Supporting Information

Difluorination of Heterobenzylic C–H Bonds with N-Fluoro-N-(fluorosulfonyl)carbamate (NFC)


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Table of Contents

S1. General Information ........................................................................................................ page 3
S2. Screening of Reaction Conditions in Fluorination of Pyridine 2a .......................... page 3-4
S3. Substrate Scope ............................................................................................................. page 5-13
S4. Mechanistic Studies ...................................................................................................... page 13-18
S5. NMR Spectra ................................................................................................................ page 19-46
S6. References ..................................................................................................................... page 47
S1. General Information

\(^1\)H, \(^{13}\)C, and \(^{19}\)F NMR spectra were measured on JEOL JNM-ECZ400S (\(^1\)H NMR: 400 MHz, \(^{13}\)C NMR: 100 MHz, \(^{19}\)F NMR: 376 MHz) spectrometers at ambient temperature. Analytical thin layer chromatography (TLC) was performed on glass plates pre-coated with silica-gel (Merck Kieselgel 60 F\(_{254}\), layer thickness 0.25 mm). Column chromatography was performed on KANTO Silica Gel 60N (spherical, neutral). High-resolution mass (HRMS) spectra were measured on a JEOL JMS-T100LP spectrometer in the electron spray ionization time-of-flight (ESI-TOF) mode. Gas chromatography-mass spectroscopy (GC-MS) analyses (using CI as ionization mode) were performed using a Shimadzu GC-MS QP2020 gas chromatograph mass spectrometer equipped with an HP-5 capillary column (0.320 i.d.; 0.25 \(\mu\)m df; 30 m; Agilent Technologies) with helium as the carrier gas. N-Fluoro-N-(fluorosulfonyl)-neopentylcarbamate (NFC) as a fluorinating reagent was synthesized according to the previous synthetic method.\(^{[1]}\)

S2. Screening of Reaction Conditions in Fluorination of Pyridine 2a

S2-1. Solvent

\[
\begin{align*}
\text{NFC (4 eq.)} & \quad \text{Na}_2\text{CO}_3 (2 \text{ eq.)} \\
2a & \quad \text{Solvent (0.1M) \quad 50^\circ \text{C, 2 h}} \\
\end{align*}
\]

To a mixture of Na\(_2\)CO\(_3\) (21.2 mg, 0.20 mmol, 2.0 equiv.) and 2a (10.7 mg, 0.10 mmol) in solvent (0.1 M, 1.0 mL) was added NFC (92.5 mg, 0.40 mmol, 4.0 equiv.)\(^{[1]}\) at room temperature under N\(_2\) atmosphere. After stirring for 2 h at 50 \(^\circ\)C, the yield and selectivity were determined by \(^{19}\)F NMR spectroscopy analysis using benzotrifluoride as an internal standard.

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<tr>
<th>Entry</th>
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<th>(^{19})F NMR yield [%]</th>
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<th>4a</th>
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<tr>
<td>1</td>
<td>AcOEt</td>
<td>0</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CH(_2)CN</td>
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<td>&gt;99</td>
<td></td>
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<tr>
<td>3</td>
<td>Toluene</td>
<td>11</td>
<td>70</td>
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<tr>
<td>4</td>
<td>CH(_2)CICH(_2)Cl</td>
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<tr>
<td>5</td>
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<td>trace</td>
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<tr>
<td>6</td>
<td>DMF</td>
<td>56</td>
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S2-2. Base

To a mixture of organic/inorganic base (0.20 mmol, 2.0 equiv.) and 2a (10.7 mg, 0.10 mmol) in AcOEt or CH₃CN (0.1 M, 1.0 mL) was added NFC (92.5 mg, 0.40 mmol, 4.0 equiv.) at room temperature under N₂ atmosphere. After stirring for 2 h at 50 °C, the yield and selectivity were determined by ¹⁹F NMR spectroscopy analysis using benzotrifluoride as an internal standard.

<table>
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<th>Entry</th>
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<th>¹⁹F NMR yield [%]</th>
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<tr>
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<td>Na₂CO₃</td>
<td>CH₃CN</td>
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S2-3. Equivalence

To a mixture of Li₂CO₃ (Y equiv.) and 2a (10.7 mg, 0.10 mmol) in CH₃CN (0.1 M, 1.0 mL) was added NFC (X equiv.) at room temperature under N₂ atmosphere. After stirring for 2 h at 50 °C, the yield and selectivity were determined by ¹⁹F NMR spectroscopy analysis using benzotrifluoride as an internal standard.

<table>
<thead>
<tr>
<th>Entry</th>
<th>NFC [eq.]</th>
<th>Li₂CO₃ [eq.]</th>
<th>¹⁹F NMR yield [%]</th>
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</tr>
<tr>
<td>5</td>
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<td>1.0</td>
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S3. Substrate Scope

S3-1. Direct Fluorination of N-Heterocycles using with NFC

\[
\begin{array}{c}
\text{NFC (4.0 eq.)} \\
\text{Li}_{2}CO_{3} (2.0 eq.) \\
\text{Temp., Time} \\
\text{CH}_{3}CN or AcOEt (0.1M) \\
\end{array}
\]

The title compound was obtained from 4-ethylpyridine following the procedure above (\(\text{CH}_{3}CN, 50 \, ^{\circ}\text{C}, 2\) h). The yield and ratio of compounds (>99%, mono-F/di-F = <1/<99) were determined by \(^{19}\text{F}\) NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography \((n\text{-hexane/EtOAc} = 7/1)\) gave the compound (12.6 mg, 88% yield) as a yellow oil. The product is known and the following data are identical to those given in corresponding literature.\(^{[2-3]}\)

\(^{1}\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.69 \((d, J = 4.8\) Hz, 2H), 7.38 \((d, J = 4.8\) Hz, 2H), 1.89 \((t, J = 18.0\) Hz, 3H); \(^{19}\text{F}\) NMR (376 MHz, CDCl\(_3\)) \(\delta\) -91.1 \((q, J = 17.3\) Hz, 2F).

4-(1,1-Difluoro-2-phenylpropyl)pyridine (4b)

The title compound was obtained from 4-(3-phenylpropyl)pyridine following the procedure above \((\text{CH}_{3}CN, 50 \, ^{\circ}\text{C}, 10\) h). The yield and ratio of compounds (93%, mono-F/di-F = <1/<99) were determined by \(^{19}\text{F}\) NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography \((n\text{-hexane/EtOAc} = 3/1)\) gave the compound (16.7 mg, 72% yield) as a yellow oil.

\(^{1}\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.71 \((t, J = 4.2\) Hz, 2H), 7.39 \((t, J = 4.2\) Hz, 2H), 7.25 \((d, J = 4.2\) Hz, 2H), 7.20 \((t, J = 8.0\) Hz, 1H), 7.13 \((d, J = 8.4\) Hz), 2.75-2.80 \((m, 2\) H), 2.33-2.47 \((m, 2\) H); \(^{19}\text{F}\) NMR (376 MHz, CDCl\(_3\)) \(\delta\) -99.19 \((t, J = 17.3\) Hz, 2F); \(^{13}\text{C}\) NMR (100MHz, CDCl\(_3\)) \(\delta\) 150.43, 145.32 \((t, J_{\text{C-F}} = 28.0\) Hz), 139.85, 128.72, 128.30, 126.51, 121.30 \((t, J_{\text{C-F}} = 241.9\) Hz), 119.66 \((t, J_{\text{C-F}} = 5.5\) Hz), 40.48 \((t, J_{\text{C-F}} = 26.5\) Hz), 28.52 \((t, J_{\text{C-F}} = 4.0\) Hz); HRMS (ESI-TOF) calcd for C\(_{14}\)H\(_{14}\)F\(_{2}\)N [M+H]\(^{+}\): 234.1094, found:234.1090.

4-(Difluorophenyl)methyl)pyridine (4c)

The title compound was obtained from 4-(benzyl)pyridine following the procedure above \((\text{CH}_{3}CN, 50 \, ^{\circ}\text{C}, 2\) h). The yield and ratio of compounds (73%, mono-F/di-F = <1/<99) were determined by \(^{19}\text{F}\) NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography \((\text{CH}_{2}\text{Cl}_{2})\) gave the compound (13.1 mg, 64% yield) as a yellow oil. The product is
known and the following data are identical to those given in corresponding literature.\[^{[4]}\]

\[^{[4]}\] 1H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.70 (d, \(J = 5.6\) Hz, 1H), 7.41-7.50 (m, 7H); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -92.5 (s, 2F).

**4-(1,1-Difluoro-1-(4′-nitrophenyl)methyl)pyridine (4d)**

The title compound was obtained from 4-((4′-nitrophenyl)methyl)pyridine following the procedure above (CH\(_3\)CN, 50 °C, 2 h). The yield and ratio of compounds (99%, mono-F/di-F = <1/>99) were determined by \(^{19}\)F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/EtOAc =5/1) gave the compound (18.4 mg, 86% yield) as a white solid.

\[^{1}\] 1H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.50 (d, \(J = 5.8\) Hz, 2H), 8.31 (d, \(J = 9.0\) Hz, 2H), 7.71 (d, \(J = 9.0\) Hz, 2H), 7.12 (d, \(J = 5.8\) Hz, 2H); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -93.63 (s, 2F); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 150.68, 149.22, 144.47 (t, \(J = 29.8\) Hz), 142.28 (t, \(J = 28.8\) Hz), 126.97 (t, \(J = 5.8\) Hz), 124.12, 119.90 (t, \(J = 5.3\) Hz), 118.42 (t, \(J = 243.4\) Hz); HRMS (ESI-TOF) calcd for C\(_{12}\)H\(_8\)F\(_2\)N\(_2\)O\(_2\) [M+Na\(^+\)]\(^{+}\): 273.04515, found: 273.04410.

**5,5-Difluoro-5,6,7,8-tetrahydroisoquinoline (4e)**

The title compound was obtained from 5,6,7,8-tetrahydroisoquinoline following the procedure above (CH\(_3\)CN, 50 °C, 2 h). The yield and ratio of compounds (99%, mono-F/di-F = <1/>99) were determined by \(^{19}\)F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/EtOAc =2/1) gave the compound (14.0 mg, 83% yield) as a yellow oil. 4e was not identified through ESI-MS (TOF, HRMS), but was identified through GC-MS (CI, LRMS).

\[^{1}\] 1H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.53 (d, \(J = 4.8\) Hz, 1H), 8.48 (s, 1H), 7.50 (d, \(J = 4.8\) Hz, 1H), 2.81 (s, 2H), 2.22-2.32 (m, 2H), 1.98-2.05 (m, 2H); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -87.7 (t, \(J = 11.3\) Hz, 2F); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 150.69, 148.15, 139.95 (t, \(J_{CF} = 26.7\) Hz), 132.84 (t, \(J_{CF} = 5.7\) Hz), 119.38, 118.57 (t, \(J_{CF} = 237.4\) Hz), 33.08 (t, \(J_{CF} = 23.3\) Hz), 25.55, 19.70 (t, \(J_{CF} = 4.8\) Hz); LRMS (CI) calcd for C\(_9\)H\(_{10}\)F\(_2\)N [M+H\(^+\)]\(^{+}\): 170.08, found: 170.00.

**4-(1,1-Difluoro-2-methylpropyl)pyridine (4f)**

The title compound was obtained from 4-(2-methylpropyl)pyridine following the procedure above (CH\(_3\)CN, 50 °C, 10 h). The yield and ratio of compounds (74%, mono-F/di-F = <1/>99) were determined by \(^{19}\)F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/EtOAc =4/1) gave the compound (8.0 mg, 48% yield) as a colorless oil. 4f was not identified through ESI-MS (TOF, HRMS), but was identified through GC-MS (CI, LRMS).

\[^{1}\] 1H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.76 (d, \(J = 4.4\) Hz, 2H), 7.42 (d, \(J = 4.6\) Hz, 2H), 2.30 (m, 1H), 0.98 (d, \(J = 6.8\) Hz, 6H); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -106.56 (d, \(J = 13.9\) Hz, 2F); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 149.68, 145.27 (t, \(J = 28.5\) Hz), 123.19 (t, \(J = 245.6\) Hz), 120.56 (t, \(J = 5.7\) Hz), 36.19 (t, \(J = 25.6\) Hz), 15.65 (t, \(J = 4.3\) Hz); LRMS (CI) calcd for C\(_9\)H\(_{12}\)F\(_2\)N [M+H\(^+\)]\(^{+}\): 172.09, found: 172.00.
4-(1,1-Difluoro-2-phenylpropyl)pyridine (4g)

The title compound was obtained from 4-(2-phenylpropyl)pyridine following the procedure above (CH₃CN, 50 °C, 10 h). The yield and ratio of compounds (69%, mono-F/di-F = <1/>99) were determined by ¹⁹F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (CH₂Cl₂) gave the compound (14.0 mg, 60% yield) as a yellow oil. The product is known in the literature.[⁵]

¹H NMR (400 MHz, CDCl₃) δ 8.56 (d, J = 6.4 Hz, 2H), 7.22-7.24 (m, 3H), 7.04-7.10 (m, 4H), 3.35-3.44 (m, 1H), 1.47 (d, J = 6.8 Hz, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -101.03 (dd, J = 242.5, 11.7 Hz, 1F), -106.36 (dd, J = 242.9, 85.0 Hz, 1F).

4-(1,1-Difluoro-2,2-dimethylpropyl)pyridine (4h)

The title compound was obtained from 4-(2,2-dimethylpropyl)pyridine following the procedure above (0.050 mmol, AcOEt, 50 °C, 18 h). The yield and ratio of compounds (65%, mono/di-F = 13/87) were determined by ¹⁹F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/EtOAc =4/1) solely gave the difluorinated compound (4.2 mg, 45% yield) as a yellow oil. 4h was not identified through ESI-MS (TOF, HRMS), but was identified through GC-MS (CI, LRMS).

¹H NMR (400 MHz, CDCl₃) δ 8.68 (d, J = 4.0 Hz, 2H), 7.33 (d, J = 4.4 Hz, 2H), 1.03 (s, 9H); ¹⁹F NMR (376 MHz, CDCl₃) δ -108.2 (s, 2F); LRMS (CI) calcd for C₁₀H₁₄F₂N [M+H]⁺: 186.11, found: 186.05.

4-(1,1-Difluoroethyl)quinoline (4i)

The title compound was obtained from 4-ethylquinoline following the procedure above (0.050 mmol, AcOEt, 75 °C, 10 h). The yield and ratio of compounds (75%, mono-F/di-F = <1/>99) were determined by ¹⁹F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/EtOAc =8/1) gave the compound (5.2 mg, 45% yield) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 8.97 (brs, 1H), 8.20 (t, J = 7.6 Hz, 2H), 7.77 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 2.13 (t, J = 18.6 Hz, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -86.51 (q, J = 18.4 Hz, 2F); ¹³C NMR (100 MHz, CDCl₃) δ 149.89, 149.01, 130.53, 129.67, 127.58, 124.75, 123.34, 121.62 (t, J_C,F = 235.5 Hz), 117.67, 117.38. 26.16 (t, J_C,F = 28.6 Hz); HRMS(ESI-TOF) calcd for C₁₀H₁₄F₂N [M+H]⁺: 230.0548, found: 230.0568.

4-(1,1-Difluoroethyl)pyrimidine (4j)

The title compound was obtained from 4-ethylpyrimidine following the procedure above (AcOEt, 75 °C, 10 h). The yield and ratio of compounds (71%, mono-F/di-F = <1/>99) were determined by ¹⁹F NMR analysis using hexafluorobenzene (δ -163) as an internal standard. Purification by silica-gel column chromatography (n-pentane/Et₂O = 5/1) afforded volatile 4j containing solvents and some impurities. 4j
was not identified through ESI-MS (TOF, HRMS), but was identified through GC-MS (Cl, LRMS).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.30 (s, 1H), 8.91 (d, $J = 5.2$ Hz, 1H), 7.65 (dd, $J = 5.2$, 1.6 Hz, 1H), 2.00 (t, $J = 18.8$ Hz, 3H); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -93.61 (q, $J = 18.6$ Hz, 2F); LRMS (Cl) calcd for C$_6$H$_2$F$_2$N$_2$ [M+H]$^+$: 145.06, found: 145.10.

4-(Difluoromethyl)pyridine (4k)

The title compound was obtained from 4-picoline following the procedure above (CH$_3$CN, 75 °C, 10 h). The yield and ratio of compounds (60%, mono-F/di-F = <1/>99) were determined by $^{19}$F NMR analysis using benzotriazol fluoride as an internal standard. Purification by silica-gel column chromatography ($n$-hexane/EtOAc =5/1) gave the compound (15.2 mg, 59% yield) as a yellow oil. The product is known and the following data are identical to those given in corresponding literature.$^{[2]}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.69 (d, $J = 4.8$ Hz, 2H), 7.36 (d, $J = 4.8$ Hz, 2H), 6.59 (t, $J = 55.8$ Hz, 1H); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -115.8 (d, $J = 55.6$ Hz, 2F).

4-(Difluoromethyl)-3-methyl-pyridine (4l)

The title compound was obtained from 3,4-lutidine following the procedure above (CH$_3$CN, 75 °C, 24 h). The yield and ratio of compounds (32%, mono-F/di-F = <1/>99) were determined by $^{19}$F NMR analysis using hexafluorobenzene (δ -163) as an internal standard. 4l was volatile, therefore purification by silica-gel column chromatography was difficult.

$^{19}$F NMR (376 MHz, CDCl$_3$, crude) $\delta$ -119.47 (d, $J = 57.9$ Hz, 2F); LRMS (Cl) calcd for C$_7$H$_2$F$_2$N [M+H]$^+$: 144.06, found: 144.15.

3-Bromo-4-(difluoromethyl)pyridine (4m)

The title compound was obtained from 3-bromo-4-picoline following the procedure above (CH$_3$CN, 75 °C, 10 h). The yield and ratio of compounds (90%, mono-F/di-F = <1/>99) were determined by $^{19}$F NMR analysis using benzotriazol fluoride as an internal standard. Purification by silica-gel column chromatography ($n$-hexane/EtOAc =10/1) gave the compound (15.1 mg, 73% yield) as a yellow liquid. The product is known and the following data are identical to those given in corresponding literature.$^{[2]}$

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.78 (s, 1H), 8.64 (d, $J = 5.2$ Hz, 1H), 7.52 (t, $J = 5.2$ Hz, 1H), 6.81 (t, $J = 54.0$ Hz, 1H); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -118.45 (d, $J = 53.0$ Hz, 2F).

3-Cyano-4-(difluoromethyl)pyridine (4n)

The title compound was obtained from 3-cyano-4-(methyl)pyridine following the procedure above (CH$_3$CN, 75 °C, 10 h). The yield and ratio of compounds (75%, mono-F/di-F = <1/>99) were determined by $^{19}$F NMR analysis using benzotriazol fluoride as an internal standard. Purification by silica-gel column chromatography ($n$-hexane/EtOAc =3/1) gave the compound (9.2 mg, 60% yield) as a yellow oil. The product is known and the following data are identical to those given in corresponding literature.$^{[6]}$
1H NMR (400 MHz, CDCl3) δ 9.01 (s, 1H), 8.97 (d, J = 3.6 Hz, 1H), 7.67 (d, J = 4.0 Hz, 1H), 6.88 (t, J = 42.8 Hz, 1H); 19F NMR (376 MHz, CDCl3) δ -116.1 (d, J = 40.2 Hz, 2F).

3,5-Dibromo-4-(difluoromethyl)pyridine (4o)

The title compound was obtained from 3,5-dibromo-4-methylpyridine following the procedure above (CH3CN, 75 °C, 10 h). The yield and ratio of compounds (71%, mono-F/di-F = <1/99) were determined by 19F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/EtOAc = 15/1) gave the compound (6.4 mg, 45% yield) as a colorless liquid, containing 10% of impurity at around -139 ppm in 19F NMR spectra.

1H NMR (400 MHz, CDCl3) δ 8.72 (s, 2H), 7.10 (t, J = 52.8 Hz, 1H); 19F NMR (376 MHz, CDCl3) δ -116.70 (d, J = 50.8 Hz, 2F); HRMS (ESI-TOF) calced for C6H3Br2F2NNa [M+H]+: 307.8498, found: 307.8501.

4-(Difluoromethyl)-2-(p-tolyl)pyridine (4p)

The title compound was obtained from 2-(p-tolyl)pyridine (0.20 mmol) following the procedure above (AcOEt, 75 °C, 24 h). The yield and the ratio of compounds (40%, mono-F/di-F = <1/99) were determined by 19F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/EtOAc = 6/1) gave the compound (14.0 mg, 32% yield) as a colorless oil.

1H NMR (400 MHz, CDCl3) δ 8.79 (d, J = 4.8 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.81 (s, 1H), 7.26-7.32 (m, 3H), 6.69 (t, J = 56.0 Hz), 2.42 (s, 3H); 19F NMR (376 MHz, CDCl3) δ -115.47 (d, J = 57.5 Hz, 2F); 13C NMR (100 MHz, CDCl3) δ 158.58, 150.43, 143.04 (t, JCF = 23.0 Hz), 139.86, 135.83, 129.78, 127.01, 118.04, 116.46, 113.33 (t, JCF = 238.6 Hz), 21.47; HRMS (ESI-TOF) calced for C16H11F2NNa [M+Na]+: 242.0757, found: 242.0758.

4-(Difluoromethyl)quinoline (4s)

The title compound was obtained from 4-quinoline following the procedure above (AcOEt, 75 °C, 18 h). The yield and ratio of compounds (71%, mono-F/di-F = <1/99) were determined by 19F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/EtOAc = 8/1) gave the compound (5.5 mg, 58% yield) as a colorless oil. The product is known and the following data are identical to those given in corresponding literature.[7]

1H NMR (400 MHz, CDCl3) δ 9.02 (d, J = 4.8 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.80 (t, J = 7.2 Hz, 1H), 7.66 (t, J = 8.4 Hz, 1H), 7.60 (d, J = 4.4 Hz, 1H), 7.16 (t, J = 54.4 Hz, 1H); 19F NMR (376 MHz, CDCl3) δ -115.0 (d, J = 53.4 Hz, 2F).

9-(Difluoromethyl)acridine (4t)

The title compound was obtained from 9-methylacridine following the procedure above (CH3CN, 75 °C, 18 h). The yield and ratio of compounds (73%, mono-F/di-F = <1/99) were determined by 19F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/EtOAc = 10/1) gave the compound (11.7 mg, 51%
yield) as a yellow powder.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.45 (d, $J = 8.8$ Hz, 2H), 8.31 (d, $J = 8.8$ Hz, 2H), 7.95 (t, $J = 54.0$ Hz, 1H), 7.84 (t, $J = 7.6$ Hz, 2H), 7.67 (dd, $J = 8.6$, 6.6 Hz, 2H); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -108.39 (d, $J = 57.9$ Hz, 2F); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 148.91, 130.84, 130.69, 130.27, 123.48, 123.33, 112.85 (t, $J_{C-F} = 237.5$ Hz); HRMS (ESI-TOF) calcd for C$_{14}$H$_{10}$F$_2$N [M+H]$^+$: 230.0781, found: 230.0768.

2-(Chloromethyl)-4-(difluoromethyl)quinazoline (4u)

2-(Chloromethyl)-4-(difuoromethyl)quinazoline (0.050 mmol) following the procedure above (AcOEt, 75 °C, 18 h). The yield and ratio of compounds (54%, mono-F/di-F = 37/63) were determined by $^{19}$F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/ EtOAc =15/1) solely gave the difluorinated compound (3.6 mg, 31% yield) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.43 (d, $J = 8.4$ Hz, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 8.02 (t, $J = 7.6$ Hz, 1H), 7.77 (t, $J = 7.6$ Hz, 1H), 6.90 (t, $J = 54.0$ Hz, 1H), 4.92 (s, 2H); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -111.7 (d, $J = 53.4$ Hz, 2F); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 160.80, 160.21 (t, $J_{C-F} = 27.3$ Hz), 151.99, 135.08, 129.26, 129.23, 125.05 (t, $J_{C-F} = 3.3$ Hz), 119.61, 116.44 (t, $J_{C-F} = 242.9$ Hz), 47.09; HRMS (ESI-TOF) calcd for C$_{10}$H$_8$ClF$_2$N$_2$ [M+H]$^+$: 229.0344, found: 229.0355.

4-(3-Fluoro-3-pentyl)pyridine (5)

4-(3-Fluoro-3-pentyl)pyridine following the procedure above (CH$_3$CN, 50 °C, 2 h). The yield and ratio of compounds (92%) were determined by $^{19}$F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/ EtOAc =10/1) gave the compound (13.2 mg, 79% yield) as a yellow oil. 5 was not identified through ESI-MS (TOF, HRMS), but was identified through GC-MS (Cl, LRMS).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.55 (d, $J = 5.2$ Hz, 2H), 7.15 (d, $J = 4.8$ Hz, 2H), 1.76-2.01 (m, 4H), 0.75 (t, $J = 7.2$ Hz, 3H); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -167.99 (m, 1F); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 151.92 (d, $J_{C-F} = 19.2$ Hz), 149.83, 120.06 (d, $J_{C-F} = 7.7$ Hz), 99.45 (d, $J_{C-F} = 141.1$ Hz), 32.98 (d, $J_{C-F} = 19.2$ Hz), 7.52 (d, $J_{C-F} = 3.9$ Hz); LRMS (Cl) calcd for C$_{10}$H$_{12}$FN [M+H]$^+$: 168.12, found: 168.10.

2-(1-Fluoro-2-phenylpropyl)pyridine (7a)

The title compound was obtained from 2-(2-phenylpropyl)pyridine following the procedure above (CH$_3$CN, 75 °C, 18 h). The yield and ratio of compounds (42%, mono-F/di-F = >99/1) were determined by $^{19}$F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (CH$_2$Cl$_2$) gave the compound (6.5 mg, 30% yield) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.55 (d, $J = 5.2$ Hz, 1H), 7.72 (t, $J = 8.0$ Hz, 1H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.17-7.30 (m, 6H), 5.55 (ddd, $J = 48.0$, 8.0, 4.0 Hz, 1H), 2.77-2.87 (m, 2H), 2.22-2.39 (m, 2H); $^{19}$F-NMR (376 MHz, CDCl$_3$) $\delta$ -186.71 (m, 1F); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 159.73 (d, $J_{C-F} = 240.0$ Hz), 149.08 (d, $J_{C-F} = 3.0$ Hz), 141.22,
136.92, 128.62, 128.56, 126.12, 122.95, 119.82 (d, \( J_{C\text{=F}} = 7.0 \) Hz), 94.02 (d, \( J_{C\text{=F}} = 170.9 \) Hz), 37.69 (d, \( J_{C\text{=F}} = 22.0 \) Hz), 31.25 (d, \( J_{C\text{=F}} = 3.0 \) Hz); HRMS (ESI-TOF) calcd for C_{14}H_{12}FNNa [M+Na]^+: 238.1008, found: 238.1035.

7-Fluoro-6,7-dihydro-5H-cyclopenta[b]pyridine (7b)

The title compound was obtained from 6,7-dihydro-5H-cyclopenta[b]pyridine (0.20 mmol) following the procedure above (CH_{3}CN, 50 °C, 24 h). The yield and ratio of compounds (55%, mono-F/di-F = 96/4) were determined by \(^{19}\)F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/EtOAc =4/1) solely gave the monofluorinated compound (11.2 mg, 41% yield) as a brown oil. The product is known and the following data are identical to those given in corresponding literature.\(^8\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.55 (d, \( J = 4.0 \) Hz, 1H), 7.65 (d, \( J = 6.0 \) Hz, 1H), 7.23-7.26 (m, 1H), 5.94 (ddd, \( J = 44.8, 5.2, 2.0 \) Hz, 1H), 3.15-3.22 (m, 1H), 2.87-2.94 (m, 1H), 2.32-2.53 (m, 2H); \(^{19}\)F-NMR (376 MHz, CDCl\(_3\)) \( \delta \) -167.54 (m, 1F).

8-Fluoro-5,6,7,8-tetrahydroquinoline (7c)

The title compound was obtained from 5,6,7,8-tetrahydroquinoline following the procedure above (CH_{3}CN, 50 °C, 24 h). The yield and ratio of compounds (85%, mono-F/di-F = 95/5) were determined by \(^{19}\)F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/EtOAc =3/1) solely gave the monofluorinated compound (12.8 mg, 78% yield) as a yellow oil. The product is known and the following data are identical to those given in corresponding literature.\(^9\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.52 (d, \( J = 4.8 \) Hz, 1H), 7.47 (d, \( J = 8.0 \) Hz, 1H), 7.18-7.22 (m, 1H), 5.55 (d, \( J = 47.2 \) Hz, 1H), 2.69-2.88 (m, 2H), 2.35-2.40 (m, 1H), 1.92-2.08 (m, 2H), 1.81-1.91 (m, 1H); \(^{19}\)F-NMR (376 MHz, CDCl\(_3\)) \( \delta \) -163.00 (m, 1F).

2-(Fluoromethyl)pyridine (7d)

The title compound was obtained from 2-picoline following the procedure above (CH_{3}CN, 75 °C, 18 h). The yield and ratio of compounds (87%, mono-F/di-F = 98/2) were determined by \(^{19}\)F NMR analysis using benzotrifluoride (\( \delta \) -63) as an internal standard. Purification by silica-gel column chromatography (n-hexane/CH_{2}Cl\(_2\) =1/1 to 2/3) gave the compound including starting material. The product is known and the following peaks are found in correspond to the literature.\(^9\)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.56 (d, \( J = 4.4 \) Hz), 7.68-7.73 (m), 7.45 (d, \( J =7.6 \) Hz), 7.20-7.24 (m), 5.47 (d, \( J = 47.2 \) Hz); \(^{19}\)F-NMR (376 MHz, CDCl\(_3\)) \( \delta \) -221.41 (t, \( J = 46.2 \) Hz, 1F).

6-(Difluoromethyl)nicotinonitrile (8e)

The title compound was obtained from 6-methylnicotinonitrile following the procedure above (CH_{3}CN, 75 °C, 24 h). The yield and ratio of compounds (89%, mono-F/di-F = 56/44) were determined by \(^{19}\)F NMR analysis using benzotrifluoride as an internal standard. Purification by
silica-gel column chromatography (n-hexane/EtOAc =7/1) gave the difluorinated compound (5.4 mg, 35% yield) as a white powder. 8e was not identified through ESI-MS (TOF, HRMS), but was identified through GC-MS (CI, LRMS).

1H NMR (400 MHz, CDCl3) δ 8.94 (s, 1H), 8.14 (m, 1H), 7.80 (m, 1H), 6.67 (t, J = 55.2 Hz, 1H); 19F-NMR (376 MHz, CDCl3) δ -1.16.94 (d, J = 55.3 Hz, 2F); 13C-NMR (100 MHz, CDCl3) δ 156.08 (t, J_{C-F} = 19.8 Hz), 152.27, 140.99, 120.43 (t, J_{C-F} = 3.1 Hz), 115.87, 112.95 (t, J_{C-F} = 242.0 Hz), 111.98; LRMS (CI) calcd for C7H5F2N2 [M+H]+: 155.04, found: 155.00

Methyl 6-(difluoromethyl)nicotinate (8f)

The title compound was obtained from methyl 6-(methyl)nicotinate following the procedure above (CH3CN, 75 °C, 24 h). The yield and ratio of compounds (93%, mono-F/di-F = 57/43) were determined by 19F NMR analysis using benzotrifluoride as an internal standard. Purification by silica-gel column chromatography (n-hexane/EtOAc =3/1) gave the difluorinated compound (5.7 mg, 38% yield) as a white solid. The product is known and the following data are identical to those given in corresponding literature.[10]

1H NMR (400 MHz, CDCl3) δ 9.24 (s, 1H), 8.45 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 6.68 (t, J = 55.2 Hz, 1H), 3.99 (s, 3H); 19F-NMR (376 MHz, CDCl3) δ -116.52 (d, J = 57.9 Hz, 2F).

2-(Difluoromethyl)pyrazine (8h)

The title compound was obtained from 2-cyano-3-(methyl)pyridine following the procedure above (CH3CN, 75 °C, 24 h). The yield and ratio of compounds (7%, mono-F/di-F = <1/>99) were determined by 19F NMR analysis using hexafluorobenzene (δ -163) as an internal standard. 8h was not identified through ESI-MS (TOF, HRMS), but was identified through GC-MS (CI, LRMS).

19F-NMR (376 MHz, CDCl3, crude) δ -96.47 (d, J = 46.2 Hz, 2F); LRMS (CI) calcd for C5H3F2N2 [M+H]+: 131.04, found: 131.15.

S3-2. Direct Fluorination of Amino Acid Derivative 2v

To a mixture of Li2CO3 (7.4 mg, 0.10 mmol, 2.0 equiv.) and 2v (23.9 mg, 0.050 mmol) in AcOEt (0.1 M, 0.5 mL) was added NFC (46.2 mg, 0.40 mmol, 4.0 equiv.) at room temperature under N2 atmosphere. After stirring for 3 h at 50 °C, the yield and selectivity were determined by 19F NMR spectroscopy analysis using benzotrifluoride as an internal standard (89%, mono-F/di-F = <1/>99). The resulting crude mixture was purified by silica-gel column chromatography to give the products 4v (15.4 mg, 60 % yield) as a white solid.

1H NMR (400 MHz, CDCl3) δ 8.60 (d, J = 4.8 Hz, 2H), 7.77 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.37 (t, J = 3.2 Hz, 3H), 7.31 (t, J = 7.2 Hz, 2H), 7.20-7.26 (m, 4H), 5.77 (d, J = 9.2 Hz, 1H),

12
5.07-5.22 (m, 3H), 4.41 (dd, $J = 10.0$ Hz, 7.6 Hz, 1H), 4.33 (dd, $J = 10.0$ Hz, 6.8 Hz, 1H), 4.10-4.18 (m, 1H); $^{19}$F NMR (376 MHz, CDCl$_3$) δ -103.78 (d, $J = 251.9$ Hz, 1F), -105.65 (d, $J = 251.9$ Hz, 1F); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.11, 155.54, 150.28, 143.59, 141.44, 134.26, 129.04, 128.86, 128.80, 127.97, 127.26, 125.05, 120.19, 118.37 (t, $J = 250.5$ Hz), 68.50, 67.75, 59.06 (t, $J = 29.0$ Hz), 47.07, 21.18, 14.32; HRMS (ESI-TOF) calcd for C$_{30}$H$_{24}$F$_2$N$_2$O$_4$[M+Na]$^+$: 537.1602, found: 537.1609.

S3-3. Gram-Scale Synthesis

To a mixture of Li$_2$CO$_3$ (750 mg, 10.14 mmol, 2.0 equiv.) and 2b (1.0 g, 5.07 mmol) in CH$_3$CN (0.1 M, 50 mL) was added NFC (4.69 g, 20.28 mmol, 4.0 equiv.) at room temperature under N$_2$ atmosphere. After stirring for 10 h at 50 °C, the yield and selectivity (88%, mono-F/di-F = <1/99) were determined by $^{19}$F NMR spectroscopy analysis using benzotrifluoride as an internal standard. The resulting crude mixture was purified by silica-gel column chromatography to give the product 4b (70%).

S4. Mechanistic Studies

S4-1. Observation of Intermediates from Pyridine Derivative and NFC (Scheme 2a)

To a mixture of 4-(tert-butyl)pyridine (13.5 mg, 0.10 mmol) in CD$_3$CN (0.1 M, 1.0 mL) was added to NFC (23.1 mg, 0.10 mmol, 1.0 equiv.) at 25 °C under N$_2$ atmosphere and stirred for 30 min. The resulting crude mixture was analyzed by $^{19}$F NMR. The complete conversion from N-F of NFC (-47 ppm) to intermediate (-132 ppm) was observed, while RSO$_2$-F was almost not changed. Under the same conditions, NFSI instead of NFC gave no chemical shift.

S4-2. Observation of intermediates from pyridine derivative and NFC in various solvents

To a mixture of 4-(tert-butyl)pyridine (13.5 mg, 0.10 mmol) in solvent (0.1 M, 1.0 mL) was added to NFC (23.1 mg, 0.10 mmol, 1.0 equiv.) at 25 °C under N$_2$ atmosphere and stirred for 30 min. The resulting crude mixture was analyzed by $^{19}$F NMR.
S4-3. Comparison in formation of intermediates from other pyridine derivatives

To a mixture of pyridines (0.050 mmol) in CH$_3$CN (0.1 M, 0.5 mL) was added NFC (0.050 mmol, 1.0 equiv.) at shown temperature under N$_2$ atmosphere and stirred for shown time. The resulting crude mixture was analyzed by $^{19}$F NMR.

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<th>Temp. [°C]</th>
<th>Time [h]</th>
<th>Ratio of NFC / intermediate in $^{19}$F NMR</th>
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<tr>
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<td>6</td>
<td>79 / 21</td>
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<td>50</td>
<td>18</td>
<td>97 / 3</td>
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</table>
S4-4. Characterization as N-acylated dihydropyridine species (Scheme 2b)[11]

\[ \begin{array}{c}
\text{N} \\
\text{O} \\
\text{O} \\
\text{N} \\
\end{array} + \begin{array}{c}
\text{N} \\
\text{O} \\
\text{N} \\
\text{O} \\
\end{array} \xrightarrow{\text{CH}_2\text{Cl}_2, 0 \, ^\circ \text{C}, 0.5 \, \text{h}} \begin{array}{c}
\text{N} \\
\text{O} \\
\text{O} \\
\text{N} \\
\end{array}
\]

To a mixture of 4-(tert-butyl)pyridine (13.5 mg, 0.10 mmol) in \( \text{CH}_2\text{Cl}_2 \) (0.1 M, 1.0 mL) was added NFC (23.1 mg, 0.10 mmol, 1.0 equiv.) at 0 °C under \( \text{N}_2 \) atmosphere and stirred for 30 min. MeMgl (0.2 mL, 0.4 mmol, 4.0 equiv., 2M in diethyl ether) was added at -78 °C, stirred for 30 min in ice bath, subsequently analyzed by \( ^{19}\text{F} \) NMR using hexafluoro-p-xylene as internal standard (43% NMR yield). Resulting crude mixture was quenched by \( \text{H}_2\text{O} \), extracted with \( \text{CH}_2\text{Cl}_2 \), combined organic layer was dried with Na\(_2\)SO\(_4\), then evaporated under reduced pressure. Resulting crude mixture was purified by silica-gel column chromatography to give the product (31% yield).

\(^1\text{H} \) NMR (400 MHz, (CD\(_3\))\(_2\)CO) \( \delta \) 6.70 (d, \( J = 8.0 \) Hz, 1H), 5.40-5.46 (m, 1H), 5.36 (d, \( J = 6.0 \) Hz, 1H), 4.79 (quin, \( J = 6.4 \) Hz, 1H), 3.83 and 3.88 (brs, 2H, 2 rotamers), 1.06 (s, 9H), 0.98 (brs, 12H); \(^{13}\text{C} \) NMR (100 MHz, (CD\(_3\))\(_2\)CO) \( \delta \) 154.62 and 153.75 (2 rotamers), 142.33 and 142.14 (2 rotamers), 125.57 and 124.79 (2 rotamers), 116.26 and 116.18 (2 rotamers), 106.13, 75.87, 49.63 and 49.35 (2 rotamers), 34.10, 32.30, 29.22, 26.86, 19.95 and 19.16 (2 rotamers); HRMS (ESI-TOF) calcd for C\(_{16}\)H\(_{27}\)NNaO\(_2\) [M+Na]\(^+\): 288.1940, found: 288.1951.
S4-5. Observation of N-Fluoro-sulfonamide anion species

![N-Fluoro-sulfonamide anion species](image)

To a mixture of NaHNF (22.0 mg, 0.10 mmol) in CH$_3$CN (0.1 M, 1.0 mL) was added base (0.10 mmol) at -78 °C under N$_2$ atmosphere and stirred for 30 min at 25 °C. The resulting crude mixture was analyzed by $^{19}$F NMR.

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<th>Comment</th>
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<td>Chemical shift change (-93 → -134 ppm)</td>
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<tr>
<td>2</td>
<td>KHMDS (in 0.5 M toluene)</td>
<td>Chemical shift change (-93 → -127 ppm)</td>
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</table>
S4-6. Reaction ratio from non-/monofluorinated pyridine derivatives (Scheme 3)

To a mixture of Li$_2$CO$_3$ (14.8 mg, 0.20 mmol, 2.0 equiv.) and 2b (19.7 mg, 0.10 mmol) in CH$_3$CN (0.1 M, 1.0 mL) was added NFC (0.40 mmol) at room temperature under N$_2$ atmosphere. After stirring for shown time at 50 °C, the yield and selectivity were monitored by $^{19}$F NMR spectroscopy analysis using benzotrifluoride as an internal standard.

To a mixture of Li$_2$CO$_3$ (7.4 mg, 0.10 mmol, 1.0 equiv.) and 3b (21.5 mg, 0.10 mmol) in CH$_3$CN (0.1 M, 1.0 mL) was added NFC (0.20 mmol) at room temperature under N$_2$ atmosphere. After stirring for 0.5 h at 50 °C, the yield and selectivity were monitored by $^{19}$F NMR spectroscopy analysis using benzotrifluoride as an internal standard.
S5. NMR Spectra

- $^1$H NMR (CDCl$_3$)
  - Compound $4a$

- $^{19}$F NMR (CDCl$_3$)
  - Compound $4a$
4l

(δ -119.47, d,
J = 57.9 Hz, 2F)

C\textsubscript{6}F\textsubscript{6} (IS)

R\textsuperscript{2}SO\textsubscript{2}-F

crude \textsuperscript{19}F NMR (CDCl\textsubscript{3})

ROCOF
crude $^{19}$F NMR (CDCl$_3$)

R'SO$_2$F

ROCOF

8i

($\delta$ -96.47, d, $J = 46.2$ Hz, 2F)

NFC (N-F)

C$_2$F$_6$ (IS)
S6. References


