Visible-light-mediated decarboxylative alkylation of 2-pyridone derivatives via a C3-selective C–H functionalization

Worawat Niwetmarin, a,b* Rungroj Saruengkhanphasit, a
Chatchakorn Eurtivong, a Chatchakorn Eurtivong, a and Somsak Ruchirawat a,b,c

a Program in Chemical Sciences, Chulabhorn Graduate Institute, Chulabhorn Royal Academy, Bangkok 10210, Thailand
b The Center of Excellence on Environmental Health and Toxicology, Commission on Higher Education, Ministry of Education, Bangkok 10400, Thailand
c Laboratory of Medicinal Chemistry, Chulabhorn Research Institute, Bangkok 10210, Thailand

Supporting Information

Table of Contents
1. General Information 2
2. Reaction optimisation 3
3. Synthesis of the compounds 9
4. Radical trapping experiment 21
5. References 21
6. 1H and 13C NMR spectra of all compounds 22
1. General Information

All reactions were performed in a Schlenk tube under an argon atmosphere at room temperature. Heat generated from the LED lamps resulted in warming of the reactions to 35 – 40 °C, and fan cooling was used to maintain this temperature. Chemicals and photocatalysts were commercially available from chemical suppliers and were used without purification. DMSO and DMA were anhydrous purchased from Sigma-Aldrich. N-Hydroxyphthalimide esters were prepared according to literature procedures.\(^1\) 2-Pyridone derivatives was prepared from 2-hydroxypyridines and the appropriate alkylating agents or aryl halides.\(^2,3\) 8 W blue LED bulbs (8 W PAR38 EVE) were purchased from HomePro (https://www.homepro.co.th). \(^1\)H NMR (300 MHz) and \(^13\)C NMR (75 MHz) were recorded on Bruker AVANCE 300 spectrometer. Chemical shifts were reported in part per million on the scale using TMS (0 ppm) as an internal standard in CDCl\(_3\) and solvent signals (2.50 ppm) in DMSO-d\(_6\). The \(^13\)C NMR chemical shifts were determined by using solvent signals (77.0 ppm in CDCl\(_3\), and 39.5 ppm in DMSO-d\(_6\)). Infrared spectra were measured using PerkinElmer FT-IR spectrometer. High resolution mass spectra (HRMS) were obtained using a Thermo Scientific orbitrap Q Exactive Focus mass spectrometer via the electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI). Melting points were measured on a Thermo Scientific digital melting point apparatus in open capillaries. Flash column chromatography was carried out using silica gel (silica gel 60, size 0.06 – 0.20 mm, 70 – 230 mesh ASTM). TLC-Aluminum sheets on silica gel 60 GF\(_{254}\) were used for monitoring the reactions. Optical rotation ([\(\alpha\])\(_D\)) was measured on an automatic polarimeter (BIOBASE BK-P2S) and is quoted in (° mL)(g dm\(^{-1}\)).
Two 8 W blue LED lamps (8 W PAR38 EVE) were purchased from HomePro (https://www.homepro.co.th). The lamps were positioned on opposite sides of the Schlenk tubes at a distance 2 – 3 cm from the tubes. Fan cooling was used to maintain the temperature. With this setup, the temperature near the tubes was at approximately 35 – 40 °C throughout the reaction time of 4 – 24 h.
2. Reaction optimisation

Under Ar atmosphere, a Schlenk tube was charged with redox active ester 2a (0.20 mmol, 2.0 eq.), and fac-Ir(ppy)$_3$ (1 mol%). Solvent (1.0 mL) and N-methyl-2-pyridone 1 (0.10 mmol, 1.0 eq.) were added. The reaction mixture was degassed by ultra-sonication for 1 min and stirred for 4 – 24 h under the irradiation of blue LEDs (8 W × 2, at approximately 2 – 3 cm away from the light source, ca. 35 °C). 2 N NaOH (5 mL) was added. The organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. NMR yield of 3a was determined as described in the tables.


\[
\begin{align*}
\text{Entry} & & \text{Additive} & & \text{Solvent} & & \text{Yield}\text{a} \\
1 & & \text{NEtPr$_2$} (2.0 \text{ eq.}) & & \text{CH$_3$CN} & & \text{traces} \\
2^b & & \text{NEtPr$_2$} (2.0 \text{ eq.}) & & \text{CH$_3$CN} & & \text{n.r.} \\
3 & & \text{NEtPr$_2$} (0.5 \text{ eq.}) & & \text{CH$_3$CN} & & \text{n.r.} \\
4 & & \text{Ascorbic acid} (2.0 \text{ eq.}) & & \text{CH$_3$CN/H$_2$O} (1:1, 0.2 \text{ M}) & & \text{n.r.} \\
\end{align*}
\]

\text{a}Determined by $^1$H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

\text{b}1 (0.50 mmol) and 2a (0.10 mmol).

---

\[\text{O} \quad \text{CH$_3$} \]

\[\text{O} \quad \text{TsN} \quad \text{O} \quad \text{N} \quad \text{O} \quad \text{TsN} \]

\[\text{[Ru(bpy)$_3$]Cl$_2$} \quad \text{1 mol%} \]

\[\text{additive} \]

\[\text{solvent (0.1 M)} \]

\[2 \times 8\text{W blue LEDs} \quad 24 \text{ h} \]

\[\text{TsN} \quad \text{O} \quad \text{N} \quad \text{CH$_3$} \]
ii) Screening of additives with \([Ir(ppy)_2(bppy)](PF_6)_2\)

\[
\text{1 (0.10 mmol)} + \text{2a (0.20 mmol)} \xrightarrow{[Ir(ppy)_2(bppy)](PF_6)_2 (2 mol\%)} \text{additive} \xrightarrow{\text{DMSO (0.1 M), } 2 \times 8W \text{ blue LEDs, } 24 \text{ h}} \text{3a}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Yield(^a)</th>
<th>Entry</th>
<th>Additive</th>
<th>Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bi(OTf)_3 (30 mol%)</td>
<td>23%</td>
<td>6</td>
<td>Ni(dme)_2Cl_2 (20 mol%)</td>
<td>40%</td>
</tr>
<tr>
<td>2</td>
<td>B(C_6F_5)_3 (10 mol%)</td>
<td>traces</td>
<td>7</td>
<td>In(OTf)_3 (30 mol%)</td>
<td>48%</td>
</tr>
<tr>
<td>3</td>
<td>B(C_6F_5)_3 (30 mol%)</td>
<td>traces</td>
<td>8</td>
<td>In(OTf)_3 (50 mol%)</td>
<td>52%</td>
</tr>
<tr>
<td>4</td>
<td>TFA (4.0 eq.)</td>
<td>18%</td>
<td>9</td>
<td>In(OTf)_3 (1.0 eq.)</td>
<td>24%</td>
</tr>
<tr>
<td>5</td>
<td>Zn(OAc)_2 (30 mol%)</td>
<td>16%</td>
<td>10</td>
<td>In(OTf)_3 (30 mol%)</td>
<td>20%(^b)</td>
</tr>
<tr>
<td>6</td>
<td>Zn(OTf)_2 (30 mol%)</td>
<td>28%</td>
<td></td>
<td>-</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

\(\text{aDetermined by } ^1\text{H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.}\)

\(\text{bThe reaction was performed under air atmosphere.}\)

iii) Solvent screening with \([Ir(ppy)_2(bppy)](PF_6)_2\)

\[
\text{1 (0.10 mmol)} + \text{2a (0.20 mmol)} \xrightarrow{[Ir(ppy)_2(bppy)](PF_6)_2 (2 mol\%)} \text{In(OTf)_3 (30 mol\%)} \xrightarrow{\text{solvent (0.1 M), } 2 \times 8W \text{ blue LEDs, } 24 \text{ h}} \text{3a}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield(^a)</th>
<th>Entry</th>
<th>Solvent</th>
<th>Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH_3CN</td>
<td>traces</td>
<td>6</td>
<td>THF</td>
<td>traces</td>
</tr>
<tr>
<td>2</td>
<td>CH_3CN</td>
<td>traces</td>
<td>7</td>
<td>DCM</td>
<td>14%</td>
</tr>
<tr>
<td>3</td>
<td>DMA</td>
<td>traces</td>
<td>8</td>
<td>toluene</td>
<td>n.r.</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>traces</td>
<td>9</td>
<td>TFE</td>
<td>13%</td>
</tr>
<tr>
<td>5</td>
<td>DMSO</td>
<td>48%</td>
<td>10</td>
<td>MeOH</td>
<td>42%</td>
</tr>
</tbody>
</table>

\(\text{aDetermined by } ^1\text{H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.}\)
iv) Screening of additives with fac-Ir(ppy)$_3$

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Yield(^a)</th>
<th>Entry</th>
<th>Additive</th>
<th>Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>53%</td>
<td>11</td>
<td>Ni(dme)$_2$Br$_2$ (20 mol%)</td>
<td>43%</td>
</tr>
<tr>
<td>2</td>
<td>In(OTf)$_3$ (30 mol%)</td>
<td>53%</td>
<td>12</td>
<td>Ni(dme)$_2$Cl$_2$ (20 mol%)</td>
<td>45%</td>
</tr>
<tr>
<td>3</td>
<td>Sc(OTf)$_3$ (30 mol%)</td>
<td>28%</td>
<td>13</td>
<td>Ni(dme)$_2$Cl$_2$ (20 mol%) dtbpy (20 mol%)</td>
<td>44%</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)$_2$ (20 mol%)</td>
<td>n.r.</td>
<td>14</td>
<td>Ni(dme)$_2$Cl$_2$ (20 mol%) dtbpy (20 mol%) K$_2$CO$_3$ (2.0 eq.)</td>
<td>35%</td>
</tr>
<tr>
<td>5</td>
<td>Mn(OAc)$_3$ (20 mol%)</td>
<td>28%</td>
<td>15</td>
<td>Cs$_2$CO$_3$ (2.0 eq.)</td>
<td>17%</td>
</tr>
<tr>
<td>6</td>
<td>Zn(OAc)$_2$ (1.0 eq.)</td>
<td>42%</td>
<td>16</td>
<td>2,6-lutidine (2.0 eq.)</td>
<td>36%</td>
</tr>
<tr>
<td>7</td>
<td>Fe(NO$_3$)$_3$9H$_2$O (30 mol%)</td>
<td>n.r.</td>
<td>17</td>
<td>Et$_3$N (2.0 eq.)</td>
<td>15%</td>
</tr>
<tr>
<td>8</td>
<td>TFA (2.0 eq.)</td>
<td>40%</td>
<td>18</td>
<td>tBuOK (2.0 eq.)</td>
<td>17%</td>
</tr>
<tr>
<td>9</td>
<td>Ascorbic acid (2.0 eq.)</td>
<td>27%</td>
<td>19</td>
<td>NaOAc (2.0 eq.)</td>
<td>26%</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$ (5 mol%)</td>
<td>35%</td>
<td>20</td>
<td>KH$_2$PO$_4$ (2.0 eq.)</td>
<td>39%</td>
</tr>
</tbody>
</table>

\(^a\) Determined by $^1$H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.
v) Varying ratios of substrates

\[
\begin{align*}
\text{1} & \quad + \quad \text{2a} & \quad \xrightarrow{\text{fac-Ir(ppy)_3 (1 mol\%)} \text{ DMSO (0.1 M)} \quad 2 \times 8W \text{ blue LEDs} \quad 4 \text{ h}} \quad \text{3a}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 (mmol)</th>
<th>2a (mmol)</th>
<th>Yield\textsuperscript{a}</th>
<th>Entry</th>
<th>1 (mmol)</th>
<th>2a (mmol)</th>
<th>Yield\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>2.0</td>
<td>53%</td>
<td>4</td>
<td>5.0</td>
<td>1.0</td>
<td>46%</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>1.5</td>
<td>36%</td>
<td>5</td>
<td>1.0</td>
<td>5.0</td>
<td>52%</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>1.0</td>
<td>27%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Determined by \textsuperscript{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.

vi) Varying reaction setup

\[
\begin{align*}
\text{1 (0.10 mmol)} & \quad + \quad \text{2a (0.20 mmol)} & \quad \xrightarrow{\text{fac-Ir(ppy)_3 (1 mol\%)} \text{ DMSO (0.1 M)} \quad 2 \times 8W \text{ blue LEDs} \quad 4 \text{ h}} \quad \text{3a}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from above</th>
<th>Yield\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Using CFL bulbs</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>No fan cooling (55 °C)</td>
<td>38%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Determined by \textsuperscript{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard.
vii) Unsuccessful products.

Attempts were made to prepare the following desired products and these compounds could not be formed in our standard conditions. It can be suggested that corresponding NHPI esters were decomposed or unstable in the reactions. For the reaction with huperzine A, no reaction was observed.

![Chemical structures of unsuccessful products.](image)

**Figure S2. Unsuccessful products.**
3. Synthesis of the compounds

General Procedure for the Decarboxylative Alkylation of 2-Pyridones.

Under Ar atmosphere, a Schlenk tube was charged with redox active ester (0.20 mmol, 2.0 eq.), pyridones (if solid, 0.10 mmol, 1.0 eq.) and fac-Ir(ppy)$_3$ (1 mol%). Anhydrous DMSO (1.0 mL) and pyridones (if liquid, 0.10 mmol, 1.0 eq.) were added. The reaction mixture was degassed by ultra-sonication for 1 min and stirred for 4 – 24 h under the irradiation of blue LEDs (8 W × 2, at approximately 2 – 3 cm away from the light source, ca. 35 °C). 2 N NaOH (5 mL) was added. The organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification of the crude by column chromatography gave the desired product.

Pyridone scope

1-Methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3a). Flash column chromatography [DCM:Et$_2$O:Et$_3$N (90:10:1 – 80:20:1)]; Yellow solid (55%, 19.1 mg). m.p. 130 – 133 °C (DCM). R$_f$ = 0.34 (DCM:Et$_2$O, 8:2). $^1$H NMR (300 MHz, Chloroform-d) δ 7.74 – 7.62 (m, 2H), 7.40 – 7.30 (m, 2H), 7.19 (dd, $J$ = 6.7, 2.0 Hz, 1H), 7.13 (dd, $J$ = 6.9, 1.7 Hz, 1H), 6.16 (t, $J$ = 6.8 Hz, 1H), 3.99 – 3.84 (m, 2H), 3.54 (s, 3H), 2.80 (tt, $J$ = 12.3, 3.4 Hz, 1H), 2.46 (s, 3H), 2.38 (td, $J$ = 12.0, 2.5 Hz, 2H), 2.02 – 1.86 (m, 2H), 1.70 – 1.54 (m, 2H). $^{13}$C NMR (75 MHz, Chloroform-d) δ 162.4, 143.5, 135.9, 133.8, 132.9, 129.6, 127.7, 105.6, 46.9, 37.9, 34.9, 30.5, 21.5. IR (v/cm$^{-1}$) 2919, 2846, 1648, 1597, 1561, 1326, 1157, 935, 769. HRMS (ESI+) calcd for C$_{18}$H$_{23}$O$_3$N$_2$S $[M+H]^+$: 347.1424, found 347.1421.

For large-scale synthesis. According to the general procedure, using the NHPI ester (1.7 g, 4.00 mmol), N-methyl-2-pyridone (0.20 mL, 2.00 mmol), fac-Ir(ppy)$_3$ (1.3 mg, 0.10 mol%), and anhydrous DMSO (20 mL). The product 3a was obtained in 43% yield.
**1-Benzyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3b).** Flash column chromatography [EtOAc:n-hexane (2:3)]; Colourless solid (39%, 16.3 mg). m.p. 160 – 164 °C (EtOAc/n-hexane). Rf = 0.21 (EtOAc:n-hexane, 2:3). 1H NMR (300 MHz, Chloroform-d) δ 7.77 – 7.57 (m, 2H), 7.44 – 7.25 (m, 7H), 7.21 (dd, J = 6.8, 2.0 Hz, 1H), 7.16 – 7.06 (m, 1H), 6.16 (t, J = 6.8 Hz, 1H), 5.13 (s, 2H), 3.99 – 3.84 (m, 2H), 2.91 – 2.72 (m, 1H), 2.46 (s, 3H), 2.37 (td, J = 12.0, 2.5 Hz, 2H), 2.01 – 1.89 (m, 2H), 1.71 – 1.51 (m, 2H). 13C NMR (75 MHz, Chloroform-d) δ 162.0, 143.5, 136.4, 136.1, 134.9, 133.7, 132.8, 129.6, 128.9, 128.2, 128.0, 127.7, 105.9, 52.5, 46.9, 35.1, 30.5, 21.5. IR (ν/cm⁻¹) 2934, 2849, 1648, 1597, 1559, 1328, 1159, 921, 764. HRMS (ESI+) calcd for C_{24}H_{27}O_{3}N_{2}S [M+H]^+: 423.1737, found 423.1737.

![Chemical Structure](image)

**1-Butyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3c).** Flash column chromatography [EtOAc:n-hexane:Et₃N (40:60:1)]; Yellow oil (39%, 15 mg). Rf = 0.38 (EtOAc:n-hexane, 1:1). 1H NMR (300 MHz, Chloroform-d) δ 7.72 – 7.61 (m, 2H), 7.39 – 7.30 (m, 2H), 7.16 (dd, J = 6.7, 1.9 Hz, 1H), 7.11 (dd, J = 6.9, 1.5 Hz, 1H), 6.15 (t, J = 6.8 Hz, 1H), 4.04 – 3.77 (m, 4H), 2.90 – 2.69 (m, 1H), 2.46 (s, 3H), 2.43 – 2.30 (m, 2H), 2.00 – 1.87 (m, 2H), 1.81 – 1.50 (m, 4H), 1.44 – 1.29 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). 13C NMR (75 MHz, Chloroform-d) δ 161.8, 143.5, 135.8, 135.2, 133.4, 132.9, 129.6, 127.7, 105.5, 50.0, 46.9, 35.0, 31.3, 30.5, 21.5, 19.9, 13.7. IR (ν/cm⁻¹) 2927, 2853, 1724, 1645, 1595, 1558, 1160, 719, 546. HRMS (ESI+) calcd for C_{21}H_{29}O_{3}N_{2}S [M+H]^+: 389.1893, found 389.1892.

![Chemical Structure](image)

**1-Allyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3d).** Flash column chromatography [EtOAc:n-hexane:Et₃N (60:40:1)]; Yellow oil (27%, 10 mg). Rf = 0.56 (EtOAc). 1H NMR (300 MHz, Chloroform-d) δ 7.67 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.22 – 7.03 (m, 2H), 7.11 – 6.80 (m, 2H), 6.11 (t, J = 7.1 Hz, 1H), 4.97 – 4.63 (m, 2H), 2.74 – 2.59 (m, 2H), 2.40 – 2.22 (m, 2H), 1.93 – 1.70 (m, 2H), 1.42 – 1.23 (m, 2H). 13C NMR (75 MHz, Chloroform-d) δ 162.1, 143.5, 135.6, 135.3, 133.4, 132.9, 129.6, 127.7, 105.5, 50.4, 46.9, 35.0, 31.3, 30.5, 21.5, 19.9, 13.7. IR (ν/cm⁻¹) 2932, 2853, 1724, 1645, 1595, 1558, 1160, 719, 546. HRMS (ESI+) calcd for C_{21}H_{29}O_{3}N_{2}S [M+H]^+: 389.1893, found 389.1892.
6.19 (t, J = 6.8 Hz, 1H), 6.02 – 5.81 (m, 1H), 5.34 – 5.11 (m, 2H), 4.56 (d, J = 5.9 Hz, 2H), 3.99 – 3.80 (m, 2H), 2.89 – 2.71 (m, 1H), 2.46 (s, 3H), 2.42 – 2.26 (m, 2H), 2.00 – 1.87 (m, 2H), 1.70 – 1.51 (m, 2H). \(^{13}\)C NMR (75 MHz, Chloroform-\(d\)) \(\delta\) 161.7, 143.5, 136.0, 134.7, 133.7, 132.9, 132.5, 129.6, 127.7, 118.5, 105.8, 51.4, 46.9, 35.0, 30.5, 21.5. IR (\(\nu/cm\)^\(-1\)) 2921, 2849, 1648, 1593, 1558, 1330, 1162, 929, 726. HRMS (ESI+) calcd for \(C_{20}H_{25}O_3N_2S\) [M+H]^+: 373.1580, found 373.1581.

[\(\text{TsN}\)]

1-Phenyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3e). Flash column chromatography [EtOAc:n-hexane:Et\(_3\)N (40:60:1)]; Colourless solid (55%, 22.6 mg). m.p. 208 – 210 °C (EtOAc/n-hexane). \(R_t\) = 0.38 (DCM:MeOH, 98:2). \(^1\)H NMR (300 MHz, Chloroform-\(d\)) \(\delta\) 7.71 – 7.63 (m, 2H), 7.54 – 7.31 (m, 7H), 7.27 (dd, \(J = 6.9\), 2.0 Hz, 1H), 7.21 (dd, \(J = 7.0\), 2.0 Hz, 1H), 6.26 (t, \(J = 6.9\) Hz, 1H), 4.02 – 3.85 (m, 2H), 2.81 (tt, \(J = 12.1\), 3.0 Hz, 2H), 2.45 (s, 3H), 2.37 (td, \(J = 12.0\), 2.5 Hz, 2H), 2.06 – 1.95 (m, 2H), 1.76 – 1.58 (m, 2H). \(^{13}\)C NMR (75 MHz, Chloroform-\(d\)) \(\delta\) 161.8, 143.5, 141.1, 136.7, 135.6, 134.1, 133.0, 129.6, 129.2, 128.4, 127.7, 126.6, 105.7, 46.9, 35.2, 30.5, 21.5. IR (\(\nu/cm\)^\(-1\)) 2921, 2844, 1653, 1606, 1556, 1340, 1161, 929, 698. HRMS (ESI+) calcd for \(C_{23}H_{25}O_3N_2S\) [M+H]^+: 409.1580, found 409.1577.

[\(\text{TsN}\)]

3-(1-Tosylpiperidin-4-yl)-2H-[1,2'-bipyridin]-2-one (3f). Flash column chromatography [EtOAc:n-hexane:Et\(_3\)N (70:30:1)]; Yellow solid (59%, 24 mg). m.p. 160 – 162 °C (EtOAc/n-hexane). \(R_t\) = 0.45 (EtOAc:n-hexane, 4:1). \(^1\)H NMR (300 MHz, Chloroform-\(d\)) \(\delta\) 8.57 (d, \(J = 4.6\) Hz, 1H), 7.91 – 7.78 (m, 2H), 7.74 (d, \(J = 7.0\) Hz, 1H), 7.71 – 7.63 (m, 2H), 7.42 – 7.28 (m, 3H), 7.20 (d, \(J = 6.7\) Hz, 1H), 6.30 (t, \(J = 6.9\) Hz, 1H), 4.04 – 3.85 (m, 2H), 2.91 – 2.73 (m, 1H), 2.51 – 2.31 (m, 5H), 2.08 – 1.92 (m, 2H), 1.74 – 1.57 (m, 2H). \(^{13}\)C NMR (75 MHz, Chloroform-\(d\)) \(\delta\) 161.6, 152.2, 149.0, 143.5, 137.6, 136.7, 134.5, 133.9, 132.9, 129.6, 127.7, 123.2, 121.6, 106.0, 46.9, 35.2, 30.5, 21.5. IR (\(\nu/cm\)^\(-1\)) 2920, 2845, 1652, 1605, 1556, 1463,
1433, 1344, 1161, 931, 796, 722. HRMS (ESI+) calcd for C_{22}H_{24}O_{3}N_{3}S [M+H]^+: 410.1533, found 410.1527.

5-Chloro-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3g). Flash column chromatography [EtOAc:n-hexane:Et$_3$N (80:20:1)]; Colourless solid (33%, 12.6 mg). m.p. 211 – 212 °C (EtOAc/n-hexane). R$_f$ = 0.35 (EtOAc:n-hexane, 4:1). $^1$H NMR (300 MHz, Chloroform-d) δ 7.74 – 7.60 (m, 2H), 7.42 – 7.32 (m, 2H), 7.25 (d, J = 2.7 Hz, 1H), 7.07 (d, J = 2.6 Hz, 1H), 4.00 – 3.83 (m, 2H), 3.51 (s, 3H), 2.77 (ddd, J = 15.3, 7.7, 3.2 Hz, 1H), 2.46 (s, 3H), 2.38 (td, J = 12.0, 2.2 Hz, 2H), 2.02 – 1.87 (m, 2H), 1.71 – 1.50 (m, 2H). $^{13}$C NMR (75 MHz, Chloroform-d) δ 160.8, 143.6, 136.9, 135.0, 133.4, 133.0, 129.6, 127.7, 112.0, 46.7, 38.0, 35.2, 30.3, 21.5. IR (ν/cm$^{-1}$) 3075, 2929, 2826, 1648, 1586, 1557, 1349, 1160, 927, 728. HRMS (ESI+) calcd for C$_{18}$H$_{22}$O$_3$N$_2$S [M+H]$^+$: 381.1034, found 381.1024.

5-Bromo-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3h). Flash column chromatography [EtOAc:Et$_3$N (99:1)]; Yellow solid (24%, 10 mg). m.p. 217 – 218 °C (EtOAc). R$_f$ = 0.39 (EtOAc). $^1$H NMR (300 MHz, Chloroform-d) δ 7.67 (d, J = 8.2 Hz, 2H), 7.41 – 7.30 (m, 3H), 7.20 – 7.07 (m, 1H), 4.03 – 3.82 (m, 2H), 3.52 (s, 3H), 2.86 – 2.67 (m, 1H), 2.47 (s, 3H), 2.43 – 2.29 (m, 2H), 2.01 – 1.85 (m, 2H), 1.66 – 1.49 (m, 2H). $^{13}$C NMR (75 MHz, Chloroform-d) δ 160.9, 143.6, 137.3, 137.1, 135.7, 133.0, 129.6, 127.7, 97.7, 46.7, 37.9, 35.2, 30.3, 21.5. IR (ν/cm$^{-1}$) 3075, 2929, 2847, 2826, 1648, 1586, 1557, 1349, 1160, 927, 728. HRMS (ESI+) calcd for C$_{18}$H$_{22}$O$_3$N$_2$BrS [M+H]$^+$:425.0529, found 425.0531.

4-Chloro-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3i). Flash column chromatography [EtOAc:Et$_3$N (99:1)]; Brown solid (60%, 23 mg). m.p. > 240 °C (decomposed)
4-Methoxy-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3j). Preparative thin-layer chromatography [DCM:MeOH (95:5)]; Yellow solid (12%, 4.7 mg). m.p. 218 – 220 °C (EtOAc). 

1H NMR (300 MHz, Chloroform-d) δ 7.75 – 7.60 (m, 2H), 7.40 – 7.32 (m, 2H), 7.19 (d, J = 7.7 Hz, 1H), 6.03 (d, J = 7.7 Hz, 1H), 3.92 – 3.79 (m, 5H), 3.49 (s, 3H), 3.16 – 3.02 (m, 1H), 2.47 (s, 3H), 2.43 – 2.25 (m, 4H), 1.61 – 1.48 (m, 2H). 

13C NMR (75 MHz, Chloroform-d) δ 164.5, 163.4, 143.3, 136.6, 133.1, 129.5, 127.8, 116.3, 94.9, 55.6, 47.4, 37.7, 33.0, 27.8, 21.5. IR (ν/cm⁻¹) 2920, 2849, 1645, 1594, 1351, 1254, 1162, 928, 720. HRMS (ESI+) calcd for C₁₉H₂₅O₄N₂S [M+H⁺]: 377.1530, found 377.1531.

3-(1-Tosylpiperidin-4-yl)pyridin-2(1H)-one (3k). Flash column chromatography [DCM:MeOH:NH₄OH (97.25:2.5:0.25)]; Colorless solid (49%, 16.4 mg). m.p. 233 – 236 °C (EtOAc). 

1H NMR (300 MHz, Chloroform-d) δ 12.66 (br s, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.30 – 7.16 (m, 2H), 6.42 – 6.10 (m, 1H), 4.00 – 3.84 (m, 2H), 2.87 – 2.68 (m, 1H), 2.48 – 2.26 (m, 5H), 2.03 – 1.84 (m, 2H), 1.78 – 1.58 (m, 2H). 

13C NMR (75 MHz, Chloroform-d) δ 164.2, 143.5, 135.9, 135.6, 132.9, 132.0, 129.6, 127.8, 106.8, 46.9, 34.5, 30.4, 21.5. IR (ν/cm⁻¹) 3581, 3477, 2916, 2844, 1639, 1619, 1562, 1324, 1164, 930, 776. HRMS (ESI+) calcd for C₁₇H₂₂O₃N₂S [M+H⁺]: 333.1267, found 333.1269.
5-Chloro-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3l). Flash column chromatography [EtOAc:Et$_3$N (99:1)]; Yellow solid (22%, 8 mg). m.p. 274 – 276 °C (EtOAc). R$_f$ = 0.39 (EtOAc). $^1$H NMR (300 MHz, Chloroform-d) δ 12.64 (s, 1H), 7.69 (d, $J$ = 8.2 Hz, 2H), 7.36 (d, $J$ = 8.0 Hz, 2H), 7.26 (d, $J$ = 2.7 Hz, 1H), 7.19 (d, $J$ = 2.5 Hz, 1H), 4.05 – 3.84 (m, 2H), 2.81 – 2.62 (m, 1H), 2.46 (s, 3H), 2.44 – 2.30 (m, 2H), 2.01 – 1.86 (m, 2H), 1.76 – 1.55 (m, 2H). $^{13}$C NMR (75 MHz, Chloroform-d) δ 162.7, 143.6, 137.2, 136.9, 132.9, 129.8, 129.6, 127.8, 113.8, 46.7, 34.9, 30.1, 21.5. IR (ν/cm$^{-1}$) 2922, 2848, 1642, 1610, 1555, 1355, 1332, 1166, 919, 868. HRMS (ESI+) calcd for C$_{17}$H$_{20}$O$_3$N$_2$ClS [M+H]$^+$: 367.0878, found 367.0875.

4-Chloro-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3m). Flash column chromatography [DCM:MeOH:NH$_4$OH (97.25:2.5:0.25)]; Brown solid (70%, 26 mg). m.p. 236 – 238 °C (DCM). R$_f$ = 0.21 (DCM:MeOH, 97.5:2.5). $^1$H NMR (300 MHz, Chloroform-d) δ 12.91 (s, 1H), 7.69 (d, $J$ = 8.1 Hz, 2H), 7.36 (d, $J$ = 8.1 Hz, 2H), 7.29 (d, $J$ = 6.9 Hz, 1H), 6.32 (d, $J$ = 7.0 Hz, 1H), 4.04 – 3.80 (m, 2H), 3.11 – 2.95 (m, 1H), 2.83 – 2.64 (m, 2H), 2.47 (s, 3H), 2.37 – 2.19 (m, 2H), 1.65 – 1.48 (m, 2H). $^{13}$C NMR (75 MHz, Chloroform-d) δ 163.8, 145.6, 143.5, 133.0, 132.4, 131.0, 129.6, 127.8, 109.5, 47.0, 37.1, 26.6, 21.6. IR (ν/cm$^{-1}$) 2922, 2853, 1628, 1334, 1251, 1157, 944, 923, 786. HRMS (ESI+) calcd for C$_{17}$H$_{20}$O$_3$N$_2$ClS [M+H]$^+$: 367.0878, found 367.0875.

1-Methyl-3-(1-tosylpiperidin-4-yl)quinolin-2(1H)-one (3n). Flash column chromatography [EtOAc:n-hexane (1:1)]; Colorless solid (76%, 30 mg). m.p. 75 – 77 °C (EtOAc). R$_f$ = 0.39 (EtOAc:n-hexane, 1:1). $^1$H NMR (300 MHz, Chloroform-d) δ 7.75 – 7.64 (m, 2H), 7.60 – 7.50 (m, 2H), 7.47 (s, 1H), 7.42 – 7.31 (m, 3H), 7.30 – 7.21 (m, 1H), 4.05 – 3.86 (m, 2H), 3.73 (s, 3H), 3.00 – 2.79 (m, 1H), 2.53 – 2.36 (m, 5H), 2.09 – 1.95 (m, 2H), 1.81 – 1.62 (m, 2H). $^{13}$C
NMR (75 MHz, Chloroform-d) δ 161.8, 143.6, 138.8, 136.0, 132.9, 129.9, 129.6, 128.5, 127.8, 122.2, 120.4, 113.9, 46.9, 35.3, 30.7, 29.9, 21.6. IR (v/cm⁻¹) 2924, 2844, 1642, 1623, 1593, 1574, 1351, 1162, 754. HRMS (ESI+) calcd for C₂₂H₂₅O₃N₂S [M+H]⁺:397.1580, found 397.1576.

3-(1-Tosylpiperidin-4-yl)quinolin-2(1H)-one (3o). Flash column chromatography [DCM:MeOH:NH₄OH (97.25:2.5:0.25)]; Colorless solid (89%, 34 mg). m.p. 304 – 305 °C (DCM). R_f = 0.25 (DCM:MeOH, 97.5:2.5). ¹H NMR (300 MHz, DMSO-d₆) δ 11.76 (s, 1H), 7.78 – 7.56 (m, 4H), 7.56 – 7.38 (m, 3H), 7.32 – 7.23 (m, 1H), 7.22 – 7.11 (m, 1H), 3.87 – 3.71 (m, 2H), 2.77 – 2.59 (m, 1H), 2.43 (s, 3H), 2.36 – 2.21 (m, 2H), 1.97 – 1.83 (m, 2H), 1.75 – 1.52 (m, 2H). ¹³C NMR (75 MHz, DMSO-d₆) δ 161.9, 144.0, 138.0, 136.7, 134.6, 133.0, 130.3, 130.0, 128.0 128.0, 122.2, 119.8, 115.1, 47.0, 35.1, 30.3, 21.5. IR (v/cm⁻¹) 2922, 2848, 1652, 1570, 1349, 1332, 1162, 1091, 935, 817. HRMS (ESI+) calcd for C₂₁H₂₃O₂N₂S [M+H]⁺: 383.1424, found 383.1422.

Alkyl NHPI ester scope

1-Methyl-3-phenethylpyridin-2(1H)-one (4a). Flash column chromatography [EtOAc:n-hexane (2:3)]; Colourless oil (20%, 8 mg). R_f = 0.31 (EtOAc:n-hexane, 2:3). ¹H NMR (300 MHz, Chloroform-d) δ 7.34 – 7.15 (m, 7H), 7.10 (d, J = 6.6 Hz, 1H), 6.08 (t, J = 6.8 Hz, 1H), 3.59 (s, 3H), 3.00 – 2.77 (m, 4H). ¹³C NMR (75 MHz, Chloroform-d) δ 163.0, 141.9, 136.0, 135.9, 132.7, 128.6, 128.3, 125.8, 105.5, 37.8, 34.4, 33.1. IR (v/cm⁻¹) 3022, 2921, 2853, 1647, 1588, 1560, 1453, 754. HRMS (ESI+) calcd for C₁₄H₁₄ON [M+H]⁺:214.1226, found 214.1231.
3-(3,4-Dimethoxyphenethyl)-1-methylpyridin-2(1H)-one (4b). Flash column chromatography [EtOAc:Et₃N (99:1)]; Brown oil (21%, 11.5 mg). Rᵣ = 0.30 (EtOAc). ¹H NMR (300 MHz, Chloroform-δ) δ 7.23 – 7.14 (m, 1H), 7.14 – 7.06 (m, 1H), 6.84 – 6.71 (m, 3H), 6.08 (t, J = 6.7 Hz, 1H), 3.86 (s, 6H), 3.58 (s, 3H), 2.94 – 2.78 (m, 4H). ¹³C NMR (75 MHz, Chloroform-δ) δ 163.0, 148.7, 147.1, 136.6, 135.9, 134.6, 132.7, 120.4, 111.9, 111.1, 105.5, 55.9, 55.8, 37.8, 34.1, 33.4. IR (ν/cm⁻¹) 2932, 2835, 1646, 1586, 1560, 1514, 1463, 1258, 1236, 1153, 1028, 763. HRMS (APCI+) calcd for C₁₆H₂₀O₃N [M+H]⁺:274.1438, found 274.1439.

3-(Heptan-4-yl)-1-methylpyridin-2(1H)-one (4c). Flash column chromatography [EtOAc:n-hexane:Et₃N (80:20:1 – 100:0:1)]; Yellow oil (20%, 8 mg). Rᵣ = 0.32 (EtOAc:n-hexane, 1:1). ¹H NMR (300 MHz, Chloroform-δ) δ 7.20 – 7.06 (m, 2H), 6.13 (t, J = 6.8 Hz, 1H), 3.56 (s, 3H), 3.03 (p, J = 7.1 Hz, 1H), 1.63 – 1.50 (m, 4H), 1.31 – 1.16 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H). ¹³C NMR (75 MHz, Chloroform-δ) δ 163.1, 148.7, 147.1, 136.6, 135.3, 134.8, 105.4, 38.4, 37.9, 36.7, 20.5, 14.3. IR (ν/cm⁻¹) 2954, 2928, 2870, 1647, 1596, 1556, 1465, 756. HRMS (ESI+) calcd for C₁₃H₂₂ON [M+H]⁺: 208.1696, found 208.1691.

3-Cyclohexyl-1-methylpyridin-2(1H)-one (4d). Flash column chromatography [EtOAc:Et₃N (99:1)]; Brown oil (31%, 12 mg). Rᵣ = 0.16 (EtOAc:n-hexane, 1:1). ¹H NMR (300 MHz, Chloroform-δ) δ 7.22 – 7.10 (m, 2H), 6.13 (t, J = 6.8 Hz, 1H), 3.55 (s, 3H), 2.99 – 2.80 (m, 1H), 1.98 – 1.72 (m, 5H), 1.53 – 1.34 (m, 2H), 1.29 – 1.07 (m, 3H). ¹³C NMR (75 MHz, Chloroform-δ) δ 162.8, 138.7, 135.1, 133.4, 105.6, 37.8, 37.5, 32.4, 26.8, 26.4. IR (ν/cm⁻¹) 2921, 2849, 1646, 1590, 1557, 1447, 758. HRMS (APCI+) calcd for C₁₂H₁₈ON [M+H]⁺: 192.1383, found 192.1384.
3-Cyclopentyl-1-methylpyridin-2(1H)-one (4e). Flash column chromatography [EtOAc:Et₃N (99:1)]; Brown oil (35%, 12.5 mg). Rₐ = 0.19 (EtOAc:n-hexane, 1:1). ¹H NMR (300 MHz, Chloroform-d) δ 7.25 – 7.11 (m, 2H), 6.12 (t, J = 6.8 Hz, 1H), 3.56 (s, 3H), 3.24 (p, J = 8.3 Hz, 1H), 2.15 – 1.94 (m, 2H), 1.83 – 1.64 (m, 4H), 1.58 – 1.42 (m, 2H). ¹³C NMR (75 MHz, Chloroform-d) δ 163.1, 137.3, 135.2, 133.3, 105.5, 40.2, 37.8, 32.0, 25.3. IR (ν/cm⁻¹) 2949, 2868, 1735, 1646, 1594, 1558, 1241, 1045, 757. HRMS (ESI+) calcd for C₁₁H₁₆O₃N [M+H]+:178.1226, found 178.1224.

1-Methyl-3-(1-phenoxyethyl)pyridin-2(1H)-one (4f). Flash column chromatography [EtOAc:n-hexane:Et₃N (50:50:1)]; Yellow oil (46%, 21 mg). Rₐ = 0.16 (EtOAc:n-hexane, 1:1). ¹H NMR (300 MHz, Chloroform-d) δ 7.46 (dd, J = 6.9, 1.6 Hz, 1H), 7.28 – 7.18 (m, 3H), 6.95 – 6.83 (m, 3H), 6.16 (t, J = 6.8 Hz, 1H), 5.64 (q, J = 6.3 Hz, 1H), 3.61 (s, 3H), 1.60 (d, J = 6.3 Hz, 3H). ¹³C NMR (75 MHz, Chloroform-d) δ 161.4, 157.5, 136.8, 134.7, 133.8, 129.4, 120.6, 115.5, 106.0, 70.1, 37.6, 21.6. IR (ν/cm⁻¹) 2976, 2929, 1650, 1596, 1560, 1493, 1236, 1086, 754. HRMS (ESI+) calcd for C₁₄H₁₆O₂N [M+H]+:230.1176, found 230.1177.

3-((3r,5r,7r)-Adamantan-1-yl)-1-methylpyridin-2(1H)-one (4g). Flash column chromatography [EtOAc:n-hexane:Et₃N (50:50:1)]; Colourless solid (49%, 24 mg). m.p. 175 – 177 °C (EtOAc). Rₐ = 0.39 (EtOAc:n-hexane, 1:1). ¹H NMR (300 MHz, Chloroform-d) δ 7.26 – 7.12 (m, 2H, H₄, H₆), 6.12 (t, J = 6.9 Hz, 1H, H₅), 3.52 (s, 3H, NCH₃), 2.14 – 2.00 (m, 9H, H₆), 1.84 – 1.70 (m, 6H). ¹³C NMR (75 MHz, Chloroform-d) δ 162.1, 140.3, 135.7, 133.9, 105.2, 39.5, 37.8, 37.1, 37.0, 28.8. IR (ν/cm⁻¹) 2900, 2848, 1641, 1582, 1570, 1552, 1342, 1211, 758. HRMS (ESI+) calcd for C₁₆H₂₂O₂N [M+H]+:244.1696, found 244.1697.
1-Methyl-3-(1-methylcyclohexyl)pyridin-2(1H)-one (4h). Flash column chromatography [EtOAc:n-hexane:Et$_3$N (50:50:1)]; Yellow solid (49%, 10 mg). m.p. 70 – 72 °C (EtOAc). $R_f$ = 0.35 (EtOAc:n-hexane, 3:7). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.29 (dd, $J = 7.1$, 2.0 Hz, 1H), 7.22 (dd, $J = 6.6$, 2.0 Hz, 1H), 6.18 – 6.07 (m, 1H), 3.53 (s, 3H), 2.22 – 2.01 (m, 2H), 1.80 – 1.35 (m, 8H), 1.32 (s, 3H). $^{13}$C NMR (75 MHz, Chloroform-d) $\delta$ 162.4, 139.6, 135.8, 135.1, 105.1, 38.3, 38.0, 35.7, 26.7 (2C), 22.6. IR (v/cm$^{-1}$) 2922, 2851, 1646, 1595, 1580, 1448, 1367, 1214, 750. HRMS (ESI+) calcd for C$_{13}$H$_{20}$ON [M+H]$^+$: 206.1539, found 206.1540.

3-(1-Hydroxy-2-methylpropan-2-yl)-1-methylpyridin-2(1H)-one (4i). Flash column chromatography [EtOAc:MeOH:Et$_3$N (99:1:1)]; Colourless solid (17%, 3 mg). m.p. 123 – 124 °C (EtOAc). $R_f$ = 0.38 (DCM:MeOH, 97.5:2.5). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.38 (dd, $J = 7.2$, 1.9 Hz, 1H), 7.26 (dd, $J = 6.5$, 2.0 Hz, 1H), 6.29 – 6.16 (m, 1H), 5.04 (s, 1H), 3.80 – 3.66 (m, 2H), 3.58 (s, 3H), 1.36 (s, 6H). $^{13}$C NMR (75 MHz, Chloroform-d) $\delta$ 163.9, 138.4, 136.4, 136.1, 106.3, 72.1, 40.5, 38.4, 24.7. IR (v/cm$^{-1}$) 3382, 2957, 2922, 2851, 1646, 1595, 1580, 1448, 1367, 1214, 778, 543. HRMS (ESI+) calcd for C$_{10}$H$_{16}$O$_2$N [M+H]$^+$: 182.1176, found 182.1177.

Cytisine scope

3-(1-Tosylpiperidin-4-yl)-N-benzyl-(-)-cytisine (5a). Flash column chromatography [EtOAc:n-hexane:Et$_3$N (40:60:1)]; Amorphous yellow solid (29%, 15 mg). m.p. 80 – 82 °C (EtOAc). $R_f$ = 0.28 (EtOAc). $[\alpha]_{D}^{27} = -122$ (c 0.97, CHCl$_3$). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.75 – 7.64 (m, 2H), 7.42 – 7.32 (m, 2H), 7.21 – 7.13 (m, 3H), 7.10 (d, $J = 7.1$, 1H), 6.99 – 6.89 (m, 2H), 5.92 (d, $J = 7.2$, 1H), 4.11 (d, $J = 15.3$, 1H), 4.01 – 3.80 (m, 3H), 3.54 – 3.34 (m, 2H), 3.00 – 2.78 (m, 4H), 2.47 (s, 3H), 2.46 – 2.27 (m, 5H), 2.11 – 1.86 (m, 3H), 1.86 – 1.57
(m, 3H). $^{13}$C NMR (75 MHz, Chloroform-d) $\delta$ 162.6, 148.9, 143.5, 138.2, 133.0, 131.2, 129.6, 128.1, 128.1, 127.8, 126.9, 104.2, 61.8, 60.1, 60.0, 50.2, 47.0, 35.4, 34.8, 30.7, 28.2, 26.0, 21.5. IR (v/cm$^{-1}$) 2926, 2844, 2797, 1639, 1587, 1559, 1351, 1162, 927, 723, 650. HRMS (ESI+) calcd for C$_{30}$H$_{36}$O$_3$N$_3$S [M+H]$^+$: 518.2472, found 518.2471.

3-(1-Tosylpiperidin-4-yl)-N-Boc-(–)-cytisine (5b). Flash column chromatography [EtOAc:Et$_3$N (99:1)]; Amorphous colourless solid (47%, 25 mg). m.p. 60 – 63 °C (EtOAc). $R_f$ = 0.28 (EtOAc). $[\alpha]_D^{27} = -97$ (c 0.83, CHCl$_3$). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.76 – 7.56 (m, 2H), 7.47 – 7.30 (m, 2H), 7.09 (d, $J = 7.1$ Hz, 1H), 6.19 – 5.93 (m, 1H), 4.53 – 4.00 (m, 3H), 3.99 – 3.70 (m, 3H), 3.22 – 2.84 (m, 3H), 2.84 – 2.62 (m, 1H), 2.51 – 2.25 (m, 6H), 2.05 – 1.76 (m, 4H), 1.72 – 1.45 (m, 2H), 1.45 – 1.02 (m, 9H). $^{13}$C NMR (75 MHz, Chloroform-d) $\delta$ 162.5, 154.4, 146.6 and 146.2 (conformers), 143.5, 133.5, 132.9, 132.0 and 131.7 (conformers), 129.6, 127.7, 105.4 and 104.6 (conformers), 80.2 and 79.6 (conformers), 51.7, 50.6, 49.1, 47.0 and 46.9 (conformers), 34.9, 34.8, 30.5, 30.3, 28.0, 27.7, 26.3, 21.5. IR (v/cm$^{-1}$) 2925, 2860, 1688, 1641, 1557, 1424, 1160, 1132, 925, 721, 582. HRMS (ESI+) calcd for C$_{28}$H$_{38}$O$_5$N$_3$S [M+H]$^+$: 528.2527, found 528.2530.

3-((3r,5r,7r)-Adamantan-1-yl)-N-Boc-(–)-cytisine (5c). Flash column chromatography [EtOAc:Et$_3$N (99:1)]; Pale yellow solid (31%, 13 mg). m.p. 187 – 190 °C (EtOAc). $R_f = 0.24$ (EtOAc:n-hexane, 1:1). $[\alpha]_D^{27} = -124$ (c 0.72, CHCl$_3$). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.14 (d, $J = 7.3$ Hz, 1H), 6.12 – 5.94 (m, 1H), 4.50 – 4.05 (m, 3H), 3.81 (dd, $J = 15.5$, 6.5 Hz, 1H), 3.20 – 2.86 (m, 3H), 2.54 – 2.32 (m, 1H), 2.14 – 1.86 (m, 11H), 1.76 (s, 6H), 1.44 – 1.11 (m, 9H). $^{13}$C NMR (75 MHz, Chloroform-d) $\delta$ 162.1, 154.5, 145.7, 136.5, 133.5 and 132.8 (conformers), 104.9 and 104.1 (conformers), 80.3 and 79.6 (conformers), 51.8 and 50.7 (conformers), 50.6 and 49.3 (conformers), 48.8, 39.5, 37.1, 36.8, 34.8, 28.8, 28.1, 28.0, 26.4. IR (v/cm$^{-1}$) 2900, 2848, 1679, 1637, 1583, 1558, 1453, 1425, 1362, 1238, 1167, 1133. HRMS (ESI+) calcd for C$_{26}$H$_{37}$O$_3$N$_2$ [M+H]$^+$: 425.2799, found 425.2794.
3-(1-Phenoxyethyl)-N-Boc-(−)-cytisine (5d). Flash column chromatography [EtOAc:Et$_3$N (99:1)]; Brown oil (10 %, 4 mg). R$_f$ = 0.38 (EtOAc). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.49 – 7.36 (m, 1H), 7.26 – 7.14 (m, 2H), 6.96 – 6.78 (m, 3H), 6.18 – 5.98 (m, 1H), 5.72 – 5.46 (m, 1H), 4.55 – 4.03 (m, 3H), 3.99 – 3.83 (m, 1H), 3.20 – 2.90 (m, 3H), 2.56 – 2.38 (m, 1H), 2.10 – 1.88 (m, 2H), 1.60 – 1.52 (m, 3H), 1.42 – 1.17 (m, 9H). $^{13}$C NMR (75 MHz, Chloroform-d) $\delta$ 161.5, 157.6, 154.4, 129.4, 120.6, 115.5, 70.6 and 70.1 (conformers), 50.4, 49.1 and 49.0 (conformers), 34.9 and 34.7 (conformers), 28.1, 27.7 and 27.5 (conformers), 26.3 and 26.1 (conformers), 21.7 and 21.5 (conformers), pyridone carbons and Boc quaternary carbon not observed. IR (ν/cm$^{-1}$) 2974, 2918, 2845, 1689, 1641, 1586, 1556, 1454, 1425, 1270, 1238, 1164, 1131, 754. HRMS (ESI+) calcd for C$_{24}$H$_{31}$O$_4$N$_2$ [M+H]+: 411.2278, found 411.2281.

Radical clock experiment

3-(But-3-en-1-yl)-1-methylpyridin-2(1H)-one (6). Flash column chromatography [EtOAc:n-hexane:Et$_3$N (80:20:1)]; Brown oil (28%, 9 mg). R$_f$ = 0.22 (EtOAc:n-hexane, 1:1). $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.25 – 7.12 (m, 2H), 6.11 (t, $J$ = 6.8 Hz, 1H), 5.87 (ddt, $J$ = 16.9, 10.2, 6.6 Hz, 1H), 5.14 – 4.92 (m, 2H), 3.56 (s, 3H), 2.73 – 2.57 (m, 2H), 2.46 – 2.30 (m, 2H). $^{13}$C NMR (75 MHz, Chloroform-d) $\delta$ 163.0, 138.2, 136.2, 135.8, 132.8, 115.0, 105.5, 77.5, 37.8, 32.2, 30.2. IR (ν/cm$^{-1}$) 2919, 2856, 1646, 1586, 1560, 912, 762. HRMS (ESI+) calcd for C$_{10}$H$_{14}$ON [M+H]$: 164.1070$, found 164.1071.
4. Radical trapping experiment

Under Ar atmosphere, a Schlenk tube was charged with redox active ester (0.20 mmol, 2.0 eq.), TEMPO (0.30 mmol, 3.0 eq.) and Ir(ppy)$_3$ (1 mol%). Anhydrous DMSO (1.0 mL) and N-methyl-2-pyridone 1 (0.10 mmol, 1.0 eq.) were added. The reaction mixture was degassed by ultra-sonication for 1 min and stirred for 4 h under the irradiation of blue LEDs (8W × 2, at approximately 2 – 3 cm away from the light source, ca. 35 °C). The organic phase was washed with water (2 × 10 mL) and brine (10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The alkyl-TEMPO adduct 8 was detected by LC-MS (calcd for C$_{21}$H$_{35}$O$_3$N$_2$S [M+H]$^+$: 395.2363, found 395.2362).

Figure S2. HRMS spectrum of the reaction crude.

5. References

6. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra of all compounds

1-Methyl-3-(1-tosylpiperidin-4-yl)pyridin-2($1H$)-one (3a).
1-Benzyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3b).
1-Butyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3c)
1-Allyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3d)
1-Phenyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3e).
3-(1-Tosylpiperidin-4-yl)-2H-[1,2'-bipyridin]-2-one (3f).
5-Chloro-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3g).
5-Bromo-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3h)
4-Chloro-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3i)
4-Methoxy-1-methyl-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3j)
3-(1-Tosylpiperidin-4-yl)pyridin-2(1H)-one (3k)
5-Chloro-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3l).
4-Chloro-3-(1-tosylpiperidin-4-yl)pyridin-2(1H)-one (3m).
1-Methyl-3-(1-tosylpiperidin-4-yl)quinolin-2(1H)-one (3n)
3-(1-Tosylpiperidin-4-yl)quinolin-2(1H)-one (3o).
1-Methyl-3-phenethylpyridin-2(1H)-one (4a)
3-(3,4-Dimethoxyphenethyl)-1-methylpyridin-2(1H)-one (4b)
3-(Heptan-4-yl)-1-methylpyridin-2(1H)-one (4c)
3-Cyclohexyl-1-methylpyridin-2(1H)-one 4d)
3-Cyclopentyl-1-methylpyridin-2(1H)-one (4e)
1-Methyl-3-(1-phenoxyethyl)pyridin-2(1H)-one (4f)
3-((3r,5r,7r)-Adamantan-1-yl)-1-methylpyridin-2(1H)-one (4g)
1-Methyl-3-(1-methylcyclohexyl)pyridin-2(1H)-one (4h)
3-(1-Hydroxy-2-methylpropan-2-yl)-1-methylpyridin-2(1H)-one (4i).
3-(1-Tosylpiperidin-4-yl)-N-benzyl-(−)-cytisine (5a).
3-(1-Tosylpiperidin-4-yl)-N-Boc-(-)-cytisine (5b).
3-((3r,5r,7r)-Adamantan-1-yl)-N-Boc-(-)-cystisine (5c).
3-(1-Phenoxyethyl)-N-Boc(--)-cytisine (5d).
3-(But-3-en-1-yl)-1-methylpyridin-2(1H)-one (7)