Hydroxyl-Directed C–H Carbonylation Enabled by Mono-N-Protected Amino Acid Ligands: An Expedient Route to 1-Isochromanones

Yi Lu, Dasheng Leow, Xisheng Wang, Keary M. Engle and Jin-Quan Yu *

Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, USA.

*To whom correspondence should be addressed. Email: yu200@scripps.edu

SUPPORTING INFORMATION

Table of Contents

General Information .......................................................................................... page S-2
Experimental Procedures ........................................................................... pages S-2 – S-15
  Table S1: Solvent Screening ................................................................. page S-3
  Table S2: Oxidant Screening ................................................................. page S-4
  Table S3: Ligand Screening ................................................................. page S-5
  Table S4: Temperature Screening .......................................................... page S-6
  General Procedures ............................................................................ page S-7
  Characterization of new compounds ...................................................... pages S-8 – S-15
References ........................................................................................................ page S-16
NMR Spectra ............................................................................................... page S-17 – S-37
**General Information**

All solvents were used as received from commercial sources without further purification. Anhydrous solvents were prepared according to standard methods. The preparation of starting materials 1a–1t has previously been described by our group based on earlier literature precedent. 1u was prepared according to a literature procedure. Reagents used to prepare these alcohol substrates were purchased from Acros, Sigma-Aldrich, TCI and Alfa-Aesar and were used as received without further purification. Commercially available amino acid ligands were purchased from Bachem, EMD, or Novabiochem. (+)-Methyl(O2C)-Leu-OH was prepared according to our group’s previous report. Palladium acetate was purchased from Sigma-Aldrich and used without further purification. Dichloromethane was purchased from Acros and used without further purification. 1H NMR and 13C NMR spectra were recorded on Bruker-AV (400 MHz and 100 MHz, respectively) and Bruker-DRX (500 MHz and 125 MHz, respectively) instruments internally referenced to TMS or residual chloroform signals. High resolution mass spectra were recorded at the Center for Mass Spectrometry, The Scripps Research Institute.
Experimental Section for Hydroxyl-Directed C–H Carbonylation

Table S1: Solvent screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>% Conv.(^a)</th>
<th>Entry</th>
<th>Solvent</th>
<th>% Conv.(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOAc</td>
<td>&lt;1</td>
<td>6</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOH</td>
<td>0</td>
<td>7</td>
<td>1,4-dioxane</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>0</td>
<td>8</td>
<td>DCM</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>&lt;1</td>
<td>9</td>
<td>C(_3)F(_6)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>n-hexanes</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) The conversion was determined by \(^1\)H NMR analysis of the crude reaction mixture using CH\(_2\)Br\(_2\) as an internal standard.

Solvent screening for hydroxyl-directed C–H carbonylation: To a 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stirring bar, were added Pd(OAc)\(_2\) (4.5 mg, 0.02 mmol), 2-methyl-1-(m-tolyl)propan-2-ol (2c) (32.8 mg, 0.20 mmol), Li\(_2\)CO\(_3\) (14.8 mg, 0.20 mmol), solvent (2 mL). The tube was evacuated then back-filled with CO (×3, balloon), capped, and heated to 80 °C for 48 hours. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the conversion was determined by \(^1\)H NMR analysis of the crude material using CH\(_2\)Br\(_2\) as an internal standard.
Table S2: Oxidant screening

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant (equiv.)</th>
<th>% Conv. (^a)</th>
<th>Entry</th>
<th>Oxidant (equiv.)</th>
<th>% Conv. (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOAc (2)</td>
<td>38</td>
<td>5</td>
<td>AgOAc (4)</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>AgOAc (3)</td>
<td>35</td>
<td>6</td>
<td>(\text{Ag}_2\text{CO}_3) (2) / Cu(OAc) (2)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Ag}_2\text{CO}_3) (2)</td>
<td>4</td>
<td>7</td>
<td>(\text{Ag}_2\text{CO}_3) (2) / Cu(OAc) (1)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Ag}_2\text{O}) (2)</td>
<td>9</td>
<td>8</td>
<td>(\text{Ag}_2\text{CO}_3) (1) / Cu(OAc) (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) The conversion was determined by \(^1\)H NMR analysis of the crude reaction mixture using CH\(_2\)Br\(_2\) as an internal standard. \(^b\) CO/N\(_2\) = 1:1.

**Oxidant screening for hydroxyl-directed C–H carbonylation:** To a 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stirring bar, were added Pd(OAc)\(_2\) (4.5 mg, 0.02 mmol), 2-methyl-1-(m-tolyl)propan-2-ol (2c) (30.0 mg, 0.20 mmol), oxidant, Li\(_2\)CO\(_3\) (14.8 mg, 0.20 mmol), dichloromethane (5.0 mL). The tube was evacuated then back-filled with CO (\(\times 3\), balloon), capped, and heated to 80 °C for 48 hours. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the conversion was determined by \(^1\)H NMR analysis of the crude material using CH\(_2\)Br\(_2\) as an internal standard.
Table S3: Ligand screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>% Conv. a</th>
<th>Entry</th>
<th>Ligand</th>
<th>% Conv. a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>_</td>
<td>35</td>
<td>9</td>
<td>Boc-Acpc-OH</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>Boc-Ile-OH·0.5 H2O</td>
<td>46</td>
<td>10</td>
<td>Boc-tert-Leu-OH</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>Boc-Ala-OH</td>
<td>27</td>
<td>11</td>
<td>Boc-Leu-OH·H2O</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>Boc-Phe-OH</td>
<td>26</td>
<td>12</td>
<td>Ac-Leu-OH</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>Boc-Ser-OH</td>
<td>5</td>
<td>13</td>
<td>Fmoc-Leu-OH</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>Boc-Nva-OH</td>
<td>54</td>
<td>14</td>
<td>Bz-Leu-OH</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>Boc-Nle-OH</td>
<td>34</td>
<td>15</td>
<td>(+)-Men-Leu-OH</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>Boc-α- Me-Ala-OH</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a The conversion was determined by 1H NMR analysis of the crude reaction mixture using CH2Br2 as an internal standard. (+)-Men-Leu-OH = (+)-Menthyl(O2C)-Leu-OH.

**Ligand screening for hydroxyl-directed C–H carbonylation:** To a 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stirring bar, were added Pd(OAc)2 (4.5 mg, 0.02mmol, 10 mol%), 2-methyl-1-phenylpropan-2-ol (2a) (30.0 mg, 0.20 mmol), ligand (0.04 mmol), AgOAc (100.1 mg, 0.60 mmol), Li2CO3 (14.8 mg, 0.20 mmol), dichloromethane (5.0mL). The tube was evacuated then back-filled with CO (×3, balloon), capped, and heated to 80 °C for 48 hours. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*, and the conversion was determined by 1H NMR analysis of the crude material using CH2Br2 as an internal standard.
Table S4: Temperature screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. [°C]</th>
<th>% Conv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>110</td>
<td>95</td>
</tr>
</tbody>
</table>

*The conversion was determined by $^1$H NMR analysis of the crude reaction mixture using CH$_2$Br$_2$ as an internal standard. (+)-Men-Leu-OH = (+)-Menthyl(O$_2$C)-Leu-OH.

**Temperature screening for hydroxyl-directed C–H carbonylation:** To a 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stirring bar, were added Pd(OAc)$_2$ (4.5 mg, 0.02 mmol, 10 mol%), 1-(3,4-dimethoxyphenyl)-2-methylpropan-2-ol (2h) (30.0 mg, 0.20 mmol), (+)-Men-Leu-OH (12.5 mg, 0.04 mmol), AgOAc (100.1 mg, 0.60 mmol), Li$_2$CO$_3$ (14.8 mg, 0.20 mmol), dichloromethane (5.0 mL). The tube was evacuated then back-filled with CO (×3, balloon), capped, and heated to different temperatures for 48 hours. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the conversion was determined by $^1$H NMR analysis of the crude material using CH$_2$Br$_2$ as an internal standard.
**General procedures**

**General procedure for hydroxyl-directed C–H carbonylation:** A 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar was charged with the phenethyl alcohol 2 (0.20 mmol), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol), Li$_2$CO$_3$ (73.8 mg, 0.20 mmol), (+)-Menthyl(O$_2$C)-Leu-OH (12.5 mg, 0.04 mmol), AgOAc (100.1 mg, 0.60 mmol), and dichloromethane (5.0 mL). The tube was evacuated then back-filled with CO (×3, balloon), capped, and heated to 110 °C for 48 hours. *A note of caution: these reactions were performed at a temperature that is well above the boiling point of DCM (approximately 40 °C), leading to substantial pressure build-up in the sealed reaction vessel. As such, proper precautions (including the use of a blast shield) should be taken when performing these experiments.* After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel flash column chromatography using hexanes/EtOAc as the eluent.
Characterization of new compounds

3,3-Dimethylisochroman-1-one (3a):

\[ \begin{align*}
\text{1H NMR (500 MHz, CDCl}_3\text{)}: & \quad \delta = 8.10 (d, J = 7.5 \text{ Hz, } 1 \text{ H}), 7.54 (td, J_1 = 7.5 \text{ Hz, } J_2 = 1.5 \text{ Hz, } 1 \text{ H}), 7.38 (t, J = 7.5 \text{ Hz, } 1 \text{ H}), 7.22 (d, J = 7.5 \text{ Hz, } 1 \text{ H}), 3.03 (s, 2 \text{ H}), 1.47 (s, 6 \text{ H}) \text{ ppm; 13C NMR (125 MHz, CDCl}_3\text{): } \delta = 165.08, 138.05, 133.74, 130.06, 127.91, 127.51, 124.81, 80.66, 39.47, 27.55 \text{ ppm; HRMS (ESI-TOF) } m/z \text{ Calcd for } C_{11}H_{13}O_2 (M+H)^+ 177.0910, \text{ found } 177.0907. 
\end{align*} \]

3,3,5-Trimethylisochroman-1-one (3b):

\[ \begin{align*}
\text{1H NMR (500 MHz, CDCl}_3\text{): } & \quad \delta = 7.98 (d, J = 7.5 \text{ Hz, } 1 \text{ H}), 7.40 (d, J = 7.5 \text{ Hz, } 1 \text{ H}), 7.27 (t, J = 7.5 \text{ Hz, } 1 \text{ H}), 2.94 (s, 2 \text{ H}), 2.31 (s, 3 \text{ H}), 1.47 (s, 6 \text{ H}) \text{ ppm; 13C NMR (125 MHz, CDCl}_3\text{): } \delta = 165.47, 136.50, 135.53, 135.11, 127.89, 126.83, 124.75, 79.84, 36.39, 27.79, 18.88 \text{ ppm; HRMS (ESI-TOF) } m/z \text{ Calcd for } C_{16}H_{21}O_3 (M+H)^+ 191.1067, \text{ found } 191.1069. 
\end{align*} \]

3,3,6-Trimethylisochroman-1-one (3c):

\[ \begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{): } & \quad \delta = 7.98 (d, J = 8.0 \text{ Hz, } 1 \text{ H}), 7.18 (d, J = 8.0 \text{ Hz, } 1 \text{ H}), 7.02 (s, 1 \text{ H}), 2.97 (s, 2 \text{ H}), 2.40 (s, 3 \text{ H}), 1.45 (s, 6 \text{ H}) \text{ ppm; 13C NMR (125 MHz, CDCl}_3\text{): } \delta = 165.20, 144.65, 138.06, 128.46, 128.33, 122.09, 80.49, 39.42, 27.52, 21.69 \text{ ppm; HRMS (ESI-TOF) } m/z \text{ Calcd for } C_{12}H_{15}O_2 (M+H)^+ 191.1067, \text{ found } 191.1069. 
\end{align*} \]
3,3,7-Trimethylisochroman-1-one (3d):

\[
\begin{align*}
\text{1H NMR (500 MHz, CDCl}_3\text{): } & \delta = 7.91 \text{ (s, 1 H), } 7.34 \text{ (d, } J = 7.5 \text{ Hz, 1 H), } 7.11 \text{ (d, } J = 7.5 \text{ Hz, 1 H), } 2.98 \text{ (s, 2 H), } 2.39 \text{ (s, 3 H), } 1.45 \text{ (s, 6 H) ppm; } \\
\text{13C NMR (125 MHz, CDCl}_3\text{): } & \delta = 165.35, 137.30, 135.04, 134.56, 130.30, 127.79, 124.48, 80.70, 39.07, 27.50, 20.95 \text{ ppm; HRMS (ESI-TOF) } m/z \text{ Calcd for } C_{12}H_{15}O_2 (M+H)^+ 191.1067, \text{ found } 191.1069.
\end{align*}
\]

3,3,6,8-Tetramethylisochroman-1-one (3e):

\[
\begin{align*}
\text{1H NMR (500 MHz, CDCl}_3\text{): } & \delta = 6.99 \text{ (s, 1 H), } 6.84 \text{ (s, 1 H), } 2.93 \text{ (s, 2 H), } 2.64 \text{ (s, 3 H), } 2.34 \text{ (s, 3 H), } 1.41 \text{ (s, 6 H) ppm; } \\
\text{13C NMR (125 MHz, CDCl}_3\text{): } & \delta = 164.51, 143.30, 142.63, 139.11, 131.77, 126.50, 120.57, 79.30, 40.50, 27.23, 21.36 \text{ ppm; HRMS (ESI-TOF) } m/z \text{ Calcd for } C_{13}H_{17}O_2 (M+H)^+ 205.1223, \text{ found } 205.1219.
\end{align*}
\]

6-Methoxy-3,3-dipropylisochroman-1-one (3f):

\[
\begin{align*}
\text{1H NMR (500 MHz, CDCl}_3\text{): } & \delta = 8.04 \text{ (d, } J = 8.5 \text{ Hz, 1 H), } 6.87 \text{ (dd, } J_1 = 8.5 \text{ Hz, } J_2 = 2.5 \text{ Hz, 1 H), } 6.69 \text{ (d, } J = 2.5 \text{ Hz, 1 H), } 3.87 \text{ (s, 3 H), } 2.98 \text{ (s, 2 H), } 1.45 \text{ (s, 6 H) ppm; } \\
\text{13C NMR (100 MHz, CDCl}_3\text{): } & \delta = 164.97, 163.85, 140.35, 132.28, 117.27, 113.03, 112.80, 80.24, 55.44, 39.72, 27.46 \text{ ppm; HRMS (ESI-TOF) } m/z \text{ Calcd for } C_{12}H_{15}O_3 (M+H)^+ 207.1016, \text{ found } 207.1021.
\end{align*}
\]
7-Methoxy-3,3-dimethylisochroman-1-one (3g):

![Structure](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.60 (d, $J$ = 2.5 Hz, 1 H), 7.14–7.08 (m, 2 H), 3.85 (s, 3 H), 2.96 (s, 2 H), 1.46 (s, 6 H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 165.15, 158.85, 130.24, 129.03, 125.51, 121.51, 112.81, 81.02, 55.55, 38.63, 27.46 ppm; HRMS (ESI-TOF) $m$/z Calcd for C$_{12}$H$_{15}$O$_3$ (M+H)$^+$ 207.1016, found 207.1017.

6,7-Dimethoxy-3,3-dimethylisochroman-1-one (3h):

![Structure](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.56 (s, 1 H), 6.66 (s, 1 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 2.95 (s, 2 H), 1.47 (s, 6 H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 165.06, 153.64, 148.21, 132.30, 116.79, 111.62, 109.79, 80.56, 56.07, 39.02, 27.46 ppm; HRMS (ESI-TOF) $m$/z Calcd for C$_{13}$H$_{17}$O$_4$ (M+H)$^+$ 237.1121, found 237.1123.

5-Fluoro-3,3-dimethylisochroman-1-one (3i):

![Structure](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.92 (d, $J$ = 8.5 Hz, 1 H), 7.39–7.34 (m, 1 H), 7.30 (td, $J_1$ = 8.5 Hz, $J_2$ = 1.0 Hz, 1 H), 3.04 (s, 2 H), 1.49 (s, 6 H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 163.91 (d, $J_{C-F}$ = 3.8 Hz), 159.43 (d, $J_{C-F}$ = 245.5 Hz), 128.24 (d, $J_{C-F}$ = 7.8 Hz), 126.61 (d, $J_{C-F}$ = 4.4 Hz), 125.71 (d, $J_{C-F}$ = 3.5 Hz), 125.11 (d, $J_{C-F}$ = 18.9 Hz), 120.30 (d, $J_{C-F}$ = 21.3 Hz), 80.66,
32.16 (d, $J_{C-F} = 2.2$ Hz), 27.68 ppm; HRMS (ESI-TOF) $m/z$ Calcd for $C_{11}H_{12}FO_{2}$ (M+H)$^+$ 195.0816, found 195.0818.

**7-Fluoro-3,3-dimethylisochroman-1-one (3j):**

![Chemical Structure](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.78$ (dd, $J_1 = 8.5$ Hz, $J_2 = 3.0$ Hz, 1 H), 7.27–7.20 (m, 2 H), 3.00 (s, 2 H), 1.46 (s, 6 H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 164.01$ (d, $J_{C-F} = 2.5$ Hz), 161.76 (d, $J_{C-F} = 245.4$ Hz), 133.72 (d, $J_{C-F} = 3.1$ Hz), 129.66 (d, $J_{C-F} = 7.4$ Hz), 126.48 (d, $J_{C-F} = 7.5$ Hz), 121.03 (d, $J_{C-F} = 21.8$ Hz), 116.52 (d, $J_{C-F} = 23.0$ Hz), 81.11, 38.73, 27.47 ppm; HRMS (ESI-TOF) $m/z$ Calcd for $C_{11}H_{12}FO_{2}$ (M+H)$^+$ 195.0816, found 195.0821.

**5-Chloro-3,3-dimethylisochroman-1-one (3k):**

![Chemical Structure](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.05$ (dd, $J_1 = 7.5$ Hz, $J_2 = 0.5$ Hz, 1 H), 7.61 (d, $J_1 = 7.5$ Hz, $J_2 = 0.5$ Hz, 1 H), 7.34 (t, $J_1 = 7.5$ Hz, $J_2 = 0.5$ Hz, 1 H), 3.12 (s, 2 H), 1.49 (s, 6 H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 164.13$, 136.00, 134.17, 133.28, 128.62, 128.10, 126.66, 80.27, 36.62, 27.71 ppm; HRMS(ESI) $m/z$ Calcd for $C_{11}H_{12}ClO_{2}$ (M+H)$^+$ 211.0526, [(M+H)+2]$^+$ 213.0496, found 211.0522, 213.0495, (M+H)$^+$: [(M+2)+H]$^+$ = 3:1.

**6-Chloro-3,3-dimethylisochroman-1-one (3l):**

![Chemical Structure](image)
1H NMR (500 MHz, CDCl₃): δ = 8.04 (d, J = 8.0 Hz, 1 H), 7.36 (dd, J₁ = 8.0 Hz, J₂ = 2.0 Hz, 1 H), 7.24 (d, J = 2.0 Hz, 1 H), 3.00 (s, 2 H), 1.47 (s, 6 H) ppm; 13C NMR (125 MHz, CDCl₃): δ = 164.18, 140.09, 139.75, 131.60, 128.00, 123.27, 80.74, 39.23, 27.51 ppm; HRMS(ESI) m/z Calcd for C₁₁H₁₂ClO₂ (M+H)+ 211.0526, found 211.0528.

7-Chloro-3,3-dimethylisochroman-1-one (3m):

\[
\text{Me} \quad \text{Cl} \quad \text{Me} 
\]

1H NMR (500 MHz, CDCl₃): δ = 8.08 (d, J = 2.0 Hz, 1 H), 7.51 (dd, J₁ = 8.0 Hz, J₂ = 2.0 Hz, 1 H), 7.18 (d, J = 8.0 Hz, 1 H), 3.00 (s, 2 H), 1.46 (s, 6 H) ppm; 13C NMR (100 MHz, CDCl₃): δ = 163.86, 136.29, 133.54, 129.38, 126.30, 80.97, 38.90, 27.51 ppm; HRMS (ESI-TOF) m/z Calcd for C₁₁H₁₂ClO₂ (M+H)+ 211.0526, found 211.0522.

5-Bromo-3,3-dimethylisochroman-1-one (3n):

\[
\text{Br} \quad \text{Me} \quad \text{Me} 
\]

1H NMR (500 MHz, CDCl₃): δ = 8.09 (dd, J₁ = 8.0 Hz, J₂ = 0.5 Hz, 1 H), 7.78 (dd, J₁ = 8.0 Hz, J₂ = 1.5 Hz, 1 H), 7.28 (td, J₁ = 8.0 Hz, J₂ = 0.5 Hz, 1 H), 3.11 (s, 2 H), 1.49 (s, 6 H) ppm; 13C NMR (100 MHz, CDCl₃): δ = 164.16, 137.79, 137.43, 129.29, 128.53, 126.83, 123.52, 80.23, 39.40, 27.68 ppm; HRMS (ESI-TOF) m/z Calcd for C₁₁H₁₂BrO₂ (M+H)+ 255.0015, [(M+H)+2]+ 257.0000, found 255.0022, 2557.0002, (M+H)+: [(M+2)+H]+ = 1:1.
7-Bromo-3,3-dimethylisochroman-1-one (3o):

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

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.24\) (d, \(J = 2.0\) Hz, 1 H), 7.66 (dd, \(J_1 = 8.0\) Hz, \(J_2 = 2.0\) Hz, 1 H), 7.12 (d, \(J = 8.0\) Hz, 1 H), 2.98 (s, 2 H), 1.46 (s, 6 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 163.72, 136.78, 136.66, 132.87, 129.62, 126.52, 121.17, 80.93, 38.95, 27.51\); HRMS (ESI-TOF) m/z Calcd for C\(_{11}\)H\(_{12}\)BrO\(_2\) (M+H)\(^+\) 255.0015, [(M+H)+2]\(^+\) 257.0000, found 255.0017, 256.9995, (M+H)\(^+\): [(M+2)+H]\(^+\) = 1:1.

3-Benzyl-3-methylisochroman-1-one (3p):

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

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.11\) (d, \(J = 7.5\) Hz, 1 H), 7.54 (td, \(J_1 = 7.5\) Hz, \(J_2 = 1.0\) Hz, 1 H), 7.38 (t, \(J = 7.5\) Hz, 1 H), 7.32–7.29 (m, 2 H), 7.27–7.23 (m, 1 H), 7.21–7.18 (m, 3 H), 3.09–2.85 (m, 4 H), 1.41 (s, 3 H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 164.84, 137.89, 135.86, 133.88, 130.54, 130.06, 128.30, 127.99, 127.52, 126.94, 125.03, 82.76, 46.26, 36.84, 25.46\) ppm; HRMS (ESI-TOF) m/z Calcd for C\(_{17}\)H\(_{17}\)O\(_2\) (M+H)\(^+\) 253.1223, found 253.1224.

3-\(\text{iso}\)-butyl-6,7-dimethoxy-3-methylisochroman-1-one (3q):

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

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.56\) (s, 1 H), 6.64 (s, 1 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 3.03 (d, \(J = 16.0\) Hz, 1 H), 2.87 (d, \(J = 16.0\) Hz, 1 H), 1.95–1.87 (m, 1 H), 1.70 (dd, \(J_1 = 14.5\) Hz, \(J_2 = 6.5\) Hz, 2 H), 1.59 (dd, \(J_1 = 14.5\) Hz, \(J_2 = 5.5\) Hz, 2 H), 1.44 (s, 3 H), 1.00 (d, \(J = 6.5\) Hz, 3 H), 0.96
(d, J = 6.5 Hz, 3 H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 164.99, 153.62, 148.17, 132.28, 117.06, 111.60, 109.83, 83.13, 56.08, 48.62, 38.17, 25.42, 24.51, 24.32, 24.08 ppm; HRMS (ESI-TOF) m/z Calcd for C₁₆H₂₃O₄ (M+H)⁺ 279.1591, found 279.1588.

6-Methoxy-3,3-dipropylisochroman-1-one (3r):

\[
\begin{align*}
\text{MeO} &- \text{n-Pr} & - \text{n-Pr} & - \text{O} \\
\end{align*}
\]

¹H NMR (500 MHz, CDCl₃): δ = 7.03 (d, J = 8.5 Hz, 1 H), 6.86 (dd, J₁ = 8.5 Hz, J₂ = 2.5 Hz, 1 H), 6.68 (d, J = 2.5 Hz, 1 H), 3.87 (s, 3 H), 2.95 (s, 2 H), 1.73–1.59 (m, 2 H), 1.48–1.32 (m, 2 H), 0.89 (t, J = 7.5 Hz, 6 H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 164.97, 163.82, 140.31, 132.16, 117.72, 112.88, 112.81, 84.56, 55.43, 39.67, 36.04, 16.88, 14.32 ppm; HRMS (ESI-TOF) m/z Calcd for C₁₆H₂₃O₃ (M+H)⁺ 263.1642, found 263.164.

Spiro[cyclohexane-1,3′-isochroman]-1′-one (3s):

\[
\begin{align*}
\text{O} &- \text{MeO} & - \text{H} & - \text{H} \\
\end{align*}
\]

¹H NMR (500 MHz, CDCl₃): δ = 8.08 (d, J = 7.5 Hz, 1 H), 7.52 (td, J₁ = 7.5 Hz, J₂ = 1.5 Hz, 1 H), 7.36 (t, J = 7.5 Hz, 1 H), 7.21 (d, J = 7.5 Hz, 1 H), 3.01 (s, 2 H), 1.92–1.88 (m, 2 H), 1.82–1.74 (m, 2 H), 1.63–1.46 (m, 5 H), 1.41–1.33 (m, 1 H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ = 165.00, 137.69, 133.68, 129.92, 128.00, 127.36, 125.19, 81.77, 38.15, 36.07, 25.28, 21.62 ppm; HRMS (ESI-TOF) m/z Calcd for C₁₄H₁₇O₂ (M+H)⁺ 217.1223, found 217.1219.
3,3,4-Trimethylisochroman-1-one (3t):

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{O} \\
\end{align*}
\]

\( ^1 \text{H NMR (500 MHz, CDCl}_3 \): \delta = 8.08 (dd, \text{J}_1 = 8.0 \text{ Hz, J}_2 = 1.5 \text{ Hz, 1 H}), 7.55 (t, \text{J}_1 = 8.0 \text{ Hz, J}_2 = 1.5 \text{ Hz, 1 H}), 7.39 (td, \text{J}_1 = 8.0 \text{ Hz, J}_2 = 1.5 \text{ Hz, 1 H}), 7.28 (d, \text{J} = 8.0 \text{ Hz, 1 H}), 2.98 (q, \text{J} = 7.0 \text{ Hz, 2 H}), 1.43 (s, 3 \text{ H}), 1.39 (s, 3 \text{ H}), 1.32 (d, \text{J} = 7.0 \text{ Hz, 3 H}) \text{ ppm}; ^{13} \text{C NMR (125 MHz, CDCl}_3 \): \delta = 164.96, 144.12, 133.93, 129.91, 127.20, 126.63, 124.13, 83.06, 41.23, 27.64, 23.89, 16.38 \text{ ppm; HRMS (ESI-TOF) m/z} \text{ Calcd for C}_{12}\text{H}_{15}\text{O}_{2} (\text{M+H})^+ 190.0994, \text{ found } 190.0995.
\]

tert-Butyl 1-oxospiro[isochroman-3,4'-piperidine]-1'-carboxylate (3u):

\[
\begin{align*}
\text{O} & \quad \text{N}^+ \text{Boc} \\
\end{align*}
\]

\( ^1 \text{H NMR (500 MHz, CDCl}_3 \): \delta = 8.08 (d, \text{J} = 8.0 \text{ Hz, 1 H}), 7.57–7.54 (m, 1 \text{ H}), 7.39 (t, \text{J} = 7.5 \text{ Hz, 1 H}), 7.24 (d, \text{J} = 8.0 \text{ Hz, 1 H}), 3.85 (br, 2 \text{ H}), 3.32 (br, 2 \text{ H}), 3.03 (s, 2 \text{ H}), 1.92 (d, \text{J} = 13.0 \text{ Hz, 2 H}), 1.68–1.62 (m, 2 \text{ H}), 1.46 (s, 9 \text{ H}) \text{ ppm; ^{13}C NMR (125 MHz, CDCl}_3 \): \delta = 164.22, 154.53, 136.81, 133.98, 129.96, 128.01, 127.59, 124.68, 79.59, 79.22, 40.0–38.5 (br, 1 \text{ C}), 38.40, 35.31, 28.27 \text{ ppm; HRMS (ESI-TOF) m/z} \text{ Calcd for C}_{18}\text{H}_{23}\text{NO}_{4}\text{Na (M+Na)}^+ 340.1519, \text{ found } 340.1520.
\]
References


NMR Spectra
Supplementary Material (ESI) for Chemical Science
This journal is (c) The Royal Society of Chemistry 2011

S-27
Supplementary Material (ESI) for Chemical Science
This journal is (c) The Royal Society of Chemistry 2011