Hindered dialkyl ether synthesis with electrogenerated carbocations

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Hindered Dialkyl Ether Synthesis with Electrogenerated Carbocations

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<td>Compound 108</td>
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Compound 141 $^{13}$C NMR ........................................................................................................ 432
Compound SI-7 $^1$H NMR ........................................................................................................ 433
Compound SI-7 $^{13}$C NMR ........................................................................................................ 434
Compound SI-16 $^1$H NMR ........................................................................................................ 435
Compound SI-16 $^{13}$C NMR ........................................................................................................ 436
Compound SI-17 $^1$H NMR ........................................................................................................ 437
Compound SI-17 $^{13}$C NMR ........................................................................................................ 438
Compound SI-18 $^1$H NMR ........................................................................................................ 439
Compound SI-18 $^{13}$C NMR ........................................................................................................ 440
Compound SI-19 $^1$H NMR ........................................................................................................ 441
Compound SI-19 $^{19}$F NMR ........................................................................................................ 442
Compound SI-19 $^{13}$C NMR ........................................................................................................ 443
Compound SI-20 $^1$H NMR ........................................................................................................ 444
Compound SI-20 $^{19}$F NMR ........................................................................................................ 445
Compound SI-20 $^{13}$C NMR ........................................................................................................ 446
A Survey of Electrochemical Decarboxylative Etherification

<table>
<thead>
<tr>
<th><strong>Compound</strong></th>
<th><strong>Reagents</strong></th>
<th><strong>Conditions</strong></th>
<th><strong>Yield</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{NaOMe}$ or $\text{NaOAc}, \text{MeOH}$</td>
<td>2.6 F/mol, 0°C</td>
<td>60-95% yield</td>
</tr>
<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{Pt(+)/Pt(-)}$, 1 A</td>
<td></td>
<td></td>
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<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{NaOMe}$ or $\text{NaOAc}, \text{MeOH}$</td>
<td>2.6 F/mol, 275 mA/cm</td>
<td>&gt;95% yield</td>
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<td>$\text{R} \text{COOH}$</td>
<td>$\text{Et}_2\text{NMeOH}$, Pt(+)/Pt(-), 200-250 mA/cm$^2$</td>
<td>0°C, 79%/73% yield</td>
<td></td>
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<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{NaOMe}$ or $\text{NaOAc}, \text{MeOH}$</td>
<td>2.6 F/mol, 100 mA/cm$^2$</td>
<td>70-93% yield</td>
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<td>$\text{R} \text{COOH}$</td>
<td>$\text{Pt(+)/Pt(-)}$, 1 A</td>
<td></td>
<td></td>
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<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{NaOMe}$ or $\text{NaOAc}, \text{MeOH}$</td>
<td>2.6 F/mol, 275 mA/cm</td>
<td>&gt;95% yield</td>
</tr>
<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{Pt(+)/Pt(-)}$, 1 A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{NaOMe}$ or $\text{NaOAc}, \text{MeOH}$</td>
<td>2.6 F/mol, 275 mA/cm</td>
<td>&gt;95% yield</td>
</tr>
<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{Pt(+)/Pt(-)}$, 1 A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{NaOMe}$ or $\text{NaOAc}, \text{MeOH}$</td>
<td>2.6 F/mol, 275 mA/cm</td>
<td>&gt;95% yield</td>
</tr>
<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{Pt(+)/Pt(-)}$, 1 A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{NaOMe}$ or $\text{NaOAc}, \text{MeOH}$</td>
<td>2.6 F/mol, 275 mA/cm</td>
<td>&gt;95% yield</td>
</tr>
<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{Pt(+)/Pt(-)}$, 1 A</td>
<td></td>
<td></td>
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<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{NaOMe}$ or $\text{NaOAc}, \text{MeOH}$</td>
<td>2.6 F/mol, 275 mA/cm</td>
<td>&gt;95% yield</td>
</tr>
<tr>
<td>$\text{R} \text{COOH}$</td>
<td>$\text{Pt(+)/Pt(-)}$, 1 A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure S1: A Survey of Electrochemical Decarboxylative Etherification
General Experimental

Tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), N,N-dimethylformamide (DMF), and acetonitrile (CH$_3$CN) were obtained by passing the previously degassed solvents through an activated alumina column. AgPF$_6$ was purchase from Alfa Aesar (lot #I17M26). AgClO$_4$ anhydrous was purchase from Alfa Aesar (lot #Y20D047). AgSbF$_6$ was purchase from Oakwood (lot #007268). "Bu$_4$NPF$_6$ was purchased from Oakwood (lot #A034292920). "Bu$_4$NCIO$_4$ (>98%) was purchased from TCI (Product #T0836). 3Å molecular sieves were purchased from Acros Organics (catalog lot #A034292920) and activated under flame dry for 30 min prior to use. 2,4,6-collidine (99%) was purchased from Sigma-Aldrich (batch # 13925DD). AgClO$_4$ was grinded prior to use. All the other reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous material. TLC was performed using 0.25 mm E. Merck Silica plates (60F-254), using short-wave UV light for visualization, and phosphomolybdic acid, Ce(SO$_4$)$_2$, acidic ethanolic anisaldehyde, or KMnO$_4$ as developing agents upon heating. NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 instruments and are calibrated using residual undeuterated solvent (CHCl$_3$ at 7.26 ppm 1H NMR, 77.16 ppm 13C NMR). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was performed using E. Merck silica gel (60, particle size 0.043–0.063 mm). High-resolution mass spectra (HRMS) were recorded on Waters LC with G2-XS TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. GCMS (EI) was recorded on Agilent 7820A GC systems and 5975 Series MSD. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected. The enantiomeric excesses were determined with Waters UPC$^2$ SFC equipped with a photodiode array detector or an Agilent Technologies 1220 Infinity II LC HPLC. Optical rotations were recorded on a Rudolph Research Analytical Autopol III Automatic Polarimeter.
List of Carboxylic Acids Substrates and References for Their Preparation.

CAS no.: 826-55-1

CAS no.: 189321-63-9

CAS no.: 58148-13-3

CAS no.: 33315-63-8

CAS no.: 36881-14-8

CAS no.: 32936-76-8

CAS no.: 24463-41-0
Ref: Patent WO 2018086592

CAS no.: 1510754-94-5

CAS no.: 33315-63-8

CAS no.: 81655-41-6

CAS no.: 5217-05-0
Ref: ACIE 2014, 53, 4945.

CAS no.: 15448-77-8

CAS no.: 2840-74-6

CAS no.: 884512-77-0

CAS no.: 80-23-8

CAS no.: 10276-09-2
Ref: JACS, 2018, 140, 16610.

CAS no.: 18720-35-9

CAS no.: 13511-38-1

CAS no.: 2271155-09-8
Ref: ACIE 2019, 58, 2134.

CAS no.: 909187-36-6
Ref: Patent WO 2006094187
Optimization of Reaction Parameters for Electrochemical Decarboxylative Etherification

All optimization reactions were carried out on 0.20 mmol scale. The crude reaction mixture was analyzed by GC/FID using n-dodecane as internal standard.

Starting conditions

```
\begin{align*}
\text{Me} & \text{CO}_2\text{H} + \text{HO} & \overset{\text{Et}_3\text{N (3.0 equiv.)}}{\overset{\text{DMF or acetone, r.t.}}{\overset{+C/-C, 10 mA, 3 h}}\text{Me} & \text{CO}_2\text{Me}} \\
3 & 4 & \text{5} & <1 \text{ yield}
\end{align*}
```

Primary evaluation of bases and electrolyte (Table S1)

<table>
<thead>
<tr>
<th>entry</th>
<th>electrolyte</th>
<th>base</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu_4NClO_4</td>
<td>K_2CO_3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>Bu_4NClO_4</td>
<td>DBU</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>Bu_4NClO_4</td>
<td>2,4,6-collidine</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Bu_4NPF_6</td>
<td>2,4,6-collidine</td>
<td>6</td>
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Evaluation of solvents (Table S2)

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<th>solvent</th>
<th>yield (%)</th>
</tr>
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<tr>
<td>1</td>
<td>Bu_4NClO_4</td>
<td>CH_3CN</td>
<td>27</td>
</tr>
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<td>2</td>
<td>Bu_4NClO_4</td>
<td>THF</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Bu_4NClO_4</td>
<td>PhCF_3</td>
<td>38</td>
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<td>4</td>
<td>Bu_4NClO_4</td>
<td>acetone</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Bu_4NClO_4</td>
<td>CH_2Cl_2</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>Bu_4NClO_4</td>
<td>CICH_2CH_2Cl</td>
<td>47</td>
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<tr>
<td>7</td>
<td>Bu_4NPF_6</td>
<td>CH_2Cl_2</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>Bu_4NPF_6</td>
<td>CICH_2CH_2Cl</td>
<td>42</td>
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</tbody>
</table>

Further evaluation of electrolytes (Table S3)

![Reaction Scheme]

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<tr>
<td>1</td>
<td>LiClO₄</td>
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<tr>
<td>2</td>
<td>n-Bu₄NOTs</td>
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</tr>
<tr>
<td>3</td>
<td>Et₄NCl</td>
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</table>

Further evaluation of bases (Table S4)

![Reaction Scheme]

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<th>base</th>
<th>yield (%)</th>
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<tr>
<td>1</td>
<td>t-BuOK</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>KOH</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>NaOAc</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>DBU</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>TMG</td>
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</tr>
<tr>
<td>6</td>
<td>2,6-lutidine</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>DABCO</td>
<td>&lt;1</td>
</tr>
<tr>
<td>8</td>
<td>DMAP</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>2,6-di-tert-butylpyridine</td>
<td>6</td>
</tr>
</tbody>
</table>

Adding 3Å molecular sieves

![Reaction Scheme]

^nBu₄NClO₄: 62% yield
^nBu₄NPF₆: 43% yield
Evaluation of additives (Table S5)

<table>
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<tr>
<th>entry</th>
<th>additive (1.5 equiv.)</th>
<th>yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>K₃Fe(CN)₆</td>
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</tr>
<tr>
<td>2</td>
<td>MnCO₃</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>ZnO</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>K$_2$SbF$_6$</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>Ag$_2$SO$_4$</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>AgPF$_6$</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>AgBF$_4$</td>
<td>72</td>
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<tr>
<td>8</td>
<td>Ag$_2$O</td>
<td>64</td>
</tr>
<tr>
<td>9</td>
<td>AgClO$_4$</td>
<td>81(78)</td>
</tr>
<tr>
<td>10</td>
<td>AgClO$_4$ (0.3 equiv.)</td>
<td>63</td>
</tr>
</tbody>
</table>

* Isolated yield

However, under the aforementioned optimized conditions for 2-methyl-2-phenylpropanoic acid 3, decarboxylative etherification of 2,2-dimethylbutanoic acid 3b proceeded in low yield.

In order to identify a more general set of conditions, further optimization efforts were undertaken on 2,2-dimethylbutanoic acid 3b.

Evaluation of additives using $^n$Bu$_4$NPF$_6$ as electrolyte (Table S6)
<table>
<thead>
<tr>
<th>entry</th>
<th>Additive (1.5 equiv.)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Br₂</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>KClO₄</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>KPF₆</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>AgPF₆</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>AgSbF₆</td>
<td>62(62)a</td>
</tr>
<tr>
<td>7</td>
<td>KSBF₆</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>NaSbF₆</td>
<td>46</td>
</tr>
</tbody>
</table>

*a Isolated yield

This optimized set of conditions for the decarboxylative etherification of non-benzylic carboxylic acid 3b was more general, and was also suitable for 2-methyl-2-phenylpropanoic acid 3.

Control experiments (Table S7)

<table>
<thead>
<tr>
<th>entry</th>
<th>Variation from standard conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No AgPF₆</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>No 3Å molecular sieves</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>No 2,4,6-collidine</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>No electric current</td>
<td>0</td>
</tr>
</tbody>
</table>
Reoptimization for compound 25 (Table S8)

\[
\begin{array}{ccc}
\text{entry} & \text{Variation from standard conditions} & \text{yield (\%)} \\
1 & \text{no deviation} & 24^a \\
2 & 2 \text{mL CH}_2\text{Cl}_2 & 32 \\
3 & 1.5 \text{mL CH}_2\text{Cl}_2 & 34 \\
4 & 1 \text{mL CH}_2\text{Cl}_2 & 25 \\
5 & 1.5 \text{mL CH}_2\text{Cl}_2, I = 7.5 \text{ mA}, 4 \text{ h} & 45(43)^a \\
6 & 1.5 \text{mL CH}_2\text{Cl}_2, I = 5 \text{ mA}, 6 \text{ h} & 36 \\
\end{array}
\]

\(^a\) Isolated yield

CH\(_2\)Cl\(_2\) Cathodic reduction

Conditions: 0.1 M \(\text{\(n\)}\text{Bu}_{4}\text{NPF}_6\), CH\(_2\)Cl\(_2\) solvent, GC working /Pt counter electrode, Ag/AgCl reference electrode. Scan rate = 200 mV/s.

**Figure S2:** The cathodic potential of the reaction of 3 and 4 was measured as -2.2 V against Ag/AgCl reference electrode, which is in agreement with the reduction of CH\(_2\)Cl\(_2\) observed in the cyclic voltammetric study.
Optimization of Reaction Parameters for Electrochemical Decarboxylative Hydroxylation

All optimization reactions were carried out on 0.20 mmol scale. The crude reaction mixture was analyzed by GC/FID using n-dodecane as internal standard.

<table>
<thead>
<tr>
<th>entry</th>
<th>base (3 eq)</th>
<th>[Ag]</th>
<th>H₂O</th>
<th>solvent</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,4,6-collidine</td>
<td>-</td>
<td>0.1 mL</td>
<td>CH₂Cl₂ 3 mL</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>2,4,6-collidine</td>
<td>Ag₂O (1.5 eq)</td>
<td>0.1 mL</td>
<td>CH₂Cl₂ 3 mL</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>Cs₂CO₃</td>
<td>Ag₂O (1.5 eq)</td>
<td>0.1 mL</td>
<td>CH₂Cl₂ 3 mL</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>2,4,6-collidine</td>
<td>Ag₂O (1.5 eq)</td>
<td>0.1 mL</td>
<td>MeCN 3 mL</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>2,4,6-collidine</td>
<td>Ag₂O (1.5 eq)</td>
<td>0.1 mL</td>
<td>DMF 3 mL</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>2,4,6-collidine</td>
<td>Ag₂O (1.5 eq)</td>
<td>0.1 mL</td>
<td>Dioxane 3 mL</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>2,4,6-collidine</td>
<td>Ag₂O (1.5 eq)</td>
<td>0.1 mL</td>
<td>Acetone 3 mL</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>2,4,6-collidine</td>
<td>-</td>
<td>0.1 mL</td>
<td>Acetone 3 mL</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>2,4,6-collidine</td>
<td>AgClO₄ (3 eq)</td>
<td>0.1 mL</td>
<td>Acetone 3 mL</td>
<td>39</td>
</tr>
<tr>
<td>10</td>
<td>2,4,6-collidine</td>
<td>-</td>
<td>0.5 mL</td>
<td>Acetone 2.5 mL</td>
<td>49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>H₂O</th>
<th>electrolyte</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,4,6-collidine (3 eq)</td>
<td>0.2 mL</td>
<td>tBu₄NCIO₄</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>2,4,6-collidine (3 eq)</td>
<td>0.3 mL</td>
<td>tBu₄NCIO₄</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>2,4,6-collidine (3 eq)</td>
<td>0.1 mL</td>
<td>tBu₄NCIO₄</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>2,4,6-collidine (1.5 eq)</td>
<td>0.1 mL</td>
<td>tBu₄NCIO₄</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>2,4,6-collidine (4.5 eq)</td>
<td>0.1 mL</td>
<td>tBu₄NCIO₄</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>2,4,6-collidine (1.5 eq)</td>
<td>0.1 mL</td>
<td>tBu₄NPF₆</td>
<td>75(70)</td>
</tr>
<tr>
<td>7</td>
<td>2,4,6-collidine (1.5 eq)</td>
<td>0.1 mL</td>
<td>Et₄NOTs</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>2,4,6-collidine (1.5 eq)</td>
<td>0.1 mL</td>
<td>tBu₄NF·H₂O</td>
<td>47</td>
</tr>
</tbody>
</table>

*a* Isolated yield
General Procedure for Electrochemical Decarboxylative Etherification (General Procedure A, Carboxylic Acid as Limiting Reagent):

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with carboxylic acid (42.4 mg, 0.2 mmol, 1 equiv.), alcohol (44.4 mg, 0.6 mmol, 3 equiv.), 2,4,6-collidine (72.6 mg, 0.6 mmol, 3 equiv.), "Bu4NPF6 (116 mg, 0.3 mmol, 1.5 equiv.), 3 Å molecular sieves (150 mg), AgPF6 (76 mg, 0.3 mmol, 1.5 equiv.), and CH2Cl2 (3.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. After pre-stirring for 15 minutes, the reaction mixture was electrolyzed at a constant current of 10 mA for 3 hours. The ElectraSyn vial cap was removed, and electrodes were rinsed with Et2O (2 mL), which was combined with the crude mixture. Then, the crude mixture was further diluted with Et2O (30 mL). The resulting mixture was washed with 2N HCl (20 mL) (for products containing pyridine moiety, washing with 2N HCl is omitted) and NaHCO3 (aq) (20 mL), dried over Na2SO4, and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) to furnish the desired product.

Graphical Guide for Electrochemical Decarboxylative Etherification:

Setting Up the ElectraSyn Device

Left: select “New Experiment”. Center: select “Constant Current”. Right: set the current to 10 mA (for a 0.2 mmol scale).
Left: no need to use a reference electrode. Center: choose “Time”. Right: set reaction time to 3h.

Left: 0.2 mmol of carboxylic acid substrate was used. Center: no alternate polarity. Right: Saving data is up to the individual.

Left: all reagents for this reaction. Center: carboxylic acid (42.4 mg). Right: t-BuOH (44.4 mg).
Left: AgPF₆ (76 mg). Center: "Bu₄NPF₆ (116 mg). Right: 3Å MS (150 mg).

Left: 2,4,6-collidine (72 mg). Center: CH₂Cl₂ from solvent system. Right: CH₂Cl₂ (3 mL).

Left: after adding CH₂Cl₂ to the vial. Center: graphite electrodes. Right: pre-stir for 15 min.
Left: start the reaction on the ElectraSyn 2.0 with a stirring speed of 700 rpm. Center: reaction completed. Right: transfer reaction mixture to a separatory funnel with Et₂O. Then the organic phase was washed with 2N HCl (aq) and sat. NaHCO₃ (aq).

Left: dried over Na₂SO₄. Center: filter off Na₂SO₄. Right: crude TLC (Hexanes: Et₂O = 100:1), top spot is the product.

Left: purified by PTLC (Hexanes: Et₂O = 100:1) Center: removal of solvent. Right: weight of vial containing product (31.0 mg, 65% yield).
Note: For volatile ether products, a rotary evaporator was operated over a water bath at 20 °C, and a high vacuum pump was avoided during the whole workup sequence.

General Procedure for Electrochemical Decarboxylative Etherification (General Procedure B, Alcohol as Limiting Reagent):

Electrochemical Decarboxylative Etherification: With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with carboxylic acid SI-3 (0.45 mmol, 3 equiv.), alcohol SI-2 (0.15 mmol, 1 equiv.), 2,4,6-collidine (81.6 mg, 0.675 mmol, 4.5 equiv.), 4Bu4NClO4 (137 mg, 0.4 mmol, 0.2 M), 3 Å molecular sieves (100 mg), AgClO4 (124 mg, 0.6 mmol, 4 equiv.), and CH2Cl2 (2.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. After pre-stirring for 15 minutes, the reaction mixture was electrolyzed under a constant current at 10 mA for 3 hours. The ElectraSyn vial cap was removed, and electrodes were rinsed with Et2O (2 mL), which was combined with crude mixture. Then, the crude mixture was further diluted with Et2O (30 mL). The resulting mixture was washed with 2N HCl (20 mL) (for products containing pyridine moiety, washing with 2N HCl is omitted) and NaHCO3(aq) (20 mL), dried over Na2SO4, and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) to furnish the desired product.

General Procedure for Electrochemical Decarboxylative Hydroxylation: (General Procedure C):

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with carboxylic acid SI-4 (28.4 mg, 0.2 mmol, 1 equiv.), 2,4,6-collidine (36.3 mg, 0.3 mmol, 1.5 equiv.), 4Bu4NPF6 (114 mg, 0.3 mmol, 0.1M), acetone (3.0 mL), and H2O (0.1 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted
into the mixture. After pre-stirring for 5 minutes, the reaction mixture was electrolyzed under a constant current of 10 mA for 3 hours. The ElectraSyn vial cap was removed and electrodes were rinsed with Et₂O (2 mL). The resulting solution was diluted with Et₂O (40 mL), and then washed with saturated aqueous NH₄Cl (20 mL) and brine (20 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) to furnish the desired product. (Note: an empty balloon is attached for a large scale reaction to balance the pressure resulting from the H₂ generation on the cathode).

**Graphic Procedure for Electrochemical Decarboxylative Hydroxylation:**

![Graphic Procedure](image)

Left: all reagents for hydroxylation reaction. Center: carboxylic acid (28.5 mg, 0.2 mmol). Right: "Bu₄NPF₆ (114 mg, 0.3 mmol).

![Graphic Procedure](image)

Left: 2,4,6-collidine (36.3 mg, 0.3 mmol). Center: acetone used in this reaction. Right: acetone (3 mL).
Left: H₂O (0.1 mL). Center: graphite electrode. Right: pre-stir the reaction mixture for 5 min.

Left: start the reaction on the ElectraSyn 2.0. Center: reaction completed. Right: crude TLC (Hexanes: EtOAc = 3:1).

Left: dilute with Et₂O (30 mL) and washed with sat. NH₄Cl (aq). Center: washed with brine. Right: dried over Na₂SO₄ and filtered.
Left: concentrated *in vacuo*. Center: purified by PTLC. Right: weight of vial containing product (16.0 mg, 70% yield).

**Experimental Procedure for Gram-Scale Electrochemical Decarboxylative Etherification**

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Ph-} & \quad \text{CO}_2\text{H} \\
\text{3} & \\
+ & \\
\text{HO} & \quad \text{Me} \\
\text{Ph} & \quad \text{Ph} \\
\text{4} & \\
\xrightarrow{2,4,6\text{-collidine, } 3\text{Å MS, } \text{Bu}_4\text{NClO}_4\text{, } +C/-C, 10 \text{ mA, rt, 15 h}} & \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{5} & \\
\end{align*}
\]

Left: reagents for etherification reaction. Center: ElectraSyn vials (25 mL). Right: Tare of the vial.
Left: 3 (394 mg, 2.4 mmol). Center: 4 (880 mg, 7.2 mmol). Right: 2,4,6-collidine (436 mg, 3.6 mmol)

Left: nBu₄NClO₄ (308 mg, 0.9 mmol). Center: 3 Å molecular sieves (450 mg). Right: CH₂Cl₂ (9 mL)

Left: after adding CH₂Cl₂ and equipped with graphite electrodes for 5 reactions. Center: After pre-stirring for 30 minutes, start the reaction on the ElectraSyn device (after 1 min). Right: reaction completed (15h).
Left: crude TLC (Hexanes: Et<sub>2</sub>O=30:1). Center: the suspension of 5 reactions was diluted with Et<sub>2</sub>O and washed with 1 N HCl. Right: dried over Na<sub>2</sub>SO<sub>4</sub>.

Left: column chromatography purification. Center: weight of empty flask. Right: weight of flask containing product (2.08 g, 72% yield).

Experimental Procedure for Gram-Scale Electrochemical Decarboxylative Hydroxylation

![Chemical reaction diagram]

Left: reagents for hydroxylation reaction. Center: ElectraSyn vials (25 mL). Right: Tare of the vial.
Left: 71 (254 mg, 1.2 mmol). Center: "Bu₄NPF₆ (139 mg, 0.36 mmol). Right: 2,4,6-collidine (218 mg, 1.8 mmol)

Left: after adding all reagents for 6 reactions. Center: acetone used in this reaction. Right: acetone (9 mL)

Left: after adding solvent and H₂O, and equipped with graphite electrodes. Center: reaction completed (12h). Right: crude TLC (Hexanes: EtOAc= 4:1).
Left: adding Et$_2$O to dilute 6 reactions and filtered, rinsed with Et$_2$O. Center: column chromatography purification. Right: weight of empty flask.

After purification. (864 mg, 65% yield).
Figure S3: <sup>a</sup>AgClO₄ (0.6 mmol) instead of AgPF₆, <sup>b</sup>°Bu₄NClO₄ (0.1 M) instead of °Bu₄NPF₆, <sup>c</sup>AgSbF₆ (0.3 mmol) instead of AgPF₆, DBU (0.6 mmol) instead of 2,4,6-collidine. <sup>d</sup>4.0 or 6.0 equiv. alcohol. <sup>e</sup>Alcohol as limiting reagent, conditions: alcohol (0.15 mmol), carboxylic acid (0.45 mmol), AgClO₄ (0.6 mmol), 2,4,6-collidine (0.675 mmol), °Bu₄NClO₄ (0.2 M), 3Å MS (100 mg), CH₂Cl₂ (2 mL), I = 10 mA, 3 h.
Unsuccessful and Challenging Substrates for Decarboxylative Etherification and Hydroxylation

**Figure S4:** "AgClO₄ (0.6 mmol) instead of AgPF₆, "BuNClO₄ (0.1 M) instead of "Bu₄NPF₆, "AgSbF₆ (0.3 mmol) instead of AgPF₆, DBU (0.6 mmol) instead of 2,4,6-collidine.

**Mechanistic Probes and Kinetic Study**

**Discussion**

**Figure S5.** (A) Probe substrates verify the intermediacy of carbocations through well-known rearrangement pathways; and (B) Kinetic and mechanistic analysis of the process, variable time normalization analysis (VTNA) method used to determine first order dependence on current (left).
Subjection of acids containing cyclobutane (96), β-alkoxy (98), and bridged substituents (100) gave rise to products that would be expected from a thermodynamically-favored ring contraction (to 97), a 1,2-hydride shift (to 99), and strain release (to 101), respectively (Figure S5 A). These studies, combined with the scope limitations (vide supra) and observation of 18O labeling (Table 2, substrate 81), confer confidence in the intermediacy of electrogenerated carbocation formation as postulated in Figure S5.

In addition to these probe experiments, a series of kinetic studies was undertaken on the model reaction (Figure 1C) to shed light on the rate-determining step, as well as the role of the silver additive (Figure S5 B). The reaction rate was found to be proportional to the current employed Figure S5 B, left) in the presence or absence of silver salt, indicating that a reaction occurring at the electrode is either involved in, or occurs before, the rate-determining step1,2. Accordingly, the rate of product formation exhibits zero-order kinetics in concentrations of both acid and alcohol substrates under the standard conditions of 10 mA current. At higher currents, the reactions on the electrode surface become fast enough, and chemical steps not associated with the electrode begin to contribute to the observed rate of product formation. Hence, at 15 mA, the reaction remains zero-order in [acid] but begins to show positive rate dependence on the concentration of alcohol (Figure S5 B, center), suggesting that carbocation capture contributes to the rate. Regarding the role of silver salt, it appears—consistent with original optimization efforts—that Ag⁺ suppresses the formation of elimination (α-methylstyrene 7) byproducts (See details below for studies investigating the role of silver in the reaction). In summary, the mechanism is likely to be the rate-limiting oxidation of a carboxylate on the anode to generate a carbocation, followed by nucleophilic attack by an alcohol to afford the ether product (Figure S5 B, right).

References:

General procedure
To a 10 mL ElectraSyn vial equipped with stir bar was added 2-methyl-2-phenylpropionic acid 3 (32.8 mg, 0.2 mmol), AgClO₄ (anhydrous, 124 mg, 0.6 mmol), nBu₄NClO₄ (103 mg, 0.3 mmol)
and 150 mg 3 Å molecular sieves (powder, flame-dried under vacuum). Dichloromethane (dry, 6 mL) was added to the vial, followed by 1-phenylethanol 4 (94 μL, 0.8 mmol) and 2,4,6-collidine (80 μL, 0.6 mmol). The vial cap, equipped with two graphite electrodes, was tightened and the mixture was subjected to 10 mA constant current conditions at a stir speed of 1000 rpm for 90 minutes during which aliquots (20 μL) were removed at indicated times.

**Sample preparation**

Each aliquot was injected into a filter vial housing and a solution of 4,4’-di-tert-butylbiphenyl in acetonitrile (0.5 mL, 1 mM) was added, the filter was inserted and the sample subjected to HPLC analysis.

**Analysis**

The samples were analyzed on an Agilent 1260 Infinity unit with a UV detector and an Agilent Eclipse Plus C18 column (3.5 μm, 4.6x100 mm). A method based on acetonitrile (A) and 0.1% formic acid in water (B) with a flow of 1 mL/min was used with the following gradient: 60% A for 2 min, 60-95% A over 1 minute, hold 95% A for 13 min, 95-60% A over 10 seconds, hold 60% for 4 minutes.

**Data**

![Graph showing concentration over time for acid and product](image)

**Figure S6:** Good reproducibility between two different ElectraSyn Pro instruments

**Standard conditions:** Alcohol (132 mM), acid (33 mM, 0.2 mmol), AgClO₄ (100 mM), 2,4,6-collidine (99.9 mM), ⁴Bu₄NClO₄ (49.5 mM), 3Å MS powder (150 mg), 6 mL CH₂Cl₂ (dry), 1000 rpm, 15 mA constant current, graphite electrodes
Figure S7: Good reproducibility between new and reused counter electrode (this electrode had been used in 4 reactions with Ag prior to the indicated run).

**Standard conditions:** Alcohol (132 mM), acid (33 mM, 0.2 mmol), AgClO₄ (100 mM), 2,4,6-collidine (99.9 mM), nBu₄NClO₄ (49.5 mM), 3Å MS powder (150 mg), 6 mL CH₂Cl₂ (dry), 1000 rpm, 10 mA constant current, graphite electrodes

Figure S8: Zero order in [acid] at 10 mA

**Standard conditions:** Alcohol (132 mM), acid (33 mM, 0.2 mmol), AgClO₄ (100 or 0 mM), 2,4,6-collidine (99.9 mM), nBu₄NClO₄ (49.5 mM), 3Å MS powder (150 mg), 6 mL CH₂Cl₂ (dry), 1000 rpm, 10 mA constant current, graphite electrodes
Figure S9: Zero order in [acid] at 15 mA

**Standard conditions:** Alcohol (132 mM), acid (33 mM, 0.2 mmol), AgClO₄ (100 or 0 mM), 2,4,6-collidine (99.9 mM), "nBu₄NClO₄ (49.5 mM), 3Å MS powder (150 mg), 6 mL CH₂Cl₂ (dry), 1000 rpm, 15 mA constant current, graphite electrodes

Figure S10: Zero order in [alcohol] at 10 mA

**Standard conditions:** Alcohol (132 mM), acid (33 mM, 0.2 mmol), AgClO₄ (100 or 0 mM), 2,4,6-collidine (99.9 mM), "nBu₄NClO₄ (49.5 mM), 3Å MS powder (150 mg), 6 mL CH₂Cl₂ (dry), 1000 rpm, 10 mA constant current, graphite electrodes
Figure S11: The effect of [alcohol] at 15 mA

**Standard conditions:** Alcohol (132 mM), acid (33 mM, 0.2 mmol), AgClO$_4$ (100 or 0 mM), 2,4,6-collidine (99.9 mM), "Bu$_4$NCIO$_4$ (49.5 mM), 3Å MS powder (150 mg), 6 mL CH$_2$Cl$_2$ (dry), 1000 rpm, 15 mA constant current, graphite electrodes

Figure S12: The effect of [alcohol] at 20 mA

**Standard conditions:** Alcohol (132 mM), acid (33 mM, 0.2 mmol), AgClO$_4$ (100 or 0 mM), 2,4,6-collidine (99.9 mM), "Bu$_4$NCIO$_4$ (49.5 mM), 3Å MS powder (150 mg), 6 mL CH$_2$Cl$_2$ (dry), 1000 rpm, 15 mA constant current, graphite electrodes
Figure S13: No product formation in absence of base and fast decomposition of acid at low [base] in the presence of Ag

**Standard conditions:** Alcohol (132 mM), acid (33 mM, 0.2 mmol), AgClO₄ (100 or 0 mM), 2,4,6-collidine (99.9 mM), "Bu₄NClO₄ (49.5 mM), 3Å MS powder (150 mg), 6 mL CH₂Cl₂ (dry), 1000 rpm, 10 mA constant current, graphite electrodes

Figure S14: Increased rates with increased current

**Standard conditions:** Alcohol (132 mM), acid (33 mM, 0.2 mmol), AgClO₄ (100 or 0 mM), 2,4,6-collidine (99.9 mM), "Bu₄NClO₄ (49.5 mM), 3Å MS powder (150 mg), 6 mL CH₂Cl₂ (dry), 1000 rpm, constant current, graphite electrodes
Figure S15: Relative reaction rates under different conditions (normalized to rate for standard conditions with Ag at 10 mA)

**Standard conditions:** Alcohol (132 mM), acid (33 mM, 0.2 mmol), AgClO₄ (100 or 0 mM), 2,4,6-collidine (99.9 mM), "Bu₄NClO₄ (49.5 mM), 3Å MS powder (150 mg), 6 mL CH₂Cl₂ (dry), 1000 rpm, constant current, graphite electrodes
Figure S16: Relative rate of acid disappearance under different conditions (normalized to rate for standard conditions with Ag at 10 mA)

**Standard conditions:** Alcohol (132 mM), acid (33 mM, 0.2 mmol), AgClO₄ (100 or 0 mM), 2,4,6-collidine (99.9 mM), tBu₄NClO₄ (49.5 mM), 3Å MS powder (150 mg), 6 mL CH₂Cl₂ (dry), 1000 rpm, constant current, graphite electrodes

![Figure S16](image)

Figure S17: Concentration of α-methylstyrene over time under different conditions at 20 mA

**Standard conditions:** Alcohol (132 mM), acid (33 mM, 0.2 mmol), AgClO₄ (100 or 0 mM), 2,4,6-collidine (99.9 mM), tBu₄NClO₄ (49.5 mM), 3Å MS powder (150 mg), 6 mL CH₂Cl₂ (dry), 1000 rpm, 20 mA constant current, graphite electrodes

**Cyclic Voltammetry Analysis**
Cyclic voltammetry was recorded with 3 mm disc glassy carbon working electrode, platinum plate counter electrode and aqueous Ag/AgCl reference electrode. Scan rate: 200 mV/s.
**Figure S18**: Cyclic voltammograms at 200 mV/s in DCM. Carboxylic acid 3 (20 mM) + \text{"}Bu_4NPF_6 (50 mM).

**Figure S19**: Cyclic voltammograms at 200 mV/s in DCM. Carboxylic acid 3 (5 mM) + 2,4,6-collidine (15 mM) + \text{"}Bu_4NPF_6 (50 mM).
Figure S20: Cyclic voltammograms at 200 mV/s in DCM. Carboxylic acid 3 (5 mM) + 2,4,6-collidine (15 mM) + $^6$Bu$_4$NPF$_6$ (50 mM) + AgPF$_6$ (7.5 mM).

Figure S21: Cyclic voltammograms at 200 mV/s in DCM. $^6$Bu$_4$NPF$_6$ (50 mM) + AgPF$_6$ (7.5 mM).

Discussion: No clear oxidation of carboxylic acid 3 was observed in the absence nor presence of 2,4,6-collidine, whereas slight change of the cyclic voltammogram was indeed observed after the addition of 2,4,6-collidine. Addition of AgPF$_6$ to the mixture of acid and 2,4,6-collidine led to the appearance of a broad oxidation peak around 2.2 V. However, a similar peak was observed in
the cyclic voltammogram of AgPF$_6$ by itself, indicating that the peak is not likely to be the oxidation of carboxylic acid.

**Divided Cell Experiment**

![Divided Cell Experiment](image)

**Experiment with Ag additive in anodic chamber**

Anodic and cathodic chamber are separated by custom-made syrindrical PTFE frit. To the anode chamber (see the picture above) was added compound 3 (66 mg, 0.4 mmol), alcohol 4 (147 mg, 1.2 mmol, 3.0 eq), 2,4,6-collidine (145 mg, 1.2 mmol, 3.0 eq), nBu$_4$NPF$_6$ (349 mg, 0.9 mmol), 3 Å molecular sieves (300 mg), AgPF$_6$ (152 mg, 0.3 mmol), and CH$_2$Cl$_2$ (9.0 mL). To the cathode chamber was added compound 3 (33 mg, 0.2 mmol), alcohol 4 (73 mg, 0.6 mmol, 3.0 eq), 2,4,6-collidine (73 mg, 0.6 mmol, 3.0 eq), nBu$_4$NPF$_6$ (116 mg, 0.3 mmol), 3 Å molecular sieves (150 mg), and CH$_2$Cl$_2$ (3.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. The reaction mixture was electrolyzed under a constant current at 10 mA for 4 hours. After the reaction, the ElectraSyn vial cap was removed, and electrodes were rinsed with Et$_2$O (3 mL), which was combined with crude mixture. Then, the combined mixture from anode and cathode chamber was further diluted with Et$_2$O (60 mL). The
resulting mixture was washed with 2N HCl (30 mL) and NaHCO₃(aq) (30 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography (silica, 50:1 Hexanes: Et₂O) afforded 104.0 mg (72%) of product 5.

Experiment with Ag additive in cathodic chamber
To the anode chamber was added compound 3 (66 mg, 0.4 mmol), alcohol 4 (147 mg, 1.2 mmol, 3.0 eq), 2,4,6-collidine (145 mg, 1.2 mmol, 3.0 eq), tBu₄NPF₆ (349 mg, 0.9 mmol), 3 Å molecular sieves (300 mg), and CH₂Cl₂ (9.0 mL). To the cathode chamber was added compound 3 (33 mg, 0.2 mmol), alcohol 4 (73 mg, 0.6 mmol, 3.0 eq), 2,4,6-collidine (73 mg, 0.6 mmol, 3.0 eq), tBu₄NPF₆ (116 mg, 0.3 mmol), 3 Å molecular sieves (150 mg), AgPF₆ (152 mg, 0.3 mmol), and CH₂Cl₂ (3.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. The reaction mixture was electrolyzed under a constant current at 10 mA for 4 hours. After the reaction, the ElectraSyn vial cap was removed, and electrodes were rinsed with Et₂O (3 mL), which was combined with crude mixture. Then, the combined mixture from anode and cathode chamber was further diluted with Et₂O (60 mL). The resulting mixture was washed with 2N HCl (30 mL) and NaHCO₃(aq) (30 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography (silica, 50:1 Hexanes: Et₂O) afforded 7.2 mg (5%) of product 5.

Troubleshooting: Frequently Asked Questions

Question 1:
Are there any precautions that need to be taken for running this reaction?

Answer:
We used all the reagents without any special handling. But the 3Å molecular sieves were flame dried under vacuum for 10 min under vacuum prior to use. The reaction was performed under air without degassing, however, an empty balloon is attached for a large scale reaction of hydroxylation to balance the pressure resulting from the H₂ generation on the cathode.

Question 2:
Is stirring crucial for this reaction?

Answer:
Because the etherification reaction is heterogeneous, stirring is critical—without stirring, the potential of the reaction is high, leading to low yields. Our preferred stirring rate is from 600 to 1000 rpm.

**Question 3:**
What is the byproduct of this reaction?

**Answer:**
We have mentioned the common byproducts that we observed for etherification in the manuscript. In addition, one of the major byproducts when using difluorophenylacetic acid as electrophile is difluoro(phenyl)methyl 2,2-difluoro-2-phenylacetate, which is resulted from the nucleophilic attack of the difluoro-phenylacetic acid towards the corresponding carbocation.

**Question 4:**
What can I do if lots of starting materials remain after electrolysis?

**Answer:**
You can increase the reaction time, use a higher current to get a higher conversion. Alternatively, using more alcohol coupling partners such as 6 equiv. usually helps to get a better yield.

**Question 5:**
How do I monitor the reaction?

**Answer:**
We have evaluated the reaction time on the standard substrate, which indicates 3h is enough for full conversion in 0.2 mmol scale. So we chose to leave the reaction for each substrate for 3h without monitoring. But if you want to speed up the process, you can use TLC analysis with UV visualization (254 nm) to see the starting material if it is UV active and I₂ stain for non-UV active substrates.

**Question 6:**
Does longer reaction time cause decrease of yield?

**Answer:**
We left the reaction running for 6h during optimization and no significant decrease of yield was observed.

**Question 7:**
Are the etherification products volatile?

**Answer:**
Some etherification products that have low molecular weight or no functionalities are volatile. You can use Et₂O for work up and purification and keep the temperature of rotavap water bath below 30 °C.

**Question 8:**
How to clean up the electrodes after the reaction?

**Answer:**
Normally, after the reaction, you observe Ag plating on the cathode. To remove Ag plating, you can simply use a blade to scrape the graphite electrode. However, we didn’t observe appreciable ill effect to the yield even without removing Ag plating.

**Question 9:**
This is a heterogeneous reaction. Does the yield drop in a larger scale?

**Answer:**
We obtained similar yield when scaling up the reaction to gram scale. Larger scale was not tested.

**Question 10:**
What's the limitation of current decarboxylative C-O bond forming reaction?

**Answer:**
“Non-activated” (we define “activated” carboxylic acids to be some acid substrates bearing stabilizing elements for the electrogenerated carbon cation such as phenyl group, N, O, Si heteroatom) primary and secondary carboxylic acids without any stabilizing effect for the corresponding carbon cation are generally not compatible probably because the electrogenerated carbocation doesn’t have a high enough lifetime to be attacked by the alcohol nucleophile; instead, it undergoes elimination, rearrangement etc. Tertiary alcohols gave low yield when they coupled with tertiary carboxylic acids to generate steric hindered tertiary alkyl-alkyl ethers. Please see “Unsuccessful or Challenging Substrates in This Study” section (see page 35) for the problematic substrates we’ve tried.

**Question 11:** How do we choose an appropriate conditions for the synthesis of hindered ether?

**Answer:** General procedure A and B are differentiated by which reagents (acid or alcohol) are used as limiting reagent. The criteria for how to choose conditions is first dependent on the value of the substrates. More specifically, if the carboxylic acid is much more precious, you should choose General procedure A. As for how to choose the [Ag], based on our experience, AgClO₄ is suitable for benzylic carboxylic acids, while AgSbF₆ is preferred for non-activated carboxylic
acids. AgPF$_6$ is generally effective for all substrates, but yields are slightly lower than using AgClO$_4$ and AgSbF$_6$ respectively. We don’t have a clear rule for how to choose the base, but 2,4,6-collidine is proven to be a general base for all types of substrates. Only in a few examples of non-activated carboxylic acids, we found that DBU gave better yields than 2,4,6-collidine.

**Question 12:** Can we use other electrodes?

**Answer:** Among a variety of electrodes we have tested for both cathode and anode, we found nickel foam can be used as cathode instead of graphite to give the product in a comparable yield. However, the anode selection is more narrow as we found electrodes such as Pt, RVC, glass carbon etc gave much lower yield than graphite when they were used as anode.

**Question 13:** How can we scale up these reactions?

**Answer:** You can scale up to gram-scale for both of the etherification and hydroxylation according to the procedure we provided (pages 29–33). An even larger scale reaction hasn’t been tested. For gram-scale reaction, there are some extra tricks that need to be pointed out. First, the amount of electrolyte and base can be reduced without affecting the yield. Second, we found that double the concentration actually gave a better yield compared to the small scale reaction. Third, the reaction time can be shortened.

**Question 14:** Why do we need a pre-stir of 15 min before starting the reaction?

**Answer:** We have not determined the exact role of the pre-stir; we only know for certain that it improves yields relative to omitting this step. It’s possible that the pre-stir helps mitigate low kinetic solubility of the reagents, or that it gives the molecular sieves an opportunity to trap adventitious water before the reaction begins.

**Experimental Procedures and Characterization Data**

**Compound 5**

\[
\text{Me} - \text{Me} - \text{Me} \quad \text{Me} \quad \text{O} \quad \text{Ph}
\]

**(R)-(2-(1-phenylethoxy)propan-2-yl)benzene**

Following General Procedure A. Purification by flash column chromatography (silica, gradient elution, 50:1 Hexanes: Et$_2$O to 5:1 Hexanes: Et$_2$O) afforded 37.0 mg (77%) of the title compound 5 and 42.6 mg (58%) of the starting material (R)-1-phenylethanol 4.

**Physical State:** colorless oil.
\[ ^1 \text{H NMR (600 MHz, CDCl}_3 \]: } \delta 7.48 (d, J = 7.3 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.32 – 7.26 (m, 5H), 7.23 – 7.18 (m, 1H), 4.31 (q, J = 6.5 Hz, 1H), 1.52 (s, 3H), 1.38 (s, 3H), 1.33 (d, J = 6.5 Hz, 3H).

\[ ^{13} \text{C NMR (151 MHz, CDCl}_3 \]: } \delta 147.6, 147.0, 128.2, 128.1, 127.0, 126.6, 126.2, 125.8, 78.1, 71.9, 31.7, 27.2, 26.6.

\[ \text{GC/MS (EI): } m/z \text{ (%) } 240 (0.003\%), 225 (7\%), 119 (100\%), 105 (100\%), 91 (68\%). \]

\[ [\alpha]_D^{24} = 153.6 \text{ (c = 1.0, CHCl}_3 \). \]

\[ \text{TLC: } R_f = 0.3 \text{ (50:1 Hexanes: Et}_2\text{O). } \]

**Compound 10**

\[
\text{Ph} \quad \text{Me} \quad \text{O} \\
\big/\big/ \big/ \\
\text{Me} \quad \text{O} \quad \text{Me} \\
\text{Ph} \quad \text{Me} \quad \text{Me}
\]

1-Phenylethyl 2-methyl-2-phenylpropanoate

Following General Procedure A, no 2,4,6-collidine. Purification by PTLC (silica, 8:1 Hexanes: Et\(_2\)O) afforded 29.0 mg (54\%) of the title compound 10.

**Physical State:** colorless oil.

\[ ^1 \text{H NMR (600 MHz, CDCl}_3 \]: } \delta 7.35 – 7.21 (m, 8H), 7.19 – 7.14 (m, 2H), 5.86 (q, J = 6.6 Hz, 1H), 1.61 (s, 3H), 1.58 (s, 3H), 1.44 (d, J = 6.8 Hz, 3H).

\[ ^{13} \text{C NMR (151 MHz, CDCl}_3 \]: } \delta 175.9, 144.7, 141.9, 128.5, 128.4, 127.7, 126.7, 125.90, 125.87, 72.6, 46.7, 26.6, 26.5, 22.3.

\[ \text{TLC: } R_f = 0.40 \text{ (8:1 Hexanes:Et}_2\text{O). } \]

Note: when using \((R)-1\)-phenylethan-1-ol as the nucleophile, the product 7 was isolated as racemic (er = 50:50).

**Chiral HPLC:** Chiralpak IA 4.6 x 250 mm; 5:95 i-PrOH : Hexanes, 0.5 mL/min, 212 nm; \(t_R\) (minor) = 7.5 min, \(t_R\) (major) = 8.5 min, 50:50 er.

\((rac)-1\)-phenylethan-1-ol as the nucleophile

---

Signal 2: DAD1 B, Sig=210.4 Ref=off

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %
---|-----|------|-------|-----|-----|
1  7.531 MM 0.3014 2.89417e4 1600.47656 50.5401
2  8.578 MM 0.3041 2.83231e4 1552.33069 49.4599

(R)-1-phenylethan-1-ol as the nucleophile

Signal 2: DAD1 B, Sig=210.4 Ref=off

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %
---|-----|------|-------|-----|-----|
1  7.530 VB 0.2111 1.98400e4 1402.32031 50.8606
2  8.569 BV R 0.2147 1.91686e4 1321.73340 49.1394
Compound 16

\[
\begin{array}{c}
\text{O} \\
\text{Me}
\end{array}
\]

\text{1-}((R)-1\text{-phenylethoxy)adamantane}

Following General Procedure A. Purification by PTLC (silica, 50:1 Hexanes: Et\text{2}O) afforded 33.4 mg (65\%) of the title compound 16.

\text{Physical State: colorless oil.}

\text{1H NMR (600 MHz, CDCl}_{3}: \delta 7.36 (d, J = 7.4 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 4.83 (q, J = 6.5 Hz, 1H), 2.08 (s, 3H), 1.72 (q, J = 11.5 Hz, 6H), 1.59 – 1.55 (m, 6H), 1.37 (d, J = 6.6 Hz, 3H).

\text{13C NMR (151 MHz, CDCl}_{3}: \delta 147.9, 128.2, 126.6, 125.7, 73.6, 67.9, 42.7, 36.6, 30.7, 26.9.

\text{GC/MS (EI): m/z (%)} 256 (0.03\%), 241 (17\%), 135 (100\%), 105 (89\%), 95 (23\%).

\text{TLC: } R_{f} = 0.4 (30:1 Hexanes: Et\text{2}O).

[\alpha]_{D}^{24} = 58.0 (c = 0.33, CHCl}_{3}.

Compound 17

\[
\begin{array}{c}
\text{BocN} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array}
\]

tert-butyl \((R)-4\text{-methyl-4-(1-phenylethoxy)piperidine-1-carboxylate}

Following General Procedure A without 2N HCl work up (washed twice with H\text{2}O), using AgSbF\text{6} (103 mg, 1.5 equiv.), DBU (91.2 mg, 3.0 equiv.) instead of AgPF\text{6} and 2,4,6-collidine respectively. Purification by PTLC (silica, 4:1 Hexanes: EtOAc) afforded 28.7 mg (45\%) of the title compound 17.

\text{Physical State: colorless oil.}

\text{1H NMR (600 MHz, CDCl}_{3}: \delta 7.35 – 7.28 (m, 3H), 7.24 – 7.19 (m, 1H), 4.61 (q, J = 6.5 Hz, 1H), 3.69 (s, 1H), 3.49 (s, 1H), 3.25 (t, J = 12.5 Hz, 1H), 2.95 (s, 1H), 1.80 (d, J = 13.7 Hz, 1H), 1.63 (d, J = 14.0 Hz, 1H), 1.44 – 1.40 (m, 10H), 1.37 (d, J = 6.5 Hz, 3H), 1.36 – 1.31 (m, 1H), 1.08 (s, 3H).
$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 155.0, 147.1, 128.4, 126.9, 125.8, 79.3, 73.3, 69.8, 40.0, 36.6, 28.6, 26.9, 26.0.

HRMS (ESI-TOF): calc’d for C$_{19}$H$_{29}$NNaO$_3$ [M + Na]$^+$: 342.2040; found 342.2044.

TLC: R$_f$ = 0.63 (3:1 Hexanes: EtOAc).

Chiral HPLC: Chiralpak IG 4.6 x 250 mm; 5% MeOH/CO$_2$, 0.5 mL/min, 212 nm; $t_R$ (minor) = 2.11 min, $t_R$ (major) = 2.37 min, 95% ee.
(1-((1-methycyclohexyl)oxy)ethyl)benzene

Following General Procedure A, using AgSbF₆ (103 mg, 1.5 equiv.), DBU (91.2 mg, 3.0 equiv.) instead of AgPF₆ and 2,4,6-collidine respectively. Purification by PTLC (silica, 30:1 Hexanes: Et₂O) afforded 23.6 mg (54%) of the title compound 18.

**Physical State:** colorless oil.

**¹H NMR (600 MHz, CDCl₃):** δ 7.38 – 7.35 (m, 2H), 7.32 – 7.28 (m, 2H), 7.22 – 7.19 (m, 1H), 4.66 (q, J = 6.5 Hz, 1H), 1.78 – 1.71 (m, 1H), 1.69 – 1.57 (m, 3H), 1.48 – 1.35 (m, 5H), 1.33 – 1.22 (m, 4H), 1.04 (s, 3H).

**¹³C NMR (151 MHz, CDCl₃):** δ 147.9, 128.2, 126.6, 125.9, 75.3, 69.1, 37.7, 37.3, 27.0, 26.0, 25.8, 22.8, 22.6.

**GC/MS (EI):** m/z 218 (0.5%), 203 (2%), 105 (100%), 77 (15%).

**TLC:** Rₛ = 0.56 (20:1 Hexanes: Et₂O).

**Compound 19**

![Structure of Compound 19]
(R)-(1-((1-methylcyclopentyl)oxy)ethyl)benzene

Following General Procedure A, using AgSbF$_6$ (103 mg, 1.5 equiv.), DBU (91.2 mg, 3.0 equiv.) instead of AgPF$_6$ and 2,4,6-collidine respectively. Purification by PTLC (silica, 50:1 Hexanes: Et$_2$O) afforded 16.3 mg (40%) of the title compound 19.

**Physical State:** colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.35 (d, $J$ = 6.7 Hz, 2H), 7.30 (t, $J$ = 7.6 Hz, 2H), 7.21 (t, $J$ = 7.2 Hz, 1H), 4.59 (q, $J$ = 6.6 Hz, 1H), 1.93 – 1.86 (m, 1H), 1.81 – 1.69 (m, 2H), 1.63 – 1.54 (m, 2H), 1.53 – 1.42 (m, 2H), 1.37 (d, $J$ = 6.6 Hz, 3H), 1.36 – 1.28 (m, 1H), 1.21 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 147.6, 128.2, 126.6, 125.7, 85.8, 71.0, 39.1, 38.6, 26.9, 25.0, 24.1, 23.9.

**GC/MS (EI):** m/z (%) 204 (0.9%), 105 (100%), 99 (3%), 83 (4%), 77 (13%).

**TLC:** R$_f$ = 0.3 (30:1 Hexanes: Et$_2$O).

$[\alpha]_D^{24} = 57.1$ (c = 1.0, CHCl$_3$).

**Compound 20**

(1-(1-butylcyclobutoxy)ethyl)benzene

Following General Procedure A, using AgSbF$_6$ (103 mg, 1.5 equiv.), DBU (91.2 mg, 3.0 equiv.) instead of AgPF$_6$ and 2,4,6-collidine respectively. Purification by PTLC (pure Hexanes) afforded 24.0 mg (52%) of the title compound 20.

**Physical State:** colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36 (d, $J$ = 7.3 Hz, 2H), 7.31 (t, $J$ = 7.6 Hz, 2H), 7.22 (t, $J$ = 7.3 Hz, 1H), 4.52 (q, $J$ = 6.5 Hz, 1H), 2.09 (q, $J$ = 10.1 Hz, 1H), 1.99 (q, $J$ = 10.2 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.76 – 1.69 (m, 1H), 1.69 – 1.61 (m, 2H), 1.56 – 1.43 (m, 2H), 1.40 (d, $J$ = 6.5 Hz, 3H), 1.37 – 1.24 (m, 2H), 1.24 – 1.11 (m, 2H), 0.85 (t, $J$ = 7.0 Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 146.8, 128.3, 126.9, 126.1, 80.2, 70.9, 36.7, 33.0, 32.6, 26.0, 25.5, 23.2, 14.2, 13.2.

**GC/MS (EI):** m/z (%) 232 (0.005%), 127 (4%), 105 (100%), 85 (3%), 77 (8%).

**TLC:** R$_f$ = 0.4 (50:1 Hexanes: Et$_2$O).
\[ [\alpha]b^{24} = 52.4 \ (c = 1.0, \text{CHCl}_3). \]

**Compound 21**

\( (R)-((1-(1-\text{phenethylcyclobutoxy})\text{ethyl})\text{benzene} \)

Following General Procedure A, using AgSbF\(_6\) (103 mg, 1.5 equiv.) instead of AgPF\(_6\). Purification by PTLC (pure Hexanes) afforded 23.0 mg (41%) of the title compound 21.

**Physical State:** colorless oil.

\(^1\text{H NMR (600 MHz, CDCl}_3\); \(\delta 7.40 (d, J = 7.4 \text{ Hz}, 2H), 7.34 (t, J = 7.6 \text{ Hz}, 2H), 7.27 (t, J = 7.4 \text{ Hz}, 1H), 7.23 (t, J = 7.5 \text{ Hz}, 2H), 7.15 (t, J = 7.4 \text{ Hz}, 1H), 6.98 (d, J = 7.4 \text{ Hz}, 2H), 4.57 (q, J = 6.5 \text{ Hz}, 1H), 2.62 (td, J = 13.0, 4.8 \text{ Hz}, 1H), 2.50 (td, J = 13.0, 4.8 \text{ Hz}, 1H), 2.17 (q, J = 10.0 \text{ Hz}, 1H), 2.07 (q, J = 10.0 \text{ Hz}, 1H), 1.97 – 1.80 (m, 4H), 1.77 – 1.67 (m, 1H), 1.55 – 1.49 (m, 1H), 1.45 (d, J = 6.5 \text{ Hz}, 3H). 

\(^{13}\text{C NMR (151 MHz, CDCl}_3\); \(\delta 146.6, 143.0, 128.5, 128.5, 128.4, 127.1, 126.2, 125.7, 80.1, 71.3, 39.3, 32.9, 32.6, 30.0, 26.2, 13.2.

**GC/MS (EI):** m/z (%) 175 (2%), 130 (5%), 105 (100%), 91 (27%), 77 (14%).

**TLC:** \( R_f = 0.3 \) (50:1 Hexanes: Et\(_2\)O).

\[ [\alpha]b^{24} = 55.5 \ (c = 1.0, \text{CHCl}_3). \]

**Compound 22**

\( (R)-((1-(\text{tert-butoxy})\text{ethyl})\text{benzene} \)

Following General Procedure B. Purification by PTLC (silica, 100:1 Hexanes: Et\(_2\)O) afforded 16.4 mg (61%) of the title compound 22.

**Physical State:** colorless oil.

\(^1\text{H NMR (500 MHz, CDCl}_3\); \(\delta 7.35 (d, J = 7.3 \text{ Hz}, 2H), 7.30 (t, J = 7.6 \text{ Hz}, 2H), 7.20 (t, J = 7.2 \text{ Hz}, 1H), 4.66 (q, J = 6.5 \text{ Hz}, 1H), 1.37 (d, J = 6.6 \text{ Hz}, 3H), 1.16 (s, 9H).
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 147.7, 128.2, 126.6, 125.7, 74.3, 70.0, 28.7, 26.9.
GC/MS (EI): m/z (%) 178 (0.07%), 163 (30%), 105 (100%), 77 (20%), 57 (30%).
TLC: $R_f = 0.4$ (Hexanes).
$[\alpha]_D^{24} = 65.8 (c = 1.0, \text{CHCl}_3)$.

**Compound 23**

(R)-(1-(tert-pentyloxy)ethyl)benzene

Following General Procedure A, using AgSbF$_6$ (103 mg, 1.5 equiv.) instead of AgPF$_6$.
Purification by PTLC (silica, 30:1 Hexanes: Et$_2$O) afforded 23.8 mg (62%) of the title compound 23.

**Physical State:** colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.37 – 7.33 (m, 2H), 7.32 – 7.27 (m, 2H), 7.20 (ddt, $J = 7.7, 6.7, 1.3$ Hz, 1H), 4.64 (q, $J = 6.5$ Hz, 1H), 1.60 – 1.53 (m, 1H), 1.49 – 1.42 (m, 1H), 1.36 (d, $J = 6.5$ Hz, 3H), 1.10 (s, 3H), 1.05 (s, 3H), 0.87 (t, $J = 7.5$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 147.9, 128.2, 126.6, 125.7, 76.5, 69.6, 34.2, 26.9, 26.1, 25.8, 8.8.

GC/MS (EI): m/z (%) 177 (1%), 163 (8%), 105 (100%), 77 (13%).
TLC: $R_f = 0.50$ (20:1 Hexanes: Et$_2$O).
$[\alpha]_D^{24} = +282.7 (c = 1.0, \text{CHCl}_3)$.

**Compound 24**

(R)-(4-methyl-4-(1-phenylethoxy)pentyl)benzene

Following General Procedure A, using AgSbF$_6$ (103 mg, 1.5 equiv.), DBU (91.2 mg, 3.0 equiv.) instead of AgPF$_6$ and 2,4,6-collidine respectively. Purification by PTLC (pure Hexanes) afforded 19.7 mg (35%) of the title compound 24.

**Physical State:** colorless oil.
Compound 25

(1-((1-chloro-2-methylpropan-2-yl)oxy)ethyl)benzene

Following General Procedure A, using AgClO$_4$ (124 mg, 3 equiv.), $n$Bu$_4$NClO$_4$ (0.1 M) instead of AgPF$_6$ and $n$Bu$_4$NPF$_6$ respectively, the amount of alcohol was 4 equiv., 1.5 mL CH$_2$Cl$_2$, I = 7.5 mA, 4 h. Purification by PTLC (silica, 30:1 Hexanes: Et$_2$O) afforded 18.5 mg (43%) of the title compound 25.

Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.37 – 7.28 (m, 4H), 7.22 (ddt, $J = 7.6, 6.6, 1.5$ Hz, 1H), 4.69 (q, $J = 6.5$ Hz, 1H), 3.49 (d, $J = 11.1$ Hz, 1H), 3.38 (d, $J = 11.1$ Hz, 1H), 1.40 (d, $J = 6.5$ Hz, 3H), 1.23 (s, 3H), 1.20 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 146.9, 128.4, 127.0, 125.7, 76.1, 70.8, 52.7, 26.7, 24.7, 24.4.

GC/MS (EI): m/z (%) 197 (5%), 163 (4%), 105 (100%), 77 (22%).

TLC: $R_f$ = 0.47 (20:1 Hexanes: Et$_2$O).

Compound 26

((2-methylhex-5-en-2-yl)oxy)cyclohexane
Following General Procedure A using AgClO₄ (124 mg, 3 equiv.), "Bu₄NClO₄ (0.1 M) instead of AgPF₆ and "Bu₄NPF₆ respectively and the amount of alcohol was 6 equiv. Purification by PTLC (50:1 Hexanes: EtOAc) afforded 16.8 mg (43%) of the title compound 26.

**Physical State:** colorless oil.

**1H NMR (600 MHz, CDCl₃):** δ 5.84 (ddt, J = 16.8, 9.8, 6.6 Hz, 1H), 5.01 (d, J = 17.1 Hz, 1H), 4.92 (d, J = 17.1 Hz, 1H), 3.39 – 3.28 (m, 1H), 2.11 (q, J = 7.5 Hz, 2H), 1.78 – 1.69 (m, 4H), 1.55 – 1.50 (m, 3H), 1.25 (t, J = 7.4 Hz, 4H), 1.15 (s, 6H), 1.13 – 1.08 (m, 1H).

**13C NMR (151 MHz, CDCl₃):** δ 139.5, 114.0, 75.0, 69.9, 40.8, 35.7, 28.8, 26.4, 25.8, 25.2.

**GC/MS (EI):** m/z (%) 181 (0.2%), 141 (18%), 97 (16%), 81 (12%), 59 (100%).

**TLC:** R_f = 0.3 (50:1 Hexanes: EtOAc).

**Compound 27**

![Chemical structure of compound 27](image)

1-(tert-butyl) 2-methyl (2S,4R)-4-((1-(4-fluorophenyl)cyclohexyl)oxy)pyrrolidine-1,2-dicarboxylate

Following General Procedure A without 2N HCl work up (washed twice with H₂O), using AgClO₄ (124 mg, 3 equiv.), "Bu₄NClO₄ (0.1 M) instead of AgPF₆ and "Bu₄NPF₆ respectively. Purification by PTLC (3:1 Hexanes: EtOAc) afforded 39.0 mg (46%) of the title compound 27.

**Physical State:** colorless oil.

**1H NMR (600 MHz, CDCl₃, for two rotamers):** δ 7.38 – 7.35 (m, 2H), 7.03 – 6.99 (m, 2H), 4.33 – 4.22 (m, 1H), 3.86 – 3.79 (m, 1H), 3.64 (s, 1.21H), 3.62 (s, 1.75H), 3.45 – 3.30 (m, 1H), 3.22 – 3.11 (m, 1H), 2.16 – 1.96 (m, 3H), 1.84 – 1.57 (m, 6H), 1.57 – 1.49 (m, 2H), 1.42 (s, 3.47H), 1.37 (s, 5.82H), 1.30 – 1.20 (m, 1H).

**13C NMR (151 MHz, CDCl₃, for two rotamers):** δ 173.6, 173.4, 162.89, 162.87, 161.3, 161.2, 154.5, 153.7, 141.53, 141.45, 128.20, 128.15, 115.21, 115.16, 115.1, 115.0, 80.14, 80.11, 77.8, 77.6, 70.3, 69.5, 57.8, 57.4, 52.4, 52.24, 52.21, 52.0, 37.8, 37.1, 36.5, 36.2, 36.1, 28.5, 28.4, 25.7, 22.42, 22.36.

**19F NMR (376 MHz, CDCl₃, for two rotamers):** δ -115.57, -115.67.

**HRMS (ESI-TOF):** calc’d for C₂₃H₃₂FNO₅Na [M + Na]⁺: 444.2157; found 444.2165.
TLC: R\textsubscript{f} = 0.49 (3:1 Hexanes: EtOAc).
[\alpha]\textsubscript{D}\textsuperscript{24} = -3.5 (c = 1.0, CHCl\textsubscript{3}).

**Compound 28**

1-(\textit{tert}-butyl) 2-methyl (2\textit{S},4\textit{R})-4-((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)oxy)pyrrolidine-1,2-dicarboxylate

Following General Procedure A without 2N HCl work up (washed twice with H\textsubscript{2}O), using AgClO\textsubscript{4} (124 mg, 3 equiv.), "Bu\textsubscript{4}NClO\textsubscript{4} (0.1 M) instead of AgPF\textsubscript{6} and "Bu\textsubscript{4}NPF\textsubscript{6} respectively. Purification by PTLC (3:1 Hexanes: EtOAc) afforded 52.9 mg (54%) of the title compound 28.

**Physical State**: colorless oil.

\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}, for two rotamers): \(\delta\ 7.79 - 7.77\) (m, 2H), 7.46 - 7.35 (m, 2H), 4.39 - 4.30 (m, 1H), 4.03 - 3.85 (m, 1H), 3.66 (s, 0.93H), 3.65 (s, 1.75H), 3.60 - 3.51 (m, 1H), 3.37 - 3.23 (m, 1H), 2.28 - 2.12 (m, 1H), 1.99 - 1.94 (m, 1H), 1.54 - 1.49 (m, 6H), 1.44 (s, 4H), 1.39 (s, 5H), 1.34 (s, 12H).

\textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{3}, for two rotamers): \(\delta\ 173.7, 173.4, 154.5, 153.8, 149.6, 149.5, 135.0, 125.32, 125.28, 84.0, 83.9, 80.2, 78.1, 77.9, 71.3, 70.5, 58.0, 57.6, 53.2, 53.1, 52.3, 52.1, 38.3, 37.4, 29.5, 29.1, 28.9, 28.5, 28.4, 25.02, 24.99, 24.97.

HRMS (ESI-TOF): calc’d for C\textsubscript{26}H\textsubscript{40}BNO\textsubscript{7}Na [M + Na]\textsuperscript{+}: 511.2826; found 511.2841.

TLC: R\textsubscript{f} = 0.39 (3:1 Hexanes: EtOAc).
[\alpha]\textsubscript{D}\textsuperscript{24} = +10.2 (c = 1.0, CHCl\textsubscript{3}).

**Compound 29**

methyl 2-(cyclohexyloxy)-2-phenylacetate
Following General Procedure A, using AgClO$_4$ (124 mg, 3 equiv.), $^+$Bu$_4$NClO$_4$ (0.1 M) instead of AgPF$_6$ and $^+$Bu$_4$NPF$_6$ respectively and the amount of alcohol was 6 equiv. Purification by PTLC (50:1 Hexanes: EtOAc) afforded 20.4 mg (41%) of the title compound 29.

**Physical State:** colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.47 (d, $J = 7.5$ Hz, 2H), 7.35 (t, $J = 7.3$ Hz, 2H), 7.33 – 7.30 (m, 1H), 5.05 (s, 1H), 3.71 (s, 3H), 3.35 (td, $J = 9.7$, 9.3, 4.5 Hz, 1H), 1.98 (d, $J = 11.4$ Hz, 1H), 1.88 (d, $J = 11.9$ Hz, 1H), 1.80 – 1.67 (m, 2H), 1.52 (s, 1H), 1.46 – 1.35 (m, 2H), 1.26 – 1.16 (m, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 172.2, 137.5, 128.7, 128.5, 127.2, 78.2, 52.4, 32.3, 32.3, 25.8, 24.3.

GC/MS (EI): $m/z$ (%) 248 (0.02%), 189 (30%), 121 (11%), 107 (100%), 55 (11%).

TLC: $R_f$ = 0.3 (50:1 Hexanes: EtOAc).

**Compound 30**

![1-chloro-4-((1R)-2-methyl-1-(1-phenylethoxy)propyl)benzene](image)

Following General Procedure A, Purification by PTLC (silica, 100:1 Hexanes: Et$_2$O) afforded 42.5 mg (74%) of the title compound 30.

**Physical State:** colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$, for both diastereomers) (the integration at 4.10 ppm, 3.67 ppm indicated the ratio of the two isomers of 30 to be 1:1): $\delta$ 7.38 – 7.26 (m, 5H), 7.26 – 7.24 (m, 4H), 7.24 – 7.19 (m, 5H), 7.17 (d, $J = 8.3$ Hz, 2H), 7.12 (d, $J = 8.3$ Hz, 2H), 4.35 (q, $J = 6.3$ Hz, 1H), 4.14 (q, $J = 6.5$ Hz, 1H), 4.10 (d, $J = 6.9$ Hz, 1H), 3.67 (d, $J = 7.6$ Hz, 1H), 1.98 – 1.91 (m, 1H), 1.90 – 1.82 (m, 1H), 1.43 (d, $J = 6.4$ Hz, 3H), 1.37 (d, $J = 6.5$ Hz, 3H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.79 (d, $J = 6.8$ Hz, 3H), 0.62 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$, for both diastereomers): $\delta$ 144.5, 143.8, 140.5, 133.1, 132.8, 129.1, 128.9, 128.5, 128.4, 128.2, 128.1, 128.0, 127.6, 127.1, 126.9, 126.2, 84.4, 83.6, 75.1, 74.7, 34.9, 34.9, 24.6, 22.1, 19.4, 19.1, 18.9.

GC/MS (EI): $m/z$ (%) 288 (0.02%), 247 (2%), 245 (7%), 125 (8%), 105 (21%).

TLC: $R_f$ = 0.4 (100:1 Hexanes: Et$_2$O).
**Compound 31**

![Structure of Compound 31](image)

*tert*-butyl 4-((1,2,3,4-tetrahydronaphthalen-1-yl)oxy)piperidine-1-carboxylate

Following General Procedure A without 2N HCl work up (washed twice with H₂O), using AgClO₄ (124 mg, 3 equiv.), "Bu₄NClO₄ (0.1 M) instead of AgPF₆ and "Bu₄NPF₆ respectively. Purification by PTLC (4:1 Hexanes: EtOAc) afforded 45.1 mg (68%) of the title compound 31.

**Physical State**: colorless oil.

**¹H NMR (600 MHz, CDCl₃)**: δ 7.35 – 7.31 (m, 1H), 7.19 – 7.14 (m, 2H), 7.10 – 7.06 (m, 1H), 4.53 (t, J = 5.1 Hz, 1H), 3.82 (s, 2H), 3.73 (tt, J = 8.1, 3.7 Hz, 1H), 3.19 – 3.07 (m, 2H), 2.83 (dt, J = 16.7, 5.9 Hz, 1H), 2.71 (ddd, J = 16.7, 7.9, 5.7 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.94 – 1.91 (m, 2H), 1.84 (s, 1H), 1.75 – 1.71 (m, 1H), 1.67 – 1.56 (m, 3H), 1.46 (s, 9H).

**¹³C NMR (151 MHz, CDCl₃)**: δ 155.0, 137.6, 137.5, 129.1, 127.5, 126.0, 79.6, 72.9, 72.7, 41.4, 32.8, 31.0, 29.3, 29.2, 28.6, 19.2.

**HRMS (ESI-TOF)**: calc’d for C₂₀H₂₉NO₃Na [M + Na]⁺: 354.2040; found 354.2043.

**TLC**: Rf = 0.58 (3:1 Hexanes: EtOAc).

**Compound 32**

![Structure of Compound 32](image)

((R)-((1-phenylethoxy)methylene)dibenzene

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), "Bu₄NClO₄ (0.1 M) instead of AgPF₆ and "Bu₄NPF₆ respectively. Purification by PTLC (50:1 Hexanes: Et₂O) afforded 46.1 mg (80%) of the title compound 32.

**Physical State**: colorless oil.

**¹H NMR (600 MHz, CDCl₃)**: δ 7.39 – 7.26 (m, 14H), 7.23 – 7.17 (m, 1H), 5.26 (s, 1H), 4.46 (q, J = 6.5 Hz, 1H), 1.49 (d, J = 6.5 Hz, 3H).
Compound 33

2-((bicyclo[2.2.1]heptan-2-yl)oxy)-2,3-dihydro-1H-indene

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively. Purification by PTLC (20:1 Hexanes: Et₂O) afforded 26.0 mg (57%) of the title compound 33.

Physical State: colorless oil.

1H NMR (600 MHz, CDCl₃): δ 7.21 – 7.18 (m, 2H), 7.16 – 7.13 (m, 2H), 4.39 (tt, J = 6.9, 5.7 Hz, 1H), 3.51 (dt, J = 7.0, 1.7 Hz, 1H), 3.15 (ddd, J = 15.9, 13.0, 6.8 Hz, 2H), 2.94 (ddd, J = 16.1, 10.8, 5.7 Hz, 2H), 2.33 (d, J = 4.9 Hz, 1H), 2.27 – 2.20 (m, 1H), 1.63 – 1.54 (m, 2H), 1.51 (tdd, J = 12.1, 4.9, 3.4 Hz, 1H), 1.47 – 1.37 (m, 2H), 1.10 (ddq, J = 9.7, 2.9, 1.5 Hz, 1H), 1.08 – 0.97 (m, 2H).

13C NMR (151 MHz, CDCl₃): δ 141.3, 141.2, 126.5, 124.8, 124.8, 81.1, 78.0, 41.0, 40.1, 40.1, 39.8, 35.3, 35.0, 28.7, 24.9.

GC/MS (EI): m/z (%) 228 (5%), 117 (67%), 95 (100%), 67 (13%).

TLC: Rf = 0.47 (20:1 Hexanes: Et₂O).

Compound 34

(1-(cyclohexyloxy)ethyl)benzene
Following General Procedure A. Purification by PTLC (silica, 20:1 Hexanes: Et₂O) afforded 2.9 mg (7%) of the title compound 34.

**Physical State**: colorless oil.

**¹H NMR (600 MHz, CDCl₃)**: δ 7.33–7.32 (m, 4H), 7.27–7.23 (m, 1H), 4.59 (q, J = 6.5 Hz, 1H), 3.16 (tt, J = 9.7, 3.9 Hz, 1H), 1.97 (d, J = 12.4 Hz, 1H), 1.78–1.64 (m, 3H), 1.54–1.48 (m, 1H), 1.40 (d, J = 6.5 Hz, 3H), 1.34–1.24 (m, 2H), 1.21–1.10 (m, 3H).

**¹³C NMR (151 MHz, CDCl₃)**: δ 145.3, 128.4, 127.2, 126.2, 75.0, 74.4, 33.6, 32.0, 26.0, 25.0, 24.6, 24.4.

**GC/MS (EI)**: m/z (%) 204 (0.01%), 189 (21%), 105 (100%), 99 (7%), 77 (13%).

**TLC**: R_f = 0.42 (20:1 Hexanes: Et₂O).

**Compound 35**

![2-((adamantan-1-yl)oxy)tetrahydrofuran]

Following General Procedure A. Purification by PTLC (silica, 50:1 Hexanes: EtOAc) afforded 25.8 mg (58%) of the title compound 35.

**Physical State**: colorless oil.

**¹H NMR (600 MHz, CDCl₃)**: δ 5.54 (dd, J = 5.5, 1.8 Hz, 1H), 3.94 (q, J = 7.7 Hz, 1H), 3.78 (td, J = 7.8, 5.4 Hz, 1H), 2.12 (s, 3H), 2.03–1.96 (m, 1H), 1.96–1.88 (m, 1H), 1.86–1.74 (m, 8H), 1.64–1.59 (m, 6H).

**¹³C NMR (151 MHz, CDCl₃)**: δ 97.4, 73.3, 66.7, 43.0, 36.5, 33.6, 30.8, 24.1.

**GC/MS (EI)**: m/z (%) 222 (0.1%), 152 (28%), 135 (48%), 95 (100%), 71 (21%).

**TLC**: R_f = 0.2 (50:1 Hexanes: EtOAc).

**Compound 36**

![tert-butyl 2-(cyclohexyloxy)morpholine-4-carboxylate]

Following General Procedure A. Purification by PTLC (silica, 6:1 Hexanes: EtOAc) afforded 31.4 mg (55%) of the title compound 36.
**Physical State**: colorless oil.

**1H NMR (600 MHz, CDCl₃)**: δ 4.63 (s, 1H), 3.93 (s, 1H), 3.75 – 3.56 (m, 2H), 3.52 – 3.44 (m, 2H), 3.39 – 2.93 (m, 2H), 1.87 (s, 2H), 1.73 (s, 2H), 1.53 – 1.48 (m, 1H), 1.45 (s, 9H), 1.41 – 1.35 (m, 1H), 1.29 – 1.18 (m, 4H).

**13C NMR (151 MHz, CDCl₃)**: δ 155.1, 95.2, 94.4, 80.1, 75.4, 61.9, 47.1, 43.8, 42.7, 33.7, 31.8, 29.8, 28.5, 25.8, 24.3, 24.1.

**GC/MS (EI)**: m/z (%) 285 (0.6%), 147 (15%), 130 (17%), 102 (80%), 73 (55%), 57 (34%).

**TLC**: R_f = 0.4 (6:1 Hexanes: EtOAc).

**Compound 37**

![Structure of Compound 37](image)

**2-(1-((2,3-dihydro-1H-inden-2-yl)oxy)ethyl)isoindoline-1,3-dione**

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively. Purification by PTLC (2:1 Hexanes: EtOAc) afforded 50.4 mg (82%) of the title compound 37.

**Physical State**: white solid.

**m.p.:** 124 – 126 °C.

**1H NMR (600 MHz, CDCl₃)**: δ 7.94 – 7.86 (m, 2H), 7.79 – 7.73 (m, 2H), 7.20 – 7.10 (m, 4H), 5.74 (q, J = 6.4 Hz, 1H), 4.46 – 4.35 (m, 1H), 3.25 (dd, J = 16.0, 6.7 Hz, 1H), 3.10 – 3.00 (m, 2H), 2.94 (dd, J = 16.0, 5.6 Hz, 1H), 1.79 (d, J = 6.3 Hz, 3H).

**13C NMR (151 MHz, CDCl₃)**: δ 168.1, 140.8, 140.3, 134.4, 131.9, 126.7, 126.7, 124.8, 124.7, 123.7, 78.5, 76.9, 39.8, 39.0, 19.7.

**HRMS (ESI-TOF)**: calc’d for C₁₉H₁₇NO₃Na [M + Na]^+: 330.1101; found 330.1112.

**TLC**: R_f = 0.47 (3:1 Hexanes: EtOAc).

**Compound 38**

![Structure of Compound 38](image)
1-isobutyl-4-((1R)-1-(1-phenylethoxy)ethyl)benzene

Following General Procedure A. Purification by PTLC (silica, 50:1 Hexanes: Et₂O) afforded 50.8 mg (90%) of the title compound 38.

**Physical State:** colorless oil.

**¹H NMR (600 MHz, CDCl₃, for both diastereomers):** (the integration at 1.93 ppm, 1.88 ppm indicated the ratio of the two isomers of 38 to be 1:1): δ 7.40 – 7.34 (m, 2H), 7.34 – 7.27 (m, 7H), 7.27 – 7.17 (m, 5H), 7.15 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 4.59 – 4.51 (m, 2H), 4.32 – 4.21 (m, 2H), 2.51 (d, J = 7.2 Hz, 2H), 2.46 (d, J = 7.2 Hz, 2H), 1.93 – 1.91 (m, 1H), 1.88 – 1.83 (m, 1H), 1.49 (d, J = 6.4 Hz, 6H), 1.40 (d, J = 7.7 Hz, 6H), 0.95 (d, J = 6.6 Hz, 6H), 0.92 (d, J = 6.6 Hz, 6H).

**¹³C NMR (151 MHz, CDCl₃, for both diastereomers):** δ 144.5, 144.4, 141.5, 141.4, 140.9, 140.7, 129.3, 129.1, 128.6, 128.3, 127.5, 127.2, 126.5, 126.2, 126.2, 74.6, 74.5, 74.5, 45.3, 45.3, 30.4, 30.3, 24.9, 24.8, 23.2, 22.9, 22.6, 22.6, 22.5.

**GC/MS (EI):** m/z (%) 282 (0.04%), 177 (16%), 161 (31%), 105 (100%), 91 (12%).

**TLC:** \( R_f = 0.4 \) (50:1 Hexanes: Et₂O).

**Compound 39**

(3S,4aR,6aR,6bS,8aS,12aR,14aR,14bS)-11-(cyclohexyloxy)-4,4,6a,8a,11,14b-heptamethyl-14-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicen-3-yl acetate

Following General Procedure A, using AgSbF₆ (103 mg, 1.5 equiv.), DBU (91.2 mg, 3.0 equiv.) instead of AgPF₆ and 2,4,6-collidine respectively. Purification by PTLC (100% CH₂Cl₂) afforded 40.0 mg (35%) of the title compound 39.

**Physical State:** colorless oil.

**¹H NMR (600 MHz, CDCl₃ for two diastereomers)** (the integration at 5.62 ppm, 5.59 ppm indicated the ratio of the two isomers of 39 to be 1:1): δ 5.62 (s, 1H), 5.59 (s, 1H), 4.52 – 4.49 (m, 2H), 3.44 – 3.28 (m, 2H), 2.81 – 2.77 (m, 2H), 2.41 – 2.31 (m, 3H), 2.12 (td, J = 13.8, 4.7 Hz,
1H), 2.043 (s, 3H), 2.040 (s, 3H), 2.02 – 1.97 (m, 1H), 1.93 (t, J = 13.3 Hz, 1H), 1.86 – 1.77 (m, 2H), 1.74 – 1.67 (m, 10H), 1.67 – 1.61 (m, 6H), 1.61 – 1.53 (m, 5H), 1.52 – 1.47 (m, 3H), 1.45 – 1.38 (m, 7H), 1.38 – 1.35 (m, 4H), 1.33 (s, 3H), 1.32 – 1.21 (m, 9H), 1.20 – 1.14 (m, 13H), 1.14 – 1.10 (m, 9H), 1.09 – 0.95 (m, 5H), 0.87 (s, 12H), 0.843 (s, 3H), 0.836 (s, 3H), 0.80 (d, J = 1.8 Hz, 1H), 0.78 (d, 1.8 Hz, 1H).

13C NMR (151 MHz, CDCl3 for two diastereomers): δ 200.4, 200.3, 171.2, 171.1, 170.8, 169.4, 128.3, 128.0, 80.8, 80.7, 75.8, 73.4, 69.62, 69.58, 61.84, 61.81, 55.2, 55.1, 49.1, 46.6, 45.5, 43.49, 43.48, 41.7, 38.9, 38.2, 37.9, 37.1, 36.0, 35.7, 35.6, 35.5, 33.5, 33.4, 32.84, 32.81, 32.7, 31.9, 28.7, 28.4, 28.20, 28.18, 27.7, 26.64, 26.62, 26.5, 26.4, 25.8, 25.7, 25.34, 25.32, 24.9, 24.8, 23.72, 23.69, 23.52, 23.50, 21.4, 21.3, 18.9, 18.8, 17.5, 16.8, 16.5.


TLC: Rf = 0.66 (3:1 Hexanes: EtOAc).

**Compound 40**

1-chloro-2-(2-methoxyethoxy)-2-methylpropane

Following General Procedure A, using AgClO4 (124 mg, 3 equiv.), nBu4NClO4 (0.1 M) instead of AgPF6 and nBu4NPF6 respectively. Purification by PTLC (50:1 Hexanes: Et2O) afforded 16.0 mg (48%) of the title compound 40.

Physical State: colorless oil.

1H NMR (600 MHz, CDCl3): δ 3.56 – 3.50 (m, 4H), 3.48 (s, 2H), 3.38 (s, 3H), 1.28 (s, 6H).

13C NMR (151 MHz, CDCl3): δ 74.8, 72.4, 61.6, 59.3, 51.5, 23.7.

GC/MS (EI): m/z (%) 151 (0.6%), 117 (50%), 91 (30%), 59 (100%), 55 (40%).

TLC: Rf = 0.4 (30:1 Hexanes: Et2O).

**Compound 41**

(4-butoxy-4-methylpentyl)benzene

Following General Procedure A. Purification by PTLC (silica, 50:1 Hexanes: Et2O) afforded 27.6 mg (59%) of the title compound 41.
Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.28 (t, $J = 7.5$ Hz, 2H), 7.22 – 7.15 (m, 3H), 3.26 (t, $J = 6.6$ Hz, 2H), 2.61 (t, $J = 7.7$ Hz, 2H), 1.71 – 1.63 (m, 2H), 1.53 – 1.46 (m, 4H), 1.38 – 1.32 (m, 2H), 1.13 (s, 6H), 0.92 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 142.8, 128.5, 128.4, 125.8, 74.2, 60.9, 40.0, 36.5, 32.9, 25.9, 25.7, 19.6, 14.1.

GC/MS (EI): m/z (%) 219 (1%), 160 (20%), 115 (35%), 104 (100%), 91 (55%), 59 (89%).

TLC: $R_f$ = 0.5 (30:1 Hexanes: Et$_2$O).

**Compound 42**

![Chemical Structure of Compound 42]

$N$-((4$R$,4$aR$,6$S$,8$aR$)-8a-(2,4-difluorophenyl)-4-methyl-6-(((2-phenylpropan-2-yl)oxy)methyl)-4,4$a$,5,6,8$a$-hexahydropyrano[3,4-$c$][1,3]thiazin-2-yl)benzamide

Following General Procedure B. Purification by PTLC (silica, 1:1 Hexanes: EtOAc) afforded 56.0 mg (68%) of the title compound 42.

Physical State: Pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.23 (d, $J = 7.6$ Hz, 2H), 7.55 – 7.49 (m, 2H), 7.48 – 7.42 (m, 4H), 7.39 – 7.33 (m, 2H), 7.28 – 7.23 (m, 1H), 6.98 – 6.85 (m, 2H), 4.19 (d, $J = 12.2$ Hz, 1H), 3.86 – 3.80 (m, 2H), 3.39 (dd, $J = 9.6$, 6.2 Hz, 1H), 3.28 (dd, $J = 7.1$, 3.4 Hz, 1H), 3.15 (dd, $J = 9.6$, 5.1 Hz, 1H), 2.97 – 2.90 (m, 1H), 1.75– 1.68 (m, 2H), 1.57 (d, $J = 2.7$ Hz, 6H), 1.27 (d, $J = 7.0$ Hz, 4H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 163.0 (dd, $J = 251.5$, 12.6 Hz), 158.7 (dd, $J = 248.4$, 11.5 Hz), 145.9, 132.0, 131.1 (dd, $J = 9.4$, 5.6 Hz), 129.3, 128.3, 128.2, 128.1, 127.0, 126.7, 125.8, 124.4, 112.3 (d, $J = 20.6$ Hz), 105.7 (t, $J = 26.9$ Hz), 73.2, 66.1, 61.2 (d, $J = 6.9$ Hz), 37.7, 36.5, 31.8, 28.7, 27.9, 23.5, 17.1.

HRMS (ESI): calc’d for $C_{31}H_{33}F_2N_2O_3S$ [M + H]$^+$: 551.2174; found 551.2150.

TLC: $R_f$ = 0.72 (1:1, Heptanes: EtOAc).
Compound 43

\[
\text{4-methoxy-3,5-dimethyl-2-(((2-phenylpropan-2-yl)oxy)methyl)pyridine}
\]

Following General Procedure A without 2N HCl work up, using AgClO\(_4\) (124 mg, 3 equiv.), "Bu\(_4\)NCIO\(_4\) (0.1 M) instead of AgPF\(_6\) and "Bu\(_4\)NPF\(_6\) respectively. Purification by PTLC (3:1 Hexanes: EtOAc) afforded 28.4 mg (50\%) of the title compound 43.

**Physical State:** colorless oil.

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 8.21 (s, 1H), 7.51 (d, \(J = 7.7\) Hz, 2H), 7.36 (t, \(J = 7.5\) Hz, 2H), 7.28 – 7.26 (m, 1H), 4.31 (s, 2H), 3.75 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H), 1.65 (s, 6H).

\(^13\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 164.3, 156.4, 149.1, 145.9, 128.4, 127.2, 126.1, 125.8, 65.7, 59.9, 28.4, 13.4, 11.1.

GC/MS (EI): m/z (%) 167 (100\%), 152 (35\%), 138 (51\%), 123 (43\%), 92 (44\%).

TLC: \(R_f = 0.2\) (3:1 Hexanes: EtOAc).

Compound 44

\[
\text{tert-butyl 2-(((4R,6S)-2,2-dimethyl-6-(((2-phenylpropan-2-yl)oxy)methyl)-1,3-dioxan-4-yl)acetate}
\]

Following General Procedure A without 2N HCl work up (washed twice with H\(_2\)O), using AgClO\(_4\) (124 mg, 3 equiv.), "Bu\(_4\)NCIO\(_4\) (0.1 M) instead of AgPF\(_6\) and "Bu\(_4\)NPF\(_6\) respectively. Purification by PTLC (4:1 Hexanes: EtOAc) afforded 39.4 mg (52\%) of the title compound 44.

**Physical State:** colorless oil.

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.41 – 7.39 (m, 2H), 7.33 – 7.30 (m, 2H), 7.25 – 7.22 (m, 1H), 4.32 – 4.24 (m, 1H), 4.06 – 3.98 (m, 1H), 3.27 (dd, \(J = 9.1, 5.1\) Hz, 1H), 3.02 (dd, \(J = 9.0, 6.7\) Hz, 1H), 2.42 (dd, \(J = 15.0, 7.3\) Hz, 1H), 2.31 (dd, \(J = 15.0, 5.9\) Hz, 1H), 1.74 (dt, \(J = 12.8, 2.5\) Hz, 1H), 1.52 (d, \(J = 2.2\) Hz, 6H), 1.45 (s, 12H), 1.34 (s, 3H), 1.17 – 1.11 (m, 1H).
\(^{13}\text{C NMR (151 MHz, CDCl}_3\):} \(\delta 170.4, 146.2, 128.2, 127.0, 126.0, 98.8, 80.7, 76.8, 68.6, 66.8, 66.2, 43.0, 34.3, 30.1, 28.5, 28.24, 28.22, 19.9.

**HRMS (ESI-TOF):** calcd for \(\text{C}_{22}\text{H}_{34}\text{O}_5\text{Na}\) \([\text{M + Na}]^+\): 401.2298; found 401.2299.

**TLC:** \(R_f = 0.65\) (3:1 Hexanes: EtOAc).

\([\alpha]_D^{24} = -6.0\) (\(c = 1.0, \text{CHCl}_3\)).

**Compound 45**

\[\text{5-}((3,5-\text{diethyl}-1-(2-((2-\text{phenylpropan-2-yl})\text{oxy})\text{ethyl})\text{-1H-} \text{pyrazol-4-yl})\text{oxy})\text{isophthalonitrile}\]

Following General Procedure B. Purification by PTLC (silica, 1:1 heptanes: EtOAc) afforded 27.0 mg (42%) of the title compound 45.

**Physical State:** Pale yellow oil.

\(^1\text{H NMR (500 MHz, CDCl}_3\):} \(\delta 7.56 (t, J = 1.4 \text{ Hz, 1H}), 7.41 (d, J = 1.3 \text{ Hz, 2H}), 7.30 - 7.26 (m, 2H), 7.24 - 7.19 (m, 3H), 4.14 (t, J = 5.4 \text{ Hz, 2H}), 3.53 (t, J = 5.4 \text{ Hz, 2H}), 2.60 (q, J = 7.7 \text{ Hz, 2H}), 2.40 (q, J = 7.6 \text{ Hz, 2H}), 1.48 (s, 6H), 1.16 - 1.06 (m, 6H).

\(^{13}\text{C NMR (126 MHz, CDCl}_3\):} \(\delta 160.0, 145.6, 144.2, 136.5, 131.3, 128.4, 128.2, 127.0, 125.5, 122.5, 116.3, 115.2, 77.3, 62.1, 50.1, 28.2, 19.0, 16.8, 13.0, 12.9.

**HRMS (ESI):** calcd for \(\text{C}_{26}\text{H}_{29}\text{N}_4\text{O}\) \([\text{M + H}]^+\): 429.2285; found 429.2267.

**TLC:** \(R_f = 0.6\) (1:1 Heptanes: EtOAc).

**Compound 46**

\[\text{1-}((1-\text{methylcyclobutoxy})\text{ethyl})\text{-2-}((\text{trifluoromethyl})\text{benzene}\]

Following General Procedure A, using AgSbF\(_6\) (103 mg, 1.5 equiv.) instead of AgPF\(_6\). Purification by PTLC (silica, 50:1 Hexanes: EtOAc) afforded 31.1 mg (60%) of the title compound 46.
Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.48 (d, $J = 7.9$ Hz, 1H), 8.18 (q, $J = 7.8$ Hz, 2H), 7.94 (t, $J = 7.6$ Hz, 1H), 5.58 – 5.53 (m, 1H), 2.75 (q, $J = 10.1$ Hz, 1H), 2.63 (q, $J = 10.2$ Hz, 1H), 2.50 – 2.43 (m, 1H), 2.40 – 2.32 (m, 1H), 2.30 – 2.20 (m, 1H), 2.16 – 2.08 (m, 1H), 2.01 (d, $J = 6.4$ Hz, 3H), 1.82 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 146.7, 132.2, 128.4, 126.8, 125.7 (q, $J = 30.2$ Hz), 125.2 (q, $J = 5.9$ Hz), 124.7 (q, $J = 271.8$ Hz), 77.9, 66.7, 34.7, 34.5, 26.6, 24.6, 12.6.

GC/MS (EI): m/z (%) 258 (0.07%), 230 (15%), 173 (23%), 153 (68%), 133 (54%).

TLC: $R_f$ = 0.3 (50:1 Hexanes: EtOAc).

**Compound 47**

![Compound 47](attachment:image)

4-((tert-butoxy)-1-tosylpiperidine

Following General Procedure B. Purification by PTLC (silica, 3:1 Hexanes: EtOAc) afforded 18.2 mg (39%) of the title compound 47.

Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.64 (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 3.45 – 3.36 (m, 3H), 2.71 (t, $J = 11.8$ Hz, 2H), 2.43 (s, 3H), 1.81 – 1.72 (m, 2H), 1.63 – 1.57 (m, 2H), 1.11 (s, 9H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 143.5, 133.6, 129.7, 127.8, 73.8, 65.9, 44.3, 33.6, 28.4, 21.7.

HRMS (ESI-TOF): calc’d for C$_{16}$H$_{26}$NO$_3$S [M + H]$^+$: 312.1633; found 312.1635.

TLC: $R_f$ = 0.2 (4:1 Hexanes: EtOAc).

**Compound 48**

![Compound 48](attachment:image)
(1S,2R,4R)-2-(tert-butoxy)-4-methyl-1-(prop-1-en-2-yl)cyclohexane

Following General Procedure B. Purification by PTLC (silica, 50:1 Hexanes: Et₂O) afforded 10.0 mg (32%) of the title compound 48.

Physical State: colorless oil.

^1H NMR (400 MHz, CDCl₃): δ 4.67 (d, J = 6.0 Hz, 2H), 3.03 (td, J = 10.2, 3.9 Hz, 1H), 2.02 – 1.89 (m, 2H), 1.79 – 1.74 (m, 1H), 1.70 (s, 3H), 1.68 – 1.61 (m, 1H), 1.28 (s, 2H), 1.20 (s, 9H), 1.16 – 1.03 (m, 2H), 0.95 (d, J = 6.5 Hz, 3H).

^13C NMR (151 MHz, CDCl₃): δ 150.2, 108.6, 76.0, 73.4, 44.8, 41.2, 39.0, 34.1, 31.5, 29.2, 20.8, 19.7.

GC/MS (EI): m/z (%) 210 (2%), 154 (14%), 136 (16%), 97 (69%), 57 (100%).

TLC: R_f = 0.3 (50:1 Hexanes: Et₂O).

[α]D²⁴ = -27.3 (c = 0.2, CHCl₃).

Compound 49

(2-((propan-2-yl-d7)oxy)propan-2-yl)benzene

Following General Procedure A. Purification by PTLC (silica, 30:1 Hexanes: Et₂O) afforded 30.2 mg (82%) of the title compound 49.

Physical State: colorless oil.

^1H NMR (600 MHz, CDCl₃): δ 7.49 (d, J = 7.4 Hz, 2H), 7.33 (t, J = 7.7 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 1.55 (s, 6H).

^13C NMR (151 MHz, CDCl₃): δ 147.1, 128.0, 127.0, 126.4, 76.8, 65.0 – 64.7 (m), 29.1, 23.8 (dt, J = 38.3, 19.3 Hz).

GC/MS (EI): m/z (%) 185 (0.06%), 170 (49%), 122 (100%), 91 (33%), 77 (17%).

TLC: R_f = 0.39 (20:1 Hexanes: Et₂O).

Compound 50
benzyl 3-((2-(4-chlorophenyl)propan-2-yl)oxy)azetidine-1-carboxylate

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), "Bu₄NClO₄ (0.1 M) instead of AgPF₆ and "Bu₄NPF₆ respectively. Purification by PTLC (3:1 Hexanes: EtOAc) afforded 50.1 mg (70%) of the title compound 50.

Physical State: colorless oil.

¹H NMR (600 MHz, CDCl₃): δ 7.36 – 7.26 (m, 9H), 5.07 (s, 2H), 4.12 – 4.02 (m, 3H), 3.97 – 3.92 (m, 2H), 1.48 (s, 6H).

¹³C NMR (151 MHz, CDCl₃): δ 156.5, 144.5, 136.8, 133.2, 128.7, 128.6, 128.13, 128.06, 127.2, 78.0, 66.8, 62.5, 58.7, 28.6.

HRMS (ESI-TOF): calc’d for C₂₀H₂₃ClNO₃ [M + H]⁺: 360.1361; found 360.1362.

TLC: Rf = 0.35 (3:1 Hexanes: EtOAc).

Compound 51

1-((3S,8S,9S,10R,13S,14S,17S)-10,13-dimethyl-3-((2-phenylpropan-2-yl)oxy)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethenone

Following General Procedure B. Purification by PTLC (silica, 50:1 Hexanes: Et₂O) afforded 35.2 mg (54%) of the title compound 51.

Physical State: colorless oil.

¹H NMR (600 MHz, CDCl₃): δ 7.48 (d, J = 7.3 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 5.17 (d, J = 5.1 Hz, 1H), 3.10 – 3.03 (m, 1H), 2.49 (t, J = 8.9 Hz, 1H), 2.29 (t, J = 13.3 Hz, 1H), 2.19 – 2.11 (m, 2H), 2.10 (s, 3H), 2.01 (d, J = 11.1 Hz, 1H), 1.93 (d, J = 19.5 Hz, 1H), 1.72 (dt, J = 13.3, 3.6 Hz, 1H), 1.65 – 1.59 (m, 4H), 1.55 (d, J = 12.6 Hz, 6H), 1.45 – 1.30 (m, 4H), 1.22 – 1.05 (m, 3H), 0.97 (s, 3H), 0.91 – 0.83 (m, 2H), 0.60 (s, 3H).

¹³C NMR (151 MHz, CDCl₃): δ 209.6, 147.0, 141.8, 127.9, 127.0, 126.3, 120.8, 76.9, 73.1, 63.8, 57.1, 50.1, 44.1, 41.8, 38.9, 37.7, 36.6, 31.9, 31.9, 31.6, 30.9, 29.5, 28.8, 24.6, 22.9, 21.1, 19.4, 13.3.

TLC: R_f = 0.2 (50:1 Hexanes: Et_2O).
[α]D^24 = -0.5 (c = 1.0, CHCl_3).

**Compound 52**

(2,5)-1,7,7-trimethyl-2-((2-phenylpropan-2-yl)oxy)bicyclo[2.2.1]heptane

Following General Procedure B. Purification by PTLC (silica, pure hexanes) afforded 27.0 mg (66%) of the title compound 52.

**Physical State**: colorless oil.

**^1H NMR (600 MHz, CDCl_3)**: δ 7.51 (d, J = 7.3 Hz, 2H), 7.33 (t, J = 7.7 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 3.61 (dt, J = 9.3, 2.5 Hz, 1H), 2.21 – 2.15 (m, 1H), 2.02 – 1.96 (m, 1H), 1.73 – 1.65 (m, 1H), 1.57 (t, J = 4.5 Hz, 1H), 1.49 (d, J = 11.7 Hz, 6H), 1.30 (s, 1H), 1.20 (d, J = 28.5 Hz, 1H), 1.04 (dd, J = 13.0, 3.4 Hz, 1H), 0.83 (s, 3H), 0.76 (d, J = 10.2 Hz, 6H).

**^13C NMR (151 MHz, CDCl_3)**: δ 148.4, 127.9, 126.6, 126.1, 77.0, 76.0, 49.5, 47.1, 45.5, 40.0, 29.7, 28.6, 27.9, 26.9, 20.0, 19.0, 14.0.

**GC/MS (EI)**: m/z (%) 272 (0.01%), 153 (44%), 135 (7%), 119 (100%), 109 (81%), 91 (38%).

**TLC**: R_f = 0.5 (50:1 Hexanes: Et_2O).

[α]D^24 = -22.5 (c = 0.5, CHCl_3).

**Compound 53**

(3aR,5R,6S,6aR)-6-((2-(4-chlorophenyl)propan-2-yl)oxy)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole
Following General Procedure A without 2N HCl work up (washed twice with H2O), using AgClO4 (124 mg, 3 equiv.), tBu4NClO4 (0.1 M) instead of AgPF6 and tBu4NPF6 respectively. Purification by PTLC (4:1 Hexanes: EtOAc) afforded 43.2 mg (52%) of the title compound 53.

Physical State: colorless oil.

1H NMR (600 MHz, CDCl3): δ 7.42 – 7.38 (m, 2H), 7.32 – 7.28 (m, 2H), 5.85 (d, J = 3.7 Hz, 1H), 4.34 (d, J = 3.7 Hz, 1H), 4.33 – 4.28 (m, 1H), 4.13 – 4.09 (m, 2H), 4.06 (d, J = 3.3 Hz, 1H), 3.99 (dd, J = 8.6, 6.3 Hz, 1H), 1.60 (s, 3H), 1.57 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H), 1.34 – 1.32 (s, 3H), 1.26 – 1.24 (s, 3H).

13C NMR (151 MHz, CDCl3): δ 144.9, 133.2, 128.4, 127.3, 111.8, 109.0, 105.1, 84.9, 81.4, 77.6, 75.7, 72.4, 67.4, 28.3, 27.8, 27.0, 26.8, 26.4, 25.6.


TLC: Rf = 0.54 (3:1 Hexanes: EtOAc).

[a]D24 = -16.4 (c = 1.0, CHCl3).

Compound 54

1-(1-(tert-butoxy)ethyl)-4-isobutylbenzene

Following General Procedure A, Purification by PTLC (silica, 100:1 Hexanes: Et2O) afforded 19.5 mg (42%) of the title compound 54.

Physical State: colorless oil.

1H NMR (600 MHz, CDCl3): δ 7.24 (d, J = 7.9 Hz, 2H), 7.07 (d, J = 7.9 Hz, 2H), 4.63 (q, J = 6.5 Hz, 1H), 2.44 (d, J = 7.2 Hz, 2H), 1.89 – 1.80 (m, 1H), 1.36 (d, J = 6.5 Hz, 3H), 1.16 (s, 9H), 0.89 (d, J = 6.6 Hz, 6H).

13C NMR (151 MHz, CDCl3): δ 144.9, 139.9, 128.9, 125.5, 74.2, 69.9, 45.3, 30.4, 28.7, 26.8, 22.6.

GC/MS (EI): m/z (%) 234 (4%), 219 (11%), 163 (100%), 161 (25%), 57 (18%).

TLC: Rf = 0.4 (100:1 Hexanes: Et2O).
Compound 55

1-((tert-butoxy)-2-methylpropyl)-4-chlorobenzene

Following General Procedure A. Purification by PTLC (silica, 100:1 Hexanes: Et₂O) afforded 31.0 mg (65%) of the title compound 55.

Physical State: colorless oil.

^1H NMR (600 MHz, CDCl₃): δ 7.25 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 4.06 (d, J = 6.8 Hz, 1H), 1.75 – 1.66 (m, J = 6.6 Hz, 1H), 1.07 (s, 9H), 0.92 (d, J = 6.7 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H).

^13C NMR (151 MHz, CDCl₃): δ 144.4, 132.1, 128.5, 127.9, 78.9, 74.1, 36.0, 28.9, 19.3, 19.0.

GC/MS (EI): m/z (%) 240 (0.004%), 197 (18%), 141 (100%), 125 (13%), 57 (51%).

TLC: R_f = 0.3 (100:1 Hexanes: Et₂O).

Compound 56

(1-(1-methylecyclohexyl)oxy)ethyl)benzene

Following General Procedure A. Purification by PTLC (silica, 100:1 Hexanes: Et₂O) afforded 22.7 mg (52%) of the title compound 56.

Physical State: colorless oil.

^1H NMR (600 MHz, CDCl₃): δ 7.36 (d, J = 7.4 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 4.66 (q, J = 6.5 Hz, 1H), 1.79 – 1.72 (m, 1H), 1.62 (d, J = 31.1 Hz, 2H), 1.49 – 1.36 (m, 7H), 1.33 – 1.24 (m, 3H), 1.05 (s, 3H).

^13C NMR (151 MHz, CDCl₃): δ 147.9, 128.2, 126.6, 125.8, 75.3, 69.1, 37.7, 37.3, 27.0, 26.0, 25.8, 22.8, 22.6.

GC/MS (EI): m/z (%) 218 (0.8%), 203 (3%), 114 (11%), 105 (100%), 77 (10%).

TLC: R_f = 0.4 (100:1 Hexanes: Et₂O).
Compound 57

1-(2-((2-methylnonadecan-2-yl)oxy)propan-2-yl)-4-(trifluoromethyl)benzene

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively. Purification by PTLC (10:1 Hexanes: Et₂O) afforded 44.5 mg (46%) of the title compound 57.

Physical State: colorless oil.

1H NMR (600 MHz, CDCl₃): δ 7.60 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 1.45 – 1.41 (m, 2H), 1.40 – 1.36 (m, 2H), 1.27 (d, J = 5.8 Hz, 34H), 1.01 (s, 6H), 0.88 (t, J = 7.1 Hz, 3H).

13C NMR (151 MHz, CDCl₃): δ 155.1 (q, J = 1.3 Hz), 128.7 (q, J = 30.2 Hz), 126.0, 124.9 (q, J = 4.5 Hz), 124.5 (q, J = 271.8 Hz), 77.2, 75.6, 45.40, 32.1, 31.75, 30.41, 29.9, 29.8, 29.5, 28.8, 24.5, 22.9, 14.3.

19F NMR (400 MHz, CDCl₃): δ -62.51.

GC/MS (EI): m/z (%) 297 (0.01%), 280 (3%), 187 (100%), 159 (9%), 69 (23%).

TLC: Rf = 0.3 (10:1 Hexanes: Et₂O).

Compound 58

1-((tert-butoxy)adamantane

Following General Procedure A. Purification by PTLC (silica, 30:1 Hexanes: Et₂O) afforded 27.1 mg (65%) of the title compound 58.

Physical State: white solid.

m.p.: 49 – 51 °C.

1H NMR (600 MHz, CDCl₃): δ 2.09 (s, 3H), 1.87 (d, J = 3.1 Hz, 6H), 1.60 (t, J = 3.2 Hz, 6H), 1.29 (s, 9H).

13C NMR (151 MHz, CDCl₃): δ 74.2, 74.0, 45.4, 36.6, 32.4, 31.2.

GC/MS (EI): m/z (%) 208 (0.2%), 193 (8%), 152 (37%), 135 (82%), 95 (100%).
TLC: $R_f = 0.47$ (20:1 Hexanes: Et$_2$O).

**Compound 59**

![Chemical structure of Compound 59]

1-((2,6-dimethyloct-7-en-2-yl)oxy)-1-methylcyclohexane

Following General Procedure A, using AgSbF$_6$ (103 mg, 1.5 equiv.), DBU (91.2 mg, 3.0 equiv.) instead of AgPF$_6$ and 2,4,6-collidine respectively. Purification by PTLC (silica, pure Hexanes) afforded 14.1 mg (28%) of the title compound 59.

**Physical State**: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.71 (ddd, $J = 17.5, 10.3, 7.5$ Hz, 1H), 5.04 – 4.82 (m, 2H), 2.12 (dq, $J = 13.9, 6.9$ Hz, 1H), 1.71 – 1.61 (m, 4H), 1.47 – 1.38 (m, 5H), 1.36 – 1.21 (m, 16H), 0.99 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 145.2, 112.3, 75.7, 74.8, 45.9, 40.8, 40.7, 37.9, 37.4, 29.4, 29.3, 26.2, 22.9, 22.1, 20.3.

GC/MS (EI): $m/z$ (%) 252 (0.2%), 155 (16%), 114 (20%), 97 (100%), 83 (38%).

TLC: $R_f = 0.3$ (Hexanes).

**Compound 60**

![Chemical structure of Compound 60]

((cyclohexyloxy)difluoromethyl)benzene

Following General Procedure A, using AgClO$_4$ (124 mg, 3 equiv.), $^+$Bu$_4$NClO$_4$ (0.1 M) instead of AgPF$_6$ and $^+$Bu$_4$NP$_6$ respectively, and the amount of alcohol was 6 equiv. Purification by PTLC (neutral aluminum oxide, pure Hexanes) afforded 20.8 mg (46%) of the title compound 60.

**Physical State**: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.62 (d, $J = 7.2$ Hz, 2H), 7.48 – 7.37 (m, 3H), 4.50 – 4.40 (m, 1H), 2.03 – 1.92 (m, 2H), 1.83 – 1.75 (m, 2H), 1.62 – 1.56 (m, 2H), 1.42 – 1.34 (m, 2H), 1.31 – 1.20 (m, 2H).
\[ ^{13}\text{C NMR (151 MHz, CDCl}_3\]): \delta 135.2 (t, J = 33.1 Hz), 130.4, 128.4, 125.6 (t, J = 3.6 Hz), 123.3 (t, J = 257.1 Hz), 73.9, 33.5, 25.5, 24.1. \]

\[ ^{19}\text{F NMR (376 MHz, CDCl}_3\): -66.27. \]

GC/MS (EI): m/z (%) 226 (0.1%), 127 (100%), 99 (29%), 77 (17%), 54 (10%).

TLC: \( R_f = 0.4 \) (50:1 Hexanes: Et\(_2\)O).

**Compound 61**

![Compound 61 structure]

**benzyl 3-(difluoro(phenyl)methoxy)azetidine-1-carboxylate**

Following General Procedure A, using AgClO\(_4\) (124 mg, 3 equiv.), \( ^{4}\text{Bu}_4\text{NClO}_4 \) (0.1 M) instead of AgPF\(_6\) and \( ^{4}\text{Bu}_4\text{NPF}_6 \) respectively. Purification by PTLC (neutral aluminum oxide, pure Hexanes) afforded 15.3 mg (23%) of the title compound 61.

**Physical State**: colorless oil.

\[ ^{1}\text{H NMR (600 MHz, CDCl}_3\]: \delta 7.63 – 7.58 (m, 2H), 7.49 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.38 – 7.30 (m, 5H), 5.19 – 5.13 (m, 1H), 5.11 (s, 2H), 4.38 – 4.31 (m, 2H), 4.15 (dd, J = 10.2, 4.5 Hz, 2H). \]

\[ ^{13}\text{C NMR (151 MHz, CDCl}_3\): \delta 156.4, 136.6, 133.3 (q, J = 31.7 Hz), 131.1, 128.7, 128.6, 128.3, 128.2, 125.5 (q, J = 4.5 Hz), 123.1 (q, J = 261.2 Hz), 67.1, 63.1 (q, J = 6.0 Hz), 57.3. \]

\[ ^{19}\text{F NMR (400 MHz, CDCl}_3\): \delta -68.85. \]

**HRMS (ESI-TOF)**: calc’d for C\(_{18}\)H\(_{18}\)F\(_2\)NO\(_3\) [M + H]**: 334.1255; found 334.1259.

TLC: \( R_f = 0.2 \) (Hexanes, aluminum TLC).

**Compound 62**

![Compound 62 structure]

**(2,2,2-trifluoro-1-methoxy-1-(1-phenylethoxy)ethyl)benzene**

Following General Procedure A without 2N HCl work up (washed twice with H\(_2\)O), using AgClO\(_4\) (124 mg, 3 equiv.), \( ^{4}\text{Bu}_4\text{NClO}_4 \) (0.1 M) instead of AgPF\(_6\) and \( ^{4}\text{Bu}_4\text{NPF}_6 \) respectively,
and the amount of alcohol was 4 equiv. Purification by PTLC (silica, 30:1 Hexanes: Et₂O) afforded 54.8 mg (88%) of the title compound 62.

**Physical State:** colorless oil.

**H NMR (600 MHz, CDCl₃, for two diastereomers)** (the integration at 5.32 ppm, 4.96 ppm indicated the ratio of the two isomers of 62 to be 1:1): δ 7.81 – 7.71 (m, 2H), 7.71 – 7.63 (m, 2H), 7.48 – 7.23 (m, 16H), 5.32 (q, J = 6.4 Hz, 1H), 4.96 (q, J = 6.5 Hz, 1H), 3.13 (s, 3H), 2.97 (s, 3H), 1.60 (d, J = 6.5 Hz, 3H), 1.53 (d, J = 6.5 Hz, 3H).

**C NMR (151 MHz, CDCl₃, for two diastereomers):** δ 145.0, 144.4, 134.9, 134.2, 129.7, 129.6, 128.8, 128.7, 128.5, 128.3, 128.14, 128.10, 127.4, 127.3, 126.3, 125.7, 123.0 (q, J = 290.8 Hz), 122.5 (q, J = 291.1 Hz), 100.0 (q, J = 40.3 Hz), 99.8 (q, J = 40.1 Hz), 72.4, 71.8 (d, J = 1.7 Hz), 52.2, 51.9 (d, J = 1.7 Hz), 25.5, 24.9.

**F NMR (376 MHz, CDCl₃, for two diastereomers):** δ -76.84, -78.04.

**GC/MS (EI):** m/z (%) 295 (0.2%), 241 (0.1%), 189 (37%), 105 (100%), 77 (32%).

**TLC:** Rᵢ = 0.47 (20:1 Hexanes: Et₂O).

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**Compound 63**

![Image](image_url)

(1-(tert-butoxy)-2,2,2-trifluoro-1-methoxyethyl)benzene

Following General Procedure A without 2N HCl work up (washed twice with H₂O), using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively, and the amount of alcohol was 4 equiv. Purification by PTLC (silica, 30:1 Hexanes: Et₂O) afforded 22.0 mg (42%) of the title compound 63.

**Physical State:** colorless oil.

**H NMR (600 MHz, CDCl₃):** δ 7.70 – 7.68 (m, 2H), 7.39 – 7.33 (m, 3H), 3.57 – 3.54 (m, 3H), 1.28 (s, 9H).

**C NMR (151 MHz, CDCl₃):** δ 137.2, 129.3, 129.0, 127.6, 122.8 (q, J = 292.2 Hz), 99.3 (q, J = 29.5 Hz), 78.8, 52.0 (d, J = 2.2 Hz), 30.5.

**F NMR (376 MHz, CDCl₃):** δ -76.72.

**GC/MS (EI):** m/z (%) 189 (84%), 137 (100%), 105 (41%), 77 (35%), 57 (45%).

**TLC:** Rᵢ = 0.57 (20:1 Hexanes: Et₂O).
Compound 64

1-(((E)-1,1-difluoro-4-phenylbut-3-en-2-yl)oxy)adamantane
Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively, and the amount of alcohol was 4 equiv. Purification by PTLC (silica, 30:1 Hexanes: Et₂O) afforded 32.6 mg (51%) of the title compound 64.

Physical State: colorless oil.

¹H NMR (500 MHz, CDCl₃): δ 7.41 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.25 (d, J = 7.9 Hz, 1H), 6.75 (d, J = 16.0 Hz, 1H), 6.21 (dd, J = 16.1, 6.0 Hz, 1H), 5.60 (td, J = 56.2, 4.3 Hz, 1H), 4.54 – 4.33 (m, 1H), 2.16 (s, 3H), 1.87 – 1.76 (m, 6H), 1.67 – 1.58 (m, 6H).

¹³C NMR (126 MHz, CDCl₃): δ 136.5, 133.6, 128.8, 128.1, 128.6, 125.1, 115.91 (t, J = 252.0 Hz), 75.1, 70.3 (t, J = 25.2 Hz), 42.5, 36.4, 30.8.

¹⁹F NMR (376 MHz, CDCl₃): δ -123.91 (d, J = 281.3 Hz), -128.95 (d, J = 281.3 Hz).

GC/MS (EI): m/z (%) 318 (0.3%), 267 (15%), 147 (14%), 135 (100%), 93 (10%).

TLC: Rₓ = 0.4 (30:1 Hexanes: Et₂O).

Compound 65

(2-((1,3-difluoropropan-2-yl)oxy)propan-2-yl)benzene
Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively, and the amount of alcohol was 4 equiv. Purification by PTLC (silica, 50:1 Hexanes: Et₂O) afforded 18.0 mg (42%) of the title compound 65.

Physical State: colorless oil.

¹H NMR (600 MHz, CDCl₃): δ 7.49 (d, J = 7.4 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 4.40 – 4.33 (m, 2H), 4.33 – 4.24 (m, 2H), 3.71 – 3.62 (m, 1H), 1.61 (s, 6H).
$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 145.1, 128.3, 127.8, 126.3, 82.1 (d, J = 166.1 Hz), 82.0 (d, J = 166.1 Hz), 78.0, 69.6 (t, J = 20.2 Hz), 28.4.

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -231.04.

GC/MS (EI): m/z (%) 199 (100%), 121 (49%), 119 (52%), 91 (47%), 77 (25%).

TLC: $R_f$ = 0.4 (100:1 Hexanes: Et$_2$O).

Compound 66

![Chemical Structure]

2-(2-((2-((4-chlorophenyl)propan-2-yl)oxy)ethoxy)ethoxy)ethan-1-ol

Following General Procedure A, using AgClO$_4$ (124 mg, 3 equiv.), $^4$Bu$_4$NClO$_4$ (0.1 M) instead of AgPF$_6$ and $^4$Bu$_4$NPF$_6$ respectively. Purification by PTLC (100% Et$_2$O) afforded 36.0 mg (59%) of the title compound 66.

Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.38 – 7.33 (m, 2H), 7.30 – 7.26 (m, 2H), 3.73 – 3.71 (m, 2H), 3.69 – 3.65 (m, 2H), 3.64 – 3.57 (m, 6H), 3.31 (t, J = 5.8 Hz, 2H), 2.60 (s, 1H), 1.51 (s, 6H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 144.9, 132.8, 128.4, 127.5, 76.6, 72.6, 71.0, 70.7, 70.5, 62.3, 61.9, 28.4.

HRMS (ESI-TOF): calc’d for C$_{15}$H$_{23}$ClO$_4$Na $[M + Na]^+$: 325.1177; found 325.1188.

TLC: $R_f$ = 0.29 (Et$_2$O).

Compound 67

![Chemical Structure]

$\text{tert-Butyl } 3-(2-((1-chloro-2-methylpropan-2-yl)oxy)ethoxy)ethoxy)propanoate$

Following General Procedure B without 2N HCl work up (washed twice with H$_2$O). Purification by PTLC (silica, 1:1 Hexanes: Et$_2$O) afforded 23.2 mg (48%) of the title compound 67.

Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 3.71 (t, J = 6.6 Hz, 2H), 3.66 – 3.63 (m, 2H), 3.61 – 3.58 (m, 4H), 3.54 – 3.52 (m, 2H), 3.46 (s, 2H), 2.50 (t, J = 6.6 Hz, 2H), 1.44 (s, 9H), 1.26 (s, 6H).
\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 171.1, 80.6, 74.8, 70.9, 70.8, 70.5, 67.1, 61.8, 51.6, 36.4, 28.2, 23.7.

HRMS (ESI-TOF): calc’d for C\(_{15}\)H\(_{29}\)ClO\(_5\)Na [M + Na]\(^+\): 347.1596; found 347.1602.

TLC: \(R_f = 0.39\) (3:1 Hexanes: EtOAc).

**Compound 68**

\(\text{tert-butyl} \quad (R)-3\)-(2-(2-(1,3-dio xoisoindolin-2-yl)ethoxy)ethoxy)ethoxy)propanoate\)

Following General Procedure B. Purification by PTLC (silica, 2:1 Hexanes: EtOAc) afforded 34.8 mg (57%) of the title compound 68.

**Physical State**: colorless oil.

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.86 (d, \(J = 8.5\) Hz, 2H), 7.74 (d, \(J = 8.5\) Hz, 2H), 5.60 (q, \(J = 6.3\) Hz, 1H), 3.69 – 3.48 (m, 10H), 2.46 (t, \(J = 6.6\) Hz, 2H), 1.80 (d, \(J = 6.3\) Hz, 3H), 1.43 (s, 9H).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 171.0, 168.1, 134.3, 131.9, 123.6, 80.6, 78.8, 70.7, 70.4, 70.3, 68.5, 67.0, 36.4, 28.2, 19.4.

HRMS (ESI-TOF): calc’d for C\(_{21}\)H\(_{29}\)NO\(_7\)Na [M + Na]\(^+\): 430.1842; found 430.1842.

TLC: \(R_f = 0.3\) (2:1 Hexanes: EtOAc).

**Compound 69**

\(\text{tert-butyl} \quad 4\)-(2-(2-(3\)-(tert-butoxy)-3-oxoproxy)ethoxy)ethoxy)-4-methylpiperidine-1-carboxylate\)

Following General Procedure A without 2N HCl work up (washed twice with H\(_2\)O), using AgSbF\(_6\) (103 mg, 1.5 equiv.), DBU (91.2 mg, 3.0 equiv.) instead of AgPF\(_6\) and 2,4,6-collidine respectively. Purification by PTLC (silica, 1:1 Hexanes: EtOAc) afforded 21.7 mg (25%) of the title compound 69.

**Physical State**: colorless oil.
\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 3.73 – 3.69 (m, 4H), 3.65 – 3.62 (m, 2H), 3.62 – 3.58 (m, 4H), 3.47 (t, \(J = 5.3\) Hz, 2H), 3.13 (s, 2H), 2.50 (t, \(J = 6.6\) Hz, 2H), 1.71 (d, \(J = 14.2\) Hz, 2H), 1.44 (s, 9H), 1.44 (s, 9H), 1.42 – 1.37 (m, 2H), 1.15 (s, 3H).

\(^13\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 171.1, 155.1, 80.6, 79.4, 71.8, 71.1, 70.8, 70.6, 67.1, 60.6, 39.8, 36.4, 35.7, 28.6, 28.2, 24.6.

HRMS (ESI-TOF): calc’d for C\(_{22}\)H\(_{42}\)NO\(_7\) [M + H]\(^+\): 432.2956; found 432.2952.

TLC: \(R_f = 0.49\) (1:1 Hexanes: EtOAc).

**Compound 78**

![Compound 78](image)

2-methyl-5-phenylpentan-2-ol

Following General Procedure C. Purification by PTLC (silica, 3:1 Hexanes: EtOAc) afforded 18.5 mg (52%) of the title compound 78.

**Physical State:** colorless oil.

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.29 (t, \(J = 7.6\) Hz, 2H), 7.22 – 7.15 (m, 3H), 2.63 (t, \(J = 7.7\) Hz, 2H), 1.74 – 1.67 (m, 2H), 1.55 – 1.49 (m, 2H), 1.21 (s, 6H).

\(^13\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 142.6, 128.5, 128.4, 125.9, 71.1, 43.6, 36.5, 29.4, 26.4.

GC/MS (EI): m/z (%) 160 (12%), 145 (13%), 104 (100%), 91 (39%), 59 (36%).

TLC: \(R_f = 0.2\) (3:1 Hexanes: EtOAc).

**Compound 79**

![Compound 79](image)

2-methyl-5-phenoxypentan-2-ol

Following General Procedure C. Purification by PTLC (silica, 4:1 Hexanes: EtOAc) afforded 25.6 mg (66%) of the title compound 79.

**Physical State:** colorless oil.

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.28 (t, \(J = 6.8\) Hz, 2H), 6.94 (t, \(J = 7.3\) Hz, 1H), 6.90 (d, \(J = 7.9\) Hz, 2H), 3.99 (t, \(J = 6.4\) Hz, 2H), 1.92 – 1.84 (m, 2H), 1.68 – 1.63 (m, 2H), 1.27 (s, 6H).

\(^13\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 159.1, 129.6, 120.8, 114.6, 70.8, 68.4, 40.4, 29.5, 24.5.
GC/MS (EI): m/z (%) 194 (2%), 176 (5%), 120 (15%), 94 (100%), 55 (46%).

TLC: R_f = 0.3 (4:1 Hexanes: EtOAc).

**Compound 80**

![Diagram of 3,5-dimethyladamantan-1-ol]

3,5-dimethyladamantan-1-ol

Following General Procedure C. Purification by PTLC (silica, 4:1 Hexanes: EtOAc) afforded 34.2 mg (95%) of the title compound **80**.

**Physical State**: colorless oil.

**1H NMR (400 MHz, CDCl_3)**: δ 2.21 – 2.14 (m, 1H), 1.56 (s, 2H), 1.44 (s, 1H), 1.39 – 1.24 (m, 8H), 1.11 (s, 2H), 0.86 (s, 6H).

**13C NMR (151 MHz, CDCl_3)**: δ 70.0, 51.6, 50.6, 43.9, 42.6, 33.9, 31.2, 30.0.

**GC/MS (EI)**: m/z (%) 180 (53%), 165 (21%), 123 (100%), 109 (95%), 91 (18%).

TLC: R_f = 0.3 (4:1 Hexanes: EtOAc).

**Compound 81**

![Diagram of methyl 4-hydroxybicyclo[2.2.2]octane-1-carboxylate]

methyl 4-hydroxybicyclo[2.2.2]octane-1-carboxylate

Following General Procedure C. Purification by PTLC (silica, 4:1 Hexanes: EtOAc) afforded 22.7 mg (61%) of the title compound **81**.

**Physical State**: colorless oil.

**1H NMR (600 MHz, CDCl_3)**: δ 3.63 (s, 3H), 1.97 – 1.87 (m, 6H), 1.69 – 1.61 (m, 6H), 1.36 (s, 1H).

**13C NMR (151 MHz, CDCl_3)**: δ 177.9, 69.4, 51.9, 38.5, 33.4, 29.7.

**GC/MS (EI)**: m/z (%) 184 (2%), 155(8%), 124 (100%), 109 (13%), 95 (18%).

**GC/MS (EI)(^{18}O)**: m/z (%) 186 (1%), 155 (9%), 126 (52%), 124 (13%), 115 (22%).

TLC: R_f = 0.3 (4:1 Hexanes: EtOAc).
Compound 82

*tert*-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate

Following General Procedure C. Purification by PTLC (silica, 1:1 Hexanes: EtOAc) afforded 13.8 mg (32%) of the title compound 82.

Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 3.69 (s, 2H), 3.23 (s, 2H), 1.54 (q, $J$ = 5.0, 4.4 Hz, 4H), 1.45 (s, 9H), 1.26 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 155.0, 79.5, 68.2, 40.6, 38.6, 30.2, 28.6.

GC/MS (EI): m/z (%) 215 (3%), 141 (34%), 126 (37%), 82 (44%), 57 (100%).

TLC: R$_f$ = 0.2 (2:1 Hexanes: EtOAc).

Compound 83

4-methyl-1-tosylpiperidin-4-ol

Following General Procedure C. Purification by PTLC (silica, 1:1 Hexanes: EtOAc) afforded 37.3 mg (69%) of the title compound 83.

Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.63 (d, $J$ = 8.2 Hz, 2H), 7.30 (d, $J$ = 8.0 Hz, 2H), 3.51 – 3.42 (m, 2H), 2.68 (t, $J$ = 13.0 Hz, 2H), 2.42 (s, 3H), 1.71 (t, $J$ = 10.5 Hz, 2H), 1.63 – 1.56 (m, 2H), 1.21 (s, 3H), 1.06 (s, 1H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 143.5, 133.4, 129.8, 127.8, 67.1, 42.5, 38.0, 30.5, 21.6.

HRMS (ESI-TOF): calc’d for C$_{13}$H$_{20}$NO$_3$S [M + H]$^+$: 270.1164; found 270.1167.

TLC: R$_f$ = 0.3 (2:1 Hexanes: EtOAc).
Compound 84

2-(4-bromophenyl)propan-2-ol

Following General Procedure C. Purification by PTLC (silica, 3:1 Hexanes: EtOAc) afforded 28.5 mg (67%) of the title compound 84.

Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.45 (d, $J = 8.5$ Hz, 2H), 7.36 (d, $J = 8.5$ Hz, 2H), 1.73 (s, 1H), 1.56 (s, 6H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 148.3, 131.4, 126.5, 120.7, 72.5, 31.9.

GC/MS (EI): m/z (%) 216 (10%), 214 (10%), 201 (94%), 199 (100%), 115 (33%), 91 (23%).

TLC: $R_f = 0.5$ (3:1 Hexanes: EtOAc).

Compound 85

2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol

Following General Procedure C. Purification by PTLC (silica, 3:1 Hexanes: EtOAc) afforded 28.8 mg (55%) of the title compound 85.

Physical State: white solid.

m.p.: 118 – 120 °C.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.80 (d, $J = 8.0$ Hz, 2H), 7.50 (d, $J = 8.1$ Hz, 2H), 1.73 (s, 1H), 1.58 (s, 6H), 1.34 (s, 12H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 152.4, 135.0, 128.4, 123.8, 83.9, 72.8, 31.8, 25.0.

GC/MS (EI): m/z (%) 262 (0.7%), 247 (83%), 158 (87%), 144 (100%), 77 (20%).

TLC: $R_f = 0.34$ (3:1 Hexanes: EtOAc).
Compound 86

3-hydroxy-2,2,3-trimethylcyclopentanone

Following General Procedure C. Purification by PTLC (silica, 1:1 Hexanes: EtOAc) afforded 15.1 mg (53%) of the title compound 86.

Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 2.50 – 2.40 (m, 1H), 2.37 – 2.29 (m, 1H), 2.09 – 1.94 (m, 2H), 1.30 (s, 3H), 1.25 (s, 1H), 1.03 (s, 3H), 0.93 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 221.8, 80.0, 53.1, 33.93, 33.85, 23.0, 21.7, 16.2.

GC/MS (EI): m/z (%) 142 (40%), 127 (3%), 109 (63%), 99 (60%), 71 (100%).

TLC: $R_f$ = 0.19 (3:1 Hexanes: EtOAc).

Compound 87

(4aS,10aR)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-ol$^{2,3}$

Following General Procedure C. Purification by PTLC (silica, 4:1 Hexanes: EtOAc) afforded 13.1 mg (24%) of compound 87-major and 4.4 mg (8%) compound 87-minor.

Compound 87-major

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.18 (d, $J = 8.2$ Hz, 1H), 7.01 (dd, $J = 8.2$, 2.1 Hz, 1H), 6.92 – 6.90 (m, 1H), 2.98 – 2.87 (m, 2H), 2.86 – 2.81 (m, 1H), 2.30 – 2.23 (m, 1H), 2.11 (ddt, $J = 12.9$, 6.9, 1.9 Hz, 1H), 1.88 (dt, $J = 12.5$, 3.3, 1.4 Hz, 1H), 1.81 – 1.74 (m, 1H), 1.73 – 1.64 (m, 2H), 1.61 (dd, $J = 12.6$, 1.9 Hz, 1H), 1.49 – 1.36 (m, 2H), 1.24 (s, 6H), 1.23 (s, 3H), 1.16 (s, 3H).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta 146.5, 145.8, 134.9, 127.1, 124.7, 124.1, 72.6, 52.6, 42.9, 38.4, 38.1, 33.6, 30.5, 24.7, 24.12, 24.10, 23.1, 20.7, 18.1.\)

**GC/MS (EI):** m/z (%) 272 (4%), 257 (4%), 239 (100%), 157 (21%), 91 (19%).

**TLC:** \(R_f = 0.42\) (3:1 Hexanes: EtOAc).

**Compound 87-minor**

\((1S,4aS,10aR)-7\)-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-ol\(^2,3\)

**Physical State:** white solid.

**m.p.:** 64 – 66 °C.

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta 7.18\) (d, \(J = 8.2\) Hz, 1H), 7.01 – 6.99 (m, 1H), 6.92 – 6.89 (m, 1H), 3.02 – 2.96 (m, 1H), 2.94 – 2.87 (m, 1H), 2.83 (p, \(J = 6.9\) Hz, 1H), 2.33 – 2.30 (m, 1H), 2.07 – 1.99 (m, 1H), 1.97 (dt, \(J = 13.8, 3.6\) Hz, 1H), 1.95 – 1.84 (m, 1H), 1.76 – 1.72 (m, 1H), 1.64 – 1.60 (m, 1H), 1.48 – 1.40 (m, 3H), 1.31 (d, \(J = 0.9\) Hz, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta 146.9, 145.8, 134.8, 127.0, 124.1, 124.0, 72.4, 48.8, 40.9, 38.3, 37.3, 33.6, 30.9, 29.6, 24.6, 24.2, 24.1, 18.6, 18.1.

**GC/MS (EI):** m/z (%) 272 (13%), 257 (19%), 239 (100%), 157 (51%), 91 (20%).

**TLC:** \(R_f = 0.58\) (3:1 Hexanes: EtOAc).

**Compound 88**

\(2-(4-(1\)-hydroxyethyl\)phenyl\)isoindolin-1-one\)

Following General Procedure C. Purification by PTLC (silica, 1:1 Hexanes: EtOAc) afforded 20.1 mg (40%) of the title compound 88.

**Physical State:** colorless oil.
$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.93 (d, $J = 7.5$ Hz, 1H), 7.86 – 7.82 (m, 2H), 7.62 – 7.57 (m, 1H), 7.52 (d, $J = 7.7$ Hz, 2H), 7.46 – 7.42 (m, 2H), 4.96 – 4.90 (m, 1H), 4.86 (s, 2H), 1.87 (s, 1H), 1.52 (d, $J = 6.4$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 167.7, 142.1, 140.2, 138.8, 133.3, 132.2, 128.6, 126.4, 124.3, 122.8, 119.7, 70.1, 50.9, 25.3.

HRMS (ESI-TOF): calc’d for C$_{16}$H$_{16}$NO$_2$ [M + H]$^+$: 254.1181; found 254.1176.

TLC: $R_f$ = 0.2 (3:1 Hexanes: EtOAc).

**Compound 89**

![Chemical structure of Compound 89]

difluoro(phenyl)methyl methyl succinate

Following General Procedure A, 3 equiv. of 4-methoxy-4-oxobutanoic acid was used as nucleophile, using AgClO$_4$ (124 mg, 3 equiv.), $^\circ$Bu$_4$NClO$_4$ (0.1 M) instead of AgPF$_6$ and $^\circ$Bu$_4$NPF$_6$ respectively. Purification by PTLC (silica, 5:1 Hexanes: EtOAc) afforded 16.0 mg (31%) of the title compound 89.

**Physical State**: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.63 – 7.61 (m, 2H), 7.53 – 7.47 (m, 1H), 7.47 – 7.43 (m, 2H), 3.68 (s, 3H), 2.76 (dd, $J = 7.3$, 6.2 Hz, 2H), 2.63 (dd, $J = 7.4$, 6.1 Hz, 2H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 172.1, 167.2, 132.0 (t, $J = 30.2$ Hz), 131.2, 128.6, 125.6 (t, $J = 4.5$ Hz), 121.7 (t, $J = 265.5$ Hz), 52.1 (d, $J = 2.4$ Hz), 29.6, 28.4.

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -69.01.

HRMS (ESI-TOF): calc’d for C$_{12}$H$_{12}$F$_2$O$_4$Na [M + Na]$^+$: 281.0596; found 281.0599.

TLC: $R_f$ = 0.46 (3:1 Hexanes: EtOAc).

**Compound 90**

![Chemical structure of Compound 90]

difluoro(phenyl)methyl 4-chlorobenzoate
Following General Procedure A, 3 equiv. of 4-chlorobenzoic acid was used as nucleophile, using AgClO₄ (124 mg, 3 equiv.), ₆Bu₄NClO₄ (0.1 M) instead of AgPF₆ and ₆Bu₄NPF₆ respectively. Purification by PTLC (silica, 10:1 Hexanes: EtOAc) afforded 20.0 mg (36%) of the title compound 90.

**Physical State:** white solid.

**m.p.:** 61 – 63 °C.

**¹H NMR (600 MHz, CDCl₃):** δ 8.03 – 7.96 (m, 2H), 7.71 – 7.69 (m, 2H), 7.55 – 7.50 (m, 1H), 7.50 – 7.42 (m, 4H).

**¹³C NMR (151 MHz, CDCl₃):** δ 160.6, 141.1, 133.0 (t, J = 30.3 Hz), 131.7, 131.3, 129.3, 128.7, 127.0, 125.6 (t, J = 4.5 Hz), 122.3 (t, J = 265.5 Hz).

**¹⁹F NMR (376 MHz, CDCl₃):** δ -68.73.

**GC/MS (EI): m/z (%)** 282 (11%), 139 (100%), 127 (47%), 96 (96%), 77 (45%).

**TLC:** R_f = 0.68 (3:1 Hexanes: EtOAc).

**Compound 91**

![Image of Compound 91]

1-chloro-4-(2-fluoropropan-2-yl)benzene

Following General Procedure A, KF (42 mg, 3.6 equiv.) was used as nucleophile, AgClO₄ (124 mg, 3 equiv.) was used instead of AgPF₆ and 18-crown-6 (190 mg, 3.6 equiv.) was used as additive. Purification by PTLC (silica, 100% Hexanes) afforded 11.9 mg (35%) of the title compound 91.

**Physical State:** colorless oil.

**¹H NMR (600 MHz, CDCl₃):** δ 7.35 – 7.29 (m, 4H), 1.69 (s, 3H), 1.65 (s, 3H).

**¹³C NMR (151 MHz, CDCl₃):** δ 144.5 (d, J = 22.4 Hz), 133.3, 128.5, 125.5 (d, J = 9.1 Hz), 95.4 (d, J = 169.5 Hz), 29.4 (d, J = 25.7 Hz).

**¹⁹F NMR (376 MHz, CDCl₃):** δ -137.65.

**GC/MS (EI): m/z (%)** 172 (21%), 157 (100%), 137 (23%), 75 (21%).

**TLC:** R_f = 0.45 (Hexanes).
**Compound 92**

1-fluoroadamantane

Following General Procedure A, KF (42 mg, 3.6 equiv.) was used as nucleophile, AgClO₄ (124 mg, 3 equiv.) was used instead of AgPF₆ and 18-crown-6 (190 mg, 3.6 equiv.) was used as additive. Purification by PTLC (silica, 100% Hexanes) afforded 18.0 mg (58%) of the title compound **92**.

**Physical State**: white solid (sublimation at room temperature).

**1H NMR (600 MHz, CDCl₃)**: δ 2.28 – 2.18 (m, 3H), 1.89 (dd, J = 5.7, 3.0 Hz, 6H), 1.68 – 1.56 (m, 6H).

**13C NMR (151 MHz, CDCl₃)**: δ 92.7 (d, J = 183.2 Hz), 42.9 (d, J = 17.0 Hz), 36.0, 31.6 (d, J = 9.9 Hz).

**19F NMR (376 MHz, CDCl₃)**: δ -128.70.

**GC/MS (EI)**: m/z (%) 154 (53%), 135 (0.6%), 111 (18%), 97 (100%), 79 (20%).

**TLC**: Rf = 0.47 (Hexanes).

**Compound 93**

*tert*-butyl 4-fluoro-4-methylpiperidine-1-carboxylate

Following General Procedure A without 2N HCl work up (washed twice with H₂O), KF (42 mg, 3.6 equiv.) was used as nucleophile, AgClO₄ (124 mg, 3 equiv.) was used instead of AgPF₆ and 18-crown-6 (190 mg, 3.6 equiv.) was used as additive. Purification by PTLC (silica, 10:1 Hexanes: EtOAc) afforded 7.8 mg (18%) of the title compound **93**.

**Physical State**: colorless oil.

**1H NMR (600 MHz, CDCl₃)**: δ 3.86 (s, 2H), 3.10 (t, J = 12.4 Hz, 2H), 1.85 – 1.74 (m, 2H), 1.64 – 1.54 (m, 2H), 1.45 (s, 9H), 1.36 (d, J = 21.4 Hz, 3H).

**13C NMR (151 MHz, CDCl₃)**: δ 154.9, 92.5 (d, J = 168.3 Hz), 79.7, 39.9, 36.4 (d, J = 22.0 Hz), 28.6, 27.2 (d, J = 24.2 Hz).
\[ \text{\(^{19}\text{F NMR (376 MHz, CDCl}_3\)}\): } \delta -153.97. \\
\text{GC/MS (EI): } m/z (\%) 217 (1\%), 144 (14\%), 116 (11\%), 57 (100\%). \\
\text{TLC: } R_f = 0.61 (3:1 \text{ Hexanes: EtOAc}).

**Compound 94**

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\]

\[ \text{2-(1-fluoroethyl)isoindoline-1,3-dione} \]

Following General Procedure A, KF (42 mg, 3.6 equiv.) was used as nucleophile, AgClO\(_4\) (124 mg, 3 equiv.) was used instead of AgPF\(_6\) and 18-crown-6 (190 mg, 3.6 equiv.) was used as additive. Purification by PTLC (silica, 100% CH\(_2\)Cl\(_2\)) afforded 24.0 mg (62\%) of the title compound 94.

**Physical State:** white solid.

**m.p.:** 134 – 136 °C.

\[ \text{\(^1\text{H NMR (600 MHz, CDCl}_3\)}\): } \delta 7.97 – 7.87 (m, 2H), 7.83 – 7.72 (m, 2H), 6.35 (dq, \(J = 48.2, 6.3\) Hz, 1H), 2.00 (dd, \(J = 20.7, 6.3\) Hz, 3H).

\[ \text{\(^{13}\text{C NMR (151 MHz, CDCl}_3\)}\): } \delta 166.9, 134.8, 131.7, 124.0, 87.3 (d, \(J = 198.4\) Hz), 18.3 (d, \(J = 28.0\) Hz).

\[ \text{\(^{19}\text{F NMR (376 MHz, CDCl}_3\)}\): } \delta -140.04.

\[ \text{GC/MS (EI): } m/z (\%) 193 (1\%), 178 (2\%), 173 (100\%), 146 (9\%), 76 (47\%). \\
\text{TLC: } R_f = 0.45 (3:1 \text{ Hexanes: EtOAc}).

**Compound 95**

\[
\begin{array}{c}
\text{HN} \\
\text{O} \\
\text{Me} \\
\text{O}
\end{array}
\]

\[ \text{N-(adamantan-1-yl)-2-phenylacetamide} \]

Following General Procedure A, 3 equiv. of phenylacetonitrile was used as nucleophile, using AgClO\(_4\) (124 mg, 3 equiv.), \(^{\text{t}}\text{Bu}_4\text{NClO}_4\) (0.1 M) instead of AgPF\(_6\) and \(^{\text{t}}\text{Bu}_4\text{NPF}_6\) respectively.
Purification by PTLC (silica, 1:1 Hexanes: Et₂O) afforded 7.5 mg (14%) of the title compound 95.

**Physical State:** white solid.

**m.p.:** 172 – 174 °C.

**1H NMR (600 MHz, CDCl₃):** δ 7.36 – 7.32 (m, 2H), 7.29 – 7.26 (m, 1H), 7.25 – 7.23 (m, 2H), 5.02 (s, 1H), 3.48 (s, 2H), 2.06 – 2.00 (m, 3H), 1.91 (d, J = 3.0 Hz, 6H), 1.64 (t, J = 3.2 Hz, 6H).

**13C NMR (151 MHz, CDCl₃):** δ 170.2, 135.7, 129.4, 129.0, 127.3, 52.0, 45.2, 41.6, 36.4, 29.5.

**HRMS (ESI-TOF):** calced for C₁₈H₂₄NO [M + H]⁺: 270.1852; found 270.1853.

**TLC:** Rₓ = 0.32 (3:1 Hexanes: EtOAc).

**Compound 97**

![Chemical Structure](image)

**1-(butoxy(1-ethylicyclopropyl)methyl)-4-chlorobenzene**

Following General Procedure A, using AgSbF₆ (103 mg, 1.5 equiv.) instead of AgPF₆.

Purification by PTLC (50:1 Hexanes: Et₂O) afforded 21.3 mg (40%) of the title compound 97.

**Physical State:** colorless oil.

**1H NMR (600 MHz, CDCl₃):** δ 7.35 – 7.26 (m, 2H), 7.26 – 7.20 (m, 2H), 4.13 (s, 1H), 3.26 (qt, J = 9.2, 6.5 Hz, 2H), 1.59 – 1.42 (m, 3H), 1.35 (ddt, J = 13.4, 10.0, 6.7 Hz, 2H), 1.13 (dq, J = 14.7, 7.4 Hz, 1H), 0.91 – 0.83 (m, 6H), 0.55 (ddd, J = 9.5, 4.9, 3.5 Hz, 1H), 0.43 (dt, J = 8.5, 4.3 Hz, 1H), 0.32 – 0.23 (m, 2H).

**13C NMR (151 MHz, CDCl₃):** δ 139.9, 129.0, 128.2, 83.7, 69.3, 32.2, 26.9, 25.2, 19.6, 14.1, 10.7, 8.9, 7.8.

**GC/MS (EI):** m/z (%) 266 (0.1%), 238 (24%), 197 (19%), 182 (44%), 166 (62%), 141(100%).

**TLC:** Rₓ = 0.4 (30:1 Hexanes: Et₂O).
Compound 99

$$\text{O}$$

$$\text{BnO}$$

$$\text{Me}$$

$$\text{OMe}$$

$$\text{Me}$$

((1-(2-methoxyethoxy)-2-methylpropoxy)methyl)benzene

Following General Procedure A, using AgSbF$_6$ (103 mg, 1.5 equiv.) instead of AgPF$_6$. Purification by PTLC (10:1 Hexanes: Et$_2$O) afforded 31.0 mg (65%) of the title compound 99.

**Physical State**: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.39 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 4.69 (d, $J$ = 11.8 Hz, 1H), 4.55 (d, $J$ = 11.8 Hz, 1H), 4.28 (d, $J$ = 7.3 Hz, 1H), 3.73 (dt, $J$ = 10.8, 4.7 Hz, 1H), 3.66 (ddd, $J$ = 10.7, 5.4, 4.1 Hz, 1H), 3.58 – 3.53 (m, 2H), 3.40 (s, 3H), 2.01 (dq, $J$ = 13.7, 6.8 Hz, 1H), 0.96 (dd, $J$ = 6.8, 4.7 Hz, 6H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 128.5, 127.9, 127.6, 107.5, 72.2, 68.1, 64.5, 59.2, 31.1, 18.1, 18.0.

GC/MS (EI): m/z (%) 162 (4%), 131 (5%), 107 (4%), 91 (100%), 59 (13%).

TLC: $R_f$ = 0.3 (10:1 Hexanes: Et$_2$O).

Compound 101

3-methylene-1-phenylocyclopentan-1-ol

Following General Procedure C. Purification by PTLC (silica, 5:1 Hexanes: EtOAc) afforded 5.9 mg (17%) of the title compound 101.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.50 (d, $J$ = 7.4 Hz, 2H), 7.36 (t, $J$ = 7.4 Hz, 2H), 7.27 (t, $J$ = 7.4 Hz, 1H), 5.01 (broad s, 2H), 2.85 (dq, $J$ = 16.3, 2.5 Hz, 1H), 2.78-2.64 (m, 2H), 2.85 (dq, $J$ = 16.9, 2.5 Hz, 1H), 2.55 (dd, $J$ = 16.3, 9.2 Hz, 1H), 2.22-2.07 (m, 2H), 1.70 (broad s, 2H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 150.2, 145.9, 128.5, 127.3, 125.3, 107.6, 82.4, 48.8, 41.1, 30.6.


TLC: $R_f$ = 0.4 (5:1 Hexanes: EtOAc).
**Compound 102**

1-butoxy-1-methylcyclohexane

Following General Procedure A, using AgSbF₆ (103 mg, 1.5 equiv.), DBU (91.2 mg, 3.0 equiv.) instead of AgPF₆ and 2,4,6-collidine respectively. Purification by PTLC (silica, 30:1 Hexanes: Et₂O) afforded 14.3 mg (42%) of the title compound 102.

**Physical State:** colorless oil.

**¹H NMR (600 MHz, CDCl₃):** δ 3.29 (t, J = 6.6 Hz, 2H), 1.72 – 1.65 (m, 2H), 1.61 – 1.48 (m, 5H), 1.42 – 1.35 (m, 4H), 1.32 – 1.22 (m, 3H), 1.10 (s, 3H), 0.92 (t, J = 7.4 Hz, 3H).

**¹³C NMR (151 MHz, CDCl₃):** δ 73.1, 60.1, 36.7, 33.0, 26.0, 24.8, 22.4, 19.8, 14.2.

**GC/MS (EI):** m/z (%) 170 (6%), 155 (3%), 127 (22%), 71 (100%).

**TLC:** Rₔ = 0.47 (20:1 Hexanes: Et₂O).

**Compound 103**

2-(((2-phenylpropan-2-yl)oxy)methyl)pyridine

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively. Purification by PTLC (silica, 3:1 Hexanes: EtOAc) afforded 17.7 mg (39%) of the title compound 103.

**Physical State:** colorless oil.

**¹H NMR (600 MHz, CDCl₃):** δ 8.56 (s, 1H), 8.51 (d, J = 4.9 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 7.7 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.31 – 7.26 (m, 2H), 4.25 (s, 2H), 1.65 (s, 6H).

**¹³C NMR (151 MHz, CDCl₃):** δ 148.6, 148.2, 145.7, 135.8, 135.3, 128.6, 127.4, 125.9, 123.6, 77.7, 62.8, 28.5.

**GC/MS (EI):** m/z (%) 212 (17%), 118 (76%), 103 (46%), 92 (100%), 65 (20%).

**TLC:** Rₔ = 0.3 (3:1 Hexanes: EtOAc).
Compound 104

1-(4-nitrophenoxy)adamantane

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively. Purification by PTLC (silica, 4:1 Hexanes: Et₂O) afforded 38.0 mg (63%) of the title compound 104.

Physical State: white solid.

m.p.: 50 – 52 °C.

¹H NMR (600 MHz, CDCl₃): δ 8.18 – 8.11 (m, 2H), 7.43 – 7.37 (m, 2H), 3.65 (t, J = 6.7 Hz, 2H), 2.91 (t, J = 6.7 Hz, 2H), 2.15 – 2.08 (m, 3H), 1.68 (d, J = 3.0 Hz, 6H), 1.65 – 1.53 (m, 6H).

¹³C NMR (151 MHz, CDCl₃): δ 148.0, 146.6, 130.0, 123.5, 72.5, 60.1, 41.6, 37.3, 36.5, 30.6.

GC/MS (EI): m/z (%) 301 (0.01%), 271 (3%), 150 (5%), 135 (100%), 79 (9%).

TLC: Rᵣ = 0.65 (3:1 Hexanes: EtOAc).

Compound 105

(methoxymethylene)dibenzene

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively and the amount of MeOH was 6 equiv. Purification by PTLC (silica, pure Hexanes) afforded 33.5 mg (85%) of the title compound 105.

Physical State: colorless oil.

¹H NMR (500 MHz, CDCl₃): δ 7.39 – 7.31 (m, 8H), 7.28 – 7.24 (m, 2H), 5.26 (s, 1H), 3.40 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 142.2, 128.5, 127.6, 127.1, 85.6, 57.2.

GC/MS (EI): m/z (%) 198 (75%), 167 (100%), 121 (74%), 105 (38%), 77 (38%).

TLC: Rᵣ = 0.4 (50:1 Hexanes: Et₂O).
**Compound 106**

1-chloro-4-(1-methoxy-2-methylpropyl)benzene

Following General Procedure A, using AgClO$_4$ (124 mg, 3 equiv.), $n$Bu$_4$NClO$_4$ (0.1 M) instead of AgPF$_6$ and $n$Bu$_4$NP$_6$ respectively and the amount of MeOH was 6 equiv. Purification by PTLC (silica, 100:1 Hexanes: Et$_2$O) afforded 31.7 mg (80%) of the title compound 106.

**Physical State:** colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.31 (d, $J =$ 8.4 Hz, 2H), 7.18 (d, $J =$ 8.4 Hz, 2H), 3.74 (d, $J =$ 7.1 Hz, 1H), 3.18 (s, 3H), 1.87 (hept, $J =$ 6.8 Hz, 1H), 0.97 (d, $J =$ 6.6 Hz, 3H), 0.73 (d, $J =$ 6.8 Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 139.8, 133.1, 128.9, 128.4, 89.2, 57.2, 34.8, 18.9.

GC/MS (EI): m/z (%) 198 (0.7%), 157 (32%), 155 (100%), 139 (10%), 91 (15%).

TLC: $R_f$ = 0.4 (100:1 Hexanes: Et$_2$O).

**Compound 107**

**tert-butyl 4-methoxy-4-methylpiperidine-1-carboxylate**

Following General Procedure A, using AgClO$_4$ (124 mg, 3 equiv.), $n$Bu$_4$NClO$_4$ (0.1 M) instead of AgPF$_6$ and $n$Bu$_4$NP$_6$ respectively, and MeOH (3 mL) as solvent. Purification by PTLC (silica, 8:1 Hexanes: EtOAc) afforded 21.5 mg (47%) of the title compound 107.

**Physical State:** colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 3.69 (d, $J =$ 13.1 Hz, 2H), 3.19 (s, 3H), 3.12 (t, $J =$ 12.2 Hz, 2H), 1.71 (d, $J =$ 13.7 Hz, 2H), 1.45 (s, 9H), 1.44 – 1.38 (m, 2H), 1.15 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 155.1, 79.4, 71.7, 48.8, 40.0, 35.4, 28.6, 23.9.

GC/MS (EI): m/z (%) 229 (2%), 141 (62%), 126 (51%), 82 (58%), 57 (100%).

HRMS (ESI-TOF): calc’d for C$_{12}$H$_{23}$NO$_3$Na [M + Na]$^+$: 252.1576; found 252.1575.
TLC: $R_f = 0.3$ (8:1 Hexanes: EtOAc).

**Compound 108**

benzyl 4-[(1-methyl-1-phenylethoxy)methyl]piperidine-1-carboxylate

Following General Procedure A. Purification by PTLC (silica, 2:1 Hexanes: EtOAc) afforded 31.8 mg (43%) of the title compound 108.

**Physical State**: colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.37-7.11 (m, 10H), 5.03 (s, 2H), 4.08 (broad s, 2H), 2.90 (d, $J$ = 6.1 Hz, 2H), 2.69 (broad s, 2H), 1.77 – 1.52 (m, 4H), 1.43 (s, 6H), 1.02 (d, $J$ = 13.0 Hz, 2H).

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 155.4, 146.4, 137.1, 128.6, 128.3, 128.0, 127.9, 127.0, 125.8, 76.25, 67.2, 67.1, 44.1, 36.9, 29.2, 28.4.

HRMS (ESI-TOF): calc’d for C$_{23}$H$_{30}$NO$_3$ [M + H]$^+$: 368.2226, found: 368.2244.

TLC: $R_f = 0.65$ (2:1 Hexanes: EtOAc).

**Compound 109**

2-phenyl-4-(((2-phenylpropan-2-yl)oxy)methyl)thiazole

Following General Procedure B (0.6 mmol scale). Purification by PTLC afforded 102 mg (55%) of the title compound 109.

**Physical State**: white solid.

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.85 (m, 2H), 7.45 (m, 2H), 7.35-7.25 (m, 5H), 7.20 (m, 2H), 4.40 (s, 2H), 1.60 (s, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 168.1, 156.3, 150.0, 133.8, 129.9, 128.9, 128.3, 127.1, 126.5, 125.8, 114.4, 77.6, 62.2, 26.5.

HRMS (ESI-TOF): calc’d for C$_{19}$H$_{20}$NOS [M + H]$^+$: 310.1260; found 310.1245.

TLC: $R_f = 0.7$ (7:3 heptane: MTBE).
Compound 110

5-bromo-2-(((2-phenylpropan-2-yl)oxy)methyl)benzofuran

Following General Procedure B (0.6 mmol scale). Purification by PTLC afforded 130 mg (63%) of the title compound 110.

Physical State: colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.66 (m, 1H), 7.55-7.50 (m, 2H), 7.41 (m, 2H), 7.35-7.25 (m, 3H), 6.57 (m, 1H), 4.32 (s, 2H), 1.66 (s, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 157.1, 153.9, 145.4, 130.4, 128.4, 127.3, 126.9, 125.9, 123.5, 115.7, 112.7, 104.0, 78.1, 58.6, 28.4.

HRMS (ESI-TOF): calc’d for C$_{18}$H$_{18}$BrO$_2$ [M + H]$^+$: 345.0490; found 345.0484.

TLC: $R_f$ = 0.8 (7:3 Heptane: MTBE).

Compound 111

2-(((2-phenylpropan-2-yl)oxy)methyl)quinoline

Following General Procedure B (0.6 mmol scale). Purification by PTLC afforded 84 mg (51%) of the title compound 111.

Physical State: colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.19 (m, 1H), 8.01 (m, 1H), 7.82 (m, 1H), 7.77 (m, 1H), 7.69 (m, 1H), 7.60-7.50 (m, 3H), 7.37 (m, 2H), 7.25 (m 1H), 4.59 (s, 2H), 1.70 (s, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 160.3, 147.4, 145.9, 136.5, 129.4, 128.9, 128.3, 127.6, 127.4, 127.1, 126.0, 125.8, 119.4, 77.7, 67.0, 28.4.

HRMS (ESI-TOF): calc’d for C$_{19}$H$_{20}$NO [M + H]$^+$: 278.1539; found 278.1550.

TLC: $R_f$ = 0.4 (7:3 Heptane: MTBE).
Compound 112

![Structure of Compound 112]

2-(((2-phenylpropan-2-yl)oxy)methyl)quinoxaline

Following General Procedure B (0.6 mmol scale). Purification by PTLC afforded 52 mg (31%) of the title compound 112.

Physical State: colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.12 (s, 1H), 8.12 (m, 1H), 8.01 (m, 1H), 7.75 (m, 2H), 7.53 (m, 2H), 7.39 (m, 2H), 7.29 (m, 1H), 4.61 (s, 2H), 1.71 (s, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 154.4, 145.4, 144.8, 142.0, 141.6, 130.0, 129.4, 129.3, 129.0, 128.5, 127.3, 125.8, 78.1, 65.5, 28.3.

HRMS (ESI-TOF): calc’d for C$_{18}$H$_{19}$N$_2$O [M + H]$^+$: 279.1492; found 279.1501.

TLC: $R_f$ = 0.5 (7:3 Heptane: MTBE).

Compound 113

![Structure of Compound 113]

(2-((3-phenylprop-2-yn-1-yl)oxy)propan-2-yl)benzene

Following General Procedure A. Purification by PTLC (silica, 10:1 Hexanes: Et$_2$O) afforded 14.5 mg (29%) of the title compound 113.

Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.51 – 7.47 (m, 2H), 7.43 (dd, $J$ = 6.7, 2.9 Hz, 2H), 7.37 (t, $J$ = 7.7 Hz, 2H), 7.29 (dq, $J$ = 5.9, 2.3, 1.6 Hz, 4H), 4.08 (s, 2H), 1.63 (s, 6H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 145.5, 131.9, 128.5, 128.3, 128.3, 127.3, 126.0, 123.1, 86.7, 85.1, 78.3, 52.5, 28.6.

GC/MS (EI): m/z (%) 235 (50%), 192 (63%), 115 (100%), 105 (20%), 91 (27%).

TLC: $R_f$ = 0.3 (10:1 Hexanes: Et$_2$O).
Compound 114


Following General Procedure B. Purification by PTLC (40:1 Hexanes: Et2O) afforded 79.1 mg (71%) of the title compound 114.

Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.39 – 7.34 (m, 4H), 7.34 – 7.30 (m, 4H), 7.26 – 7.22 (m, 2H), 5.58 (s, 1H), 3.38 – 3.31 (m, 1H), 1.97 (dt, $J$ = 12.6, 3.4 Hz, 1H), 1.92 (d, $J$ = 10.5 Hz, 1H), 1.85 – 1.77 (m, 1H), 1.74 – 1.63 (m, 3H), 1.58 – 0.96 (m, 24H), 0.91 (d, $J$ = 6.6 Hz, 3H), 0.88 (dd, $J$ = 6.6, 2.7 Hz, 6H), 0.83 (s, 3H), 0.66 (s, 3H), 0.57 (td, $J$ = 12.4, 4.0 Hz, 1H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 143.2, 128.4, 127.3, 127.2, 80.3, 76.5, 56.6, 56.4, 54.6, 45.0, 42.7, 40.2, 39.7, 37.2, 36.3, 35.9, 35.6, 35.2, 32.3, 29.0, 28.6, 28.4, 28.2, 24.4, 24.0, 23.0, 22.7, 21.4, 18.8, 12.5, 12.2.

GC/MS (EI): m/z (%) 491 (1%), 387 (4%), 371 (8%), 215 (10%), 119 (100%), 91 (34%).

TLC: $R_f$ = 0.3 (40:1 Hexanes: Et2O).

$[\alpha]_D^{24}$ = 8.3 (c = 1.0, CHCl$_3$).

Compound 115

(2-(cyclohexyloxy)propan-2-yl)benzene

Following General Procedure A, using AgClO$_4$ (124 mg, 3 equiv.), $^\circ$Bu$_4$NClO$_4$ (0.1 M) instead of AgPF$_6$ and $^\circ$Bu$_4$NPF$_6$ respectively and the amount of alcohol was 6 equiv. Purification by PTLC (silica, pure Hexanes) afforded 29.6 mg (68%) of the title compound 115.

Physical State: colorless oil.
Compound 116

benzyl 4-(1-methyl-1-phenylethoxy)piperidine-1-carboxylate

Following General Procedure A. Purification by PTLC (silica, 2:1 Hexanes: EtOAc) afforded 32.7 mg (46%) of the title compound 116.

Physical State: colorless oil.

1H NMR (400 MHz, CDCl₃): δ 7.50 – 7.45 (m, 2H), 7.37 – 7.24 (m, 8H), 5.11 (s, 2H), 3.88 – 3.78 (broad s, 2H), 3.38 (dt, J = 8.4, 4.4 Hz, 1H), 3.03 (ddd, J = 13.2, 9.5, 3.5 Hz, 2H), 1.68 – 1.58 (broad m, 2H), 1.55 (s, 6H), 1.53 – 1.41 (m, 2H).

13C NMR (151 MHz, CDCl₃): δ 155.4, 146.8, 137.1, 128.6, 128.1, 128.0, 127.9, 127.2, 126.2, 77.1, 68.4, 67.1, 41.9, 33.7, 29.0.

HRMS (ESI-TOF): calc’d for C_{22}H_{28}NO₃ [M + H]^+: 354.2069, found: 354.2096.

TLC: R_f = 0.6 (2:1 Hexanes: EtOAc).

Compound 117

benzyl 3-(1-methyl-1-phenylethoxy)piperidine-1-carboxylate

Following General Procedure A. Purification by PTLC (silica, 2:1 Hexanes: EtOAc) afforded 21.4 mg (30%) of the title compound 117.

Physical State: colorless oil.

1H NMR (400 MHz, CDCl₃, 2 rotamers): δ 7.57 – 7.39 (m, 2H), 7.39 – 7.24 (m, 8H), 5.05 (s, 2H), 4.09 – 3.66 (m, 2H), 3.3 – 2.7 (m, 3H), 1.86 – 1.19 (m, 11H).
\[ \text{Compound 118} \]

**benzyl 3-(1-methyl-1-phenylethoxy)pyrrolidine-1-carboxylate**

Following General Procedure A, using AgClO\(_4\) (124 mg, 3 equiv.), \(\text{nBu}4\text{NClO}_4\) (0.1 M) instead of AgPF\(_6\) and \(\text{nBu}4\text{NPF}_6\) respectively. Purification by PTLC (silica, 2:1 Hexanes: EtOAc) afforded 22.0 mg (32%) of the title compound **118**.

**Physical State**: colorless oil.

\[ \text{1H NMR (600 MHz, CDCl}_3\text{, 2 rotamers): } \delta 7.42 (d, J = 7.9 Hz, 2H), 7.38 – 7.24 (m, 8H), 5.11 (s, 2H), 3.87 – 3.84 (m, 1H), 3.61-3.39 (m, 2H), 3.37 – 3.20 (m, 2H), 1.91-1.85 (m, 2H), 1.55 – 1.53 (4 s, 6H). \]

\[ \text{13C NMR (151 MHz, CDCl}_3\text{, 2 rotamers): } \delta 155.4, 146.6, 137.0, 128.6, 128.1, 128.0, 127.9, 127.2, 126.2, 67.7, 67.1, 50.6, 44.2, 32.9, 30.1, 28.8, 28.7, 23.9, 23.4. \]

**HRMS (ESI-TOF)**: calc’d for C\(_{22}\)H\(_{27}\)NO\(_3\)Na [M + Na]\(^+\): 376.1889, found: 376.1896.

**TLC**: \(R_f = 0.59\) (2:1 Hexanes: EtOAc).

\[ \text{Compound 119} \]

**benzyl 3-(1-methyl-1-phenylethoxy)azetidine-1-carboxylate**

Following General Procedure A, using AgClO\(_4\) (124 mg, 3 equiv.), \(\text{nBu}4\text{NClO}_4\) (0.1 M) instead of AgPF\(_6\) and \(\text{nBu}4\text{NPF}_6\) respectively. Purification by PTLC (silica, 2:1 Hexanes: EtOAc) afforded 22.0 mg (34%) of the title compound **119**.

**Physical State**: colorless oil.
\( ^1\text{H NMR (400 MHz, CDCl}_3\): } \delta 7.42 - 7.27 (m, 10H), 5.07 (s, 2H), 4.16 - 4.08 (m, 1H), 4.04 (dd, \( J = 9.1, 6.7 \) Hz, 2H), 3.95 (dd, \( J = 9.1, 4.9 \) Hz, 2H), 1.50 (s, 6H).

\( ^{13}\text{C NMR (151 MHz, CDCl}_3\): } \delta 156.5, 145.9, 136.8, 128.6, 128.5, 128.1, 128.0, 127.4, 125.7, 78.4, 66.8, 62.5, 58.8, 28.7.

HRMS (ESI-TOF): calc’d for \( \text{C}_{20}\text{H}_{24}\text{NO}_3 \) [M + H]⁺: 326.1756, found: 326.1765.

TLC: \( R_f = 0.53 \) (2:1 Hexanes: EtOAc).

**Compound 120**

![Compound 120](image)

1,3-dimethyl-5-(1-phenylethoxy)adamantane

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), \( ^{4}\text{Bu}_4\text{NCIO}_4 \) (0.1 M) instead of AgPF₆ and \( ^{4}\text{Bu}_4\text{NPFO} \) respectively. Purification by PTLC (silica, 1:1 Hexanes: CH₂Cl₂) afforded 47.0 mg (83%) of the title compound 120.

**Physical State**: colorless oil.

\( ^1\text{H NMR (400 MHz, CDCl}_3\): } \delta 7.35 (d, \( J = 7.3 \) Hz, 2H), 7.30 (t, \( J = 7.5 \) Hz, 2H), 7.20 (t, \( J = 7.2 \) Hz, 1H), 4.81 (q, \( J = 6.5 \) Hz, 1H), 2.12 (p, \( J = 3.2 \) Hz, 1H), 1.55 (dd, \( J = 10.7, 1.5 \) Hz, 2H), 1.45 (d, \( J = 10.7 \) Hz, 1H), 1.40 – 1.30 (m, 6H), 1.30 – 1.18 (m, 4H), 1.09 (s, 2H), 0.83 (s, 3H), 0.82 (s, 3H).

\( ^{13}\text{C NMR (151 MHz, CDCl}_3\): } \delta 147.7, 128.2, 126.6, 125.7, 75.3, 68.1, 50.9, 49.0, 48.5, 42.9, 41.2, 33.7, 33.6, 31.1, 30.3, 30.3, 26.9.

GC/MS (EI): m/z (%) 269 (7%), 163 (100%), 123 (10%), 105 (60%), 91 (5%), 77 (10%), 55 (5%).

TLC: \( R_f = 0.59 \) (1:1 Hexanes: CH₂Cl₂).

**Compound 121**

![Compound 121](image)
(1-(1-(trifluoromethyl)cyclohexyl)oxy)ethyl)benzene

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively, and the amount of alcohol was 4 equiv. Purification by PTLC (silica, 50:1 Hexanes: Et₂O) afforded 15.2 mg (28%) of the title compound 121.

**Physical State**: colorless oil.

**¹H NMR (600 MHz, CDCl₃)**: δ 7.36 – 7.30 (m, 4H), 7.24 (t, J = 6.9 Hz, 1H), 4.89 (q, J = 6.4 Hz, 1H), 1.95 (t, J = 17.5 Hz, 2H), 1.59 – 1.46 (m, 5H), 1.44 (d, J = 6.4 Hz, 3H), 1.31 – 1.27 (m, 1H), 1.14 – 1.05 (m, 1H), 0.96 – 0.86 (m, 1H).

**¹³C NMR (151 MHz, CDCl₃)**: δ 145.9, 128.4, 127.1, 126.8 (q, J = 288.4 Hz), 125.8, 77.2 (q, J = 25.6 Hz), 72.2, 30.1, 27.0, 26.0, 25.1, 20.6, 20.3.

**GC/MS (EI)**: m/z (%) 272 (0.2%), 257 (26%), 107 (100%), 105 (80%), 79 (27%).

**TLC**: Rₓ = 0.5 (40:1 Hexanes: Et₂O).

**Compound 122**

(1-(cyclohexyloxy)-2,2,2-trifluoro-1-methoxyethyl)benzene

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively, and the amount of alcohol was 4 equiv. Purification by PTLC (silica, 30:1 Hexanes: Et₂O) afforded 49.6 mg (86%) of the title compound 122.

**Physical State**: colorless oil.

**¹H NMR (600 MHz, CDCl₃)**: δ 7.69 – 7.61 (m, 2H), 7.44 – 7.36 (m, 3H), 4.07 – 3.95 (m, 1H), 3.37 (s, 3H), 1.97 – 1.83 (m, 2H), 1.81 – 1.74 (m, 2H), 1.58 – 1.47 (m, 3H), 1.33 – 1.25 (m, 3H).

**¹³C NMR (151 MHz, CDCl₃)**: δ 134.9, 129.5, 128.8, 128.0, 122.9 (q, J = 291.0 Hz), 99.5 (q, J = 29.7 Hz), 72.2, 51.7, 34.1, 33.2, 25.7, 24.4, 24.3.

**¹⁹F NMR (376 MHz, CDCl₃)**: δ -77.32.

**GC/MS (EI)**: m/z (%) 257 (0.06%), 219 (3%), 189 (100%), 137 (70%), 105 (32%).

**TLC**: Rₓ = 0.53 (20:1 Hexanes: Et₂O).
Compound 123

(2,2,2-trifluoro-1-(1-phenylethoxy)ethyl)benzene

Following General Procedure A, using AgClO$_4$ (124 mg, 3 equiv.), $^4$Bu$_4$NClO$_4$ (0.1 M) instead of AgPF$_6$ and $^4$Bu$_4$NPF$_6$ respectively, and the amount of alcohol was 4 equiv. Purification by PTLC (silica, 50:1 Hexanes: Et$_2$O) afforded 29.1 mg (52%) of the title compound 123.

Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$, for both diastereomers) (the integration at 4.62 ppm, 4.44 ppm indicated the ratio of the two isomers of 123 to be 1:1): $\delta$ 7.47 – 7.27 (m, 15H), 7.25 – 7.13 (m, 5H), 4.83 – 4.75 (m, 1H), 4.62 (q, $J = 6.7$ Hz, 1H), 4.44 (q, $J = 6.8$ Hz, 1H), 4.38 – 4.25 (q, $J = 6.7$ Hz, 1H), 1.54 (d, $J = 6.4$ Hz, 3H), 1.48 (d, $J = 6.5$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$, for both diastereomers): $\delta$ 142.4, 141.7, 133.8, 133.0, 129.7, 129.2, 128.9; 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 127.9, 126.8, 126.5, 124.7 (q, $J = 283.9$ Hz), 123.9 (q, $J = 280.9$ Hz), 78.8, 77.2 (q, $J = 31.7$ Hz), 76.8 (q, $J = 31.7$ Hz), 75.9, 24.4, 23.4.

$^{19}$F NMR (376 MHz, CDCl$_3$, for both diastereomers): $\delta$ -76.10, -76.71.

GC/MS (EI) for one diastereomer: m/z (%) 265 (0.2%), 159 (26%), 121 (100%), 105 (100%), 77 (35%).

GC/MS (EI) for the other diastereomer: m/z (%) 265 (15%), 159 (100%), 121 (49%), 105 (75%), 77 (18%).

TLC: $R_f = 0.4$ (40:1 Hexanes: Et$_2$O).

Compound 124

(1-((1,1,3,3,3-hexafluoropropan-2-yl)oxy)ethyl)benzene

Following General Procedure A, HFIP (3 mL) instead of CH$_2$Cl$_2$ as solvent, no AgClO$_4$ and 3Å molecular sieves. Purification by PTLC (silica, 30:1 Hexanes: Et$_2$O) afforded 34.8 mg (64%) of the title compound 124.

Physical State: colorless oil.
\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta 7.45 - 7.31\) (m, 5H), 4.85 (q, \(J = 6.5\) Hz, 1H), 3.99 (hept, \(J = 6.0\) Hz, 1H), 1.60 (d, \(J = 6.5\) Hz, 3H).

\(^1\)C NMR (151 MHz, CDCl\(_3\)): \(\delta 139.6, 129.1, 129.0, 127.3, 123.2 - 120.3\) (m), 81.5, 73.0 (p, \(J = 32.1\) Hz), 23.3.

\(^1\)F NMR (376 MHz, CDCl\(_3\)): \(\delta -73.54\) (dq, \(J = 304.6, 9.4\) Hz).

GC/MS (EI): m/z (%) 272 (11%), 257 (100%), 105 (69%), 77 (23%).

TLC: \(R_f = 0.53\) (20:1 Hexanes: Et\(_2\)O).

**Compound 125**

(2-((1,1,1-trifluoropropan-2-yl)oxy)propan-2-yl)benzene

Following General Procedure A, using AgClO\(_4\) (124 mg, 3 equiv.), \(^{\text{Bu}}\text{NCIO}_4\) (0.1 M) instead of AgPF\(_6\) and \(^{\text{Bu}}\text{NPF}_6\) respectively, and the amount of alcohol was 4 equiv. Purification by PTLC (silica, 40:1 Hexanes: Et\(_2\)O) afforded 20.5 mg (44%) of the title compound 125.

**Physical State**: colorless oil.

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta 7.49\) (d, \(J = 8.6\) Hz, 2H), 7.35 (t, \(J = 7.6\) Hz, 2H), 7.28 (t, \(J = 7.3\) Hz, 1H), 3.80 – 3.71 (m, 1H), 1.62 (s, 3H), 1.59 (s, 3H), 1.12 (d, \(J = 6.4\) Hz, 3H).

\(^1\)C NMR (151 MHz, CDCl\(_3\)): \(\delta 144.8, 128.2, 127.7, 126.5, 125.4\) (q, \(J = 282.4\) Hz), 78.6, 67.5 (q, \(J = 30.7\) Hz), 29.6, 26.8, 16.4.

\(^1\)F NMR (376 MHz, CDCl\(_3\)): \(\delta -78.47\).

GC/MS (EI): m/z (%) 232 (0.2%), 217 (100%), 119 (29%), 91 (24%), 77 (16%).

TLC: \(R_f = 0.5\) (40:1 Hexanes: Et\(_2\)O).

**Compound 126**

(2-(2,2,2-trifluorooethoxy)propan-2-yl)benzene
Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively, and the amount of alcohol was 4 equiv. Purification by PTLC (silica, pure Hexanes) afforded 21.6 mg (50%) of the title compound 126.

**Physical State**: colorless oil.

**¹H NMR (600 MHz, CDCl₃)**: δ 7.43 (d, J = 7.3 Hz, 2H), 7.37 (t, J = 7.7 Hz, 2H), 7.30 (d, J = 7.3 Hz, 1H), 3.52 (q, J = 8.7 Hz, 2H), 1.60 (s, 6H).

**¹³C NMR (151 MHz, CDCl₃)**: δ 144.4, 128.7, 127.7, 125.9, 123.8 (q, J = 277.8 Hz), 78.6, 61.7 (q, J = 34.2 Hz), 28.1.

**¹⁹F NMR (376 MHz, CDCl₃)**: δ -74.37.

**GC/MS (EI)**: m/z (%) 218 (0.6%), 203 (100%), 119 (11%), 105 (9%), 91 (13%).

**TLC**: Rᵥ = 0.4 (100:1 Hexanes: Et₂O).

**Compound 127**

4,4,5,5-tetramethyl-2-(4-((1,1,1-trifluoropropan-2-yl)oxy)propan-2-yl)phenyl)-1,3,2-dioxaborolane

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), nBu₄NClO₄ (0.1 M) instead of AgPF₆ and nBu₄NPF₆ respectively, and the amount of alcohol was 4 equiv. Purification by PTLC (silica, 10:1 Hexanes: Et₂O) afforded 24.4 mg (34%) of the title compound 127.

**Physical State**: colorless oil.

**¹H NMR (600 MHz, CDCl₃)**: δ 7.81 – 7.79 (m, 2H), 7.50 – 7.48 (m, 2H), 3.73 (p, J = 6.5 Hz, 1H), 1.61 (s, 3H), 1.58 (s, 3H), 1.35 (s, 12H), 1.11 (d, J = 6.5 Hz, 3H).

**¹³C NMR (151 MHz, CDCl₃)**: δ 147.9, 134.7, 133.6, 125.8, 125.3 (q, J = 281.9 Hz), 84.0, 78.6, 67.7 (q, J = 30.7 Hz), 29.8, 26.7, 25.0 (d, J = 5.5 Hz), 16.3 (q, J = 2.4 Hz).

**¹⁹F NMR (376 MHz, CDCl₃)**: δ -78.45.

**GC/MS (EI)**: m/z (%) 358 (0.2%), 343 (100%), 245 (36%), 145 (52%).

**TLC**: Rᵥ = 0.26 (20:1 Hexanes: Et₂O).
Compound 128

1-(1-ethoxy-2,2,2-trifluoroethoxy)adamantane

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), Bu₄NClO₄ (0.1 M) instead of AgPF₆ and Bu₄NPF₆ respectively, and the amount of alcohol was 4 equiv. Purification by PTLC (silica, 30:1 hexanes: Et₂O) afforded 40.0 mg (72%) of the title compound 128.

Physical State: colorless oil.

¹H NMR (600 MHz, CDCl₃): δ 4.97 (q, J = 4.3 Hz, 1H), 3.81 – 3.67 (m, 2H), 2.20 – 2.17 (m, 3H), 1.86 – 1.78 (m, 6H), 1.68 – 1.59 (m, 6H), 1.23 (t, J = 7.1 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃): δ 122.4 (q, J = 285.5 Hz), 90.4 (q, J = 34.6 Hz), 76.0, 62.1, 42.3, 36.2, 30.8, 15.5.

¹⁹F NMR (376 MHz, CDCl₃): δ -80.74.

GC/MS (EI): m/z (%) 278 (0.2%), 209 (2%), 151 (0.5%), 135 (100%), 95 (26%).

TLC: R_f = 0.50 (20:1 Hexanes: Et₂O).

Compound 129

1-chloro-4-(2-methyl-1-((1,1,1-trifluoropropan-2-yl)oxy)propyl)benzene

Following General Procedure A, using AgClO₄ (124 mg, 3 equiv.), Bu₄NClO₄ (0.1 M) instead of AgPF₆ and Bu₄NPF₆ respectively, and the amount of alcohol was 4 equiv. Purification by PTLC (40:1 Hexanes: Et₂O) afforded 29.6 mg (53%, dr=1.5:1) of the title compound 129.

Physical State: colorless oil.

¹H NMR (600 MHz, CDCl₃, for both diastereomers) (the integration at 4.12 ppm, 4.00 ppm indicated the ratio of the two isomers of 129 to be 1.7:1): δ 7.32 (t, J = 8.2 Hz, 5.3H), 7.21 (d, J = 8.3 Hz, 5.4H), 4.12 (d, J = 7.9 Hz, 1.0H), 4.00 (d, J = 7.2 Hz, 1.7H), 3.65 – 3.55 (m, 2.7H), 1.94 – 1.84 (m, 2.7H), 1.30 (d, J = 6.4 Hz, 5.0H), 1.12 (d, J = 6.6 Hz, 3.1H), 1.05 (d, J = 6.6 Hz, 3.0H), 0.99 (d, J = 6.6 Hz, 5.1H), 0.74 (d, J = 6.8 Hz, 4.9H), 0.68 (d, J = 6.8 Hz, 3.0H).
\[ ^{13}C\text{ NMR (151 MHz, CDCl}_3\text{, for both diastereomers): } \delta 139.3, 138.6, 133.8, 133.7, 129.1, 129.1, 128.6, 128.5, 125.9 (q, } J = 283.9 \text{ Hz), 124.9 (q, } J = 280.9 \text{ Hz), 88.7, 85.4, 71.7 (q, } J = 30.0 \text{ Hz), 71.0 (q, } J = 31.1 \text{ Hz), 35.1, 34.9, 19.0, 19.0, 18.9, 18.9, 15.4 (q, } J = 2.1 \text{ Hz), 12.8 (q, } J = 2.1 \text{ Hz).} \]

\[ ^{19}F\text{ NMR (376 MHz, CDCl}_3\text{, for both diastereomers): } \delta -78.04, -79.12. \]

\[ \text{GC/MS (EI) for one diastereomer: } m/z (\%) 280 (0.5\%), 239 (32\%), 237 (100\%), 141 (35\%), 113 (16\%). \]

\[ \text{GC/MS (EI) for the other diastereomer: } m/z (\%) 280 (0.7\%), 239 (33\%), 237 (100\%), 141 (24\%), 113 (10\%). \]

\[ \text{TLC: } R_f = 0.4 \text{ (100:1 Hexanes: Et}_2\text{O).} \]

**Compound 130**

\[ \text{2-(2,2-difluoro-1-(1-(4-isobutylphenyl)ethoxy)ethyl)naphthalene} \]

Following General Procedure A, using AgClO\(_4\) (124 mg, 3 equiv.), \(\text{Bu}_4\text{NCIO}_4\) (0.1 M) instead of AgPF\(_6\) and \(\text{Bu}_4\text{NPF}_6\) respectively, and the amount of alcohol was 4 equiv. Purification by PTLC (50:1 Hexanes: Et\(_2\)O) afforded 30.2 mg (41\%, dr = 1:1) of the title compound 130.

**Physical State**: colorless oil.

\[ ^{1}H\text{ NMR (600 MHz, CDCl}_3\text{, for both diastereomers): the integration at 2.52 ppm, 2.41 ppm indicated the ratio of the two isomers of 130 to be 1:1: } \delta 7.93 – 7.73 \text{ (m, 8H), 7.56 – 7.46 (m, 5H), 7.42 (dd, } J = 8.3, 1.7 \text{ Hz, 1H), 7.23 – 7.12 (m, 6H), 7.05 – 6.99 (m, 2H), 5.89 (td, } J = 55.8, 28.5 \text{ Hz, 1H), 5.88 (td, } J = 55.8, 28.5 \text{ Hz, 1H), 4.76 (q, } J = 6.4 \text{ Hz, 1H), 4.68 (td, } J = 10.0, 4.9 \text{ Hz, 1H), 4.48 (ddd, } J = 11.6, 10.2, 4.4 \text{ Hz, 1H), 4.39 (q, } J = 6.5 \text{ Hz, 1H), 2.52 (d, } J = 7.3 \text{ Hz, 2H), 2.41 (d, } J = 7.2 \text{ Hz, 2H), 1.94 – 1.86 (m, 1H), 1.84 – 1.76 (m, 1H), 1.56 (d, } J = 6.4 \text{ Hz, 3H), 1.49 (d, } J = 6.5 \text{ Hz, 3H), 0.95 (dd, } J = 6.6, 0.9 \text{ Hz, 6H), 0.86 (dd, } J = 6.6, 3.2 \text{ Hz, 6H).} \]

\[ ^{13}C\text{ NMR (151 MHz, CDCl}_3\text{): } 141.6, 141.2, 140.2, 139.5, 133.8, 133.3, 133.1, 133.0, 132.3, 132.3, 129.5, 129.2, 128.6, 128.3, 128.2, 128.2, 128.2, 127.9, 127.8, 127.6, 126.6, 126.6, 126.5, 126.5, 126.4, 126.3, 125.5, 125.3, 117.8, 116.2 (t, } J = 120.8 \text{ Hz), 114.5 (t, } J = 121.8 \text{ Hz), 78.5 (t, } J = 24.2 \text{ Hz), 77.9 (t, } J = 24.2 \text{ Hz), 77.6, 75.4, 45.3, 45.2, 30.4, 30.3, 24.5, 22.9, 22.6, 22.5, 22.5.} \]
\(^{19}\)F NMR (400 MHz, CDCl\(_3\)): \(\delta\) -124.91, -125.31, -128.22.

GC/MS (EI) for one diastereomer: m/z (%) 368 (2%), 192 (35%), 177 (23%), 161 (100%), 117 (93%).

GC/MS (EI) for the other diastereomer: m/z (%) 368 (1%), 192 (30%), 177 (17%), 161 (100%), 117 (86%).

TLC: \(R_f = 0.4\) (50:1 Hexanes: Et\(_2\)O).

**Compound 131**

![NHbz](./images/NHbz.png)

benzyl (tetrahydrofuran-2-yl)carbamate

The title product was synthesized by following General Procedure A with 2-(((benzyloxy)carbonyl)amino)-5-hydroxypentanoic acid as starting material\(^4\) (53 mg, 0.2 mmol) to yield the title product as a colorless oil (19 mg, 44%). Spectral data matched those published\(^5\).

\(^1\)H NMR data are reported here for convenience:

\(^1\)H NMR (500 MHz, CDCl\(_3\)):

\(\delta\) 7.40 – 7.28 (m, 5H), 5.57 (m, 1H), 5.25 – 5.03 (m, 3H), 3.90 (ddd, \(J = 8.4, 7.0, 6.7\) Hz, 1H), 3.83 (ddd, \(J = 8.4, 7.0, 6.7\) Hz, 1H), 2.19 (m, 1H), 1.93 (m, 2H), 1.68 (m, 1H).

**Compound 132**

![Me](./images/Me.png)

2-phenylpropan-2-ol

Following General Procedure C. Purification by PTLC (silica, 4:1 Hexanes: EtOAc) afforded 21.0 mg (77%) of the title compound 132.

**Physical State:** colorless oil.

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Compound 133

2-(4-chlorophenyl)propan-2-ol

The title product was synthesized by following General Procedure C with 2-(4-chlorophenyl)-2-methylpropanoic acid (39.6 mg, 0.2 mmol) to yield the title product as a colorless oil (25.8 mg, 76%). Spectral data matched the one published\(^6\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.41 (d, J = 8.6 \text{ Hz}, 2H), 7.29 (d, J = 8.6 \text{ Hz}, 2H), 1.94 (s, 1H), 1.55 (s, 6H)\). \(^8\)

Compound 134

1-methylcyclohexan-1-ol

Following General Procedure C. Purification by PTLC (silica, 8:1 Hexanes: EtOAc) afforded 16.0 mg (70%) of the title compound 134.

Physical State: colorless oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 1.62 – 1.38 (m, 9H), 1.27 (dq, J = 15.2, 6.1, 4.6 \text{ Hz}, 1H), 1.18 (s, 3H)\).

\(^13\)C NMR (126 MHz, CDCl\(_3\)): \(\delta 70.0, 39.5, 29.6, 25.7, 22.8\).

GC/MS (EI): m/z (%) 114 (5%), 99 (18%), 81 (23%), 71 (100%), 58 (28%).

TLC: \(R_f = 0.3\) (6:1 Hexanes: EtOAc).

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Compound 135

1-(4-fluorophenyl)cyclohexanol
Following General Procedure C. Purification by PTLC (silica, 4:1 Hexanes: EtOAc) afforded 36.0 mg (92%) of the title compound 135.

Physical State: white solid.

m.p.: 72 – 74 ºC.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.47 (dd, $J = 8.2$, 5.6 Hz, 2H), 7.01 (t, $J = 8.6$ Hz, 2H), 1.86 – 1.70 (m, 7H), 1.68 – 1.59 (m, 3H), 1.34 – 1.23 (m, 1H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 161.8 (d, $J = 244.8$ Hz), 145.3 (d, $J = 3.3$ Hz), 126.5 (d, $J = 7.9$ Hz), 115.0 (d, $J = 20.9$ Hz), 73.0, 39.1, 25.6, 22.3.

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -117.05.

GC/MS (EI): m/z (%) 194 (17%), 176 (39%), 151 (100%), 109 (36%).

TLC: $R_f = 0.58$ (3:1 Hexanes: EtOAc).

Compound 136

1-(4-methoxyphenyl)cyclohexanol
Following General Procedure C. Purification by PTLC (silica, 3:1 Hexanes: EtOAc) afforded 29.0 mg (70%) of the title compound 136.

Physical State: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.43 (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.9$ Hz, 2H), 3.80 (s, 3H), 1.87 – 1.68 (m, 7H), 1.67 – 1.58 (m, 3H), 1.35 – 1.23 (m, 1H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 158.4, 141.8, 125.9, 113.6, 72.9, 55.4, 39.0, 25.7, 22.4.

HRMS (ESI-TOF): calc’d for C$_{13}$H$_{19}$O$_2$ [M + H]$^+$: 207.1380; found 207.1384.

TLC: $R_f = 0.47$ (3:1 Hexanes:EtOAc).
Compound 138

1-chloro-2-methylpropan-2-ol

Following General Procedure C. The yield (84%) was detected by GC-FID.

Compound 138

(3S,4aR,6aR,6bS,8aS,12aR,14aR,14bS)-11-hydroxy-4,4,6a,6b,8a,11,14b-heptamethyl-14-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropenic-3-yl acetate

Following General Procedure C. Purification by PTLC (silica, 1:1 Hexanes: EtOAc) afforded 38.0 mg (39%) of compound (11S)-138 and 34.0 mg (35%) of compound (11R)-138.

Compound (11S)-138

(3S,4aR,6aR,6bS,8aS,11S,12aR,14aR,14bS)-11-hydroxy-4,4,6a,6b,8a,11,14b-heptamethyl-14-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropenic-3-yl acetate

Physical State: white solid.

m.p.: 242 – 244 °C.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.63 (s, 1H), 4.51 (dd, $J = 11.8, 4.7$ Hz, 1H), 2.78 (dt, $J = 13.6, 3.7$ Hz, 1H), 2.37 (dd, $J = 13.7, 3.9$ Hz, 1H), 2.34 (s, 1H), 2.04 (s, 3H), 2.00 (td, $J = 13.6, 4.5$ Hz, 1H), 1.86 – 1.80 (m, 2H), 1.75 – 1.49 (m, 6H), 1.50 – 1.28 (m, 9H), 1.27 – 1.10 (m, 10H), 1.09 – 0.96 (m, 2H), 0.87 (s, 9H), 0.79 (dd, $J = 12.0, 1.9$ Hz, 1H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 200.2, 171.2, 169.9, 128.3, 80.8, 69.5, 61.8, 55.1, 46.7, 45.6, 44.4, 43.4, 38.9, 38.2, 37.1, 35.6, 34.1, 32.8, 32.0, 31.7, 28.4, 28.2, 26.6, 26.1, 23.7, 23.6, 21.5, 18.8, 17.5, 16.8, 16.5.

HRMS (ESI-TOF): calc’d for C$_{31}$H$_{49}$O$_4$ [M + H]$^+$: 485.3625; found 485.3628.
**TLC:** \( R_f = 0.41 \) (1:1 Hexanes: EtOAc).

\([\alpha]_D^{24} = +485.5 \) (\( c = 1.0 \), CHCl₃).

**Compound (11\( R \))-138**

(3\( S \),4\( aR \),6\( aR \),6\( bS \),8\( aS \),11\( R \),12\( aR \),14\( aR \),14\( bS \))-11-hydroxy-4,4,6\( a \),6\( b \),8\( a \),11,14b-heptamethyl-14-oxo-1,2,3,4,4\( a \),5,6\( a \),6\( b \),7,8,8\( a \),9,10,11,12,12\( a \),14,14\( a \),14\( b \)-icosahydropicen-3-yl acetate

**Physical State:** white solid.

**m.p.:** 279 – 281 °C.

**\( ^{1}H\) NMR (600 MHz, CDCl₃):** \( \delta \) 5.59 (s, 1H), 4.51 (dd, \( J = 11.8, 4.7 \) Hz, 1H), 2.78 (dt, \( J = 13.7 \) Hz, 1H), 2.36 (s, 1H), 2.12 (td, \( J = 13.5, 4.4 \) Hz, 1H), 2.07 – 2.04 (m, 4H), 1.98 (t, \( J = 13.2 \) Hz, 1H), 1.82 (td, \( J = 13.8, 4.8 \) Hz, 1H), 1.74 – 1.58 (m, 5H), 1.51 – 1.45 (m, 3H), 1.44 – 1.39 (m, 3H), 1.37 (s, 3H), 1.24 (s, 3H), 1.22 – 1.18 (m, 1H), 1.16 (s, 3H), 1.13 (s, 3H), 1.09 – 0.98 (m, 3H), 0.87 (s, 6H), 0.86 (s, 3H), 0.80 (d, \( J = 11.6 \) Hz, 1H).

**\( ^{13}C\) NMR (151 MHz, CDCl₃):** \( \delta \) 200.3, 171.1, 168.8, 128.4, 80.7, 71.5, 61.8, 55.1, 49.6, 45.8, 45.6, 43.5, 38.9, 38.4, 38.2, 37.1, 35.6, 32.8, 32.6, 28.3, 28.2, 26.52, 26.48, 25.3, 23.7, 23.5, 21.4, 18.9, 17.5, 16.8, 16.5.

**HRMS (ESI-TOF):** calc’d for \( C_{31}H_{49}O_4 \) [M + H]⁺: 485.3625; found 485.3632.

**TLC:** \( R_f = 0.29 \) (1:1 Hexanes: EtOAc).

\([\alpha]_D^{24} = +417.4 \) (\( c = 1.0 \), CHCl₃).

The structure of compound (11\( R \))-138 was unambiguously determined by an X-ray diffraction analysis (see the CIF file).

**Compound 139**

1-(4-chlorophenyl)cyclohexan-1-ol
Following General Procedure C. Purification by PTLC (silica, 5:2 Heptane:EtOAc) afforded 30.1 mg (72%) of the title compound 139.

Physical State: colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.54 – 7.37 (m, 2H), 7.37 – 7.27 (m, 2H), 1.85 – 1.67 (m, 7H), 1.67 – 1.59 (m, 3H), 1.36 – 1.21 (m, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 147.95, 132.40, 128.23, 126.14, 72.90, 38.79, 25.37, 22.06.

TLC: $R_f = 0.6$ (3:1 Heptane:EtOAc).

**Compound 140**

![Compound 140](image)

1-(4-chlorophenyl)cyclobutan-1-ol

Following General Procedure C. Purification by PTLC (silica, 5:3 Heptane:EtOAc) afforded 24.6 mg (68%) of the title compound 140.

Physical State: colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.50 – 7.42 (m, 2H), 7.40 – 7.32 (m, 2H), 2.61 – 2.49 (m, 2H), 2.45 – 2.32 (m, 2H), 2.13 – 1.99 (m, 1H), 2.00 (s, 1H), 1.72 (dtt, $J = 11.4, 8.8, 7.5$ Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 144.78, 132.99, 128.51, 126.46, 76.60, 37.02, 12.90.

TLC: $R_f = 0.5$ (3:1 Heptane:EtOAc).

**Compound 141**

![Compound 141](image)

1-(4-methoxyphenyl)cyclobutan-1-ol

Following General Procedure C. Purification by PTLC (silica, 2:1 Heptane:EtOAc) afforded 25.3 mg (71%) of the title compound 141.

Physical State: colorless oil.

$^1$H NMR (400 MHz, Benzene-$_d_6$) δ 7.36 – 7.28 (m, 2H), 6.82 (d, $J = 8.8$ Hz, 2H), 3.35 (s, 3H), 2.45 – 2.31 (m, 2H), 2.25 – 2.12 (m, 2H), 1.93 – 1.75 (m, 1H), 1.60 – 1.46 (m, 1H).

$^{13}$C NMR (101 MHz, Benzene-$_d_6$) δ 159.29, 139.44, 126.60, 113.99, 76.59, 54.85, 37.54, 13.32.
Discussion, Experimental Procedures, and Characterization for Applications

In the below section we detail 12 real-world applications in which we used the currently-reported decarboxylative etherification to synthesize 12 molecules of industrial, biomedical, or academic interest. We compare these syntheses to previously-reported literature routes. Because starting materials for respective routes to the same compound differ, comparisons inherently cannot be direct; however, we believe that the dramatic improvements in overall yield, step-count, and reaction time are quite compelling.

The kinase inhibitor intermediate 1 in Figure 1A that was previously accessed in 3.4% overall yield, in 3 steps, over 6 days, can now be prepared in 51% overall yield (63% for ether bond formation), in 2 steps, over 15 hours\(^9\). Glycogen phosphorylase inhibitors accessed from the hindered ether-containing amino acid 11 were previously prepared in 31% overall yield, in 5 steps, over 2.5 days\(^{10}\). Now, they are accessible in 32% yield, in 1 step, over 3 hours. Wipf's elegant synthesis of the anti-tumor marine natural product trunkamide A relied on access to the serine-derived ether 12 which required 7 steps, proceeding in 37% overall yield after >3 days of effort\(^{11}\). Alternatively, the same ether could be prepared in a single step, in 3 hours from commercially available Z-Ser-OMe (40% isolated yield). A recent report from Bristol-Meyers Squibb (BMS) on the synthesis of macrocyclic HIV-inhibitors utilized intermediate 13, which required a 6-step route proceeding in 24% overall yield after 2 days, and necessitated expensive and moisture-sensitive reagents\(^{12}\). In stark contrast, 13 can be prepared by our method in a single step (21% yield, 3 h). Cyclohexanone derivatives such as 14, which have found use as intermediates for the synthesis of liquid crystals, were synthesized through a 4-step sequence in 47% yield over 2 days\(^{13}\). Etherification through \textit{via} the carboxylic acid enables a single step, 3-hour preparation in 42% yield. The simple brominated tertiary ether 15 used as an intermediate for the preparation of muscarinic acetylcholine receptor antagonists was accessed through a low-yielding (<2%), 2-step procedure requiring >5 days of reaction time\(^{14}\). The same structure can now be accessed in a single step (81% yield, 3 h).

During a recent campaign targeting GPR120 modulators, BMS employed a 7-step route to 72 (involving a variety of labor intensive reactions including the use of mercury) that proceeded in \textit{ca.} 21% overall yield after 4 days\(^{15,16}\). In contrast, commercially available 70 could
be subjected to decarboxylative methoxylation to deliver 72 after ester hydrolysis in two steps over 9 hours (56% overall yield). The same starting material could be used to access bridged system 73 in a single decarboxylative step using water as the nucleophile (66% yield, 3 h); this compound was previously prepared in a 9-step process required more than 5 days (ca. 15% overall yield)\textsuperscript{16}. Signal Pharmaceuticals, in the pursuit of JNK kinase inhibitors, prepared amino-ether 74 in a 7-step process, commencing with 71 proceeding in 12% overall yield after 3 days of reaction time\textsuperscript{17}. This simple structure could instead be accessed in 2 intuitive steps (31% overall yield, 24 h) from the same starting material: Electrochemical methoxylation with a basic workup to hydrolyze the resulting ester, followed by Curtius rearrangement. Semi-ester starting materials such as 70 and 71 could also allow us to rapidly access valuable chemical space through decarboxylative hydroxylation. For instance, tertiary alcohol 75 (another GPR120 modulator intermediate) was historically prepared in a 14-step sequence requiring more than 9 days of labor in 5% overall yield by employing a range of inconvenient or expensive reagents including TMSCHN\textsubscript{2}, BF\textsubscript{3}, LiAlH\textsubscript{4}, Dess-Martin periodinane, and Pd\textsuperscript{18}. Striking truncation of this sequence could be achieved by a 2-step sequence (22% overall, 27 h) involving electrochemical hydroxylation (with basic workup to hydrolyze the remaining ester), followed by decarboxylative Giese-type chemistry. The same logic could be applied to alcohol 76, of use as an intermediate in the liquid-crystal arena, that was previously synthesized in a 7-step sequence (8% overall yield, 62 h)\textsuperscript{19}. Thus, a Ni-catalyzed decarboxylative Negishi coupling of 71, followed by hydrolysis and electrochemical hydroxylation, furnished 76 in only 3 steps (17 % overall). The modularity of the routes to 75 and 76 are notable and, aside from reducing overall step count, the pathways enabled by this electrochemical approach allow for more convenient exploration of diverse chemical space. Finally, studies in the synthesis of steroidal dehydrogenase inhibitors required the semi-synthesis of enoxolone analogs 77. A 5-step sequence from the natural product (enoxolone) featuring Barton decarboxylative halogenation was required (procedures and diastereomeric ratio were not reported), which could be streamlined in a single step from the same starting material (61% yield, 3 h, 1.1:1 dr)\textsuperscript{20}.

References:


**Price of commercial carboxylic acids used in the applications.**

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{H} \\
\text{Me} & \quad \text{CO}_2\text{H} \\
\text{Me} & \quad \text{CO}_2\text{H} \\
\text{Me} & \quad \text{CO}_2\text{H} \\
\text{Me} & \quad \text{CO}_2\text{H} \\
\end{align*}
\]

- CAS no.: 826-55-1 $10/5g \text{ (Combi-Blocks Inc)}$
- CAS no.: 189321-63-9 $22.08/g \text{ (Fisher Scientific)}$
- CAS no.: 24463-41-0 $72/g \text{ (Astatech Inc)}$
- CAS no.: 18720-35-9 $35/g \text{ (Combi-Blocks Inc)}$
- CAS no.: 10276-09-2 $93.28/g \text{ (Fisher Scientific)}$
- CAS no.: 32936-76-8 $120/g \text{ (Combi-Blocks Inc)}$
- CAS no.: 5217-05-0 $277.83/0.5g \text{ (VWR Intl)}$
- CAS no.: 15448-77-8 $430/g \text{ (eNovation Chemicals LLC)}$
Synthetic routes for the preparation of some expensive carboxylic acids.

Application for Etherification No. 1

Previous synthesis of intermediate of aurora kinase modulator (compound 1) (ref. WO2011088045 A1).

Scheme for the synthesis of compound 1

Compound SI-7

1-benzyl 2-methyl (2S,4R)-4-(1-methylcyclobutoxy)pyrrolidine-1,2-dicarboxylate

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with SI-5 (23 mg, 0.2 mmol, 1 equiv.), SI-6 (168 mg, 0.6 mmol, 3 equiv.), AgSbF$_6$ (103 mg, 1.5 equiv.), DBU (92.1 mg, 3 equiv.), $^4$Bu$_4$NPF$_6$ (232 mg, 0.6 mmol), 3 Å molecular sieves (150 mg), and CH$_2$Cl$_2$ (3.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. The reaction mixture was pre-stirred for 30 min and electrolyzed under constant current at 10 mA for 3 hours. After the reaction, the ElectraSyn vial cap was removed, and electrodes were rinsed with Et$_2$O (2 mL), which was combined with crude mixture. Then, the crude mixture was further diluted with Et$_2$O (30 mL).
The resulting mixture was washed with 2N HCl (20 mL) and saturated NaHCO₃ aq. (20 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) (3:1 Hexanes:EtOAc, v/v) to give the product SI-7 as a colorless oil (44.0 mg, 63% yield).

**Physical State**: colorless oil.

**¹H NMR (600 MHz, CDCl₃, for two rotamers)**: \( \delta \) 7.42 – 7.27 (m, 5H), 5.20 – 5.01 (m, 2H), 4.49 – 4.42 (m, 1H), 4.25 – 4.12 (m, 1H), 3.81 – 3.70 (m, 2.5H), 3.55 (s, 1.5H), 3.51 – 3.34 (m, 1H), 2.33 – 2.15 (m, 1H), 2.14 – 1.99 (m, 3H), 1.92 – 1.81 (m, 2H), 1.76 – 1.66 (m, 1H), 1.65 – 1.50 (m, 2H), 1.37 – 1.29 (m, 3H).

**¹³C NMR (151 MHz, CDCl₃, for two rotamers)**: \( \delta \) 173.4, 173.3, 155.1, 154.4, 136.7, 136.6, 128.6, 128.5, 128.14, 128.09, 128.06, 128.0, 77.5, 77.4, 70.5, 69.7, 67.3, 67.2, 58.0, 57.8, 53.6, 53.0, 52.5, 52.2, 38.4, 37.4, 34.9, 34.8, 24.3, 12.6.

**HRMS (ESI-TOF)**: calc’d for \( \text{C}_{19}\text{H}_{26}\text{NO}_5 \) [M + H]⁺: 348.1805; found 348.1813.

**TLC**: \( R_f = 0.27 \) (3:1 Hexanes:EtOAc).

\( [\alpha]_D^{24} = -148.7 \) (c = 1.0, CHCl₃).

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**Compound 1**

benzyl (2S,4R)-2-(hydroxymethyl)-4-(1-methylcyclobutoxy)pyrrolidine-1-carboxylate

A solution of ester SI-7 (18 mg, 0.052 mmol, 1 equiv.) in THF (2 mL) was cooled to 0 °C. 4 M LiBH₄ in THF (52 \( \mu \)L, 0.207 mmol, 4 equiv.) was added. After stirring overnight at room temperature the reaction was quenched by adding water (5 mL), and hydrochloric acid (1 N) was added until neutral pH. The aqueous phase was extracted with ethyl acetate (15 mL \( \times \) 3), the combined organic layers were dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) (1:1 Hexanes: EtOAc, v/v) to give the product as a colorless oil (13.4 mg, 81% yield).

**Physical State**: colorless oil.

**¹H NMR (600 MHz, CDCl₃)**: \( \delta \) 7.38 – 7.29 (m, 5H), 5.15 (s, 2H), 4.32 (dd, \( J = 8.6, 2.9 \) Hz, 1H), 4.23 – 4.14 (m, 1H), 4.10 – 4.07 (m, 1H), 3.73 (ddd, \( J = 10.9, 7.8, 2.8 \) Hz, 1H), 3.59 (ddd, \( J = 10.9, 7.8, 2.8 \) Hz, 1H), 3.59 (ddd, \( J =
11.1, 7.4, 2.7 Hz, 1H), 3.50 (qd, J = 11.6, 4.4 Hz, 2H), 2.14 – 1.98 (m, 3H), 1.89 – 1.83 (m, 2H), 1.77 – 1.67 (m, 2H), 1.60 – 1.50 (m, 1H), 1.32 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 157.3, 136.6, 128.7, 128.2, 128.1, 77.2, 70.0, 67.5, 67.0, 59.7, 54.3, 36.5, 35.0, 24.3, 12.7.

HRMS (ESI-TOF): calc’d for C$_{18}$H$_{26}$NO$_4$ [M + H]$^+$: 320.1856; found 320.1860.

TLC: $R_f$ = 0.47 (1:2 Hexanes:EtOAc).

$[\alpha]_D^{24} = -97.9$ (c = 1.0, CHCl$_3$).

Application for Etherification No. 2

Previous synthesis of intermediate of Glycogen phosphorylase inhibitors (compound 11) (ref. WO2006052722 A1).

Scheme for the synthesis of compound 11

Compound 11

methyl N-((benzyloxy)carbonyl)-O-(1-methylcyclopentyl)-L-threoninate

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with SI-8 (25.6 mg, 0.2 mmol, 1 equiv.), SI-9 (160 mg, 0.6 mmol, 3 equiv.), AgSbF$_6$ (103 mg, 0.3 mmol, 1.5 equiv.), DBU (92.1 mg, 0.6 mmol, 3 equiv.), $^{10}$Bu$_4$NPF$_6$ (232 mg, 0.6 mmol, 0.2M), 3 Å molecular sieves (150 mg), and CH$_2$Cl$_2$ (3.0 mL). The ElectraSyn vial cap
equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. The reaction mixture was electrolyzed under constant current at 10 mA for 3 hours. After the reaction, the ElectraSyn vial cap was removed, and electrodes were rinsed with Et₂O (2 mL), which was combined with crude mixture. Then, the crude mixture was further diluted with Et₂O (30 mL). The resulting mixture was washed with 2N HCl (20 mL) and saturated NaHCO₃ aq. (20 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) (4:1 Hexanes:EtOAc, v/v) to give the product 11 as a colorless oil (22.3 mg, 32% yield).

**Physical State:** colorless oil.

**¹H NMR (600 MHz, CDCl₃):** δ 7.40 – 7.32 (m, 5H), 5.55 (d, J = 9.6 Hz, 1H), 5.13 (s, 2H), 4.23 (dd, J = 9.6, 1.9 Hz, 1H), 4.19 (qd, J = 6.2, 1.9 Hz, 1H), 3.73 (s, 3H), 1.74 – 1.70 (m, 1H), 1.67 – 1.61 (m, 3H), 1.56 – 1.53 (m, 2H), 1.39 – 1.35 (m, 2H), 1.22 (d, J = 6.2 Hz, 3H), 1.17 (s, 3H).

**¹³C NMR (151 MHz, CDCl₃):** δ 171.8, 156.9, 136.5, 128.7, 128.3, 128.3, 85.6, 68.4, 67.2, 60.1, 52.4, 39.2, 38.4, 24.8, 23.8, 23.7, 21.0.


**TLC:** Rₓ = 0.3 (4:1 Hexanes:EtOAc).

[α]D²⁴ = 5.5 (c = 0.5, CHCl₃).

**Application for Etherification No. 3**


![Scheme for the synthesis of compound 12](image-url)
Compound 12

(2S)-2-(benzyloxycarbonylamino)-3-(1,1-dimethylallyloxy)propionic acid methyl ester

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with SI-10 (23 mg, 0.2 mmol, 1 equiv.), SI-11 (152 mg, 0.6 mmol, 3 equiv.), AgClO$_4$ (124 mg, 3 equiv.), 2,4,6-collidine (72.7 mg, 0.6 mmol, 3 equiv.), $n$Bu$_4$NClO$_4$ (103 mg, 0.3 mmol, 0.1M), 3 Å molecular sieves (150 mg), and CH$_2$Cl$_2$ (3.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. The reaction mixture was pre-stirred for 30 min and electrolyzed under constant current at 5 mA for 3 hours. After the reaction, the ElectraSyn vial cap was removed, and electrodes were rinsed with Et$_2$O (2 mL), which was combined with crude mixture. Then, the crude mixture was further diluted with Et$_2$O (30 mL). The resulting mixture was washed with 2N HCl (20 mL) and saturated NaHCO$_3$ aq. (20 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) (4:1 Hexanes:EtOAc, v/v) to give the product 12 as a white solid (26.0 mg, 40% yield).

Physical State: white solid.

m.p.: 42 – 44 °C.

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.42 – 7.29 (m, 5H), 5.70 (dd, $J = 17.9$, 10.6 Hz, 1H), 5.61 (d, $J = 8.9$ Hz, 1H), 5.20 – 5.05 (m, 4H), 4.45 (dt, $J = 8.9$, 3.1 Hz, 1H), 3.81 – 3.67 (m, 4H), 3.53 (dd, $J = 9.2$, 3.3 Hz, 1H), 1.21 (s, 3H), 1.20 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 171.2, 156.2, 143.1, 136.4, 128.7, 128.31, 128.28, 114.4, 75.6, 67.1, 62.9, 54.7, 52.5, 25.7, 25.6.

TLC: $R_f = 0.25$ (CH$_2$Cl$_2$).

[$\alpha$]$_D^{24}$ = +9.3 (c = 0.95, CHCl$_3$).

Application for Etherification No. 4

Previous synthesis of the intermediate of macrocyclic HIV-inhibitor (compound 13) (ref. US20150232481 AI).
Scheme for the synthesis of compound 13

**Compound 13**

tert-butyl 4-methyl-4-((5-oxohexyl)oxy)piperidine-1-carboxylate

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with **SI-12** (49 mg, 0.2 mmol, 1 equiv.), **SI-13** (70 mg, 0.6 mmol, 3 equiv.), AgSbF₆ (103 mg, 0.3 mmol, 1.5 equiv.), DBU (92.1 mg, 0.6 mmol, 3 equiv.), nBu₄NPF₆ (232 mg, 0.6 mmol, 0.2 M), 3 Å molecular sieves (150 mg), and CH₂Cl₂ (3.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. The reaction mixture was pre-stirred for 30 min and electrolyzed under constant current at 10 mA for 3 hours. After the reaction, the ElectraSyn vial cap was removed, and electrodes were rinsed with Et₂O (2 mL), which was combined with crude mixture. Then, the crude mixture was further diluted with Et₂O (30 mL). The resulting mixture was washed with H₂O (20 mL) twice, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) (4:1 Hexanes:EtOAc, v/v) to give the product 13 as a colorless oil (13.2 mg, 21% yield).

**Physical State:** colorless oil.

**¹H NMR (600 MHz, CDCl₃):** δ 3.69 (d, J = 13.1 Hz, 2H), 3.30 (t, J = 6.3 Hz, 2H), 3.10 (t, J = 12.1 Hz, 2H), 2.46 (t, J = 7.4 Hz, 2H), 2.14 (s, 3H), 1.74 – 1.67 (m, 2H), 1.67 – 1.62 (m, 2H), 1.55 – 1.50 (m, 2H), 1.45 (s, 9H), 1.39 (ddd, J = 13.7, 11.5, 4.5 Hz, 2H), 1.14 (s, 3H).
$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 209.1, 155.1, 79.4, 71.3, 60.4, 43.7, 40.0, 35.8, 30.09, 30.05, 28.6, 24.7, 21.0.

HRMS (ESI-TOF): calc’d for C$_{17}$H$_{31}$NO$_4$Na [M + Na]$^+$: 336.2145; found 336.2151.

TLC: $R_f = 0.21$ (3:1 Hexanes:EtOAc).

**Application for Etherification No. 5**

Previous synthesis of intermediate of liquid crystals material (compound 14) (ref. WO2017116213 A1).

Scheme for the synthesis of compound 14

**Compound 14**

4-butoxy-4-methylcyclohexan-1-one

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with SI-14 (32 mg, 0.2 mmol, 1 equiv.), n-BuOH (360 mg, 4.8 mmol, 24 equiv.), AgSbF$_6$ (103 mg, 0.3 mmol, 1.5 equiv.), 2,4,6-collidine (72.7 mg, 0.6 mmol, 3 equiv.), $^4$Bu$_4$NPF$_6$ (232 mg, 0.6 mmol, 0.2 M), 3 Å molecular sieves (150 mg), and CH$_2$Cl$_2$ (3.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. The reaction mixture was pre-stirred for 30 min and electrolyzed under constant current at 10 mA for 3 hours. After the reaction, the ElectraSyn vial cap was removed, and electrodes were rinsed with Et$_2$O (2 mL), which was combined with crude mixture. Then, the crude mixture was further diluted with Et$_2$O (30 mL). The resulting mixture was washed with H$_2$O (20 mL)
twice, dried over Na$_2$SO$_4$, and concentrated \textit{in vacuo}. The crude material was purified by preparative thin-layer chromatography (PTLC) (5:1 Hexanes:EtOAc, v/v) to give the product 14 as a colorless oil (15.6 mg, 42% yield).

**Physical State**: colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): δ 3.39 (t, $J = 6.4$ Hz, 2H), 2.61 (td, $J = 14.1$, 5.9 Hz, 2H), 2.19 – 2.11 (m, 4H), 1.68 (td, $J = 14.0$, 4.5 Hz, 2H), 1.61 – 1.54 (m, 2H), 1.46 – 1.37 (m, 2H), 1.23 (s, 3H), 0.93 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (151 MHz, CDCl$_3$): δ 212.5, 71.6, 61.0, 37.1, 36.1, 32.8, 24.3, 19.8, 14.2.

GC/MS (EI): m/z (%) 184 (8%), 169 (0.6%), 127 (74%), 71 (100%), 55 (29%).

**TLC**: $R_f = 0.54$ (3:1 Hexanes:EtOAc).

**Application for Etherification No. 6**

Previous synthesis of the intermediate of muscarinic acetylcholine receptor antagonist (compound 15) (ref. WO2005104745 A2).

Scheme for the synthesis of compound 15

**Compound 15**

(2-(2-bromoethoxy)propan-2-yl)benzene

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with 3 (33 mg, 0.2 mmol, 1 equiv.), SI-15 (75 mg, 0.6 mmol, 3 equiv.), AgClO$_4$ (124 mg, 0.6 mmol, 3.0 equiv.), NBS, PPh$_3$, 2,4,6-collidine, nBu$_4$NClO$_4$, 3 Å MS, CH$_2$Cl$_2$ (3 mL) +Cl/-C, 10 mA, 3h. The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. The
reaction mixture was pre-stirred for 30 min and electrolyzed under constant current at 10 mA for 3 hours. After the reaction, the ElectraSyn vial cap was removed, and electrodes were rinsed with Et₂O (2 mL), which was combined with crude mixture. Then, the crude mixture was further diluted with Et₂O (30 mL). The resulting mixture was washed with H₂O (20 mL) twice, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) (20:1 Hexanes:Et₂O, v/v) to give the product 15 as a colorless oil (39.5 mg, 81% yield).

**Physical State:** colorless oil.

**¹H NMR (600 MHz, CDCl₃):** δ 7.47 – 7.42 (m, 2H), 7.38 – 7.33 (m, 2H), 7.29 – 7.24 (m, 1H), 3.49 – 3.46 (m, 2H), 3.43 – 3.40 (m, 2H), 1.57 (s, 6H).

**¹³C NMR (151 MHz, CDCl₃):** δ 145.8, 128.4, 127.3, 125.9, 63.4, 31.4, 28.4.

**GC/MS (EI):** m/z (%) 242 (0.1%), 227 (100%), 118 (63%), 91 (41%), 77 (28%).

**TLC:** Rₜ = 0.45 (20:1 Hexanes:Et₂O).

### Application for Methoxylation No. 1


![Scheme for the synthesis of compound 72](image)

**Compound SI-16**

![Compound SI-16](image)
methyl 4-methoxybicyclo[2.2.1]heptane-1-carboxylate

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with carboxylic acid 70 (39.6 mg, 0.2 mmol, 1 equiv.), 2,4,6-collidine (72.6 mg, 0.6 mmol, 3 equiv.), 3Å MS (150 mg), MeOH (3.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. The reaction mixture was electrolyzed under constant current at 10 mA for 3 hours. After the reaction, the ElectraSyn vial cap was removed and electrodes were rinsed with Et₂O (2 mL). The resulting solution was diluted with Et₂O (40 mL), and then washed with saturated aqueous NH₄Cl (20 mL) and brine (20 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) (30:1 Hexanes:Et₂O, v/v) to furnish the desired product SI-16 (24.7 mg, 67% yield).

Physical State: colorless oil.

¹H NMR (600 MHz, CDCl₃): δ 3.67 (s, 3H), 3.31 (s, 3H), 2.10 – 2.02 (m, 2H), 1.87 – 1.80 (m, 2H), 1.78 (s, 2H), 1.76 – 1.71 (m, 2H), 1.64 – 1.59 (m, 2H).

¹³C NMR (151 MHz, CDCl₃): δ 176.0, 86.8, 53.0, 51.8, 48.6, 43.2, 32.7, 31.3.

GC/MS (EI): m/z (%) 169 (2%), 155 (21%), 141 (24%), 125 (100%), 109 (18%).

TLC: Rf = 0.3 (30:1 Hexanes:Et₂O).

Compound 72

4-methoxybicyclo[2.2.1]heptane-1-carboxylic acid

In a 25 mL round bottom flask, SI-16 (36.8 mg, 0.2 mmol, 1.0 eq) and NaOH (32.0 mg, 0.8 mmol, 4.0 eq) was added to a mixture of solvents (6 mL, EtOH/H₂O = 1:1). After stirred for 6 h at 60 °C, the reaction was then poured into 1 M HCl aq. to acidify to pH 1, and the aqueous phase was extracted with EtOAc (3 × 10 mL), washed with brine (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The desired product 72 (28.6 mg, 84% yield) was purified by preparative thin-layer chromatography (PTLC) (1:1 Hexanes:EtOAc, v/v).

Physical State: colorless oil.

¹H NMR (500 MHz, CDCl₃): δ 3.31 (s, 3H), 2.10 (td, J = 13.8, 5.7 Hz, 2H), 1.89 – 1.82 (m, 2H), 1.81 (s, 2H), 1.79 – 1.73 (m, 2H), 1.67 – 1.59 (m, 2H).

¹³C NMR (126 MHz, CDCl₃): δ 181.9, 87.0, 52.9, 48.4, 43.2, 32.5, 31.3.
GC/MS (EI): m/z (%) 170 (0.3%), 141 (21%), 125 (100%), 97 (20%), 67 (6.4%).
TLC: Rf = 0.2 (1:1 Hexanes: EtOAc).

Application for Hydroxylation No. 1


Synthesis of compound 73, developed herein:

Compound 73

4-methoxybicyclo[2.2.1]heptane-1-carboxylic acid

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with compound 70 (39.6 mg, 0.2 mmol, 1 eq), 2,4,6-collidine (36.3 mg, 0.3 mmol, 1.5 equiv.), “Bu4NPF6 (116 mg, 0.3 mmol, 0.1M), acetone (3.0 mL), and H2O (0.1 mL). The ElectraSyn vial cap, equipped with anode (graphite) and cathode (graphite), were inserted into the mixture. The reaction mixture was electrolyzed under a constant current of 10 mA for 3 hours. After the reaction, the ElectraSyn vial cap was removed and electrodes were rinsed with
Et₂O (2 mL). The obtained suspension was diluted with Et₂O (40 mL), and the combined organic phase was washed with saturated aqueous NH₄Cl solution (20 mL), brine (20 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was purified by preparative thin-layer chromatography (PTLC) (3:1 Hexanes:EtOAc, v/v) to furnish the desired product 73 (22.4 mg, 66% yield).

**Physical State**: colorless oil.

**¹H NMR (500 MHz, CDCl₃)**: δ 3.64 (s, 3H), 2.60 (s, 1H), 2.13 – 1.99 (m, 2H), 1.80 – 1.59 (m, 8H).

**¹³C NMR (126 MHz, CDCl₃)**: δ 176.0, 81.8, 51.8, 49.1, 46.8, 35.4, 33.0.

**GC/MS (EI)**: m/z (%) 155 (0.2 %), 139 (7%), 127 (16%), 111 (100%), 95 (13%).

**TLC**: Rₚ = 0.2 (1:1 Hexanes: EtOAc).

**Application for Methoxylation No. 2**

Previous synthesis of the intermediate of JNK protein kinase inhibitors (compound 74) (ref. WO2012145569 A1).

**Scheme for the synthesis of compound 74**

**Compound SI-17**

**4-methoxybicyclo[2.2.2]octane-1-carboxylic acid**
With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with carboxylic acid 71 (42.4 mg, 0.2 mmol, 1 equiv.), 2,4,6-collidine (72.6 mg, 0.6 mmol, 3 equiv.), 3Å MS (150 mg), MeOH (3.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. The reaction mixture was electrolyzed under constant current at 10 mA for 3 hours. When completion, the reaction mixture was transferred to a 50 mL flask and solvent was removed in vacuo. And then NaOH (32mg, 0.8 mmol, 4 equiv.), EtOH (3 mL), H2O (3 mL) were added to the flask. The reaction mixture was stirred at 60 °C for 6 h. After completion, the mixture was extracted with Et₂O to remove the organic impurities, the aqueous layer was acidified with 2M aq. HCl to pH=1 and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) (1:1 Hexanes:EtOAc, v/v) to give the desired product SI-17 (25.0 mg, 68% yield).

**Physical State:** colorless oil

**¹H NMR (600 MHz, CDCl₃):** δ 3.18 (s, 3H), 1.97 – 1.91 (m, 6H), 1.72 – 1.66 (m, 6H).

**¹³C NMR (151 MHz, CDCl₃):** δ 183.0, 73.6, 49.3, 38.2, 29.2, 28.8.

**HRMS (ESI-TOF):** calc’d for C₁₀H₁₆O₃Na [M + Na]⁺: 207.0997; found 207.0998.

**TLC:** Rₗ = 0.2 (1:1 Hexanes: EtOAc).

**Compound 74**

![4-methoxybicyclo[2.2.2]octan-1-amine](image)

**4-methoxybicyclo[2.2.2]octan-1-amine**

A suspension of SI-17 (36.8 mg, 0.2 mmol, 1 equiv.) in toluene (2 mL) was treated with triethylamine (42 µL, 0.3 mmol, 1.5 eq) and diphenylphosphoryl azide (66 mg, 0.24 mmol, 1.2 equiv.) under argon atmosphere. The solution was slowly and warmed to 90 °C and stirred at 90 °C for 9 h, then concentrated in vacuo to remove toluene. The residue was cooled on an ice bath and treated with 6N hydrochloric acid (2 mL). The bath was removed and the mixture was stirred at room temperature for 6h. After completion, the mixture was extracted with Et₂O to remove the organic impurities, the aqueous layer was basified with saturated NaHCO₃ (aq), and then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude material was purified by preparative thin-
layer chromatography (PTLC) (1:3 Hexanes:EtOAc, v/v) to give the desired product 74 (13.9 mg, 45% yield).

**Physical State:** colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 3.16 (s, 3H), 1.86 – 1.68 (m, 6H), 1.68 – 1.59 (m, 6H), 1.55 – 1.14 (m, 2H).

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 73.0, 49.4, 46.7, 35.6, 29.9.

GC/MS (EI): m/z (%) 155 (5 %), 125 (25%), 112 (32%), 96 (22%), 69 (100%).

**TLC:** $R_f = 0.1$ (2:1 Hexanes:EtOAc).

**Application for Hydroxylation No. 2**


**Scheme for the synthesis of compound 75**

![Scheme for the synthesis of compound 75](image-url)
Compound SI-18

4-hydroxybicyclo[2.2.2]octane-1-carboxylic acid
With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with carboxylic acid 71 (42.4 mg, 0.2 mmol, 1 equiv.), 2,4,6-collidine (36.3 mg, 0.3 mmol, 1.5 equiv.), \(^{n}\)Bu\(_4\)PF\(_6\) (114 mg, 0.3 mmol, 0.1M), acetone (3.0 mL), and H\(_2\)O (0.1 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. The reaction mixture was electrolyzed under a constant current of 10 mA for 3 hours. After completion, the reaction mixture was transferred to a 50 mL flask and the solvent was removed under a reduced pressure on a rotary evaporator. A solution of NaOH (32 mg, 0.8 mmol, 4 equiv.) in EtOH (3 mL) and H\(_2\)O (3 mL) was added to the residue. The reaction mixture was stirred at 60 °C for 6 h. After completion, the reaction mixture was extracted with Et\(_2\)O (3 x 20 mL). Etherial layer was discarded, while the aqueous layer was acidified with 1N aq. HCl to pH = 4. The reaction mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) (3:1 Hexanes:EtOAc, v/v) to give the desired product SI-18 (15.3 mg, 45% yield).

Physical State: colorless oil.

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 2.02 – 1.92 (m, 6H), 1.75 – 1.66 (m, 6H), 1.58 (s, 1H).

\(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 181.7, 69.4, 38.2, 33.3, 29.6.

GC/MS (EI): m/z (%) 170 (6%), 152 (11%), 124 (100%), 109 (14%), 70 (65%).

TLC: \(R_f = 0.2\) (1:1 Hexanes: EtOAc).

Compound 75

methyl 3-(4-hydroxybicyclo[2.2.2]octan-1-yl)propanoate
To a stirred solution of carboxylic acid SI-18 (36 mg, 0.212 mmol, 1.0 eq), \(N\)-hydroxyptalimide (NHPI) (38 mg, 0.23 mmol, 1.1 eq) in anhydrous CH\(_2\)Cl\(_2\) (0.5 mL) was added dropwise DIC (36
μL, 0.25 mmol, 1.2 eq). The reaction was monitored by TLC; and usually it was completed within 2 hours. After consumption of the starting material, the solvent was removed under a reduced pressure on a rotary evaporator; and dried on a high-vacuum line (1 ppm) for at least 5 minutes to remove the residual solvents. Dry LiCl (27.6 mg, 0.64 mmol, 3.0 eq), Zn powder (27.6 mg, 0.42 mmol, 2.0 eq), and Ni(ClO₄)₂•6H₂O (15.7 mg, 0.042 mmol, 0.2 eq) were added to the residue. Note: due to its hydroscope nature, LiCl can be difficult to weigh on small scale. However, excess LiCl is not detrimental to the success of the reaction were added. A stir bar was added, the culture tube was evacuated and backfilled with argon. Methyl acrylate (38.4 μL, 0.42 mmol, 2.0 eq) was added to the reaction mixture via syringe. Next, MeCN (0.6 mL) was added, and the mixture was stirred at room temperature for overnight. After 12 hours, H₂O (4 mL) and sat. aq. NH₄Cl solution (4 mL) were added. The mixture was extracted with EtOAc (3 x 30 mL), and the combined organic phase dried over NaSO₄. Evaporation of the solvent under a reduced pressure afforded a crude material that was purified by preparative thin-layer chromatography (PTLC) (3:1 Hexanes:EtOAc, v/v) to yield the pure product 75 (22.0 mg, 49% yield).

**Physical State:** colorless oil.

**¹H NMR (600 MHz, CDCl₃):** δ 3.65 (s, 3H), 2.21 (t, J = 6.3 Hz, 3H), 1.64 – 1.59 (m, 6H), 1.53 – 1.47 (m, 6H), 1.47 – 1.42 (m, 2H).

**¹³C NMR (151 MHz, CDCl₃):** δ 174.8, 69.5, 51.7, 35.4, 34.1, 31.9, 30.1, 29.3.

**GC/MS (EI):** m/z (%) 212 (4%), 194 (28%), 166 (42%), 143 (40%), 125 (44%), 111 (100%), 95 (27%), 83 (66%).

**TLC:** R_f = 0.3 (3:1 Hexanes:EtOAc).

**Application for Hydroxylation No. 3**

Synthesis of compound 76, developed in this work:

**Compound SI-19**

methyl 4-(3,4-difluorophenyl)bicyclo[2.2.2]octane-1-carboxylate

preparation of bis(3,4-difluorophenyl)zinc solution in THF

Diarylzinc reagent were prepared in a manner similar to that report by Knochel and coworkers.
LiBr (636.0 mg, 25.0 mmol, 1.25 eq) was added to a 50.0 ml round-bottom flask. The flask was flame-dried under vacuum (to remove water), cooled to a room temperature and backfilled with argon. Magnesium turnings (435.0 mg, 18 mmol, 1.5 equiv.) and THF (anhydrous, 6.0 mL) were added, and the mixture was stirred vigorously for 5 min. DIBAL–H (1.0 M in THF, 0.12 mL, 0.12 mmol, 0.01 eq) was added via syringe, and the mixture was stirred vigorously for another 5 min. The flask was cooled to 0 °C in an ice/water bath, and 4-bromo-1,2-difluorobenzene (2.316 g, 12.0 mmol, 1.0 eq) was added via syringe. After 10 minutes the bath was removed, and the mixture was stirred at room temperature until a full consumption of the starting aryl bromide (as determined by GC/MS spectrum). Titration of the obtained Grignard reagent with I$_2$ in THF (2 mL) afforded the concentration of 1.28 M.

A Schlenk flask equipped with a stir bar was first flame-dried under vacuum, cooled to a room temperature, and backfilled with nitrogen. ZnBr$_2$ (1.013 g, 4.5 mmol, 1.0 eq) was added. The reaction flask was placed under vacuum again, and heated a heat gun to remove the residual water in ZnBr$_2$. After cooling to a room temperature, the flask was backfilled with nitrogen; and anhydrous THF (8.0 mL) was added. The mixture was vigorously stirred for 5-10 min, until a clear solution was formed. ArMgBr•LiBr (1.28 M, 7.0 ml, 9.0 mmol, 2.0 eq) was added dropwise via a syringe. Often a white precipitate forms during the addition. After addition, the reaction mixture was stirred for another 10 minutes at room temperature to obtain Ar$_2$Zn reagent (c = 0.38 M, determined by titration).

A flame-dried tube was charged with carboxylic acid 71 (42.4 mg, 0.2 mmol, 1.0 eq), 3,4,5,6-tetrachloro-N-hydroxyphthalimide (TCNHP) (66 mg, 0.22 mmol, 1.1 eq), DMAP (2.4 mg, 0.1 eq), and CH$_2$Cl$_2$ (1 mL). DIC (36 μL, 0.24 mmol, 1.2 eq) was added dropwise to a stirred reaction mixture. The reaction was stirred for 2 hours at room temperature, and controlled by TLC. After consumption of the starting material, the solvent was removed under a reduced pressure on a rotary evaporator, and dried on a high-vacuum line (1 ppm) for at least 5 minutes to remove residual solvent. ZnBr$_2$ (45.0 mg, 0.2 mmol, 1.0 eq), Ni(dpm)$_2$•xH$_2$O (18.6 mg, 0.04 mmol, 0.2 eq) were added at once to the reaction flask. The flask was evacuated and back-filled with argon, followed by an addition of DMI (1.2 mL) via a syringe. The mixture was stirred for 5 minutes at room temperature, and then was was placed into an ice/water bath. The stirring was continued for another 5 minutes. Ar$_2$Zn in THF (1.6 mL, 0.38 M, 0.6 mmol) was added in one
portion at 0 °C, and the stirring was continued for 2 min at 0 °C. The reaction mixture was removed from the ice/water bath and was allowed to stir at room temperature for 10 h. The mixture was diluted with EtOAc or Et₂O (40 mL) and quenched with 1N HCl (to pH = 3). The organic layer was washed with H₂O (20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under a reduced pressure. The crude material was purified by preparative thin-layer chromatography (PTLC) (50:1 Hexanes:EtOAc, v/v) to afford the title product SI-19 (18.5 mg, 33% yield).

**Physical State:** colorless oil.

**1H NMR (600 MHz, CDCl₃):** δ 7.14 – 6.95 (m, 3H), 3.67 (s, 3H), 1.98 – 1.89 (m, 6H), 1.85 – 1.75 (m, 6H)

**13C NMR (151 MHz, CDCl₃):** δ 178.3, 150.2 (dd, \( J = 237.1, 12.1 \) Hz), 148.5 (dd, \( J = 237.1, 12.1 \) Hz), 146.5 (t, \( J = 4.5 \) Hz), 121.4 (dd, \( J = 5.8, 3.5 \) Hz), 116.8 (d, \( J = 16.6 \) Hz), 114.8 (d, \( J = 16.6 \) Hz), 51.9, 39.1, 34.7, 31.9, 28.8.

**19F NMR (400 MHz, CDCl₃):** δ -138.46 (d, \( J = 21.6 \) Hz), -142.68 (d, \( J = 21.5 \) Hz).

**GC/MS (EI):** m/z (%) 280 (16%), 220 (100%), 205 (6%), 191 (30%), 127 (50%).

**TLC:** \( R_f = 0.4 \) (50:1 Hexanes:EtOAc).

**Compound SI-20**

![Image of compound SI-20]

**4-(3,4-difluorophenyl)bicyclo[2.2.2]octane-1-carboxylic acid**

In a 25 mL round bottom flask, SI-19 (54.0 mg, 1.9 mmol, 1.0 eq) and LiOH•H₂O (40.0 mg, 9.5 mmol, 5.0 eq) were placed. THF (1.5 mL), MeOH (0.75 mL) and water (0.75 mL) were added. The reaction mixture was stirred for 6 h at room temperature. The pH of the reaction mixture was adjusted to 1 by adding aq. HCl dropwise. The reaction mixture was extracted with EtOAc (3 x 10 mL). Water layer was discarded, while the organic phase was washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The obtained crude product was purified by preparative thin-layer chromatography (PTLC) (5:1 Hexanes:EtOAc, v/v) to afford the pure desired product SI-20 (39.1 mg, 76% yield).
Physical State: colorless oil.

^1^H NMR (600 MHz, CDCl\textsubscript{3}): δ 7.16 – 6.91 (m, 3H), 2.00 – 1.89 (m, 6H), 1.87 – 1.78 (m, 6H)

^1^3^C NMR (151 MHz, CDCl\textsubscript{3}): δ 183.6, 150.2 (dd, \(J = 234.05, 13.59\) Hz), 148.6 (dd, \(J = 234.05, 12.08\) Hz), 146.3 (t, \(J = 4.2\) Hz), 121.4 (dd, \(J = 5.9, 3.3\) Hz), 116.8 (d, \(J = 16.6\) Hz), 114.8 (d, \(J = 17.4\) Hz), 38.9, 34.7, 31.8, 28.6.

^1^9^F NMR (376 MHz, CDCl\textsubscript{3}): δ -138.37 (d, \(J = 21.6\) Hz), -142.56 (d, \(J = 20.9\) Hz).

GC/MS (EI): m/z (%) 266 (69%), 237 (48%), 220 (53%), 166 (20%), 127 (82%).

TLC: \(R_f = 0.2\) (1:1 Hexanes: EtOAc).

**Compound 76**

![Structure](image)

4-(3,4-difluorophenyl)bicyclo[2.2.2]octan-1-ol

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) was charged with SI-20 (25.8 mg, 0.1 mmol, 1 eq), 2,4,6-collidine (35.2 mg, 0.3 mmol, 3 eq), ^6^Bu\textsubscript{4}NP\textsubscript{6} (116 mg, 0.3 mmol, 0.1 M), acetone (3.0 mL), and H\textsubscript{2}O (0.1 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) was inserted into the mixture. The reaction mixture was electrolyzed under a constant current of 10 mA for 3 hours under a stirring. After the reaction, the ElectraSyn vial cap was removed and electrodes were rinsed with Et\textsubscript{2}O (2 mL). The resulting suspension was diluted with Et\textsubscript{2}O (40 mL), washed with saturated aqueous NH\textsubscript{4}Cl (20 mL) and brine (20 mL). The organic phase was dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated in vacuo. The crude material was purified by preparative thin-layer chromatography (PTLC) (2:1 Hexanes:EtOAc, v/v) to furnish the desired product 76 (15.7 mg, 68% yield).

Physical State: colorless oil.

^1^H NMR (600 MHz, CDCl\textsubscript{3}): δ 7.13 – 7.01 (m, 2H), 7.01 – 6.96 (m, 1H), 1.97 – 1.86 (m, 6H), 1.82 – 1.73 (m, 6H).

^1^3^C NMR (151 MHz, CDCl\textsubscript{3}): δ 150.1 (dd, \(J = 246.9, 12.1\) Hz), 148.5 (dd, \(J = 246.1, 12.1\) Hz), 145.9 (t, \(J = 4.4\) Hz), 121.4 (dd, \(J = 6.0, 3.3\) Hz), 116.7 (d, \(J = 16.6\) Hz), 114.8 (d, \(J = 17.5\) Hz), 69.7, 34.3, 33.7.

^1^9^F NMR (600 MHz, CDCl\textsubscript{3}): δ -138.46 (d, \(J = 21.7\) Hz), -142.64 (d, \(J = 21.6\) Hz).
GC/MS (EI): m/z (%) 238 (20%), 220 (7%), 168 (100%), 153 (28%), 127(37%).

TLC: $R_f = 0.3$ (2:1 Hexanes:EtOAc).

Application for Hydroxylation No. 4

Literature synthesis of 11-\(\beta\)-hydroxysteroid dehydrogenase 1 inhibitor (compound 77) (ref. WO2008071169 A2):

Synthesis of compound 77 developed in this work:

Compound 77

\[ (4aS,6aS,6bR,8aR,10S,12aS,12bR,14bR)-2,10-dihydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-1,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,14b-octadecahydropicen-13(2H)-one \]
With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) was charged with **SI-21** (94 mg, 0.2 mmol, 1 eq), 2,4,6-collidine (35.2 mg, 0.3 mmol, 1.5 eq), **^6^**Bu4NPF6 (116 mg, 0.3 mmol, 1.5 eq), acetone (3.0 mL), and H2O (0.1 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) was inserted into the mixture. The reaction mixture was electrolyzed under a constant current of 10 mA for 3 hours. After the reaction, the ElectraSyn vial cap was removed, and the electrodes were rinsed with Et2O (2 mL). The resulting solution was diluted with Et2O (40 mL). The organic phase was washed with 1N HCl (20 mL), saturated aq. NaHCO3 (20 mL), dried over Na2SO4, and concentrated *in vacuo*. The crude material was purified by preparative thin-layer chromatography (PTLC) (1:2 Hexanes:EtOAc, v/v) to furnish the desired products (2S)-77 (25.8 mg, 29% yield) and (2R)-77 (28.4 mg, 32% yield).

**Compound (2S)-77**

![Compound 2S-77 structure](attachment:compound_2S-77.png)

(2S,4aS,6aS,6bR,8aR,10S,12aS,12bR,14bR)-2,10-dihydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-1,3,4,4a,5,6a,6b,7,8,8a,9,10,11,12,12a,12b,14b-octadecahydropicen-13(2H)-one

**Physical State**: white solid.

**m.p.**: > 270 °C.

**1H NMR (600 MHz, CDCl3)**: δ 5.63 (s, 1H), 3.22 (dd, J = 11.3, 5.0 Hz, 1H), 2.78 (dt, J = 13.5, 3.6 Hz, 1H), 2.38 – 2.34 (m, 1H), 2.32 (s, 1H), 2.00 (td, J = 13.6, 4.6 Hz, 1H), 1.89 – 1.78 (m, 2H), 1.73 – 1.51 (m, 6H), 1.49 – 1.37 (m, 4H), 1.37 – 1.26 (m, 6H), 1.26 – 1.16 (m, 4H), 1.14 (s, 3H), 1.13 (s, 3H), 1.06 – 0.93 (m, 5H), 0.88 (s, 3H), 0.80 (s, 3H), 0.69 (dt, J = 13.9, 3.5 Hz, 1H).

**13C NMR (151 MHz, CDCl3)**: δ 200.4, 169.8, 128.4, 78.9, 69.5, 62.0, 55.1, 46.7, 45.6, 44.4, 43.5, 39.3, 37.2, 35.7, 34.1, 32.9, 32.0, 31.7, 28.4, 28.2, 27.5, 26.6, 26.1, 23.7, 18.9, 17.6, 16.5, 15.7.

**HRMS (ESI-TOF)**: calc’d for C29H47O3 [M + H]+: 443.3520; found 443.3523.

**TLC**: Rf = 0.39 (2:1, EtOAc:Hexanes).

[α]D^24 = +450.9 (c = 1.0, CHCl3).

**Compound (2R)-77**
(2R,4aS,6aS,6bR,8aR,10S,12aS,12bR,14bR)-2,10-dihydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-1,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12a,12b,14b-octadecahydropicen-13(2H)-one

**Physical State**: white solid.

**m.p.**: 249 – 251 °C.

**1H NMR (600 MHz, CDCl₃)**: δ 5.59 (s, 1H), 3.22 (dd, J = 11.2, 5.1 Hz, 1H), 2.77 (dt, J = 13.5, 3.6 Hz, 1H), 2.33 (s, 1H), 2.12 (td, J = 13.6, 4.6 Hz, 1H), 2.07 – 2.03 (m, 1H), 1.97 (t, J = 13.3 Hz, 1H), 1.82 (td, J = 13.8, 4.8 Hz, 1H), 1.71 – 1.56 (m, 6H), 1.50 – 1.44 (m, 3H), 1.43 – 1.35 (m, 7H), 1.24 (s, 3H), 1.21 – 1.18 (m, 1H), 1.13 (s, 3H), 1.12 (s, 3H), 1.04 – 0.95 (m, 5H), 0.86 (s, 3H), 0.80 (s, 3H), 0.69 (dd, J = 11.9, 1.8 Hz, 1H).

**13C NMR (151 MHz, CDCl₃)**: δ 200.4, 168.8, 128.4, 78.9, 71.5, 61.9, 55.0, 49.5, 45.8, 45.6, 43.4, 39.3, 38.4, 37.2, 35.6, 32.9, 32.6, 28.3, 28.2, 27.4, 26.53, 26.49, 25.3, 23.6, 18.9, 17.6, 16.5, 15.7.

**HRMS (ESI-TOF)**: calc’d for C₂₉H₄₇O₃ [M + H]^+: 443.3520; found 443.3514.

**TLC**: Rᵣ = 0.25 (2:1, EtOAc:Hexanes).

\([\alpha]_D^{24} = +370.1\) (c = 1.0, CHCl₃).

**X-Ray of Compound (2R)-77**

CCDC 1918528

The single crystal X-ray diffraction studies were carried out on a Bruker Smart APEX II CCD diffractometer equipped with Cu Kα radiation (λ =1.54178 Å). Crystals of the subject compound were used as received (grown from acetone/hexanes/Et₂O). A 0.2 x 0.2 x 0.2 mm piece of a colorless crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using φ and θ scans. Crystal-to-detector distance was 40 mm and exposure time was 1, 2, 3 seconds depending on the 2θ range per frame using a scan width of 1.00°. Data collection was 100 % complete to 67.679° in θ. A total of 44094 reflections were collected covering the indices, -19<=h<=18, -33<=k<=33, -8<=l<=8. 5820 reflections were found to be symmetry independent, with a Rint of 0.0306.
Indexing and unit cell refinement indicated a **Primitive, Orthorhombic** lattice. The space group was found to be $P2_12_12_2$. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

**Notes:** Absolute stereochemistry was conclusively assigned ($\text{Flack} = -0.03(3)$). The solvent in the pores was disordered, a total of 214 electrons were squeezed from the unit cell. This is approximately 4 solvent molecules per unit cell.

![Structure](image)

Table 1. Crystal data and structure refinement for $(2R)$-77.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Identification code</strong></td>
<td>$(2R)$-77</td>
</tr>
<tr>
<td><strong>Empirical formula</strong></td>
<td>$C_{29}H_{46}O_3$</td>
</tr>
<tr>
<td><strong>Molecular formula</strong></td>
<td>$C_{29}H_{46}O_3$</td>
</tr>
<tr>
<td><strong>Formula weight</strong></td>
<td>442.66</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>100.0 K</td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
<td>1.54178 Å</td>
</tr>
<tr>
<td><strong>Crystal system</strong></td>
<td>Orthorhombic</td>
</tr>
<tr>
<td><strong>Space group</strong></td>
<td>$P2_12_12_2$</td>
</tr>
<tr>
<td><strong>Unit cell dimensions</strong></td>
<td>$a = 15.6402(8)$ Å, $\alpha = 90^\circ$</td>
</tr>
<tr>
<td></td>
<td>$b = 27.8107(15)$ Å, $\beta = 90^\circ$</td>
</tr>
</tbody>
</table>
\[ c = 7.0298(4) \, \text{Å} \quad \gamma = 90^\circ. \]

**Volume**

3057.7(3) Å³

**Z**

4

**Density (calculated)**

0.962 Mg/m³

**Absorption coefficient**

0.464 mm⁻¹

**F(000)**

976

**Crystal size**

0.2 x 0.2 x 0.2 mm³

**Crystal color, habit**

clear colourless block

**Theta range for data collection**

3.178 to 70.292°.

**Index ranges**

\(-19\leq h \leq 18, -33\leq k \leq 33, -8\leq l \leq 8\)

**Reflections collected**

44094

**Independent reflections**

5820 [R(int) = 0.0306]

**Completeness to theta = 67.679°**

100.0 %

**Absorption correction**

Semi-empirical from equivalents

**Max. and min. transmission**

0.7533 and 0.6664

**Refinement method**

Full-matrix least-squares on F²

**Data / restraints / parameters**

5820 / 0 / 298

**Goodness-of-fit on F²**

1.043

**Final R indices [I>2sigma(I)]**

R1 = 0.0280, wR2 = 0.0745

**R indices (all data)**

R1 = 0.0285, wR2 = 0.0752

**Absolute structure parameter**

-0.03(3)

**Extinction coefficient**

n/a

**Largest diff. peak and hole**

0.171 and -0.130 e.Å⁻³

---

**X-Ray of Compound (11R)-138**

**CCDC 1903823**

The single crystal X-ray diffraction studies were carried out on a Bruker Microstar APEX II CCD diffractometer equipped with Cu Kα radiation (\(\lambda = 1.54178 \, \text{Å}\)). Crystals of the subject compound were used as received (grown from CH₂Cl₂/Ethyl Acetate). A 0.025 x 0.025 x 0.125 mm piece of a colorless crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using \(\phi\) and \(\omega\) scans. Crystal-to-detector distance was 45 mm and exposure time was 4, 10, and 30 seconds depending on the 2θ range per frame using a scan width of 1.20°. Data collection was 98.4 % complete to 67.679° in 2θ. A total of 16527 reflections were collected covering the indices, \(-8\leq h \leq 5, -17\leq k \leq 11, -30\leq l \leq 25\). 4963 reflections were found to be symmetry independent, with a Rₘᵢ of 0.0265.
Indexing and unit cell refinement indicated a Primitive, Orthorhombic lattice. The space group was found to be \(P2_12_12_1\). The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Absolute Structure Parameter: 0.05(4) (Conclusive)

![Crystal structure diagram](image)

Table 1. Crystal data and structure refinement for (11R)-138.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>(11R)-138</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C31 H48 O4</td>
</tr>
<tr>
<td>Formula weight</td>
<td>484.69</td>
</tr>
<tr>
<td>Temperature</td>
<td>100.0 K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>(P2_12_12_1)</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>(a = 7.2653(2)) Å, (\alpha = 90^\circ)</td>
</tr>
<tr>
<td></td>
<td>(b = 14.7204(5)) Å, (\beta = 90^\circ)</td>
</tr>
<tr>
<td></td>
<td>(c = 25.3911(8)) Å, (\gamma = 90^\circ)</td>
</tr>
<tr>
<td>Volume</td>
<td>2715.53(15) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.186 Mg/m³</td>
</tr>
<tr>
<td>Description</td>
<td>Value</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.594 mm(^{-1})</td>
</tr>
<tr>
<td>F(000)</td>
<td>1064</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.125 x 0.025 x 0.025 mm(^3)</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>3.470 to 69.705(^{\circ})</td>
</tr>
<tr>
<td>Index ranges</td>
<td>(-8\leq h\leq 5, -17\leq k\leq 11, -30\leq l\leq 25)</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>16527</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4963 [R(int) = 0.0265]</td>
</tr>
<tr>
<td>Completeness to theta = 67.679(^{\circ})</td>
<td>98.4 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.7533 and 0.6932</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F(^2)</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>4963 / 0 / 325</td>
</tr>
<tr>
<td>Goodness-of-fit on F(^2)</td>
<td>1.049</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0286, wR2 = 0.0764</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0289, wR2 = 0.0767</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>0.05(4)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.222 and -0.151 e.Å(^{-3})</td>
</tr>
</tbody>
</table>
Compound 1 $^{13}$C NMR
Compound 5 $^1$H NMR
Compound 5 $^{13}$C NMR
Compound 10 $^1$H NMR

Ph

Me

O

O

Ph

Me

Me

S153
Compound 10 $^{13}$C NMR

Ph
Me
O
O
Ph
Me
Me

144.7
141.9
128.5
128.4
127.7
125.9

-72.6
-46.7
26.6
26.5
22.3

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)
**Compound 11 \(^1\)H NMR**

![NMR Spectrum Image]

The NMR spectrum shows the chemical shifts and multiplet patterns for the protons of Compound 11. The spectrum is crucial for identifying the molecular structure and analyzing chemical reactions.
Compound 11 $^{13}$C NMR
Compound 12 $^1$H NMR
Compound 12 $^{13}$C NMR
Compound 13 $^1$H NMR
Compound 13 $^{13}$C NMR

![Compound 13 $^{13}$C NMR spectrum](image-url)

S160
Compound 14 $^1$H NMR

![NMR Spectrum](image-url)
Compound 14 $^{13}$C NMR
Compound 15 $^1$H NMR
Compound 15 $^{13}$C NMR

$\text{Me} \quad \text{Me} \quad \text{Br}$
Compound 16 $^1$H NMR

- $7.36$, $7.31$, $7.28$, $7.26$, $7.19$
- $4.84$, $4.82$, $4.81$
- $2.08$, $1.75$, $1.61$, $1.58$, $1.57$, $1.36$

$^1$H NMR spectrum of Compound 16 with chemical shifts indicated.
Compound 16 $^{13}$C NMR

$\begin{align*}
\text{O} & \quad -147.9 \\
\text{Me} & \quad 128.2, 126.6, 125.7 \\
\text{Me} & \quad -73.6, -67.9 \\
\text{Me} & \quad -42.7, -36.6, -30.7, -28.9
\end{align*}$
Compound 17 $^1$H NMR
Compound 17 $^{13}$C NMR
Compound 18 \(^1\)H NMR

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[1.10, 1.13, 2.79, 7.62, 8.28\] ppm
Compound 18 $^{13}$C NMR
Compound 19 $^1$H NMR
Compound 19 $^{13}\text{C}$ NMR

\[
\begin{align*}
\text{Me} & \quad (p)_{p}m \\
\text{Me} & \\
\end{align*}
\]
Compound 20 $^1$H NMR
Compound 20 $^{13}$C NMR
Compound 21 $^1$H NMR
Compound 21 $^{13}$C NMR
Compound 22 \(^1\)H NMR

{Chemical structure and NMR spectrum with峰峰标号和化学位移值}
Compound 22 $^{13}$C NMR

\[
\begin{array}{c}
\text{Me} \quad \text{O} \quad \text{Me} \\
\text{Me} \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{array}
\]

Chemical shifts in ppm:
- 147.7
- 128.6
- 125.7
- 74.3
- 70.0
- 28.7
Compound 23 $^1$H NMR
Compound 23 $^{13}$C NMR

![Compound 23 $^{13}$C NMR spectrum](image)

S180
Compound 24 $^1$H NMR

![NMR Spectrum](image)

S181
Compound 24 $^{13}$C NMR

![NMR spectrum of Compound 24]
Compound 25 $^1$H NMR
Compound 25 $^{13}$C NMR
Compound 26 $^1$H NMR

![NMR Spectrum Diagram]
Compound 27 $^1$H NMR
Compound 27 $^{19}$F NMR
Compound 27 $^{13}$C NMR
Compound 28 $^1$H NMR
Compound 28 $^{13}$C NMR

The image shows a $^{13}$C NMR spectrum with chemical shifts ranging from -135.0 to 173.4 ppm. The spectrum is accompanied by a structural formula of Compound 28, which includes a benzyl group, a boronate ester, a tetrazole ring, and a carbamate group. The peaks correspond to various carbon atoms in the compound, providing information about their chemical environment and electronic properties.
Compound 29 $^1$H NMR

![NMR Spectrum](image-url)
Compound 29 $^{13}$C NMR

![NMR spectrum of Compound 29](image)

-172.2, -137.5, 128.7, 127.2, 127.0, 126.0, 125.4, 29.2, 52.4, 32.3, 32.3, 25.8, 24.3
Compound 30 $^1$H NMR

S194
Compound 30 $^{13}$C NMR
Compound 31 $^1$H NMR

S196
Compound 31 $^{13}$C NMR

BocN

O

$^{13}$C NMR spectrum showing resonance peaks at various ppm values.
Compound 32 $^1$H NMR
Compound 32 $^{13}$C NMR
Compound 33 $^1$H NMR

S200
Compound 33 $^{13}$C NMR
Compound 34 $^1$H NMR
Compound 34 $^{13}$C NMR

![Compound 34 $^{13}$C NMR spectrum](image)
Compound 35 $^1$H NMR
Compound 35 $^{13}$C NMR
Compound 36 $^1$H NMR
Compound 36 $^{13}$C NMR
Compound 37 $^1$H NMR

O
N
Me

O

Me

O

\[
\begin{array}{c}
\text{S208}
\end{array}
\]
Compound 37 $^{13}$C NMR

NMR spectrum showing chemical shifts.
Compound 38 $^1$H NMR
Compound 38 $^{13}$C NMR

[Chemical structure image]

S211
Compound 39 \(^1\)H NMR
Compound 40 $^1$H NMR
Compound 40 $^{13}$C NMR

![NMR Spectrogram](image-url)

-74.8 ppm
-72.4 ppm
-61.6 ppm
-59.3 ppm
-51.5 ppm
-23.7 ppm
Compound 41 $^1$H NMR
Compound 41 $^{13}$C NMR

\[
\begin{aligned}
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{Me}
\end{aligned}
\]
Compound 42 $^1$H NMR
Compound 42 $^{13}$C NMR
Compound 43 $^1$H NMR

S220
Compound 43 $^{13}$C NMR
Compound 44 $^1$H NMR
Compound 44 $^{13}$C NMR

![NMR Spectrum]

The NMR spectrum shows the chemical shifts for various carbon atoms in Compound 44. The spectrum is characterized by multiple peaks at different ppm values, indicating the presence of different carbon environments in the molecule.
Compound 45 $^1$H NMR

![Compound 45 $^1$H NMR Spectrogram](image-url)
Compound 45 $^{13}$C NMR

![Compound 45 $^{13}$C NMR Spectrum]
Compound 46 $^1$H NMR

-0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0 10.5 11.0 11.5 12.0 12.5
-1.0 -0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0 10.5 11.0 11.5 12.0 12.5

$^1$H NMR spectrum of Compound 46 showing chemical shifts and peak areas. The structural formula of Compound 46 is also shown.
Compound 46 $^{13}$C NMR
Compound 47 $^1$H NMR

- $7.65$, $7.31$
- $4.33$, $3.92$
- $2.72$, $2.42$
- $1.62$
- $1.11$

[Diagram of the compound with chemical shifts indicated]
Compound 47 $^{13}$C NMR
Compound 48 $^1$H NMR
Compound 48 $^{13}$C NMR
Compound 49 $^1$H NMR
Compound 49 $^{13}$C NMR

-147.1
-128.0
-127.0
-126.4
-76.8
-65.0
-64.8
-64.7
29.1
24.1
24.0
23.8
23.7
23.6

S233
Compound 50 $^1$H NMR

![NMR Spectroscopy Diagram]

S234
Compound 50 $^{13}$C NMR

S235
Compound 51 $^1$H NMR
Compound 51 $^{13}$C NMR

![Compound 51 13C NMR Diagram]
Compound 52 $^1$H NMR
Compound 52 $^{13}$C NMR

![NMR Spectrum of Compound 52]
Compound 53 $^1$H NMR
Compound 53 $^{13}$C NMR

S241
Compound 54 $^1$H NM

---

S242
Compound 54 $^{13}$C NMR

![Compound 54 $^{13}$C NMR spectrum](image)
Compound 55 $^1$H NMR

![NMR spectrum of Compound 55]
Compound 55 $^{13}$C NMR

![Compound 55 $^{13}$C NMR spectrum](image)
Compound 56 $^1$H NMR

The image shows a 1H NMR spectrum for Compound 56. The spectrum displays various peaks at different chemical shifts, which are indicated by the resonance positions on the x-axis (ppm) and the corresponding intensities on the y-axis. The spectrum is used to analyze the molecular structure of the compound by identifying the chemical shift of hydrogen nuclei in a molecule. The peaks at specific positions correspond to different hydrogen atoms within the molecule, allowing for the structural elucidation of the compound.
Compound 56 $^{13}$C NMR

\[ \text{Me} \text{O} \text{Me} \]

$^{13}$C NMR

- $-147.9$
- $-128.2$
- $-126.6$
- $-75.3$
- $-69.1$
- $37.3$
- $27.0$
- $22.8$
- $22.6$

S247
Compound 57 $^1$H NMR

$^1$H NMR spectrum of Compound 57 showing chemical shifts in ppm.
Compound 57 $^{19}$F NMR
Compound 57 $^{13}$C NMR
Compound 58 $^1$H NMR

S251
Compound 58 $^{13}$C NMR

$$\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{Me} \\
\text{Me}
\end{array}$$
Compound 59 $^1$H NMR
Compound 59 $^{13}$C NMR
Compound 60 $^1$H NMR
Compound 60 $^{19}$F NMR

$^1$H NMR: 
-66.27
Compound 60 $^{13}$C NMR

![Chemical structure](image)

**13C NMR Spectrogram**

S257
Compound 61 $^1$H NMR

![Compound 61 $^1$H NMR spectrum]
Compound 61 $^{19}$F NMR
Compound 61 $^{13}$C NMR

![Compound 61 $^{13}$C NMR spectrum](image-url)
Compound 62 $^1$H NMR
Compound 62 $^{19}$F NMR
Compound 62 $^{13}$C NMR

F3C OMe Me

S263
Compound 63 $^1$H NMR

S264
Compound 63 $^{19}$F NMR

![Compound 63 $^{19}$F NMR spectrum](image)
Compound 63 $^{13}$C NMR
Compound 64 $^1$H NMR
Compound 64 $^{19}$F NMR
Compound 64 $^{13}\text{C}$ NMR

![Carbon-13 NMR spectrum](image)
Compound 65 $^1$H NMR

O

S270
Compound 65 $^{19}$F NMR

![Compound 65 $^{19}$F NMR diagram]
Compound 65 $^{13}$C NMR

![Carbon-13 NMR spectrum](image)
Compound 66 $^1$H NMR
Compound 66 $^{13}$C NMR

![Carbon-13 NMR spectrum of Compound 66](image-url)
Compound 67 $^1$H NMR
Compound 67 $^{13}$C NMR

![Chemical structure of Compound 67]

![NMR spectrum of Compound 67]
Compound 68 $^1$H NMR
Compound 68 $^{13}$C NMR
Compound 69 $^1$H NMR

The diagram shows the $^1$H NMR spectrum of Compound 69, with chemical shifts indicated along the x-axis in ppm. The spectrum is detailed with various peaks, corresponding to different chemical environments within the molecule.
Compound 69 $^{13}$C NMR
Compound 72 \(^1\)H NMR
Compound 72 $^{13}$C NMR

$\text{MeO}$

$\text{CO}_2\text{H}$
Compound 73 $^1$H NMR

\[
\text{CO}_2\text{Me} \quad \text{HO}
\]
Compound 73 $^{13}$C NMR
Compound 74 $^1$H NMR

$^1$H NMR data for Compound 74:

- $1.72$ ppm
- $1.77$ ppm
- $1.84$ ppm
- $1.85$ ppm
- $2.05$ ppm
- $2.54$ ppm
- $2.96$ ppm
- $3.00$ ppm
- $3.39$ ppm
- $3.65$ ppm
- $3.67$ ppm
- $3.71$ ppm
- $4.20$ ppm
- $5.96$ ppm
- $6.89$ ppm
- $7.09$ ppm

S285
Compound 74 $^{13}$C NMR

$^{13}$C NMR spectrum of Compound 74 showing signals at around -73.0, -49.4, -35.6, and -29.9 ppm.
Compound 75 \(^1\)H NMR

\[
\begin{align*}
&\text{H NMR} \\
&\delta (ppm) \\
&8.5-8.0 \\
&7.5-7.0 \\
&6.5-6.0 \\
&5.5-5.0 \\
&4.5-4.0 \\
&3.5-3.0 \\
&2.5-2.0 \\
&1.5-1.0 \\
&0.5-0.0 \\
&-0.5--1.0
\end{align*}
\]
Compound 75 $^{13}$C NMR

\[
\text{HO} \quad \text{CO}_2\text{Me}
\]

$^1$H NMR (ppm):

- 69.5
- 51.7
- 54.1
- 31.8
- 29.3
Compound 76 $^1$H NMR

![NMR Spectrum](image)
Compound 76 $^{19}$F NMR
Compound (2S)-77 $^1$H NMR
Compound (2S)-77 $^{13}\text{C}$ NMR
Compound (2R)-77 $^1$H NMR
Compound (2R)-77 $^{13}$C NMR
Compound 78 $^1$H NMR

$\text{Me} - \text{Me} - \text{HO}$
Compound 78 $^{13}$C NMR
Compound 79 $^1$H NMR
Compound 79 $^{13}$C NMR

$^-159.1$ $^-129.6$ $^-120.8$ $^-114.6$ $^-70.8$ $^-68.4$ $^-40.4$ $^-29.5$ $^-24.5$
Compound 80 $^{13}$C NMR

S301
Compound 81 $^1$H NMR
Compound 81 $^{13}$C NMR

-177.9
-77.2
-69.4
-51.9
-38.5
-33.4
-33.4
-28.7

S303
Compound 82 $^1$H NMR

[Diagram of Compound 82]

S304
Compound 82 $^{13}$C NMR

Me OH

Boc

-155.0

-79.5

-58.2

-49.8

-30.8
Compound 83 $^1$H NMR

S306
Compound 83 $^{13}$C NMR
Compound 84 $^1$H NMR

- Chemical structure of Compound 84 is shown.
- The NMR spectrum is displayed with the observed chemical shifts.
- The spectrum shows peaks at the following ppm values:
  - 7.46
  - 7.37
  - 7.36
  - 1.73
  - 1.56

- The peaks are labeled with corresponding chemical shifts.
- The spectrum is used to identify and characterize the compound.
Compound 84 $^{13}$C NMR

![Chemical Structure Image]

- 148.3
- 131.4
- 126.5
- 120.7
- 72.5
- 31.9
Compound 85 $^1$H NMR

![Compound 85 $^1$H NMR spectrum](image)
Compound 85 $^{13}$C NMR
Compound 86 $^1$H NMR
Compound 86 $^{13}$C NMR
Compound 87-major $^1$H NMR

![NMR spectrum of Compound 87-major $^1$H NMR]
Compound 87-major $^{13}$C NMR

![Chemical structure and NMR spectrum](image)
Compound 87-minor $^1$H NMR
Compound 87-minor $^{13}$C NMR
Compound 88 $^1$H NMR
Compound 88 $^{13}$C NMR

\[
\begin{align*}
\text{N} & \quad \text{OH} \\
\text{Me} & \quad \text{OH}
\end{align*}
\]
Compound 89 $^1$H NMR
Compound 89 $^{19}$F NMR

$\text{F} \quad \text{F}$

$\text{O} \quad \text{O} \quad \text{Me}$
Compound 89 $^{13}$C NMR
Compound 90 $^1$H NMR

1.0 - 0.5 - 0.0 - 0.5 - 1.0

S323
Compound 90 $^{19}$F NMR
Compound 90 $^{13}$C NMR
Compound 91 $^1$H NMR

![NMR Spectrum](image-url)
Compound 91 $^{19}$F NMR

-137.85 ppm
Compound 91 $^{13}$C NMR

![Compound 91 $^{13}$C NMR spectrum]

S328
Compound 92 $^1$H NMR

S329
Compound 92 $^{19}$F NMR

-128.70 ppm
Compound 92 $^{13}$C NMR

![Compound 92 $^{13}$C NMR spectrum]

S331
Compound 93 $^1$H NMR
Compound 93 $^{19}$F NMR
Compound 93 $^{13}$C NMR

$\text{Me} \quad F$
Compound 94 H NMR

S335
Compound 94 $^{19}$F NMR

$-140.04$
Compound 94 $^{13}$C NMR

$\text{Me}$

-166.9  $\sim$134.8  $\sim$131.7  $\sim$124.0  $\sim$87.9  $\sim$86.6  $\sim$18.4  $\sim$18.2

S337
Compound 95 $^1$H NMR

- δ 1.88 (1H, s)
- δ 0.96 (1H, t)
- δ 2.06 (1H, s)
- δ 3.09 (1H, m)
- δ 6.83 (1H, m)
- δ 6.59 (1H, s)
Compound 95 $^{13}$C NMR
Compound 97 $^1$H NMR
Compound 97 $^{13}$C NMR

\[ \text{Br} \quad \text{Me} \]

\[ \text{Me} \quad \text{O} \quad \text{Me} \]

\[ \text{f1 (ppm)} \]

\[ 220 \quad 210 \quad 200 \quad 190 \quad 180 \quad 170 \quad 160 \quad 150 \quad 140 \quad 130 \quad 120 \quad 110 \quad 100 \quad 90 \quad 80 \quad 70 \quad 60 \quad 50 \quad 40 \quad 30 \quad 20 \quad 10 \quad 0 \]

S341
Compound 99 $^1$H NMR

$\text{MeO} \xrightarrow{\text{BnO}} \text{Me}$

$\text{Me}$

$\text{H}$

$\text{O}$
Compound 101 $^1$H NMR

Ph

OH
Compound 101 $^{13}$C NMR

\[ \text{PhOH} \]
Compound 102 $^1$H NMR
Compound 102 $^{13}$C NMR
Compound 103 $^1$H NMR

[Chemical structure image]

- 8.56
- 7.70
- 7.37
- 7.37
- 7.37
- 2.03
- 1.95
- 1.95
- 1.89
- 1.89
- 1.03
- 0.99

ppm
Compound 103 $^{13}$C NMR

$\text{Me} \quad \text{Me} \quad \text{O} \quad \text{N}$

![Compound structure diagram]
Compound 104 $^1$H NMR

$^{1}$H NMR spectrum showing peak assignments and chemical shifts.
Compound 104 $^{13}$C NMR
Compound 105 $^1$H NMR

S352
Compound 105 $^{13}$C NMR

OMe
Compound 106 $^1$H NMR

H NMR (ppm): 7.31, 7.19, 6.31, 3.74, 3.73, 1.90, 1.89, 1.88, 1.86, 1.85, 0.87, 0.86, 0.85, 0.73, 0.72
Compound 106 $^{13}\text{C}$ NMR
Compound 107 $^1$H NMR
Compound 107 $^{13}$C NMR

$^5$Me $^3$OMe

Me OMe

Boc

-155.1

-79.4

-71.7

48.8

36.9

28.6

23.9

f1 (ppm)

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

S357
Compound 108 $^1$H NMR
Compound 108 $^{13}$C NMR

$\text{Ph}\quad\text{O}\quad\begin{array}{c}\text{Me} \\ \text{Me}\end{array}$

$\text{N}\text{Cbz}$
Compound 109 $^1$H NMR
Compound 109 $^{13}$C NMR
Compound 110 $^1$H NMR

[Diagram of the compound with labeled atoms and a graph of the NMR spectrum]
Compound 110 $^{13}\text{C}$ NMR
Compound 111 $^1$H NMR
Compound 111 $^{13}$C NMR
Compound 112 $^1$H NMR
Compound 112 $^{13}$C NMR
Compound 113 $^1$H NMR
Compound 113 $^{13}$C NMR
Compound 114 $^{13}$C NMR
Compound 115 $^1$H NMR

S372
Compound 115 $^{13}$C NMR

[Chemical structure image]
Compound 116 $^1$H NMR

[Chemical structure diagram with NMR spectrum]
Compound 116 $^{13}$C NMR

-155.4 -146.8 -137.6 -128.1 -127.9 -126.2 -77.1 -69.4 -61.9 -33.7 -29.0

CbzN

Me

Me

Ph
Compound 117 $^1$H NMR

\[
\begin{align*}
\text{CbzN} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Ph}
\end{align*}
\]
Compound 117 $^{13}$C NMR

CbzN

O

Me

Me

Ph

-155.4
-146.4
-138.6
-128.1
-127.2
67.1
-50.6
-44.2
-30.9
-28.8
-27.8
-23.4

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
Compound 118 \(^1\)H NMR

![NMR Spectrum of Compound 118](image)
Compound 118 $^{13}$C NMR
Compound 119 $^1\text{H}$ NMR

[Spectrogram image]
Compound 119 $^{13}$C NMR
Compound 120 $^1$H NMR

O

Ph

Me

Me

Me

Me

O

Me
Compound 120 $^{13}$C NMR

$$\begin{array}{c}
\text{Ph} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array}$$

$^{13}$C NMR spectrum with peaks at various ppm values.
Compound 121 $^1$H NMR

![Compound 121 $^1$H NMR spectrum](image)

S384
Compound 121 $^{19}$F NMR
Compound 121 $^{13}$C NMR
Compound 122 $^1$H NMR
Compound 122 $^{19}$F NMR

$$
\begin{align*}
\text{F}_3\text{C} & \quad \text{OMe} \\
\end{align*}
$$
Compound 122 $^{13}$C NMR

![Chemical Structure]

S389
Compound 123 $^1$H NMR
Compound 123 $^{19}$F NMR

$\text{Me} \quad \text{Ph} \quad \text{CF}_3$

$\delta_{\text{F}}$ (ppm)
Compound 123 $^{13}$C NMR
Compound 124 $^1$H NMR
Compound 124 $^{19}$F NMR

$\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{CF}_3 \\
\text{CF}_3
\end{array}$
Compound 124 $^{13}$C NMR

$\text{Me} - \text{CF}_3$
Compound 125 $^1$H NMR

[Spectrogram image of H NMR spectrum for Compound 125]
Compound 125 $^{19}$F NMR

$\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{CF}_3$

$-78.47$

S397
Compound 125 $^{13}$C NMR

![Chemical Structure Diagram]

Chemical shifts:
- C1: 144.8
- C2: 139.2
- C3: 138.5
- C4: 136.3
- C5: 125.7
- C6: 124.4
- C7: 126.0
- C8: 79.6
- C9: 67.8
- C10: 67.4
- C11: 67.2
- C12: 29.6
- C13: 26.8
- C14: 16.4

S398
Compound 126 $^1$H NMR

$\text{Me} \quad \text{Me} \quad \text{O} \quad \text{CF}_3$

$^1$H NMR spectrum with peaks at:
- 7.42 ppm
- 7.33 ppm
- 7.28 ppm
- 3.51 ppm
- 1.60 ppm

S399
Compound 126 $^{19}$F NMR

-74.37 ppm
Compound 126 $^{13}$C NMR
Compound 127 $^1$H NMR
Compound 127 $^{19}$F NMR

-78.45
Compound 127 $^{13}$C NMR
Compound 128 \(^1\)H NMR
Compound 128 $^{19}$F NMR

\[
\begin{align*}
\text{OEt} & \quad \text{CF}_3 \\
\end{align*}
\]
Compound 128 $^{13}$C NMR
Compound 129 $^1$H NMR

S408
Compound 129 $^{19}$F NMR

-78.9 (p.p.m.)
Compound 129 $^{13}$C NMR

![Carbon-13 NMR spectrum of compound 129 with characteristic peaks and assignments.]

Chloroform (CHCl$_3$)
Compound 130 $^1$H NMR
Compound 130 $^{19}$F NMR

$\text{iPr}$

$\text{CF}_2\text{H}$

$\text{Me}$
Compound 130 $^{13}$C NMR
Compound 132 $^1$H NMR

Me

Me

OH

-7.51 to -7.38 ppm

2.00 ppm

0.52 ppm

1.00 ppm
Compound 132 $^{13}$C NMR

```
OH
Me
Me
```

S415
Compound 134 $^1$H NMR

$^1$H NMR spectrum showing the chemical shifts of the protons in Compound 134. The spectrum indicates multiple peaks at various ppm values, with peaks at $0.1$, $0.3$, $0.7$, $4.1$, and $7.4$ ppm being particularly prominent. The presence of an OH group is indicated by a peak near $7.4$ ppm, while the Me group is shown by a peak near $0.7$ ppm.
Compound 134 $^{13}$C NMR

Me

OH
Compound 135 $^1$H NMR

![NMR谱图](image)

OH

F

F
Compound 13 $^{19}$F NMR

$^{19}$F NMR spectrum for Compound 13 showing a peak at -117.05 ppm.
Compound 135 $^{13}$C NMR

S420
Compound 136 $^1$H NMR
Compound 136 $^{13}$C NMR

![Compound 136 $^{13}$C NMR spectrum](image)
Compound (11S)-138 $^1$H NMR
Compound (11S)-138 $^{13}$C NMR

S424
Compound (11R)-138 $^1$H NMR
Compound (11R)-138 $^{13}$C NMR
Compound 139 $^1$H NMR
Compound 139 $^{13}$C NMR

[Schematic diagram of molecular structure with chemical shifts]

Chemical shifts: $\delta$ ppm

- 148.1
- 132.6
- 128.4
- 126.3
- 73.1
- 39.0
- 25.5
- 22.2
Compound 140 $^1$H NMR

![NMR Spectrogram](image-url)
Compound 140 $^{13}$C NMR

\[
\begin{align*}
\text{Cl} & \quad \begin{pmatrix} \text{HO} \\ \text{HO} \end{pmatrix} \\
\text{Cl} & \quad \begin{pmatrix} \text{HO} / \text{Cl} \\ \text{HO} / \text{Cl} \end{pmatrix}
\end{align*}
\]

$\delta$ ppm: -144.9, -133.1, -126.6, -76.8, -37.2, -13.1

S430
Compound 141 $^1$H NMR

[Spectrum Image]

S431
Compound 141 $^{13}\text{C}$ NMR

[Spectrogram image of compound 141's $^{13}\text{C}$ NMR spectrum with chemical shifts labeled from -159.3 to -13.3 ppm]
Compound SI-7 $^1$H NMR

![NMR Spectrum Image]

S433
Compound SI-7 $^{13}$C NMR
Compound SI-16 $^1$H NMR

S435
Compound SI-16 $^{13}$C NMR

S436
Compound SI-17 $^1$H NMR
Compound SI-17 $^{13}$C NMR

![NMR spectrum image]
Compound SI-18 $^1$H NMR
Compound SI-18 $^{13}$C NMR
Compound SI-19 $^1$H NMR

MeOOC

S441
Compound SI-19 $^{19}$F NMR
Compound SI-19 $^{13}$C NMR
Compound SI-20 $^1$H NMR
Compound SI-20 $^{19}$F NMR

HF

HOOC
Compound SI-20 $^{13}$C NMR