Organophotoredox-Enabled Cascade Cyclization
Reactions for the Construction of Cyanoalkyl
Indole[2,1-a]isoquinolinones

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Supporting Information

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1. General Information

$^1$H NMR spectra were recorded on Bruker 400 MHz spectrometer and the chemical shifts were reported in parts per million ($\delta$) relative to internal standard TMS (0 ppm) for CDCl$_3$. The peak patterns are indicated as follows: s, singlet, d, doublet, dd, doublet of doublet, t, triplet, m, multiplet, q, quartet. The coupling constants, $J$, are reported in Hertz (Hz). $^{13}$C NMR spectra were obtained at Bruker 100 MHz and referenced to the internal solvent signals (central peak is 77.160 ppm in CDCl$_3$). CDCl$_3$ and DMSO-d$_6$ was used as the NMR solvent. High-resolution mass spectra (HRMS) were acquired on Thermo Q-Exactive instrument (quadrupole mass analyzer) using electrospray ionization mode (ESI). Flash column chromatography was performed over silica gel 200-300. All reagents were weighed and handled in air at room temperature. All chemical reagents were purchased from Energy Chemical and aladdin and used without further purification. Cyclobutanone oxime esters 1 and 2-aryl-$N$-methacryloyl indoles 2 were prepared according to the previous reported protocols.$^{1-3}$

2. Optimization of the Reaction Conditions

Photocatalysts:

![Figure S1](image)

**Table S1. Screen of photosensitizers$^a$**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Photosensitizers</th>
<th>Yield (%)$^b$</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Rhodamine B</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>Eosin B</td>
<td>45</td>
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</table>
3 Eosin Y trace
4 Rose Bengal trace
5 Methylene blue trace
6 PDI trace
7 1,4-Anthraquinone trace
8 Benzoquinone trace
9\textsuperscript{c} none NR
10\textsuperscript{d} Rhodamine B NR
11\textsuperscript{e} Rhodamine B trace

\textsuperscript{a} Unless otherwise noted, reactions were carried out with 1a (0.4 mmol), 2a (0.2 mmol) and photosensitizers (2 mol\%) in MeCN (0.1 M) at room temperature under 18 W blue LEDs for 12 h. \textsuperscript{b} isolated yields based on 2a. \textsuperscript{c} Without photocatalyst. \textsuperscript{d} Without blue LED light. \textsuperscript{e} Under air.

\textbf{Table S2. Screening of solvents and additives\textsuperscript{a}}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)\textsuperscript{b}</th>
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<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>DMA</td>
<td>NR</td>
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<tr>
<td>6</td>
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<tr>
<td>7</td>
<td>DCE</td>
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<td>8</td>
<td>EtOH</td>
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<tr>
<td>9\textsuperscript{c}</td>
<td>MeCN</td>
<td>trace</td>
</tr>
<tr>
<td>10\textsuperscript{d}</td>
<td>MeCN</td>
<td>56</td>
</tr>
<tr>
<td>11\textsuperscript{e}</td>
<td>MeCN</td>
<td>54</td>
</tr>
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</table>

\textsuperscript{a} Unless otherwise noted, reactions were carried out with 1a (0.4 mmol), 2a (0.2 mmol) and Rhodamine B (2 mol\%) in solvent (0.1 M) at room temperature under 18 W blue LEDs for 24 h. \textsuperscript{b} isolated yields based on 2a. \textsuperscript{c} Cs\textsubscript{2}CO\textsubscript{3}, Na\textsubscript{2}CO\textsubscript{3}, Na\textsubscript{2}HPO\textsubscript{4}, 2,6-Lutidine and 2,4,6-trimethylpyridine were added as bases. \textsuperscript{d} NH\textsubscript{4}Cl was added as acid additive. \textsuperscript{e} CH\textsubscript{3}COOH was added as acid.
Table S3. Screen of photocatalyst loading

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rhodamine B (x mol%)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>45</td>
</tr>
<tr>
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<td>2.0</td>
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<td>3.0</td>
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<tr>
<td>5</td>
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<td>55</td>
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<tr>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.0</td>
<td>65</td>
</tr>
</tbody>
</table>

<sup>a</sup> Unless otherwise noted, reactions were carried out with, 1a (0.4 mmol), 2a (0.2 mmol) and Rhodamine B (x mol%) in MeCN (0.1 M) at room temperature under 18 W blue LEDs for 24 h. <sup>b</sup> isolated yields. <sup>c</sup> 48 h.

Table S4. Screen of mole ratios<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mole ratio (1a : 2a)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0 : 1.0</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>1.5 : 1.0</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>1.0 : 1.0</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>1.0 : 1.5</td>
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</tr>
<tr>
<td>5</td>
<td>1.0 : 2.0</td>
<td>78</td>
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<tr>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.0 : 1.5</td>
<td>82</td>
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<tr>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.0 : 1.5</td>
<td>73</td>
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<sup>a</sup> Unless otherwise noted, reactions were carried out with, 1a, 2a and Rhodamine B (2 mol%) in MeCN (0.1 M) at room temperature under 18 W blue LEDs for 48 h. <sup>b</sup> isolated yields. <sup>c</sup> Ir(ppy)<sub>3</sub>, <sup>d</sup> Ru(bpy)<sub>3</sub>Cl<sub>2</sub> • 6H<sub>2</sub>O.

Table S5. Screen of reaction time and light source<sup>a</sup>

S3
<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>Light source</th>
<th>Yield (%)</th>
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<tbody>
<tr>
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<td>24</td>
<td>18 W Blue Light</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>18 W Blue Light</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>18 W Blue Light</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>12 W Blue Light</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>30 W Blue Light</td>
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<td>6</td>
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<td>36 W Blue Light</td>
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<td>48</td>
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<td>51</td>
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<td>8</td>
<td>48</td>
<td>455 nm Light</td>
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<tr>
<td>9</td>
<td>48</td>
<td>Green Light (520-525 nm)</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>White Light</td>
<td>76</td>
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</tbody>
</table>

*Unless otherwise noted, reactions were carried out with, 1a (0.3 mol), 2a (0.2 mol) and Rhodamine B (2 mol%) in MeCN (0.1 M) at room temperature. b isolated yields.

3. General Procedure

To a Schlenk tube equipped with a magnetic stir bar was charged with Cyclobutanone Oximes 1a (0.2 mmol), N-methylpropenyl-2-phenylindole 2a (0.3 mmol) and Rhodamine B (2 mol%). The tube was sealed with a septum, evacuated and backfilled with nitrogen three times. 2.0 mL acetonitrile (MeCN) was added via syringe with gentle stirring under N₂ atmosphere. The tube was sealed and stirred under 18 W blue LEDs for 48 h. The residue was purified directly by thin layer chromatography, eluting with ethyl acetate/cyclohexane (1:5 v/v), to afford compound 3aa.

4. Characterization Data

5-(5-Methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3aa)

Colorless oil. 57.1 mg, 87% yield. H NMR (400 MHz, CDCl₃) δ 8.58 (d, J = 8.0 Hz, 1H), 7.89-7.83 (m, 1H), 7.61 (dd, J = 7.3, 1.3 Hz, 1H), 7.42-7.31 (m, 5H), 7.04 (s, 1H), 2.43 (ddd, J = 13.3, 11.4, 5.1 Hz, 1H), 2.26-2.04 (m, 2H), 1.97 (ddd, J = 13.3, 11.5, 5.1 Hz, 1H), 1.69 (s, 3H), 1.53 (ddd, J = 30.2, 13.4, 9.0, 6.8 Hz, 2H), 1.05 (mdd, J = 13.5, 11.0, 8.7, 5.2 Hz, 2H). 13C NMR (100 MHz, CDCl₃) δ 173.03, 137.90, 135.47, 135.28, 130.77, 129.27, 127.54, 126.16, 125.39, 124.85, 124.80, 123.94, 120.62, 119.48, 116.84, 103.20, 77.16, 48.70, 41.65, 29.35, 25.53, 24.62, 16.88. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

6-(5-Methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)hexanenitrile (4aa)
Colorless oil. 7.5 mg, 11% yield. 1H NMR (400 MHz, CDCl3)δ 8.6-8.55 (m, 1H), 7.91-7.83 (m, 1H), 7.65-7.58 (m, 1H), 7.39 (m, J=4.5, 3.4, 1.4 Hz, 3H), 7.37 (dd, J=5.5, 1.6 Hz, 1H), 7.33 (m, J=7.4, 1.1 Hz, 1H), 7.03 (s, 1H), 2.41 (td, J=12.8, 4.6 Hz, 1H), 2.17 (t, J=7.1 Hz, 2H), 1.92 (td, J=12.9, 4.4 Hz, 1H), 1.69 (s, 3H), 1.51-1.40 (m, 2H), 1.36-1.25 (m, 2H), 0.98 (dp, J=15.5, 5.2, 3.7 Hz, 1H), 0.88 (tdd, J=12.4, 8.1, 5.8 Hz, 1H).

13C NMR (100 MHz, CDCl3) δ 173.26, 138.33, 135.61, 135.29, 130.78, 129.21, 127.42, 126.25, 125.36, 124.90, 124.76, 123.85, 120.59, 119.73, 116.88, 103.04, 77.16, 48.51, 42.50, 29.23, 28.70, 25.03, 24.48, 17.09. HRMS (ESI) calcd for C25H22N2O (M+H)+ 343.1805, found 343.1802. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

5,5-Dimethyl-6-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)hexanenitrile (3ba)

Colorless oil. 56.2 mg, 76% yield. 1H NMR (400 MHz, CDCl3)δ 8.59 (d, J=8.0 Hz, 1H), 7.86 (dd, J=6.4, 3.1 Hz, 1H), 7.62 (d, J=7.5 Hz, 1H), 7.42 (dt, J=8.0, 3.9 Hz, 1H), 7.40-7.31 (m, 4H), 7.07 (s, 1H), 2.58 (d, J=14.3 Hz, 1H), 2.10-2.01 (m, 2H), 1.95 (dt, J=16.7, 7.2 Hz, 1H), 1.72-1.66 (m, 3H), 1.49 (dm, J=38.4, 12.7, 5.9 Hz, 2H), 0.93 (pd, J=13.2, 4.9 Hz, 2H), 0.49 (d, J=17.4 Hz, 6H). 13C NMR (100 MHz, CDCl3) δ 173.34, 138.53, 135.39, 135.33, 130.74, 128.46, 127.61, 127.39, 125.39, 124.80, 124.31, 123.84, 120.61, 119.78, 116.87, 103.22, 77.16, 53.05, 46.85, 42.67, 34.39, 32.96, 28.37, 27.73, 20.36, 17.65. HRMS (ESI) calcd for C25H22N2O (M+H)+ 371.2118, found 371.2115. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

2-(2-(5-Methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)ethoxy)acetonitrile (3ca)

Colorless oil. 55.4 mg, 84% yield. 1H NMR (400 MHz, CDCl3)δ 8.57 (dd, J=8.2, 1.1 Hz, 1H), 7.91-7.87 (m, 1H), 7.65-7.57 (m, 1H), 7.44-7.36 (m, 4H), 7.36-7.30 (m, 1H), 7.05 (s, 1H), 3.77 (dd, J=16.2, 1.4 Hz, 1H), 3.65 (dd, J=16.3, 1.2 Hz, 1H), 3.43 (dd, J=9.6, 5.9, 3.6 Hz, 1H), 3.13 (td, J=9.7, 5.0 Hz, 1H), 2.93 (dd, J=14.1, 9.8, 6.0 Hz, 1H), 2.16 (dd, J=14.3, 5.0, 3.5 Hz, 1H), 1.74 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 172.94, 136.97, 135.42, 135.32, 130.64, 129.17, 127.73, 126.36, 125.41, 124.98, 124.68, 124.09, 120.61, 116.78, 115.33, 103.14, 77.16, 68.19, 55.90, 46.51, 41.33, 29.48. HRMS (ESI) calcd for C25H18N2O2 (M+H)+ 331.1441, found 331.1439. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

2-((2-(5-Methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)ethyl)thio)acetonitrile (3da)

Colorless oil. 50.5 mg, 73% yield. 1H NMR (400 MHz, CDCl3)δ 8.56 (d, J=8.0 Hz, 1H), 7.88 (d, J=7.4 Hz, 1H), 7.61 (d, J=7.5 Hz, 1H), 7.40 (dq, J=14.8, 7.8, 6.5 Hz, 4H), 7.34 (t, J=7.4 Hz, 1H), 7.05 (s, 1H), 3.27 (d, J=17.2 Hz, 1H), 3.06 (d, J=17.1 Hz, 1H), 2.86 (m, J=11.8, 5.7 Hz, 1H), 2.48 (q, J=9.8, 9.4 Hz, 1H), 2.41-2.28 (m, 2H), 1.70 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 172.55, 136.64, 135.40, 135.26, 130.73, 129.39, 127.81, 126.21, 125.47, 125.04, 124.83, 124.19, 120.68, 116.82, 116.40, 103.44, 77.16, 48.32, 39.56, 30.34, 28.51, 16.70. HRMS (ESI) calcd for C25H18N2OS (M+H)+ 347.1213, found 347.1209. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).
Tert-butyl (cyanomethyl)(2-(5-methyl-6-oxo-5,6-dihydropyrido[2,1-a]isoquinolin-5-yl)ethyl) carbamate (3ea)

Colorless oil. 70.3 mg, 82% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.55 (dd, $J = 8.1$, 2.5 Hz, 1H), 7.93-7.82 (m, 1H), 7.59 (d, $J = 7.6$ Hz, 1H), 7.48-7.31 (m, 5H), 7.03 (s, 1H), 4.18-3.74 (m, 2H), 3.23-2.92 (m, 2H), 2.80 (d, $J = 13.9$ Hz, 1H), 2.29 (t, $J = 10.3$ Hz, 1H), 1.75-1.63 (m, 3H), 1.28 (d, $J = 5.1$ Hz, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.70, 172.16, 154.40, 153.60, 136.96, 135.28, 130.71, 129.39, 127.79, 126.09, 125.55, 124.86, 124.76, 124.13, 120.65, 116.76, 116.18, 103.49, 103.30, 81.82, 77.16, 47.11, 44.69, 44.18, 38.86, 37.74, 35.59, 35.22, 31.15, 30.46, 28.16, 27.97 (3). HRMS (ESI) calc'd for C$_{34}$H$_{36}$N$_2$O (M+H)$^+$ 430.2125, found 430.2121. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

2-(Benzhydryl)(2-(5-methyl-6-oxo-5,6-dihydropyrido[2,1-a]isoquinolin-5-yl)ethyl)amino)aceto-nitrile (3fa)

White solid. 40.5 mg, 41% yield. m.p. 138-141°C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.66-8.58 (m, 1H), 7.90 (dd, $J = 7.9$, 1.2 Hz, 1H), 7.77-7.67 (m, 1H), 7.48-7.39 (m, 2H), 7.35-7.29 (m, 1H), 7.21-7.15 (m, 2H), 7.12 (d, $J = 7.9$ Hz, 1H), 6.98-6.87 (m, 4H), 6.85-6.79 (m, 2H), 6.73 (d, $J = 6.3$ Hz, 4H), 4.29 (s, 1H), 3.96 (d, $J = 17.8$ Hz, 1H), 3.35 (d, $J = 17.8$ Hz, 1H), 2.89 (ddd, $J = 15.4$, 9.5, 6.5 Hz, 1H), 2.32-2.20 (m, 2H), 2.13 (dt, $J = 14.8$, 4.4 Hz, 1H), 1.63 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.99, 141.20, 140.26, 137.22, 135.74, 135.61, 130.84, 129.16, 128.67 (2), 128.50 (2), 127.69 (2), 127.44, 127.33, 127.11 (2), 127.08, 126.16, 125.57, 124.93, 124.85, 124.14, 120.77, 117.17, 114.99, 103.08, 87.16, 73.43, 47.64, 46.98, 39.61, 37.46, 32.04. HRMS (ESI) calc'd for C$_{37}$H$_{38}$N$_2$O (M+H)$^+$ 496.2383, found 496.2381. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

Ethyl 2-(cyanomethyl)-4-(5-methyl-6-oxo-5,6-dihydropyrido[2,1-a]isoquinolin-5-yl)butanoate (3ga)

Colorless oil. 71.2 mg, 89% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.57 (dd, $J = 8.2$, 3.1 Hz, 1H), 7.87 (dd, $J = 7.0$, 1.8 Hz, 1H), 7.61 (d, $J = 7.6$ Hz, 1H), 7.44-7.30 (m, 5H), 7.04 (s, 1H), 4.23-4.07 (m, 2H), 2.66-2.34 (m, 4H), 2.00 (dd, $J = 42.5$, 12.9, 4.6 Hz, 1H), 1.67 (d, $J = 7.0$ Hz, 3H), 1.48-1.28 (m, 2H), 1.23 (dt, $J = 18.4$, 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.61, 172.46, 172.11, 172.01, 137.40, 137.30, 135.36, 135.33, 135.29, 130.74, 130.71, 129.36, 129.31, 127.68, 126.07, 126.03, 125.45, 125.43, 124.94, 124.85, 124.82, 124.04, 124.04, 120.64, 120.62, 117.64, 117.51, 116.85, 116.80, 103.32, 103.31, 77.16, 61.61, 61.59, 48.64, 48.56, 41.47, 41.45, 38.34, 38.17, 29.93, 29.60, 27.24, 27.02, 19.30, 18.99, 14.22, 14.18. HRMS (ESI) calc'd for C$_{27}$H$_{32}$N$_2$O$_3$ (M+H)$^+$ 401.1860, found 401.1857. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

Tert-butyl (1-cyano-4-(5-methyl-6-oxo-5,6-dihydropyrido[2,1-a]isoquinolin-5-yl)butan-2-yl) carbamate (3ha)

S6
Colorless oil. 77.9 mg, 88% yield. $^1$H NMR (400 MHz, CDCl₃) δ 8.56 (dd, $J = 8.1, 4.1$ Hz, 1H), 7.92-7.82 (m, 1H), 7.61 (d, $J = 7.6$ Hz, 1H), 7.46-7.30 (m, 5H), 7.04 (s, 1H), 4.66 (d, $J = 8.1$ Hz, 0.5H), 4.49 (d, $J = 8.4$ Hz, 0.5H), 3.82-3.53 (m, 1H), 2.68-2.51 (m, 1.5H), 2.52-2.33 (m, 1.5H), 2.05 (ddddd, $J = 19.5, 17.1, 13.8, 7.7$ Hz, 1H), 1.67 (d, $J = 7.1$ Hz, 3H), 1.43 (s, 9H), 1.31-1.16 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 172.87, 172.74, 155.23, 155.08, 137.44, 137.36, 135.33, 135.31, 130.79, 130.77, 129.50, 129.41, 127.77, 126.04, 126.00, 125.52, 124.95, 124.92, 124.91, 124.88, 124.14, 124.11, 120.70, 120.69, 117.12, 117.05, 116.88, 116.85, 103.48, 80.37, 77.16, 48.70, 48.58, 47.61, 47.43, 38.02, 37.72, 30.30, 29.72, 29.53, 29.43, 28.41(3), 23.95, 23.74. HRMS (ESI) calc'd for C₃₄H₂₃N₃O (M+H)+ 444.2282, found 444.2296. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

2-(2,2,3-Trimethyl-3-((5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)methyl)cyclohexyl)acetanitrile (3ia)

Colorless oil. 27.8 mg, 34% yield. $^1$H NMR (400 MHz, CDCl₃) δ 8.65-8.59 (m, 2H), 7.87 (dddd, $J = 9.3, 6.2, 3.7$ Hz, 2H), 7.66-7.59 (m, 2H), 7.43 (m, $J = 6.5, 2.9$ Hz, 2H), 7.40-7.31 (m, 8H), 7.06 (d, $J = 1.8$ Hz, 2H), 2.69 (d, $J = 6.4$ Hz, 1H), 2.66 (d, $J = 6.6$ Hz, 1H), 2.34-2.20 (m, 4H), 2.17-2.09 (m, 1H), 2.08-1.99 (m, 4H), 1.97-1.88 (m, 1H), 1.69 (dd, $J = 5.0$ Hz, 8H), 1.29 (dd, $J = 8.7, 4.3$ Hz, 2H), 1.08-1.00 (m, 2H), 0.98 (s, 6H), 0.69 (s, 3H), 0.60 (s, 3H), 0.44 (s, 3H), 0.23 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 173.74, 173.11, 138.89, 138.30, 135.38, 130.70, 128.43, 128.35, 127.81, 127.63, 127.45, 127.24, 125.42, 125.30, 124.75, 124.71, 124.27, 124.21, 123.89, 123.86, 120.53, 120.02, 119.93, 117.01, 103.12, 103.09, 77.16, 48.03, 47.70, 47.60, 47.46, 47.03, 46.98, 46.90, 46.78, 44.59, 43.75, 35.05, 34.04, 33.73, 33.57, 28.82, 28.37, 25.56, 23.39, 22.35, 20.71, 20.40, 19.68, 18.96, 18.93. HRMS (ESI) calc'd for C₃₄H₂₃N₃O (M+H)+ 411.2431, found 411.2427. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

5-(3-(Tert-butyl)-5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3ab)

Colorless oil. 50.7 mg, 66% yield. $^1$H NMR (400 MHz, CDCl₃) δ 8.56 (d, $J = 8.0$ Hz, 1H), 7.79 (d, $J = 8.3$ Hz, 1H), 7.59 (dd, $J = 7.6, 1.3$ Hz, 1H), 7.42 (dd, $J = 8.3, 1.9$ Hz, 1H), 7.40-7.30 (m, 3H), 6.98 (s, 1H), 2.43 (ddd, $J = 13.5, 11.4, 5.1$ Hz, 1H), 2.26-2.08 (m, 2H), 1.98 (dd, $J = 13.4, 11.6, 5.0$ Hz, 1H), 1.69 (s, 3H), 1.65-1.42 (m, 2H), 1.38 (d, $J = 0.8$ Hz, 9H), 1.08 (ddddd, $J = 26.0, 15.7, 7.3, 5.2$ Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 173.28, 152.59, 137.52, 135.65, 135.21, 130.95, 125.13, 124.96, 124.74, 123.74, 122.59, 122.19, 120.49, 119.48, 116.79, 102.49, 77.16, 48.93, 41.63, 35.13, 31.37 (3), 29.39, 25.55, 24.59, 16.86. HRMS (ESI) calc'd for C₂₉H₂₈N₂O (M+H)+ 385.2274, found 385.2269. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

5-(3,5-Dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3ac)
5-(1,5-Dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3ad)

Colorless oil. 49.3 mg, 72% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.57 (d, $J = 7.9$ Hz, 1H), 7.75 (d, $J = 7.9$ Hz, 1H), 7.41-7.29 (m, 2H), 7.19 (d, $J = 8.6$ Hz, 2H), 6.97 (s, 1H), 2.44 (s, 3H), 2.43-2.37 (m, 1H), 2.25-2.06 (m, 2H), 1.96 (ddd, $J = 13.3$, 10.8, 5.9 Hz, 1H), 1.68 (s, 3H), 1.54 (dm, $J = 15.1$, 7.9, 4.2 Hz, 2H), 1.14-0.98 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.16, 139.36, 137.89, 135.71, 135.17, 130.91, 128.62, 126.47, 125.10, 124.73, 123.90, 122.16, 120.44, 119.51, 116.77, 102.39, 77.16, 48.63, 41.72, 29.33, 25.52, 24.60, 21.85, 16.86. HRMS (ESI) calcd for C$_{25}$H$_{22}$N$_2$O (M+H)$^+$ 343.1805, found 343.1795. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

5-(2,5-Dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3ae)

Colorless oil. 62.2 mg, 91% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.66-8.58 (m, 1H), 7.64 (dd, $J = 7.6$, 1.3 Hz, 1H), 7.40 (ddd, $J = 8.5$, 7.3, 1.3 Hz, 1H), 7.34 (td, $J = 7.5$, 1.1 Hz, 1H), 7.32-7.29 (m, 2H), 7.26-7.24 (m, 2H), 7.14 (s, 1H), 2.75 (s, 3H), 2.44-2.34 (m, 1H), 2.25-2.06 (m, 2H), 2.00-1.90 (m, 1H), 1.68 (s, 3H), 1.62-1.43 (m, 2H), 1.15-1.02 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.23, 139.10, 135.65, 134.69, 134.47, 131.04, 130.78, 128.33, 125.77, 124.65, 124.27 (2), 120.73, 119.53, 116.83, 109.43, 77.16, 48.64, 41.86, 29.40, 25.55, 25.08, 24.56, 16.89. HRMS (ESI) calcd for C$_{25}$H$_{22}$N$_2$O (M+H)$^+$ 343.1805, found 343.1802. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

5-(4,5-Dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3ae')

Colorless oil. 63.6 mg, 93% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.55 (d, $J = 8.0$ Hz, 1H), 7.65 (s, 1H), 7.58 (d, $J = 7.5$ Hz, 1H), 7.39-7.28 (m, 2H), 7.24 (d, $J = 1.4$ Hz, 1H), 7.19 (dd, $J = 8.2$, 1.7 Hz, 1H), 7.00 (s, 1H), 2.41 (s, 3H), 2.41-2.35 (m, 2H), 2.22-2.04 (m, 2H), 1.92 (ddd, $J = 13.4$, 10.6, 6.0 Hz, 1H), 1.64 (s, 3H), 1.51 (dtq, $J = 21.4$, 14.5, 7.2 Hz, 2H), 1.03 (dq, $J = 19.0$, 10.2, 8.7, 5.2 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.28, 137.19, 135.68, 135.31, 135.10, 130.83, 130.44, 126.09, 125.30, 124.75, 124.64, 124.19, 120.57, 119.54, 116.85, 102.96, 77.16, 48.45, 41.65, 29.46, 25.58, 24.66, 21.26, 16.91. HRMS (ESI) calcd for C$_{25}$H$_{22}$N$_2$O (M+H)$^+$ 343.1805, found 343.1800. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

5-(3-Bromo-5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3af)

Colorless oil. 49.6 mg, 61% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.56 (d, $J = 8.1$ Hz, 1H), 7.72 (d, $J = 8.2$ Hz, 1H), 7.64-7.57 (m, 1H), 7.54-7.47 (m, 2H), 7.39 (td, $J = 7.7$, 1.3 Hz, 1H), 7.34 (td, $J = 7.5$, 1.2 Hz, 1H), 7.03 (s, 1H), 2.42 (ddd, $J = 13.4$, 11.2, 5.4 Hz, 1H), 2.26-2.09 (m, 2H), 1.91 (ddd, $J = 13.4$, 11.3, 5.5 Hz, 1H), 1.68 (s, 3H), 1.54 (dp, $J = 14.1$, 6.9, 6.4 Hz, 2H), 1.14-0.97 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.18, 139.95, 135.31, 134.45, 130.94, 130.59, 129.29, 125.78, 125.49, 125.00, 123.96, 123.09, 120.78, 119.39, 116.87, 103.84, 77.16, 48.73, 41.84, 29.16, 25.48, 24.59, 16.93. HRMS (ESI) calcd for C$_{25}$H$_{19}$BrN$_2$O (M+H)$^+$ 407.0754, found 407.0750. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).
5-(3-Chloro-5-methyl-6-oxo-5,6-dihydroindolo[2,1-α]isoquinolin-5-yl)pentanenitrile (3ag)

Colorless oil. 25.3 mg, 35% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.56 (d, \(J = 8.1\) Hz, 1H), 7.79 (d, \(J = 8.3\) Hz, 1H), 7.60 (d, \(J = 7.6\) Hz, 1H), 7.37 (h, \(J = 7.8\) Hz, 4H), 7.01 (s, 1H), 2.49-2.38 (m, 1H), 2.18 (m, 1H), 1.97-1.87 (m, 1H), 1.68 (s, 3H), 1.55 (s, 3H), 1.15-0.98 (m, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.21, 139.71, 135.26, 134.95, 134.42, 130.59, 128.09, 126.31, 125.71, 125.34, 124.97, 123.53, 120.74, 119.38, 116.85, 103.72, 77.16, 48.75, 41.80, 29.15, 25.46, 24.57, 16.91. HRMS (ESI) calcd for C\(_{22}\)H\(_{19}\)ClN\(_2\)O (M+H\(^+\)) 363.1259, found 363.1256. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

5-(10-Fluoro-5-methyl-6-oxo-5,6-dihydroindolo[2,1-α]isoquinolin-5-yl)pentanenitrile (3ah)

Colorless oil. 60.9 mg, 88% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.52 (dd, \(J = 9.0\), 4.7 Hz, 1H), 7.89-7.82 (m, 1H), 7.46-7.34 (m, 3H), 7.25 (dd, \(J = 8.6\), 2.6 Hz, 1H), 7.08 (dd, \(J = 9.0\), 2.6, 0.9 Hz, 1H), 6.99 (s, 1H), 2.42 (ddd, \(J = 13.3, 11.4, 5.1\) Hz, 1H), 2.26-2.07 (m, 2H), 1.97 (ddd, \(J = 13.4, 11.5, 5.1\) Hz, 1H), 1.68 (s, 3H), 1.53 (dddd, \(J = 31.8, 13.6, 8.9, 6.6\) Hz, 2H), 1.04 (ddd, \(J = 17.2, 11.1, 9.1, 5.0\) Hz, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.83, 161.36, 159.44, 138.11, 137.00, 131.98, 131.90, 131.59, 129.62, 127.62, 126.20, 124.46, 124.06, 114.45, 117.90, 117.83, 112.96, 112.75, 106.34, 106.15, 102.72, 102.69, 77.16, 48.63, 41.63, 29.38, 25.47, 24.58, 16.88. HRMS (ESI) calcd for C\(_{22}\)H\(_{19}\)F\(_2\)N\(_2\)O (M+H\(^+\)) 347.1554, found 347.1551. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

5-(10-Chloro-5-methyl-6-oxo-5,6-dihydroindolo[2,1-α]isoquinolin-5-yl)pentanenitrile (3ai)

Colorless oil. 61.5mg, 85% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.48 (d, \(J = 8.7\) Hz, 1H), 7.85 (d, \(J = 7.5\) Hz, 1H), 7.56 (d, \(J = 2.0\) Hz, 1H), 7.46-7.35 (m, 3H), 7.32 (dd, \(J = 8.7, 2.1\) Hz, 1H), 6.96 (s, 1H), 2.42 (ddd, \(J = 13.3, 11.2, 5.4\) Hz, 1H), 2.16 (m, \(J = 16.9, 7.3\) Hz, 2H), 1.97 (ddd, \(J = 13.4, 11.3, 5.4\) Hz, 1H), 1.68 (s, 3H), 1.61-1.45 (m, 2H), 1.04 (dm, \(J = 10.6, 8.6, 5.3\) Hz, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.97, 138.09, 136.78, 133.57, 132.09, 130.34, 129.71, 127.67, 126.21, 125.40, 124.40, 124.13, 120.18, 119.44, 117.79, 102.25, 77.16, 48.72, 41.68, 29.35, 25.48, 24.59, 16.90. HRMS (ESI) calcd for C\(_{22}\)H\(_{19}\)ClN\(_2\)O (M+H\(^+\)) 363.1259, found 363.1263. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

5-(10-Bromo-5-methyl-6-oxo-5,6-dihydroindolo[2,1-α]isoquinolin-5-yl)pentanenitrile (3aj)

Colorless oil. 64.9 mg, 80% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.43 (d, \(J = 8.7\) Hz, 1H), 7.87-7.82 (m, 1H), 7.72 (d, \(J = 2.0\) Hz, 1H), 7.47-7.35 (m, 4H), 6.95 (s, 1H), 2.41 (ddd, \(J = 13.4, 11.1, 5.4\) Hz, 1H), 2.15 (qt, \(J = 16.9, 7.3\) Hz, 2H), 1.96 (ddd, \(J = 13.5, 11.2, 5.4\) Hz, 1H), 1.68 (d, \(J = 2.3\) Hz, 3H), 1.53 (ddd, \(J = 30.0, 13.4, 8.6, 6.5\) Hz, 2H), 1.04 (ddd, \(J = 14.1, 10.8, 8.8, 6.3\) Hz, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.98, 138.09, 136.64, 133.90, 132.56, 129.72, 128.08, 127.66, 126.20, 124.34, 124.14, 123.21, 119.41, 118.14, 118.12, 102.10, 77.16, 48.74, 41.67, 29.29, 25.46, 24.56, 16.87. HRMS (ESI) calcd for C\(_{22}\)H\(_{19}\)BrN\(_2\)O (M+H\(^+\)) 407.0754, found 407.0761. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).
5-(5,10-Dimethyl-6-oxo-5,6-dihyridindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3ak)

Colorless oil. 25.3 mg, 37% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.43 (d, $J = 8.3$ Hz, 1H), 7.84 (dd, $J = 6.7$, 2.1 Hz, 1H), 7.46-7.31 (m, 4H), 7.20 (dd, $J = 8.4$, 1.6 Hz, 1H), 6.96 (s, 1H), 2.47 (s, 3H), 2.42 (ddd, $J = 13.3$, 11.4, 5.2 Hz, 1H), 2.26-2.04 (m, 2H), 1.95 (ddd, $J = 13.4$, 11.4, 5.2 Hz, 1H), 1.68 (s, 3H), 1.52 (dd, $J = 30.4$, 13.5, 8.8 Hz, 2H), 1.15-0.91 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.80, 137.91, 135.51, 134.47, 133.44, 131.01, 129.14, 127.49, 126.68, 126.16, 124.97, 123.87, 120.60, 116.45, 103.01, 77.16, 48.59, 41.74, 29.30, 25.54, 24.62, 21.62, 16.89.

HRMS (ESI) calcd for C$_{23}$H$_{22}$N$_2$O (M+H)$^+$ 343.1805, found 343.1803. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

5-(5,12-Dimethyl-6-oxo-5,6-dihyridindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3al)

White solid. 50.6 mg, 74% yield. m.p. 146-148 $^\circ$C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.60 (d, $J = 7.8$ Hz, 1H), 8.03 (d, $J = 7.5$ Hz, 1H), 7.60 (d, $J = 7.4$ Hz, 1H), 7.40 (m, $J = 16.2$, 7.7 Hz, 5H), 2.66 (s, 3H), 2.39 (ddd, $J = 13.1$, 10.3, 6.1 Hz, 1H), 2.17 (dtd, $J = 24.3$, 16.7, 8.3 Hz, 2H), 2.01-1.88 (m, 1H), 1.68 (s, 3H), 1.54 (dd, $J = 21.4$, 14.1, 7.1 Hz, 2H), 1.18-1.01 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.82, 138.23, 134.15, 132.55, 130.27, 129.74, 128.20, 127.31, 126.64, 126.32, 125.85, 125.21, 124.39, 119.52, 118.50, 116.74, 114.47, 77.16, 48.45, 41.56, 29.06, 25.55, 24.57, 16.89, 11.59. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

5-(10-Chloro-3,5-dimethyl-6-oxo-5,6-dihyridindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3am)

Colorless oil. 57.9 mg, 77% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.47 (d, $J = 8.7$ Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.54 (d, $J = 2.0$ Hz, 1H), 7.29 (dd, $J = 8.7$, 2.1 Hz, 1H), 7.22-7.15 (m, 2H), 6.89 (s, 1H), 2.43 (s, 3H), 2.42-2.35 (m, 1H), 2.25-2.08 (m, 2H), 2.00-1.91 (m, 1H), 1.67 (s, 3H), 1.53 (dd, $J = 21.1$, 13.9, 6.8 Hz, 2H), 1.04 (dd, $J = 15.0$, 10.3, 5.8 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.12, 138.23, 134.15, 132.55, 129.74, 128.20, 127.31, 126.64, 126.32, 125.21, 124.39, 119.52, 118.50, 116.74, 114.47, 77.16, 48.45, 41.56, 29.06, 25.55, 24.57, 16.89, 11.59. Purification by flash chromatography (cyclohexane/ethyl acetate = 5/1).

5. Transformation of Cyanoalkylated Product

(a) Hydrolysis of β-cyanoalkylated indolo[2,1-a]isoquinoline (3aa)

3aa (164.5 mg, 0.5 mmol) was added into 10 mL RBF. H$_2$SO$_4$ (0.3 mL), CH$_3$COOH (0.5 mL) and H$_2$O (0.5 mL) were then added sequentially via syringe. The resulting mixture was heated to reflux. Upon completion of the reaction as monitored by TLC, the solvent was removed under
vacuum. The residue was purified directly by flash column chromatography, eluting with ethyl acetate/petroleum ether (1 : 2 v/v) to give product 4a.

5-(5-Methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanoic acid. Colorless oil. 156.1 mg, 90% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.59 (d, J = 8.1\) Hz, 1H), 7.89-7.80 (m, 1H), 7.60 (dd, \(J = 7.3, 1.3\) Hz, 1H), 7.38 (dd, \(J = 5.3, 1.7\) Hz, 3H), 7.37-7.35 (m, 1H), 7.35-7.32 (m, 1H), 7.02 (s, 1H), 2.46-2.36 (m, 1H), 2.22-2.06 (m, 2H), 1.93 (td, \(J = 12.9, 4.4\) Hz, 1H), 1.68 (s, 3H), 1.60-1.37 (m, 2H), 1.08-0.84 (m, 2H). 13C NMR (100 MHz, CDCl\(_3\)) \(\delta 179.47, 173.26, 138.39, 135.61, 135.29, 130.76, 129.14, 127.34, 126.25, 125.31, 124.87, 124.70, 123.82, 120.55, 116.87, 103.00, 77.16, 48.80, 42.37, 33.64, 29.20, 24.72, 24.64. HRMS (ESI) calcd for C\(_{22}\)H\(_{21}\)NO\(_3\) (M+H)\(^+\) 348.1594, found 348.1587.

(b) Esterification of \(\beta\)-cyanoalkylated indolo[2,1-\(\alpha\)]isoquinoline (3aa)

To a solution of 3aa (0.2 mmol, 65.6 mg) in methanol (3.0 mL) at 0 °C was added concentrated sulphuric acid (1.0 mL), the reaction was heated to 70 °C in a sealed tube and stirred overnight under nitrogen atmosphere. The reaction was quenched with cold water and extracted with EtOAc. The combined organic phase were dried over Na\(_2\)SO\(_4\), filtered and concentrated under vacuum. Purification by column chromatography on silica gel, get product 4b.

Methyl 5-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-\(\alpha\)]isoquinolin-5-yl)pentanoate. Colorless oil. 54.2 mg, 75% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.59 (dd, J = 8.1, 1.1\) Hz, 1H), 7.85 (dt, \(J = 7.2, 1.2\) Hz, 1H), 7.60 (dd, \(J = 7.5, 1.3\) Hz, 1H), 7.40-7.31 (m, 5H), 7.02 (s, 1H), 3.54 (s, 3H), 2.41 (ddd, \(J = 13.5, 12.3, 4.6\) Hz, 1H), 2.19-2.04 (m, 2H), 1.93 (td, \(J = 12.9, 4.3\) Hz, 1H), 1.68 (s, 3H), 1.58-1.39 (m, 2H), 1.05-0.94 (m, 1H), 0.88 (qdd, \(J = 13.1, 6.0, 4.3\) Hz, 1H). 13C NMR (100 MHz, CDCl\(_3\)) \(\delta 173.95, 173.25, 173.25, 138.40, 135.63, 135.28, 130.75, 129.12, 127.32, 126.27, 125.29, 124.88, 124.68, 123.80, 120.53, 116.86, 102.94, 77.16, 51.52, 48.80, 42.50, 33.72, 29.13, 24.98, 24.77. HRMS (ESI) calcd for C\(_{23}\)H\(_{23}\)NO\(_3\) (M+H)\(^+\) 362.1751, found 362.1755.

(c) Reduction of \(\beta\)-cyanoalkylated indolo[2,1-\(\alpha\)]isoquinoline (3aa)

3aa (0.3 mmol, 98.4 mg), NaBH\(_4\) (2.1 mmol, 79.4 mg) and NiCl\(_2\) (0.12 mmol, 15.6 mg) were added into a Schlenk tube. The reaction vessel was capped and subjected to three vacuum-purge/nitrogen-flush cycles. Then MeOH (2.3 mL) and Boc\(_2\)O (0.6 mmol, 131.0 mg) were added through the side-arm by syringe at 0 °C. The mixture was stirred at rt for 40 h. After reaction, the mixture was added diethylenetriamine (0.3 mmol, 31.0 mg) and stirred at rt for 30 min. Water (10 mL) was added and it was extracted with EtOAc (10 mL \(\times 3\)), washed with saturated brine (10 mL),
then dried over anhydrous Na$_2$SO$_4$. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography using petroleum ether/EtOAc (5 : 1) to afford the desired product 4c.

**Tert-butyl (5-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-α]isoquinolin-5-yl)pentyl)carbamate.** Colorless oil. 53.1 mg, 41% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.59 (d, $J = 8.1$ Hz, 1H), 7.88-7.82 (m, 1H), 7.65-7.55 (m, 1H), 7.38 (t, $J = 4.2$ Hz, 3H), 7.37-7.30 (m, 2H), 7.02 (s, 1H), 4.39 (s, 1H), 2.93 (d, $J = 5.8$ Hz, 2H), 2.38 (td, $J = 12.8$, 4.6 Hz, 1H), 1.91 (td, $J = 12.8$, 4.4 Hz, 1H), 1.68 (s, 3H), 1.90 (td, $J = 12.8$, 4.4 Hz, 1H), 1.40 (s, 3H), 1.31-1.22 (m, 2H), 1.22-1.06 (m, 2H), 0.96 (dtd, $J = 16.2$, 9.1, 5.0 Hz, 1H), 0.86 (ddd, $J = 18.7$, 9.9, 5.4 Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.40, 155.99, 138.55, 135.69, 135.29, 130.77, 129.11, 127.29, 126.30, 125.27, 124.87, 124.66, 123.78, 120.53, 116.88, 102.90, 79.11, 77.16, 48.85, 42.99, 40.55, 29.81, 29.09, 28.51 (3), 26.96, 25.00.

HRMS (ESI) calcd for C$_{27}$H$_{32}$N$_2$O$_3$ (M+H)$^+$ 433.2486, found 433.2471.

**Colorless oil. 53.1 mg, 41% yield.**

$\text{(d) Amidation of} \beta\text{-cyanoalkylated indolo[2,1-α]isoquinoline (3aa)}$

3aa (0.3 mmol, 98.4 mg) and K$_2$CO$_3$ (0.3 mmol, 41.5 mg) were weighed into a Schlenk tube, then 30% H$_2$O$_2$ (0.3 mL) and DMSO (1.2 mL) was added through the side-arm by syringe. The mixture was stirred at rt for 24 h. After reaction, water (10 mL) was added, and the reaction mixture was extracted with EtOAc (5 mL×3), washed with saturated brine (10 mL), then dried over anhydrous Na$_2$SO$_4$. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography using EtOAc/CH$_2$Cl$_2$ (5 : 1) to afford the desired product 4d.

**5-(5-Methyl-6-oxo-5,6-dihydroindolo[2,1-α]isoquinolin-5-yl)pentanamide.** Colorless oil. 98.6 mg, 95% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.56 (d, $J = 8.0$ Hz, 1H), 7.84 (dd, $J = 7.1$, 1.6 Hz, 1H), 7.59 (dd, $J = 7.5$, 1.3 Hz, 1H), 7.42-7.28 (m, 5H), 7.01 (s, 1H), 5.46 (d, $J = 42.6$ Hz, 2H), 2.41 (ddd, $J = 13.4$, 11.4, 5.2 Hz, 1H), 2.07-1.98 (m, 2H), 1.98-1.89 (m, 1H), 1.67 (s, 3H), 1.48 (p, $J = 7.6$ Hz, 2H), 0.94 (tddd, $J = 17.6$, 13.1, 9.4, 4.1 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.37, 173.41, 138.30, 135.64, 135.25, 130.77, 129.19, 127.36, 126.28, 125.29, 124.79, 124.73, 123.81, 120.59, 116.78, 102.98, 77.16, 48.84, 42.22, 35.39, 29.29, 25.42, 24.80. HRMS (ESI) calcd for C$_{22}$H$_{22}$N$_2$O$_2$ (M+H)$^+$ 347.1754, found 347.1740.

6. Preliminary Mechanistic Studies

(a) Radical-Trapping Experiment

To a Schlenk tube equipped with a magnetic stir bar was charged with Cyclobutanone Oximes 1a (0.3 mmol), N-methylpropenyl-2-phenylindole 2a (0.2 mmol) and Rhodamine B (2 mol%). The tube was sealed with a septum, evacuated and backfilled with nitrogen three times. 2.0 mL acetonitrile (MeCN) was added via syringe with gentle stirring under N$_2$ atmosphere. The tube was sealed and stirred under 18 W blue LEDs. It was observed that the transformation was completely inhibited by TEMPO or PhSeSePh, along with the interception of the cyanoalkyl radical species as
detected by high-resolution mass spectrometry (HRMS) (Figure S2).

\[
\text{R} = \text{p-Cl}_2\text{C}_6\text{H}_4\text{CO}
\]

<table>
<thead>
<tr>
<th>1a</th>
<th>2a</th>
<th>Rhodamine B (2 mol%)</th>
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</thead>
<tbody>
<tr>
<td>MeCN (0.1 M), rt, N\textsubscript{2}, 48 h</td>
<td>18 W Blue LEDs</td>
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</tr>
<tr>
<td>TEMPO (1.0 equiv)</td>
<td>not reaction</td>
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</table>

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<tr>
<th>Ph \text{Se} \text{CN}</th>
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<td>1a-B</td>
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<table>
<thead>
<tr>
<th>6</th>
<th>7 90%</th>
<th>detected by HRMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>[(M+H)]\textsuperscript{+}: 225.1961</td>
<td>found: 225.1967</td>
<td></td>
</tr>
</tbody>
</table>

4-(Phenylselanyl)butanenitrile (7)

Colorless oil. 40.5 mg, 90% yield. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.51 (qd, \(J = 3.9, 1.7\) Hz, 2H), 7.29 (dt, \(J = 9.5, 2.8\) Hz, 3H), 2.99 (t, \(J = 7.0\) Hz, 2H), 2.50 (td, \(J = 7.0, 2.9\) Hz, 2H), 1.99 (p, \(J = 7.1\) Hz, 2H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 133.36, 129.43, 127.64, 119.17, 77.16, 26.16, 25.79, 17.13. HRMS (ESI) calcd for C\textsubscript{27}H\textsubscript{32}N\textsubscript{2}O\textsubscript{3} (M+H)\textsuperscript{+} 226.0129, found 226.0168.

(b) Cyclic Voltammetry Experiment

Cyclic voltammetry (CV) was taken using a CHI6043E potentiostation. CV measurement of 1a was carried out in 0.1 M of \textsuperscript{+}Bu\textsubscript{4}NBF\textsubscript{4}/MeCN at a scan rate of 100 mV/s with the protection of N\textsubscript{2}. The working electrode is a glassy carbon, the counter electrode is a Pt wire, and the reference electrode is Ag/AgCl. Hence, \(E_{1a} = -1.205\) versus SCE. \(E_{2a} = -1.456\) versus SCE. \(E_{\text{ox}}\) (Rhodamine B\textsuperscript{*} / Rhodamine B\textsuperscript{-}) = -1.31 versus SCE. \(E_{\text{red}}\) (Rhodamine B\textsuperscript{*}/Rhodamine B\textsuperscript{-}) = +1.26 versus SCE. These results suggested that 1a was suitable for SET reduction in the excited state of the Rhodamine B\textsuperscript{*} and 2a was completely unsuitable for SET reduction in the excited state of the Rhodamine B\textsuperscript{*}.  

Figure S2 TEMPO or (PhSe)\textsubscript{2} trapping cyanoalkyl Free Radicals (HRMS)
Figure S3 Cyclic Voltammograms of Reaction Substrates

(b) Stern-Volmer Fluorescence Quenching Experiments

The fluorescence quenching experiment was taken using a Hitachi f-7000 fluorescence spectrophotometer (Japan). To a solution of Rhodamine B in anhydrous, N$_2$-saturated DMF (5 × 10$^{-4}$ mol/L) in a quartz cuvette, different amounts of cyclobutanone oxime ester (1a) and N-methylpropenyl-2-phenylinodole (2a) were added, respectively, and the resulting changes in fluorescence intensity (concentration of 1a and 2a: 0.025 mol/L, 0.050 mol/L, 0.100 mol/L, 0.150 mol/L, 0.200 mol/L were collected. The results are shown in Figure S4.

Figure S4 The fluorescence emission spectra of Rhodamine B with different concentration of 1a or 2a added. $I_0$ is the inherent fluorescence intensity of Rhodamine B. $I$ is the fluorescence intensity of Rhodamine B in the presence of 1a or 2a.

To a solution of Rhodamine B in anhydrous, N$_2$-saturated DMF (5 × 10^{-4} mol/L) in a quartz cuvette, different additives were added, respectively, and the resulting changes in fluorescence intensity (concentration of additive: 0.1 mol/L were collected. The results are shown in Figure S5.
**Figure S5** The fluorescence emission spectra of Rhodamine B with different concentration of additives added

### 7. References

8. NMR Spectra of Products

5-(5-Methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3aa)
6-Methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-ylhexanenitrile (4aa)
5,5-Dimethyl-6-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)hexanenitrile (3ba)
2-(2-(5-Methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)ethoxy)acetonitrile (3ca)
2-((2-(5-Methyl-6-oxo-5,6-dihydropyrido[2,1-a]isoquinolin-5-yl)ethyl)thio)acetonitrile (3da)
Tert-butyl (cyanomethyl)(2-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)ethyl) carbamate (3ea)
2-(Benzhydryl(2-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)ethyl)amino)aceto-nitrile (3fa)
Ethyl 2-(cyanomethyl)-4-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)butanoate (3ga)
Tert-butyl (1-cyano-4-(5-methyl-6-oxo-6,6-dihydroindolo[2,1-\(a\)isoquinolin-5-yl]butan-2-yl) carbamate (3ha)
2-(2,2,3-Trimethyl-3-((5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-y1)methyl)cyclopentyl)acetonitrile (3ia)
5-(3-(Tert-butyl)-5-methyl-6-oxo-5,6-dihydropyrido[2,1-\(a\)]isoquinolin-5-yl)pentanenitrile (3ab)
5-(3,5-Dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3ac)
5-(1,5-Dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3ad)
5-(2,5-Dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3ae)
5-(4,5-Dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3ae')
5-(3-Bromo-5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3af)
5-(3-Chloro-5-methyl-6-oxo-5,6-dihydropyrido[2,1-a]isoquinolin-5-yl)pentanenitrile (3ag)
5-(10-Fluoro-5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3ah)
5-(10-Chloro-5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3ai)
5-(10-Bromo-5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3aj)
5-(5,10-Dimethyl-6-oxo-5,6-dihydroindolo[2,1-α]isoquinolin-5-yl)pentanenitrile (3ak)
5-(5,12-Dimethyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanenitrile (3al)
5-(10-Chloro-3,5-dimethyl-6-oxo-5,6-dihydroindolo[2,1-\textit{a}]isoquinolin-5-yl)pentanenitrile (3am)
5-(5-Methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanoic acid (4a)
Methyl 5-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanoate (4b)
Tert-butyl (5-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentyl)carbamate (4c)
5-(5-Methyl-6-oxo-5,6-dihydroindolo[2,1-a]isoquinolin-5-yl)pentanamide (4d)
4-(Phenylselanyl)butanenitrile (7)