmPhos)₂ (14.2 mg, 0.020 mmol), methyl 4-bromobenzoate (86 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product
was purified by column chromatography on silica (40% CH$_2$Cl$_2$ in hexane) to leave methyl 4-(fluorosulfonyl)benzoate as a white crystalline solid (64.9 mg, 0.297 mmol, 74%); mp 86-87 °C; IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3055, 1726, 1440, 1408, 1277, 1207, 1092, 1014; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.28 (d, $J$ 7.8 Hz, 2H), 8.09 (d, $J$ 8.6 Hz, 2H), 3.99 (s, 3H); $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$: 65.8; $^{13}$C ($^1$H) NMR (101 MHz, CDCl$_3$) $\delta$: 164.9, 136.7 (d, $J$ 25.4 Hz), 136.5, 130.7, 128.5, 53.0; HRMS not available.

4-(Trimethylsilyl)benzenesulfonyl fluoride (4k)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl$_2$(AmPhos)$_2$ (14.2 mg, 0.020 mmol), 1-bromo-4-(trimethylsilyl)benzene (78 µL, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 µL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (10% CH$_2$Cl$_2$ in pet. ether) to leave 4-(trimethylsilyl)benzenesulfonyl fluoride as a colourless oil (70.7 mg, 0.304 mmol, 70%); IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2959, 1406, 1252, 1213, 1192, 1111, 1090; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.96 (d, $J$ 8.2 Hz, 2H), 7.77 (app dd, $J$ 8.4, 1.0 Hz, 2H), 0.33 (s, 9H); $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$: 65.9; $^{13}$C ($^1$H) NMR (101 MHz, CDCl$_3$) $\delta$: 151.3, 134.5, 133.2 (d, $J$ 24.3 Hz), 127.2, −1.4; HRMS (CI) found $m/z$ 250.0734 [M+NH$_4$]$^+$, C$_9$H$_{17}$FNO$_2$SSi requires $m/z$ 250.0728.

Methyl 3-(fluorosulfonyl)benzoate (4l)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl$_2$(AmPhos)$_2$ (14.2 mg, 0.020 mmol), methyl 3-bromobenzoate (86 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 µL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (40% CH$_2$Cl$_2$ in pet. ether) to leave methyl 3-(fluorosulfonyl)benzoate as a white crystalline solid (61.4 mg, 0.281 mmol, 70%); mp 65-66 °C; IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2963, 1720, 1601, 1445, 1402, 1286, 1273, 1207, 1125, 1082; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.66 (app t, $J$ 1.8, 1H), 8.43 (app dt, $J$ 8.0, 1.6, 1H), 8.19 (app dt, $J$ 8.0, 1.6, 1H), 7.75 (app tt, $J$ 7.9, 0.7, 1H), 3.98 (s, 3H); $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$: 66.0; $^{13}$C ($^1$H) NMR (101 MHz, CDCl$_3$) $\delta$: 164.6, 136.3, 133.7 (d, $J$ 26.0), 132.2, 132.1, 130.1, 129.6, 52.9; HRMS (CI) found $m/z$ 236.0386 [M+NH$_4$]$^+$, C$_8$H$_{11}$FNO$_4$S requires $m/z$ 236.0387.
4-(Methoxy(methyl)carbamoyl)benzenesulfonyl fluoride (4m)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl₂(AmPhos)₂ (14.2 mg, 0.020 mmol), 4-bromo-N-methoxy-N-methylbenzamide (98 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (100% CH₂Cl₂) to leave 4-(methoxy(methyl)carbamoyl)benzenesulfonyl fluoride as a colourless oil (54.4 mg, 0.220 mmol, 55%); IR νmax (neat)/cm⁻¹ 2918, 1645, 1393, 1206, 1092, 1015; ¹H NMR (400 MHz, CDCl₃) δH: 8.09 – 8.03 (m, 2H), 7.93 – 7.87 (m, 2H), 3.53 (s, 3H), 3.40 (s, 3H); ¹⁹F {¹H} NMR (377 MHz, CDCl₃) δF: 65.9; ¹³C {¹H} NMR (101 MHz, CDCl₃) δC: 167.4, 141.1, 134.4 (d, J 25.3 Hz), 129.3, 128.2, 61.5, 33.1; HRMS (CI) found m/z 248.0391 [M+H]⁺, C₉H₁₁FNO₄S requires m/z 248.0387.

Indole-5-sulfonyl fluoride (4n)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl₂(AmPhos)₂ (14.2 mg, 0.020 mmol), 5-bromoindole (78 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (50% CH₂Cl₂ in pet. ether) to leave indole-5-sulfonyl fluoride as a white crystalline solid (62.4 mg, 0.313 mmol, 78%); mp 133-134 °C; IR νmax (neat)/cm⁻¹ 3401, 1608, 1381, 1352, 1331, 1218, 1181, 1062; ¹H NMR (400 MHz, CDCl₃) δH: 8.73 (s, 1H), 8.37 (d, J 1.8 Hz, 1H), 7.78 (dd, J 8.7, 1.9 Hz, 1H), 7.57 (d, J 8.7 Hz, 1H), 7.43 (dd, J 3.3, 2.4 Hz, 1H), 6.74 (app dt, J 3.0, 1.3 Hz, 1H); ¹⁹F NMR (377 MHz, CDCl₃) δF: 68.4; ¹³C {¹H} NMR (101 MHz, CDCl₃) δC: 139.0, 127.51, 127.45, 123.5 (d, J 23.5 Hz), 123.4, 121.2, 112.1, 104.6; HRMS (CI) found m/z 199.0095 [M⁺], C₈H₆FNO₂S requires m/z 199.0103.

3-Methyl-4-oxo-3,4-dihydroquinazoline-6-sulfonyl fluoride (4o)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl₂(AmPhos)₂ (14.2 mg, 0.020 mmol), 6-bromo-3-methylquinazolin-4(3H)-one (96 mg, 0.40 mmol), anhydrous
isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (10-100% EtOAc in heptane) to provide 3-methyl-4-oxo-3,4-dihydroquinazoline-6-sulfonyl fluoride as a white solid (54 mg, 0.22 mmol, 56%); IR ν max (neat)/cm⁻¹ 1687, 1603, 1408, 1209; ¹H NMR (400 MHz, DMSO) δ H: 8.68 (d, J 2.0 Hz, 1H), 8.63 (s, 1H), 8.41 (dd, J 8.8, 2.1 Hz, 1H), 7.97 (d, J 8.6 Hz, 1H), 3.54 (s, 3H); ¹⁹F ¹H NMR (377 MHz, DMSO) δ F: 67.0; ¹³C ¹H NMR (101 MHz, DMSO) δ C: 159.6, 153.0, 152.6, 132.0, 129.8, 128.7 (d, J 25 Hz), 128.0, 121.9, 33.9; HRMS (ESI⁺) found m/z 243.0227 [M+H]⁺, C₉H₈FN₂O₃S requires m/z 243.0234.

1-Methyl-1H-indazole-5-sulfonyl fluoride (4p)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl₂(AmPhos)₂ (14.2 mg, 0.020 mmol), 5-bromo-1-methyl-1H-indazole (84 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (10-30% EtOAc in heptane) to leave 1-methyl-1H-indazole-5-sulfonyl fluoride as a white solid (67 mg, 0.31 mmol, 78%); IR ν max (neat)/cm⁻¹ 1608, 1402, 1212, 1186, 739; ¹H NMR (400 MHz, CDCl₃) δ H: 8.52 (s, 1H), 8.21 (s, 1H), 7.94 (dd, J 9.1, 1.5 Hz, 1H), 7.60 (d, J 8.8 Hz, 1H), 4.17 (s, 3H); ¹⁹F ¹H NMR (377 MHz, CDCl₃) δ F: 68.0; ¹³C ¹H NMR (101 MHz, CDCl₃) δ C: 141.7, 135.0, 124.9, 124.7, 124.6, 123.2, 110.3, 36.0; HRMS (ESI⁺) found m/z 215.0276 [M+H]⁺, C₈H₈FN₂O₂S requires m/z 215.0285.
1.6 Palladium-Catalyzed Synthesis of Pyridyl Sulfonyl Fluorides

Table S3: Optimization of Sulfonyl Fluoride Synthesis from Heteroaromatic Bromides

<table>
<thead>
<tr>
<th>Starting Material (SM)</th>
<th>Pd/L (5 mol %)</th>
<th>Base</th>
<th>Conditions(^a)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>5a</td>
<td>Pd(4AmPhos)Cl(_2)</td>
<td>NEt(_3)</td>
<td>75 °C, 16 h</td>
<td>15</td>
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<tr>
<td>5a</td>
<td>Pd(OAc)(_2), CateCXium A</td>
<td>NEt(_3)</td>
<td>75 °C, 16 h</td>
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<tr>
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<td>Pd(4AmPhos)Cl(_2)</td>
<td>NEt(_3)</td>
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<tr>
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<td>NEt(_3)</td>
<td>110 °C, 1.5 h, ⊕W</td>
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</tr>
<tr>
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<td>Cy(_3)NMe</td>
<td>110 °C, 1.5 h, ⊕W</td>
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<td>Cy(_3)NMe</td>
<td>110 °C, 1.5 h, ⊕W</td>
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<tr>
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<td>Cy(_3)NMe</td>
<td>110 °C, 1.5 h, ⊕W(^{0})</td>
<td>53</td>
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<tr>
<td>5a</td>
<td>Pd(OAc)(_2), CateCXium A</td>
<td>Cy(_3)NMe</td>
<td>110 °C, 1.5 h, ⊕W(^{0})</td>
<td>47</td>
</tr>
<tr>
<td>5c</td>
<td>Pd(4AmPhos)Cl(_2)</td>
<td>NEt(_3)</td>
<td>75 °C, 16 h</td>
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<tr>
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<td>Cy(_3)NMe</td>
<td>110 °C, 1.5 h, ⊕W(^{0})</td>
<td>50</td>
</tr>
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</table>

\(^a\) Reaction conditions: i) Aryl bromide (0.4 mmol), Pd/L (5 mol %), DABSO (0.6 eq), Base (3 eq), \(\text{PrOH (0.2 M)}\) ii) NFSI (1.5 eq), r.t., 2 h. Isolated yields shown [b] DABSO (1.0 equiv)

**General Procedure B:** Synthesis of sulfonyl fluorides from heteroaromatic bromides, DABSO and NFSI as exemplified by the preparation of 6-methoxypyridine-3-sulfonyl fluoride (6a)

An 8 mL microwave vial was charged with DABSO (96 mg, 0.4 mmol), PdCl\(_2\) (14.2 mg, 0.020 mmol) and 3-bromo-6-methoxypyridine (89 mg, 0.40 mmol). A solution of \(N,N\)-dicyclohexylmethylamine (257 \(\mu\)L, 1.2 mmol) in anhydrous isopropanol (1.6 mL) was added, the vial was sealed with a Teflon cap, sparged for 5 minutes with \(N_2\) and subject to microwave conditions at 110°C for 1 h. After cooling to r.t., NFSI (189 mg, 0.6 mmol) was added and the reaction mixture stirred for 2 h until completion. The reaction mixture was diluted with H\(_2\)O (10 mL) and extracted with EtOAc (2 \(\times\) 15 mL), dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated in vacuo to leave the crude product, which was purified by column chromatography on silica (0-30% EtOAc in heptane) to provide 6-methoxypyridine-3-sulfonyl fluoride as a white solid (36 mg, 0.19 mmol, 47%); IR \(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 1589, 1486, 1409, 1209; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.81 (s, 1H), 8.07 (dd, \(J\) 9.1, 2.6 Hz, 1H), 6.92 (d, \(J\) 8.8 Hz, 1H), 4.06 (s, 3H); \(^{19}\)F \(\{^1\}H\) NMR (377 MHz, CDCl\(_3\)) \(\delta\): 68.6; \(^{13}\)C
\[^1\text{H}\] NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\): 168.2, 149.4, 137.9, 122.5 (d, \(J = 25\) Hz), 112.1, 54.8; LRMS (AP\(^+\)) \(m/z\) 192.3 ([M+H\(^+\)], HRMS (ESI\(^+\)) compound was not stable to ionization.

5-Methoxypyridine-3-sulfonyl fluoride (6b)

\[
\text{MeO} \quad \begin{array}{c}
\text{N} \\
\text{SO}_2F
\end{array}
\]

Prepared according to general procedure B using DABSO (96 mg, 0.40 mmol), PdCl\(_2\)(AmPhos)\(_2\) (14.2 mg, 0.020 mmol), 3-bromo-5-methoxypyridine (89 mg, 0.40 mmol), anhydrous isopropanol (1.6 mL), dicyclohexylmethylamine (257 \(\mu\)L, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-30% EtOAc in heptane) to provide 5-methoxypyridine-3-sulfonyl fluoride as a white solid (36 mg, 0.19 mmol, 47%); IR \(\nu\)\(_{\text{max}}\) (neat)/\(\text{cm}^{-1}\) 1582, 1425, 1411, 1276, 1210; \[^1\text{H}\] NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 8.81 (s, 1H), 8.67 (d, \(J = 2.7\) Hz, 1H), 7.68 (dd, \(J = 2.7, 2.0\) Hz, 1H), 3.97 (s, 3H); \[^19\text{F}\] \[^1\text{H}\] NMR (377 MHz, CDCl\textsubscript{3}) \(\delta\): 67.9; \[^{13}\text{C}\] \[^1\text{H}\] NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\): 155.6, 145.4, 140.6, 130.2 (d, \(J = 24.9\) Hz), 118.2, 56.3; HRMS (ESI\(^+\)) found \(m/z\) 192.0117 [M+H\(^+\)], \(C_6H_7FNO_3S\) requires \(m/z\) 192.0125.

5-Methylpyridine-3-sulfonyl fluoride (6c)

\[
\text{Me} \quad \begin{array}{c}
\text{N} \\
\text{SO}_2F
\end{array}
\]

Prepared according to general procedure B using DABSO (96 mg, 0.40 mmol), PdCl\(_2\)(AmPhos)\(_2\) (14.2 mg, 0.020 mmol), 3-bromo-5-methylpyridine (67 mg, 0.40 mmol), anhydrous isopropanol (1.6 mL), dicyclohexylmethylamine (257 \(\mu\)L, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-10% EtOAc in heptane) to provide 5-methylpyridine-3-sulfonyl fluoride as a white solid (35 mg, 0.20 mmol, 50%); IR \(\nu\)\(_{\text{max}}\) (neat)/\(\text{cm}^{-1}\) 3030, 1568, 1406, 1208, 776; \[^1\text{H}\] NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 9.03 (s, 1H), 8.82 (s, 1H), 8.09 (s, 1H), 2.51 (s, 3H); \(^{19}\text{F}\) \[^1\text{H}\] NMR (377 MHz, CDCl\textsubscript{3}) \(\delta\): 67.9; \[^{13}\text{C}\] \[^1\text{H}\] NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\): 158.6, 146.1, 135.9, 134.9, 129.7 (d, \(J = 24.9\) Hz), 18.3; LRMS (AP\(^+\)) \(m/z\) 176.3 ([M+H\(^+\)], HRMS (ESI\(^+\)) compound was not stable to ionization.

6-Cyanopyridine-3-sulfonyl fluoride (6d)

\[
\text{NC} \quad \begin{array}{c}
\text{N} \\
\text{SO}_2F
\end{array}
\]

Prepared according to general procedure B using DABSO (96 mg, 0.40 mmol), PdCl\(_2\)(AmPhos)\(_2\) (14.2 mg, 0.020 mmol), 5-bromopicolinonitrile (89 mg, 0.40 mmol), anhydrous isopropanol (1.6 mL),
dicyclohexylmethylamine (257 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-30% EtOAc in heptane) to provide 6-cyanopyridine-3-sulfonyl fluoride as a white solid (24 mg, 0.13 mmol, 32%); IR ν_{max} (neat)/cm\(^{-1}\) 1576, 1418, 1218, 821, 649; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ\(_H\): 9.26-9.38 (d, J = 2.3 Hz, 1H), 8.49 (dd, J = 8.2, 2.3 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H); \(^{19}\)F \{\(^1\)H\} NMR (377 MHz, CDCl\(_3\)) δ\(_F\): 68.4; \(^{13}\)C \{\(^1\)H\} NMR (101 MHz, CDCl\(_3\)) δ\(_C\): 149.8, 139.4, 137.6, 132.8 (d, J = 28.6 Hz), 128.6, 115.3; HRMS (ESI\(^+\)) found m/z 186.9969 [M+H]\(^+\), C\(_6\)H\(_4\)FN\(_2\)O\(_2\)S requires m/z 186.9972.

Furo[2,3-b]pyridine-5-sulfonyl fluoride (6e)

Prepared according to general procedure B using DABSO (96 mg, 0.40 mmol), PdCl\(_2\)(AmPhos)\(_2\) (14.2 mg, 0.020 mmol), 5-bromofuro[2,3-b]pyridine (79 mg, 0.40 mmol), anhydrous isopropanol (1.6 mL), dicyclohexylmethylamine (257 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-30% EtOAc in heptane) to provide furo[2,3-b]pyridine-5-sulfonyl fluoride as an white solid (34 mg, 0.17 mmol, 42%); IR ν_{max} (neat)/cm\(^{-1}\) 1582, 1410, 1212, 774; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ\(_H\): 8.99 (d, J = 1.2 Hz, 1H), 8.61 (d, J = 2.3 Hz, 1H), 7.97 (d, J = 2.3 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H); \(^{19}\)F \{\(^1\)H\} NMR (377 MHz, CDCl\(_3\)) δ\(_F\): 69.8; \(^{13}\)C \{\(^1\)H\} NMR (101 MHz, CDCl\(_3\)) δ\(_C\): 164.4, 148.3, 144.6, 131.2, 126.0 (d, J = 26 Hz), 119.9, 106.7; HRMS (ESI\(^+\)) found m/z 201.9970 [M+H]\(^+\), C\(_7\)H\(_5\)FNO\(_3\)S requires m/z 201.9969.

Imidazo[1,2-a]pyridine-6-sulfonyl fluoride (6f)

Prepared according to general procedure B using DABSO (96 mg, 0.40 mmol), PdCl\(_2\)(AmPhos)\(_2\) (14.2 mg, 0.020 mmol), 6-bromoimidazo[1,2-a]pyridine (79 mg, 0.40 mmol), anhydrous isopropanol (1.6 mL), dicyclohexylmethylamine (257 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-100% EtOAc in heptane) to provide imidazo[1,2-a]pyridine-6-sulfonyl fluoride as an off-white solid (34 mg, 0.17 mmol, 42%); IR ν_{max} (neat)/cm\(^{-1}\) 1626, 1439, 1417, 1240, 1198; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ\(_H\): 9.00 (s, 1H), 7.87 (d, J 1.2 Hz, 1H), 7.78-7.85 (m, 2H), 7.57 (dd, J 9.8, 2.0 Hz, 1H); \(^{19}\)F \{\(^1\)H\} NMR (377 MHz, CDCl\(_3\)) δ\(_F\): 67.9; \(^{13}\)C \{\(^1\)H\} NMR (101 MHz, CDCl\(_3\)) δ\(_C\): 145.1, 137.1, 130.4, 120.4, 119.8 (d, J 29 Hz), 119.1, 114.6; HRMS (ESI\(^+\)) found m/z 201.0125 [M+H]\(^+\), C\(_7\)H\(_6\)FNO\(_2\)S requires m/z 201.0129.
Imidazo[4,5-b]pyridine-6-sulfonyl fluoride (6g)

![Imidazo[4,5-b]pyridine-6-sulfonyl fluoride](image)

Prepared according to general procedure B using DABSO (96 mg, 0.40 mmol), PdCl₂(AmPhos)₂ (14.2 mg, 0.020 mmol), 6-bromo-3-methyl-3H-imidazo[4,5-b]pyridine (85 mg, 0.40 mmol), anhydrous isopropanol (1.6 mL), dicyclohexylmethylamine (257 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (100% EtOAc) to provide 3-methyl-3H-imidazo[4,5-b]pyridine-6-sulfon fluoride as a white solid (44 mg, 0.20 mmol, 51%); IR ν max (neat)/cm⁻¹: 3033, 1602, 1425, 1397, 1252; ¹H NMR (400 MHz, CDCl₃) δ: 9.03 (s, 1H), 8.67 (d, J 2.0 Hz, 1H), 8.29 (s, 1H), 4.02 (s, 3H); ¹⁹F {¹H} NMR (377 MHz, CDCl₃) δ: 70.3; ¹³C {¹H} NMR (101 MHz, CDCl₃) δ: 151.1, 148.3, 144.2, 134.3, 128.8, 124.2 (d, J 26 Hz), 30.3; HRMS (ESI⁺) found m/z 216.0232 [M+H]⁺, C₇H₇FN₃O₂S requires m/z 216.0238.

Quinoline-3-sulfonyl fluoride (6h)

![Quinoline-3-sulfonyl fluoride](image)

Prepared according to general procedure B using DABSO (96 mg, 0.40 mmol), PdCl₂(AmPhos)₂ (14.2 mg, 0.020 mmol), 3-bromoquinoline (83 mg, 0.40 mmol), anhydrous isopropanol (1.6 mL), dicyclohexylmethylamine (257 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-50% EtOAc in heptane) to provide quinoline-3-sulfonyl fluoride as a white solid (26 mg, 0.12 mmol, 31%); IR ν max (neat)/cm⁻¹: 3071, 1618, 1587, 1421, 1210, 788; ¹H NMR (400 MHz, CDCl₃) δ: 9.36 (d, J 2.0 Hz, 1H), 8.91 (d, J 2.3 Hz, 1H), 8.29 (d, J 8.6 Hz, 1H), 7.96-8.13 (m, 2H), 7.74-7.87 (m, 1H); ¹⁹F {¹H} NMR (377 MHz, CDCl₃) δ: 68.8; ¹³C {¹H} NMR (101 MHz, CDCl₃) δ: 150.4, 146.0, 138.9, 134.2, 129.9, 129.4, 129.1, 126.3 (d, J 25.7), 125.8; HRMS (ESI⁺) found m/z 212.0169 [M+H]⁺, C₉H₆FNO₂S requires m/z 212.0176.

tert-Butyl 4-(5-(fluorosulfonyl)pyridin-2-yl)piperazine-1-carboxylate (6i)

![tert-Butyl 4-(5-(fluorosulfonyl)pyridin-2-yl)piperazine-1-carboxylate](image)

Prepared according to general procedure B using DABSO (96 mg, 0.40 mmol), PdCl₂(AmPhos)₂ (14.2 mg, 0.020 mmol), tert-butyl 4-(5-bromopyridin-2-yl)piperazine-1-carboxylate (89 mg, 0.40 mmol), anhydrous isopropanol (1.6 mL), dicyclohexylmethylamine (257 μL, 1.2 mmol) and NFSI
(189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-30% EtOAc in heptane) to provide tert-butyl 4-(5-(fluorosulfonyl)pyridin-2-yl)piperazine-1-carboxylate as a white solid (90 mg, 0.26 mmol, 65%); IR ν max (neat)/cm⁻¹ 2978, 1695, 1591, 1404, 1245, 1203; 

\[ ^1 \text{H} \] NMR (400 MHz, CDCl$_3$) δH: 8.68 (s, 1H), 7.89 (dd, J 9.2, 2.5 Hz, 1H), 6.65 (d, J 9.4 Hz, 1H), 3.71-3.86 (m, 4H), 3.46-3.65 (m, 4H), 1.49 (s, 9H); 

\[ ^{19} \text{F} \star \] \[ ^1 \text{H} \] NMR (377 MHz, CDCl$_3$) δF: 69.1; 

\[ ^{13} \text{C} \star \] \[ ^1 \text{H} \] NMR (101 MHz, CDCl$_3$) δC: 160.8, 154.5, 150.2, 137.1, 115.9 (d, J 24.9 Hz), 105.3, 80.4, 44.3, 28.4; 

HRMS (ESI⁺) found m/z 368.1045 [M+Na]$^+$, C$_{14}$H$_{20}$FN$_3$NaO$_4$S requires m/z 368.1051.

tert-Butyl 4-(4-(fluorosulfonyl)pyridin-2-yl)piperazine-1-carboxylate (6j)

Prepared according to general procedure B using DABSO (96 mg, 0.40 mmol), PdCl$_2$(AmPhos)$_2$ (14.2 mg, 0.020 mmol), tert-butyl 4-(4-bromopyridin-2-yl)piperazine-1-carboxylate (89 mg, 0.40 mmol), anhydrous isopropanol (1.6 mL), dicyclohexymethylamine (257 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-30% EtOAc in heptane) to provide tert-butyl 4-(4-(fluorosulfonyl)pyridin-2-yl)piperazine-1-carboxylate as a white solid (63 mg, 0.18 mmol, 46%); IR ν max (neat)/cm⁻¹ 2978, 1694, 1589, 1413, 1242; 

\[ ^1 \text{H} \] NMR (400 MHz, CDCl$_3$) δH: 8.44 (d, J 5.1 Hz, 1H), 7.04-7.10 (m, 2H), 3.62-3.76 (m, 4H), 3.45-3.62 (m, 4H), 1.50 (s, 9H); 

\[ ^{19} \text{F} \star \] \[ ^1 \text{H} \] NMR (377 MHz, CDCl$_3$) δF: 63.1; 

\[ ^{13} \text{C} \star \] \[ ^1 \text{H} \] NMR (101 MHz, CDCl$_3$) δC: 159.1, 154.6, 150.3, 142.6 (d, J 26 Hz), 108.8, 104.1, 80.3, 44.6, 28.4; 

HRMS (ESI⁺) found m/z 368.1037 [M+Na]$^+$, C$_{14}$H$_{20}$FN$_3$NaO$_4$S requires m/z 368.1051.

### Additional Substrates Explored with General Procedure B

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<th>less than 10% of P isolated</th>
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<th>product is potentially unstable</th>
<th>11%</th>
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1.7 Palladium-Catalyzed Synthesis of Sulfanyl Fluoride-Containing Active Pharmaceutical Ingredients

4-(5-(p-Tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonyl fluoride (4-SO$_2$F-celecoxib, 4q)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl$_2$(AmPhos)$_2$ (14.2 mg, 0.020 mmol), 1-(4-bromophenyl)-5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazole (4-bromo celecoxib, 152 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-40% EtOAc in heptane) to leave 4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonyl fluoride (4-SO$_2$F-celecoxib) as a white solid (116 mg, 0.302 mmol, 75%); IR $\nu_{\text{max}}$(neat)/cm$^{-1}$ 1597, 1500, 1471, 1372, 1237, 1212, 1161, 1135, 1096, 973, 784, 628; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.00 (d, $J$=8.80 Hz, 2H), 7.61 (d, $J$=8.80 Hz, 2H), 7.23 (d, $J$=8.22 Hz, 2H), 7.15 (d, $J$=8.22 Hz, 2H), 6.77 (s, 1H), 2.42 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ ppm 145.5, 144.8, 144.7 (q, $J$=39.2 Hz), 140.2, 131.9 (d, $J$=26.1 Hz), 129.9, 129.5, 128.7, 125.53, 125.49, 120.9 (q, $J$=269.0 Hz), 107.0, 21.3; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: 66.4 (s, 1F), −62.6 (s, 3F); HRMS (ESI$^+$) found m/z 385.0620 [M+H]$^+$, C$_{17}$H$_{13}$F$_4$N$_2$O$_2$S requires m/z 385.0628.

4-Ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzenesulfonyl fluoride (5-SO$_2$F-sildenafil, 4r)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl$_2$(AmPhos)$_2$ (14.2 mg, 0.020 mmol), 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (5-bromo sildenafil, 157 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-40 % EtOAc in heptane) to leave 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)benzenesulfonyl fluoride (5-SO$_2$F-sildenafil) as a white solid (118 mg, 0.299 mmol, 75%); IR $\nu_{\text{max}}$(neat)/cm$^{-1}$ 3329, 2961, 1682.
1534, 1490, 1280, 1207, 1158, 770, 593; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$: 10.77 (br. s., 1 H), 9.08 (d, $J$=2.3 Hz, 1 H), 8.08 (dd, $J$=9.4 Hz, 1 H), 7.25 (d, $J$=9.4 Hz, 1 H), 4.44 (q, $J$=7.0 Hz, 2 H), 4.28 (s, 3 H), 2.95 (t, $J$=7.5 Hz, 2 H), 1.67 (t, $J$=7.5 Hz, 3 H), 1.04 (t, $J$=7.3 Hz, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$: 161.1, 153.5, 147.2, 145.6, 138.2, 132.4, 132.2, 126.1 (d, $J$=26.1 Hz), 124.5, 122.0, 113.6, 66.5, 38.2, 27.6, 22.3, 14.4, 14.0; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: 66.9; HRMS (ESI$^+$) found m/z 395.1189 [M+H$^+$], C$_{17}$H$_{20}$FNO$_4$S requires m/z 395.1184.

$^\text{tert-Butyl (3S,4R)-3-}$(benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-(fluorosulfonyl)phenyl)piperidine-1-carboxylate (N-Boc-6-SO$_2$F-paroxetine, 4s)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl$_2$(AmPhos)$_2$ (14.2 mg, 0.020 mmol), $^\text{tert-Butyl (3S,4R)-3-}$(benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-iodophenyl)piperidine-1-carboxylate (N-Boc-4-iodo paroxetine, 215 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 µL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-40 % EtOAc in heptane) to leave $^\text{tert-Butyl (3S,4R)-3-}$(benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-(fluorosulfonyl)phenyl)piperidine-1-carboxylate (N-Boc-6-SO$_2$F-paroxetine) as a white solid (95 mg, 0.192 mmol, 48%); IR $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2980, 1689, 1504, 1489, 1471, 1420, 1407, 1239, 1215, 1185, 1135, 769; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$: 7.94 (d, $J$=8.2 Hz, 2 H), 7.46 (d, $J$=8.2 Hz, 2 H), 6.64 (d, $J$=8.8 Hz, 1 H), 6.33 (d, $J$=2.3 Hz, 1 H), 6.12 (dd, $J$=8.2, 2.3 Hz, 1 H), 5.90 (s, 2 H), 4.43 (br. s., 1 H), 4.29 (br. s., 1 H), 3.61 (dd, $J$=9.4, 2.9 Hz, 1 H), 3.46 (dd, $J$=9.4, 5.9 Hz, 1 H), 2.79 - 3.01 (m, 3 H), 2.10 (br. s., 1 H), 1.82 - 1.89 (m, 1 H), 1.76 (qd, $J$=12.5, 3.5 Hz, 1 H), 1.62 (m, $J$=12.3 Hz, 1 H), 1.51 (s, 9 H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$: 154.7, 153.9, 152.4, 148.3, 141.9, 131.4 (d, $J$=25.1 Hz), 128.9, 128.8, 107.9, 105.4, 101.2, 97.9, 80.0, 68.4, 45.0, 41.6, 33.4, 28.4; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: 66.1; HRMS (ESI$^+$) found m/z 494.1645 [M+H$^+$], C$_{23}$H$_{29}$FNO$_7$S requires m/z 494.1643.
**tert-Butyl ((1S,4S)-4-(3,4-dichlorophenyl)-6-(fluorosulfonyl)-1,2,3,4-tetrahydronaphthalen-1-yl)(methyl)carbamate (N-Boc-6-SO\textsubscript{2}F-sertraline, 4t)**

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl\textsubscript{2}(AmPhos)\textsubscript{2} (14.2 mg, 0.020 mmol), tert-butyl ((1S,4S)-4-(3,4-dichlorophenyl)-6-iodo-1,2,3,4-tetrahydronaphthalen-1-yl)(methyl)carbamate (N-Boc-6-iodo sertraline, 213 mg, 0.4 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 \(\mu\)L, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-40 % EtOAc in heptane) to leave tert-butyl ((1S,4S)-4-(3,4-dichlorophenyl)-6-(fluorosulfonyl)-1,2,3,4-tetrahydronaphthalen-1-yl)(methyl)carbamate (N-Boc-6-SO\textsubscript{2}F-sertraline) as a white solid (131 mg, 0.268 mmol, 67%); IR \(\nu\max\) (neat)/cm\(^{-1}\): 2980, 1686, 1470, 1412, 1391, 1367, 1345, 1321, 1217, 1161, 1140; \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 7.89 (d, \(J=7.8\) Hz, 1H), 7.63 (s., 1H), 7.49 (d, \(J=7.8\) Hz, 1H), 7.38 (d, \(J=8.2\) Hz, 1H), 7.08 (s, 1H), 6.77 (d, \(J=7.8\) Hz, 1H), 5.20-5.57 (m, 1H), 4.30 (d, \(J=2.9\) Hz, 1H), 2.68 (s, 3H), 2.22-2.41 (m, 1H), 2.07 (d, \(J=12.3\) Hz, 1H), 1.83 (dd, \(J=7.6, 4.1\) Hz, 2H), 1.54 (s, 9H); \(^{13}\)C NMR (151 MHz, CDCl\textsubscript{3}) \(\delta\): 156.3, 146.0, 145.4, 140.3, 132.8, 131.8 (d, \(J=26.1\) Hz), 130.9, 130.7, 130.5, 130.4, 128.7, 127.8, 126.7, 80.5, 54.6, 43.0, 30.2, 29.8, 28.4, 20.8; \(^{19}\)F NMR (376 MHz, CDCl\textsubscript{3}) \(\delta\): 66.1; HRMS (ESI\textsuperscript{+}) found \(m/z\) 488.0847 [M+H]\textsuperscript{+}, \(\text{C}_{22}\text{H}_{23}\text{Cl}_{2}\text{FNO}_{4}\text{S}\) requires \(m/z\) 488.0860.

**1.8 Palladium-Catalyzed Synthesis of Peptidyl Sulfonyl Fluorides**

\(N\)-Boc-4-Sulfonylfluoride phenylalanine methyl ester (4u)

Prepared according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl\textsubscript{2}(AmPhos)\textsubscript{2} (14.2 mg, 0.020 mmol), \(N\)-Boc-4-iodo phenylalanine methyl ester (162 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 \(\mu\)L, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-40 % EtOAc in heptane) to leave \(N\)-Boc-4-sulfonylfluoride phenylalanine methyl ester as a white solid (105 mg, 0.291 mmol,
73%); IR ν max (neat)/cm⁻¹: 1744, 1711, 1405, 1366, 1280, 1212, 1161, 1056, 1019, 767, 630, 594; ¹H NMR (400 MHz, CDCl₃) δH: 7.95 (d, J 8.2 Hz, 2H), 7.42 (d, J 8.2 Hz, 2H), 5.06 (d, J 7.4 Hz, 1H), 4.66 (d, J 6.2 Hz, 1H), 3.76 (s, 3H), 3.31 (dd, J 13.9, 5.7 Hz, 1H), 3.13 (dd, J 13.5, 6.4 Hz, 1H), 1.42 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δC: 171.5, 154.9, 145.2, 131.7, 131.5, 130.6, 128.5, 100.0, 80.4, 54.0, 52.6, 38.6, 28.2; ¹⁹F NMR (376 MHz, CDCl₃) δF: 66.1; HRMS (ES+) found m/z 384.0879 [M+Na]+, C₁₅H₂₀FNNaO₆S requires m/z 384.0888.

Additionally, compound 4u was prepared from N-Boc-4-bromo phenylalanine methyl ester according to general procedure A using DABSO (58 mg, 0.24 mmol), PdCl₂(AmPhos)₂ (14.2 mg, 0.020 mmol), N-Boc-4-bromo phenylalanine methyl ester (144 mg, 0.40 mmol), anhydrous isopropanol (1.5 mL), anhydrous triethylamine (167 μL, 1.2 mmol) and NFSI (189 mg, 0.6 mmol). The crude product was purified by column chromatography on silica (0-40 % EtOAc in heptane) to leave N-Boc-4-sulfonylfluoride phenylalanine methyl ester as a white solid (105 mg, 0.291 mmol, 61%). The spectra matched the desired product 4u as described above.

Methyl N²-(tert-butoxycarbonyl)-N⁶-((4-((S)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl)sulfonyl)-L-lysinate (7)

A glass reaction tube was charged with N-Boc-4-sulfonylfluoride phenylalanine methyl ester (4u, 30 mg, 0.08 mmol), dissolved in DMSO (420 μL) and treated with DIPEA (43 μL, 0.25 mmol) and methyl (tert-butoxycarbonyl)-L-lysinate (62 mg, 0.21 mmol). After 15 h at 100 °C, the reaction was allowed to cool to r.t., diluted with brine (10 mL) and extracted with EtOAc (2x15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to leave the crude product, which was purified by column chromatography on silica (0-100% EtOAc in heptane) to provide methyl N²-(tert-butoxycarbonyl)-N⁶-((4-((S)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)phenyl)sulfonyl)-L-lysinate as a colourless oil (42 mg, 0.070 mmol, 84%); IR ν max (neat)/cm⁻¹: 3291, 2979, 2362, 1745, 1697, 1161; ¹H NMR (400 MHz, CDCl₃) δH: 7.77 (d, J = 7.6 Hz, 2H), 7.27-7.34 (m, 2H), 5.11 (d, J = 7.6 Hz, 2H), 4.93 (br. s., 1H), 4.61 (d, J = 6.5 Hz, 1H), 4.23 (d, J = 4.7 Hz, 1H), 3.72 (s, 6H), 3.22 (dd, J = 13.5, 5.3 Hz, 1H), 3.08 (dd, J = 13.2, 6.2 Hz, 1H), 2.92 (q, J = 6.5 Hz, 2H), 1.67-1.79 (m, 1H), 1.53-1.62 (m, 1H), 1.45-1.53 (m, 2H), 1.36-1.45 (m, 18H), 1.29-
1.35 (m, 2H); $^{13}$C $^1$H] NMR (101 MHz, CDCl$_3$) δC: 173.1, 171.8, 155.44, 155.0, 141.5, 138.6, 130.0, 127.2, 80.1, 79.9, 54.1, 53.0, 52.3, 42.8, 38.2, 32.2, 28.9, 28.3, 28.2, 22.2; HRMS (ESI$^+$) found $m/z$ 624.2551 [M+Na]$^+$, C$_{27}$H$_{43}$N$_3$NaO$_{10}$S requires $m/z$ 624.2561.

$\text{N-Cbz-N'}\text{-Boc-Lys-Ala-Pro-(4-iodo)Phe-OMe (8)}$

$\text{N-Boc-4-iodo phenylalanine methyl ester (N-Boc-(4-iodo)Phe, 380 mg, 0.94 mmol)}$ was taken up in 20 % TFA/CH$_2$Cl$_2$ (7.5 mL) and stirred for 45 min at r.t. The solution was concentrated under reduced pressure and the resultant oil was taken up in 50 mL EtOAc and washed with sat. aq. NaHCO$_3$ (25 mL). The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated. The resultant deprotected amine was taken up in DMF (5 mL) and treated with Et$_3$N (0.26 mL, 1.88 mmol) and $\text{N-Boc-Pro-Ala-OH (269 mg, 0.94 mmol)}$. The solution was treated with HATU (441 mg, 1.13 mmol) and the resultant yellow solution was stirred at r.t. for 18 h. The reaction was quenched with sat. aq. NaHCO$_3$ (5 mL) and stirred for 30 min at r.t. The mixture was diluted with H$_2$O (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated. The crude product was purified by flash chromatography (20-100% EtOAc in heptane) to yield the desired target $\text{N-Boc-Ala-Pro-(4-iodo)Phe-OMe as a white solid (412 mg, 0.718 mmol, 77%)}$.

$\text{N-Boc-Ala-Pro-(4-iodo)Phe-OMe (308 mg, 0.54 mmol)}$ was taken up in 20 % TFA/CH$_2$Cl$_2$ (7.5 mL) and stirred for 45 min at r.t. The solution was concentrated under reduced pressure and the resultant oil was taken up in EtOAc (50 mL) and washed with sat. aq. NaHCO$_3$ (25 mL). The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated. The resultant deprotected amine was taken up in DMF (5 mL) and treated with Et$_3$N (0.15 mL, 1.07 mmol) and $\text{N-Cbz-N'-Boc-Lys-OH (204 mg, 0.54 mmol)}$. The solution was treated with HATU (253 mg, 0.65 mmol) and the resultant yellow solution was stirred at r.t. for 18 h. The reaction was quenched with sat. aq. NaHCO$_3$ (5 mL) and stirred for 30 min at r.t. The mixture was diluted with H$_2$O (50 mL) and extracted with EtOAc (2 × 50 mL). The
combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography (20-100% EtOAc in heptane) to yield the desired target N-Cbz-N'-Boc-Lys-Ala-Pro-(4-iodo)Phe-OMe as a white solid (241 mg, 0.288 mmol, 54%); IR νmax (neat)/cm⁻¹; 3305, 2975, 1670, 1525, 1486, 1455, 1402, 1250, 1171, 849; ¹H NMR (600 MHz, dmso-d₆, cis/trans isomers observed, major peaks listed) δ, 8.17 (d, J=7.04 Hz, 1H), 8.00 (d, J=7.04 Hz, 1H), 7.62 (d, J=8.22 Hz, 2H), 7.27-7.40 (m, 5H), 7.05 (d, J=8.22 Hz, 2H), 6.74 (br. s., 1H), 5.01 (s, 2H), 4.46-4.55 (m, 1H), 4.39-4.45 (m, 1H), 4.34 (dd, J=3.52, 8.22 Hz, 1H), 3.91-3.98 (m, 1H), 3.58 (s, 3H), 3.50 (d, J=6.46 Hz, 1H), 2.83-3.05 (m, 4H), 1.90-2.10 (m, 2H), 1.79-1.90 (m, 2H), 1.69-1.76 (m, 1H), 1.54-1.64 (m, 1H), 1.42-1.41 (m, 12H), 1.14-1.20 (m, 2H), 0.97-0.98 (m, 1H); ¹³C NMR (151 MHz, dmso-d₆, cis/trans isomers observed, major peaks listed) δC 171.6, 171.5, 171.4, 170.4, 165.6, 155.9, 155.5, 137.0, 136.9, 136.8, 131.6, 131.5, 128.3, 127.7, 127.6, 92.4, 77.3, 65.3, 59.0, 54.5, 53.2, 51.8, 46.6, 46.0, 40.0, 39.9, 39.8, 39.6, 39.4, 39.2, 39.1, 36.0, 31.5, 31.2, 29.1, 28.8, 28.2, 24.3, 22.8, 22.1, 17.0, 13.9; HRMS (ESI⁺) found m/z 836.2730 [M+H]⁺, C₃₇H₅₁N₆O₉ requires m/z 836.2726.

N-Cbz-N'-Boc-Lys-Ala-Pro-(4-sulfonylfluoride)Phe-OMe (4v)

Prepared according to general procedure A using DABSO (12 mg, 0.048 mmol), PdCl₂(AmPhos)₂ (2.8 mg, 0.004 mmol), N-Cbz-N'-Boc-Lys-Ala-Pro-(4-iodo)Phe-OMe (67 mg, 0.08 mmol), anhydrous isopropanol (1 mL), anhydrous triethylamine (33 μL, 0.24 mmol) and NFSI (38 mg, 0.12 mmol). The crude product was purified by column chromatography on silica (5% MeOH in CH₂Cl₂) to provide N-Cbz-N'-Boc-Lys-Ala-Pro-(4-sulfonylfluoride)Phe-OMe as a colorless oil (41 mg, 0.0518 mmol, 65 %): IR νmax (neat)/cm⁻¹; 2973, 2945, 2487, 2011, 1972, 1652, 1558; ¹H NMR (400 MHz, dmso-d₆) cis/trans isomers observed; ¹⁹F NMR (376 MHz, DMSO) δF: 66.5; ¹³C {¹H} NMR (101 MHz, dmso-d₆) cis/trans isomers observed; LRMS (ESI) m/z 792.7 ([M+H]⁺), HRMS (ESI⁺) found m/z 792.3274 [M+H]⁺, C₃₇H₅₁F₅O₁₁S requires m/z 792.3284.

1.9 Synthesis of Sulfonyl Fluorides from Grignard Reagents

General Procedure C: Synthesis of sulfonyl fluorides from Grignard reagents, DABSO and NFSI as exemplified by the preparation of 4-fluorobenzenesulfonyl fluoride (9a)
DABSO (240 mg, 1.0 mmol, 0.5 eq.) was suspended in anhydrous THF (4 mL) and the suspension purged with N₂ for 3 min. 4-Fluorophenylmagnesium bromide solution (1.84 mL, 2.0 mmol, 1.0 eq., 0.92 M in THF) was added dropwise and the mixture stirred at r.t. for 45 min. The solution was cooled to 0 °C, then NFSI (946 mg, 3.0 mmol, 1.5 eq.) was added portionwise at 0 °C and the reaction mixture stirred at r.t. for 3 h. The mixture was quenched with sat. aq. NH₄Cl and partitioned between EtOAc and brine, washing with EtOAc. The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo to leave the crude product, which was purified by column chromatography on silica (10% CH₂Cl₂ in pet. ether) to leave 4-fluorobenzenesulfonyl fluoride as a colourless oil (329.5 mg, 1.85 mmol, 93%) with spectroscopic data in accordance with the literature;¹ ¹H NMR (400 MHz, CDCl₃) δH: 8.04 (dd, J 9.0, 4.8 Hz, 2H), 7.29 (dd, J 9.0, 7.9 Hz, 2H); ¹⁹F NMR (377 MHz, CDCl₃) δF: 66.8, −99.6 (ddd, J 7.9, 4.9, 3.2 Hz); ¹³C {¹H} NMR (101 MHz, CDCl₃) δC: 166.3 (d, J 259.9 Hz), 143.1 (d, J 3.2 Hz), 129.6 (d, J 10.3 Hz), 117.0 (d, J 23.1 Hz); HRMS (CI) found m/z 178.9979 [M+H]+, C₆H₅F₂O₂S requires m/z 178.9973.

Phenylmethanesulfonyl fluoride (9b)

Prepared according to general procedure C using DABSO (240 mg, 1.0 mmol), benzylmagnesium chloride solution (1.68 mL, 2.0 mmol, 1.19 M in THF), anhydrous THF (4 mL) and NFSI (946 mg, 3.0 mmol). The crude product was purified by column chromatography on silica (10% CH₂Cl₂ in pet. ether) to leave 3-methyl-4-oxo-3,4-dihydroquinazoline-6-sulfonyl fluoride as a white crystalline solid (222.8 mg, 1.28 mmol, 64%) with spectroscopic data in accordance with the literature;²¹ ¹H NMR (400 MHz, CDCl₃) δH: 7.48 – 7.41 (m, 5H), 4.60 (d, J 3.3 Hz, 2H); ¹⁹F NMR (377 MHz, CDCl₃) δF: 51.4 (t, J 3.3 Hz); ¹³C {¹H} NMR (101 MHz, CDCl₃) δC: 130.7, 129.9, 129.3, 125.5, 56.8 (d, J 17.5 Hz); HRMS (CI) found m/z 192.0488 [M+NH₄]+, C₇H₁₁FNO₂S requires m/z 192.0489.

Cyclohexanesulfonyl fluoride (9c)

Prepared according to general procedure C using DABSO (240 mg, 1.0 mmol), cyclohexylmagnesium chloride solution (1.43 mL, 2.0 mmol, 1.40 M in THF), anhydrous THF (4 mL) and NFSI (946 mg, 3.0 mmol). The crude product was purified by column chromatography on silica (10% CH₂Cl₂ in pet. ether) to leave cyclohexanesulfonyl fluoride as a colourless oil (220.0 mg, 1.32 mmol, 66%) with.
spectroscopic data in accordance with the literature;[4] 1H NMR (400 MHz, CDCl3) δH: 3.30 (ttd, J 12.1, 3.5, 1.6 Hz, 1H), 2.30 (dddt, J 12.0, 3.8, 2.5, 1.4 Hz, 2H), 2.00 – 1.91 (m, 2H), 1.80 – 1.61 (m, 3H), 1.43 – 1.20 (m, 3H); 19F NMR (377 MHz, CDCl3) δF: 40.8; 13C {1H} NMR (101 MHz, CDCl3) δC: 61.0 (d, J 12.7 Hz), 26.5, 24.72, 24.67; HRMS (CI) found m/z 184.0807 [M+NH4]+, C6H15FNO2S requires m/z 184.0802.

4-Chlorobenzenesulfonyl fluoride (9d)

Prepared according to general procedure C using DABSO (240 mg, 1.0 mmol), 4-chlorophenylmagnesium bromide solution (2.67 mL, 2.0 mmol, 0.75 M in 2-MeTHF), anhydrous THF (4 mL) and NFSI (946 mg, 3.0 mmol). The crude product was purified by column chromatography on silica (10% CH2Cl2 in pet. ether) to leave 4-chlorobenzenesulfonyl fluoride as a white crystalline solid (278.7 mg, 1.43 mmol, 72%) with spectroscopic data in accordance with the literature;[4] mp 42-44 °C; 1H NMR (400 MHz, CDCl3) δH: 7.94 (d, J 8.8 Hz, 2H), 7.59 (d, J 8.8 Hz, 2H); 19F NMR (377 MHz, CDCl3) δF: 66.6; 13C {1H} NMR (101 MHz, CDCl3) δC: 142.1, 130.0 (d, J 25.3 Hz), 129.9, 127.9; HRMS not available.

3-Methylbenzenesulfonyl fluoride (9e)

Prepared according to general procedure C using DABSO (240 mg, 1.0 mmol), 3-methylphenylmagnesium bromide solution (3.17 mL, 2.0 mmol, 0.63 M in THF), anhydrous THF (4 mL) and NFSI (946 mg, 3.0 mmol). The crude product was purified by column chromatography on silica (10% CH2Cl2 in pet. ether) to leave 3-methylbenzenesulfonyl fluoride as a colourless oil (252.3 mg, 1.45 mmol, 73%); IR νmax (neat)/cm−1 1404, 1321, 1200, 1098; 1H NMR (400 MHz, CDCl3) δH: 7.84 – 7.78 (m, 2H), 7.61 – 7.55 (m, 1H), 7.54 – 7.47 (m, 1H), 2.47 (s, 2H); 19F NMR (377 MHz, CDCl3) δF: 65.8; 13C {1H} NMR (101 MHz, CDCl3) δC: 140.2, 136.4, 132.9 (d, J 23.7 Hz), 129.5, 128.6, 125.5, 21.3; HRMS (CI) found m/z 192.0493 [M+NH4]+, C7H13FNO2S requires m/z 192.0489.

Thiophene-2-sulfonyl fluoride (9f)

Prepared according to general procedure C using DABSO (240 mg, 1.0 mmol), 2-thienylmagnesium bromide solution (2.70 mL, 2.0 mmol, 0.74 M in THF), anhydrous THF (4 mL) and NFSI (946 mg,
3.0 mmol). The crude product was purified by column chromatography on silica (10% CH₂Cl₂ in pet. ether) to leave thiophene-2-sulfonyl fluoride as a yellow solid (258.4 mg, 1.55 mmol, 78%) with spectroscopic data in accordance with the literature;[2] mp 39-40 °C; \(^1\)H NMR (400 MHz, CDCl₃) δH: 7.87 (dd, J 3.9, 1.4 Hz, 1H), 7.81 (dd, J 5.0, 1.4 Hz, 1H), 7.1 (dd, J 5.0, 3.9 Hz, 1H); \(^{19}\)F NMR (377 MHz, CDCl₃) δF: 71.8; \(^{13}\)C \(^{1}\)H NMR (101 MHz, CDCl₃) δC: 147.1, 135.4, 134.1, 127.5; HRMS not available.
2 References


3 NMR Spectra

3.1 NMR Spectra of Aryl Bromides
3.2 NMR Spectra of Sulfonyl Fluorides Synthesized by Palladium Catalysis
3.3 NMR Spectra of Pyridyl Sulfonyl Fluorides Synthesized by Palladium Catalysis
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**Chemical Structures:**

1. ![Chemical Structure 1](image1.png)
2. ![Chemical Structure 2](image2.png)
3.4 NMR Spectra of Sulfonyle Fluoride-Containing Active Pharmaceutical Ingredients
phenylalanine methyl ester from N-BOC-4-bromo phenylalanine methyl ester
from N-BOC-4-bromo phenylalanine methyl ester
3.5 NMR Spectra of Sulfonyl Fluorides Synthesized from Grignard Reagents

\[ \text{SO}_2F \]