A metal-, oxidant-, and fluorous solvent-free synthesis of α-indolylketones enabled by umpolung strategy

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SUPPORTING INFORMATION

Contents
1. General Experimental----------------------------------------------- S2
2. Experimental Procedure------------------------------------------S2–18
3. Supplementary References-----------------------------------------S18
4. Copies of $^1$H and $^{13}$C NMR spectra--------------------------S19–74
Experimental Section

1. General Experimental

Mass-spectrometry
High-resolution mass spectra were recorded with a JEOL JMS-T100LP mass spectrometers.

NMR spectroscopy
NMR experiments were performed with a JEOL JNM-ECA500 spectrometer operating at 500 MHz and 125 MHz for \(^1\)H and \(^{13}\)C acquisitions, respectively. Chemical shifts are expressed in ppm (\(\delta\)) using residual solvent as the internal reference. For \(^1\)H NMR: CDCl$_3$, \(\delta\) 7.25; DMSO-d$_6$, \(\delta\) 2.50; acetone-d$_6$, \(\delta\) 2.02; For \(^{13}\)C NMR: CDCl$_3$, \(\delta\) 77.1; DMSO-d$_6$, \(\delta\) 39.5; acetone-d$_6$, \(\delta\) 29.1. NMR peak are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, br s= broad singlet; coupling constants in Hz; integration.

Chromatography
Reactions were monitored by thin layer chromatography (TLC) carried out on a silica gel plates (60F-254) and visualized under UV illumination at 254 or 366 nm depending on the compounds. Column chromatography was performed on silica gel (Silica Gel 63–210 mesh, Kanto Chemical Co., Ltd.).

Starting materials
The ROBIN (2-RO-3-bromoindoline, 1a), and 3-methoxyindole (3-MeOIN, 5) were prepared by reported methods.$^{51}$ 3-bromo-2-hydroxyindoline 1b, 3-bromoindole 2, and HITABs (2-hydroxyindoline-3-triethylammonium bromides, 3) were prepared by reported methods.$^{52}$ DiMeOIN (2,3-dimethoxyindoline, 4) was prepared by reported methods.$^{53}$ Enamines 6 were prepared by reported methods.$^{54}$
All substrates were used as received from commercial suppliers (Sigma-Aldrich, TCI, and Wako) and all reagents were weighed and handled in air at room temperature.
2. Experimental Procedure

Synthesis of 2-hydroxyindoline-3-triethylammonium bromides (3)

**trans-2-Hydroxy-5-bromo-1-tosylindoline-3-ammonium bromide (3d)**

To a solution of 5-bromo-1-tosylindole (701 mg, 2 mmol) and H\textsubscript{2}O (0.36 mL, 20 mmol) in acetone (20 mL) was added NBS (392 mg, 2.2 mmol). The mixture was stirred at room temperature until the complete disappearance of starting material as indicated by TLC. Et\textsubscript{3}N (0.31 mL, 2.2 mmol) was added to the mixture and stirred further 1 h. The resulting precipitate was separated by filtration, washed with acetone, and dried \textit{in vacuo} to give 3d (746.1 mg, 68\% yield).

746.1 mg, 68\% yield. colorless solid; \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}_6) \(\delta\): 8.01 (d, \(J = 8.6 \text{ Hz}, 2\)H), 7.93 (d, \(J = 8.0 \text{ Hz}, 1\)H), 7.70 (s, 1H), 7.66 (dd, \(J = 8.6, 1.8 \text{ Hz}, 1\)H), 7.41 (d, \(J = 8.0 \text{ Hz}, 2\)H), 7.32 (d, \(J = 9.2 \text{ Hz}, 1\)H), 6.35 (d, \(J = 7.4 \text{ Hz}, 1\)H), 4.83 (s, 1H), 3.33–3.46 (m, 6H), 2.34 (s, 3H), 1.02 (t, \(J = 7.4 \text{ Hz}, 9\)H); \textsuperscript{13}C NMR (125 MHz, DMSO-\textit{d}_6) \(\delta\): 145.6, 142.2, 135.9, 135.7, 133.0, 128.2, 122.9, 115.7, 115.6, 85.1, 74.9, 53.4, 21.6, 8.9; HRMS (ESI) \textit{m/z}: 467.1004, 469.0984 (Calcd for C\textsubscript{21}H\textsubscript{28}BrN\textsubscript{2}O\textsubscript{3}S \([M]\)\textsuperscript{+}: 467.1004, 469.0984).

**trans-2-Hydroxy-4-chloro-1-tosylindoline-3-ammonium bromide (3e)**

To a solution of 4-chloro-1-tosylindole (612 mg, 2 mmol) and H\textsubscript{2}O (0.36 mL, 20 mmol) in acetone (20 mL) was added NBS (392 mg, 2.2 mmol). The mixture was stirred at room temperature for 24 h. Then, Et\textsubscript{3}N (0.31 mL, 2.2 mmol) was added to the mixture and stirred further 1 h. The mixture was concentrated \textit{in vacuo} and dried \textit{in vacuo} to give 3e (942 mg, 94\% yield) without further purification.

942.0 mg, 94\% yield. colorless oil; \textsuperscript{1}H NMR (500 MHz, acetone-\textit{d}_6) \(\delta\): 7.86 (d, \(J = 8.6 \text{ Hz}, 2\)H), 7.42 (d, \(J = 8.0 \text{ Hz}, 1\)H), 7.37 (t, \(J = 8.1 \text{ Hz}, 1\)H), 7.36 (d, \(J = 8.1 \text{ Hz}, 2\)H), 7.10 (d, \(J = 8.1 \text{ Hz}, 1\)H), 6.05 (s, 1H), 5.13 (s, 1H), 2.58–2.60 (m, 6H), 2.35 (s, 3H), 1.03 (t, \(J = 6.9 \text{ Hz}, 9\)H); \textsuperscript{13}C NMR (125 MHz, acetone-\textit{d}_6) \(\delta\): 144.9, 142.1, 136.1, 132.4, 131.8, 129.8, 128.1, 127.7, 124.3, 113.2, 93.5, 48.5, 46.1, 20.6, 10.7; HRMS (ESI) \textit{m/z}: 423.1508, 425.1480 (Calcd for C\textsubscript{21}H\textsubscript{28}ClN\textsubscript{2}O\textsubscript{3}S \([M]\)\textsuperscript{+}: 423.1509, 425.1480).
**trans-2-Hydroxy-6-chloro-1-tosylindoline-3-ammonium bromide (3f)**

To a solution of 6-chloro-1-tosylindole (1.53 g, 5 mmol) and H$_2$O (0.90 mL, 50 mmol) in acetone (50 mL) was added NBS (979 mg, 5.5 mmol). The mixture was stirred at room temperature until the complete disappearance of starting material as indicated by TLC. Et$_3$N (0.77 mL, 5.5 mmol) was added to the mixture and stirred further 1 h. The resulting precipitate was separated by filtration, washed with acetone, and dried in vacuo to give 3f (1.58 g, 63% yield).

1.58 g, 63% yield. colorless solid; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 8.04 (d, $J = 8.6$ Hz, 2H), 7.98 (d, $J = 6.9$ Hz, 1H), 7.56 (d, $J = 8.6$ Hz, 1H), 7.43 (d, $J = 8.6$ Hz, 2H), 7.29 (d, $J = 2.3$ Hz, 1H), 7.22 (dd, $J = 2.3$, 8.6 Hz, 1H), 6.39 (d, $J = 6.3$ Hz, 1H), 4.84 (s, 1H), 3.31–3.46 (m, 6H), 2.35 (s, 3H), 1.03 (t, $J = 6.9$ Hz, 9H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$: 145.8, 144.1, 137.5, 135.8, 132.1, 130.7, 128.2, 124.0, 119.6, 113.3, 85.5, 74.8, 53.3, 21.6, 8.9; HRMS (ESI) m/z: 423.1511, 425.1480 (Calcd for C$_{21}$H$_{28}$ClN$_2$O$_3$S [M]+: 423.1509, 425.1480).

**trans-2-Hydroxy-1-benzenesulfonylindoline-3-ammonium bromide (3g)**

To a solution of 1-benzenesulfonylindole (5.15 g, 20 mmol) and H$_2$O (3.60 mL, 200 mmol) in acetone (200 mL) was added NBS (3.74 g, 21 mmol). The mixture was stirred at room temperature for 6 h. Et$_3$N (2.94 mL, 21 mmol) was added to the mixture and stirred further 1 h. The resulting precipitate was separated by filtration, washed with acetone, and dried in vacuo to give 3g (7.47 g, 82% yield).

7.47 g, 82% yield. colorless solid; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$: 8.15 (d, $J = 7.5$ Hz, 2H), 7.90 (d, $J = 6.9$ Hz, 1H), 7.70 (t, $J = 7.5$ Hz, 1H), 7.61 (t, $J = 7.4$ Hz, 1H), 7.57 (d, $J = 7.5$ Hz, 1H), 7.49 (t, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 8.6$ Hz, 1H), 7.15 (t, $J = 8.1$ Hz, 1H), 6.38 (d, $J = 6.9$ Hz, 1H), 4.85 (s, 1H), 3.33–3.47 (m, 6H), 1.01 (t, $J = 6.9$ Hz, 9H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$: 142.7, 139.0, 134.7, 133.0, 130.5, 130.1, 128.1, 124.1, 120.5, 113.8, 84.8, 75.4, 53.3, 8.8; HRMS (ESI) m/z: 375.1742 (Calcd for C$_{20}$H$_{27}$N$_2$O$_3$S [M]+: 375.1742).
Optimization of Reaction Conditions

Table S1. Screening of bases

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A mixture of 3a (469.4 mg, 1.0 mmol), 6a (183.5 mg, 1.1 mmol) and base (2.0 mmol) in AcOEt (10 mL) was heated at 80 °C with stirring for 4 h. After cooling to room temperature, 10% aq. HCl (10 mL) was added to the mixture. Then the mixture was heated at 80 °C for 1 h. After cooling to room temperature, the whole was extracted with AcOEt (3 x 20 mL), washed with brine (20 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt:hexane = 1:5–1:2 or CHCl$_3$:hexane = 1:1) to give 7aa.
A mixture of 3a (469.4 mg, 1.0 mmol), 6a (183.5 mg, 1.1 mmol) and Et₃N (0.28 mL, 2.0 mmol) in solvent (10 mL) was heated at indicated temperature with stirring for 4 h. After cooling to room temperature, 10% aq. HCl (10 mL) was added to the mixture. Then the mixture was heated at 80 °C for 1 h. After cooling to room temperature, the whole was extracted with AcOEt (3 x 20 mL), washed with brine (20 mL). The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt:hexane = 1:5–1:2 or CHCl₃:hexane = 1:1) to give 7aa.
A mixture of 3 (1.0 mmol), 6 (1.1 mmol) and Et$_3$N (0.28 mL, 2.0 mmol) in AcOEt (10 mL) was heated at 80 °C with stirring for 2–16 h. After cooling to room temperature, 10% aq. HCl (10 mL) was added to the mixture. Then the mixture was heated at 80 °C for 1 h. After cooling to room temperature, the whole was extracted with AcOEt (3 x 20 mL), washed with brine (20 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt:hexane = 1:5–1:2 or CHCl$_3$:hexane = 1:1) to give 7.
2-(1-Tosyl-1H-indol-3-yl)cyclohexan-1-one (7aa)

315.3 mg, 86% yield. colorless solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.95 (d, \(J = 8.1\) Hz, 1H), 7.75 (d, \(J = 8.6\) Hz, 2H), 7.51 (s, 1H), 7.31 (d, \(J = 8.0\) Hz, 1H), 7.28 (t, \(J = 8.6\) Hz, 1H), 7.20 (d, \(J = 8.1\) Hz, 2H), 7.19 (t, \(J = 8.0\) Hz, 1H), 3.79 (dd, \(J = 11.5, 5.2\) Hz, 1H), 2.45–2.55 (m, 2H), 2.33–2.39 (m, 1H), 2.32 (s, 3H), 2.12–2.19 (m, 1H), 2.00–2.08 (m, 2H), 1.80–1.90 (m, 2H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 209.1, 144.9, 135.4, 135.1, 130.5, 130.0, 126.9, 124.7, 123.8, 123.1, 120.5, 120.0, 113.8, 48.5, 42.1, 34.3, 28.1, 25.3, 21.6; HRMS (ESI) \(m/z\): 390.1139 (Calcd for C\(_{21}\)H\(_{21}\)NNaO\(_3\)S [M+Na]\(^+\): 390.1140).

2-(5-Methoxy-1-tosyl-1H-indol-3-yl)cyclohexan-1-one (7ba)

306.9 mg, 77% yield. colorless oil; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.83 (d, \(J = 9.2\) Hz, 1H), 7.71 (d, \(J = 8.6\) Hz, 2H), 7.46 (s, 1H), 7.19 (d, \(J = 8.0\) Hz, 2H), 6.88 (dd, \(J = 9.2, 2.3\) Hz, 1H), 6.72 (d, \(J = 2.9\)Hz, 1H), 3.78 (s, 3H), 3.73 (dd, \(J = 11.4, 5.7\) Hz, 1H), 2.44–2.54 (m, 2H), 2.32–2.37 (m, 1H), 2.32 (s, 3H), 2.11–2.19 (m, 1H), 2.00–2.08 (m, 2H), 1.81–1.90 (m, 2H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 209.0, 156.3, 144.8, 135.3, 131.6, 129.9, 126.8, 124.6, 120.6, 114.6, 113.4, 102.8, 55.8, 48.4, 42.0, 34.1, 28.0, 25.2, 21.6; HRMS (ESI) \(m/z\): 420.1246 (Calcd for C\(_{22}\)H\(_{23}\)NNaO\(_4\)S [M+Na]\(^+\): 420.1246).

2-(5-Chloro-1-tosyl-1H-indol-3-yl)cyclohexan-1-one (7ca)

340.4 mg, 85% yield. colorless solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.86 (d, \(J = 8.6\) Hz, 1H), 7.72 (d, \(J = 8.6\) Hz, 2H), 7.51 (s, 1H), 7.26 (d, \(J = 1.7\) Hz, 1H), 7.21–7.23 (m, 1H), 7.21 (d, \(J = 8.0\) Hz, 2H), 3.73 (dd, \(J = 12.1, 5.2\) Hz, 1H), 2.45–2.54 (m, 2H), 2.29–2.41 (m, 1H), 2.33 (s, 3H), 2.16–2.20 (m, 1H), 1.95–2.03 (m, 2H), 1.79–1.88 (m, 2H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 208.7, 145.2, 135.1, 133.5, 131.8, 130.1, 129.0, 126.9, 125.1, 124.9, 120.0, 119.8, 114.8, 48.3, 42.2, 34.3, 28.0, 25.4, 21.7; HRMS (ESI) \(m/z\): 424.0750, 426.0721 (Calcd for C\(_{21}\)H\(_{20}\)ClNNaO\(_3\)S [M+Na]\(^+\): 424.0750, 426.0721).
2-(5-Bromo-1-tosyl-1H-indol-3-yl)cyclohexan-1-one (7da)

325.0 mg, 73% yield. colorless solid; \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.82 (d, \(J = 8.6\) Hz, 1H), 7.72 (d, \(J = 8.1\) Hz, 2H), 7.50 (s, 1H), 7.42 (s, 1H), 7.36 (d, \(J = 9.2\) Hz, 1H), 7.21 (d, \(J = 8.0\) Hz, 2H), 3.73 (dd, \(J = 11.5\), 4.6 Hz, 1H), 2.46–2.55 (m, 2H), 2.33–2.36 (m, 1H), 2.33 (s, 3H), 2.17 (m, 1H), 1.95–2.04 (m, 2H), 1.84–1.88 (m, 2H); \(^1^3^C\) NMR (125 MHz, CDCl\(_3\)) \(\delta\): 208.6, 145.3, 135.1, 133.9, 132.3, 130.1, 127.6, 126.9, 125.0, 122.8, 119.9, 116.7, 115.2, 48.3, 42.2, 34.4, 28.0, 25.4, 21.7; HRMS (ESI) \(m/z\): 468.0245, 470.0224 (Calcd for C\(_{21}\)H\(_{20}\)BrNaO\(_3\)S [M+Na]\(^+\): 468.0245, 470.0224).

2-(4-Chloro-1-tosyl-1H-indol-3-yl)cyclohexan-1-one (7ea)

225.1 mg, 56% yield. colorless solid; \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.87 (d, \(J = 7.5\) Hz, 1H), 7.73(d, \(J = 8.6\) Hz, 2H), 7.50 (s, 1H), 7.23 (d, \(J = 8.1\) Hz, 2H), 7.15 (d, \(J = 7.5\) Hz, 1H), 7.14 (d, \(J = 1.2\) Hz, 1H), 4.41 (d, \(J = 11.5\) Hz, 1H), 2.51–2.57 (m, 2H), 2.45–2.48 (m, 1H), 2.34 (s, 3H), 2.19–2.23 (m, 1H), 2.03–2.06 (m, 1H), 1.79–1.97 (m, 3H); \(^1^3^C\) NMR (125 MHz, CDCl\(_3\)) \(\delta\):209.7, 145.3, 136.4, 135.0, 130.1, 127.5, 126.9, 126.5, 125.1, 124.8, 124.6, 120.5, 112.5, 49.2, 42.4, 34.5, 25.9, 21.7; HRMS (ESI) \(m/z\): 424.0751, 426.0721 (Calcd for C\(_{21}\)H\(_{20}\)ClNaO\(_3\)S [M+Na]\(^+\): 424.0750, 426.0721).

2-(6-Chloro-1-tosyl-1H-indol-3-yl)cyclohexan-1-one (7fa)

274.1 mg, 68% yield. colorless solid; \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.96 (d, \(J = 1.7\) Hz, 1H), 7.75 (d, \(J = 8.6\) Hz, 2H), 7.47 (d, \(J = 1.1\) Hz, 1H), 7.24 (d, \(J = 8.6\) Hz, 2H), 7.21 (d, \(J = 6.9\) Hz, 1H), 7.15 (dd, \(J = 8.6\), 2.3 Hz, 1H), 3.75 (dd, \(J = 12.1\), 5.8 Hz, 1H), 2.44–2.55 (m, 2H), 2.33–2.38 (m, 1H), 2.35 (s, 3H), 2.14–2.19 (m, 1H), 1.98–2.05 (m,
2H), 1.78–1.89 (m, 2H); 13C NMR (125 MHz, CDCl3) δ: 208.8, 145.3, 135.5, 135.1, 130.7, 130.1, 129.0, 126.9, 124.2, 123.8, 121.0, 120.4, 113.9, 48.3, 42.1, 34.2, 28.0, 25.3, 21.7; HRMS (ESI) m/z: 424.0750, 426.0721 (Calcd for C21H20ClNNaO3S [M+Na]+: 424.0750, 426.0721).

2-(1-(Phenylsulfonyl)-1H-indol-3-yl)cyclohexan-1-one (7ga)

325.9 mg, 92% yield. colorless oil; 1H NMR (500 MHz, CDCl3) δ: 7.96 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 7.4 Hz, 2H), 7.51–7.53 (m, 2H), 7.43 (t, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 3.80 (dd, J = 11.5, 5.2 Hz, 1H), 2.46–2.56 (m, 2H), 2.33–2.41 (m, 1H), 2.14–2.20 (m, 1H), 2.00–2.08 (m, 2H), 1.81–1.90 (m, 2H); 13C NMR (125 MHz, CDCl3) δ: 209.0, 138.3, 135.2, 133.9, 130.5, 129.4, 126.8, 124.8, 123.7, 123.2, 120.8, 120.1, 113.8, 48.4, 42.1, 34.3, 28.1, 25.3; HRMS (ESI) m/z: 376.0983 (Calcd for C20H19NNaO3S [M+Na]+: 376.0983).

2-(1-Tosyl-1H-indol-3-yl)cyclopentan-1-one (7ab)

229.0 mg, 65% yield. colorless oil; 1H NMR (500 MHz, CDCl3) δ: 7.96 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 7.5 Hz, 1H), 7.43 (s, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.22 (t, J = 6.9 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 3.51 (t, J = 9.2 Hz, 1H), 2.45–2.55 (m, 2H), 2.27–2.38 (m, 1H), 2.31 (s, 3H), 2.13–2.19 (m, 1H), 2.05–2.10 (m, 1H), 1.97–2.02 (m, 1H); 13C NMR (125 MHz, CDCl3) δ: 216.9, 145.0, 135.3, 135.3, 130.3, 130.0, 126.9, 124.9, 123.2, 123.2, 120.4, 119.7, 113.7, 46.6, 38.1, 30.7, 21.6, 21.1; HRMS (ESI) m/z: 376.0984 (Calcd for C20H19NNaO3S [M+Na]+: 376.0983).

2-(1-Tosyl-1H-indol-3-yl)cycloheptan-1-one (7ac)

323.5 mg, 85% yield. colorless solid; 1H NMR (500 MHz, CDCl3) δ: 7.93 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.28 (td, J = 8.0, 1.2 Hz, 1H), 7.20–7.23 (m, 1H), 7.21 (d, J = 8.6 Hz,
2-(1-Tosyl-1H-indol-3-yl)cyclododecan-1-one (7ad)

406.0 mg, 90% yield. colorless solid; 1H NMR (500 MHz, CDCl3) δ: 7.95 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.6 Hz, 2H), 7.51 (s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.30 (td, J = 6.9, 1.2 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 3.96 (dd, J = 12.0, 2.9 Hz, 1H), 2.52 (ddd, J = 17.2, 11.5, 2.9 Hz, 1H), 2.25–2.38 (m, 1H), 2.33 (s, 3H), 1.99–2.04 (m, 1H), 1.84–1.93 (m, 1H), 1.71–1.77 (m, 1H), 1.25–1.50 (m, 15H); 13C NMR (125 MHz, CDCl3) δ: 209.2, 144.9, 135.5, 135.1, 130.5, 135.1, 130.5, 130.0, 126.9, 125.1, 123.6, 123.5, 121.3, 119.7, 113.9, 49.0, 36.7, 29.4, 25.7, 25.4, 24.2, 24.1, 23.9, 23.5, 22.4, 22.3, 21.7; HRMS (ESI) m/z: 446.1766 (Calcd for C25H29NaO3S [M+Na]+: 446.1766).

Rel-(2S,4S)-4-(tert-butyl)-2-(1-tosyl-1H-indol-3-yl)cyclohexan-1-one (7ae)

295.7 mg, 70% yield. colorless oil; 1H NMR (500 MHz, CDCl3) δ: 7.95 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 8.6 Hz, 2H), 7.52 (s, 1H), 7.29 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 5.2 Hz, 1H), 7.20 (d, J = 8.6 Hz, 2H), 7.17–7.22 (m, 1H), 3.82 (dd, J = 12.1, 5.2 Hz, 1H), 2.53–2.58 (m, 2H), 2.35–2.41 (m, 1H), 2.32 (s, 3H), 2.18–2.25 (m, 1H), 1.74–1.82 (m, 2H), 1.57–1.67 (m, 1H), 0.96 (s, 9H); 13C NMR (125 MHz, CDCl3) δ: 209.2, 144.9, 135.5, 135.1, 130.5, 130.0, 126.9, 124.6, 123.9, 123.1, 120.6, 119.9, 113.8, 47.8, 47.6, 41.7, 35.8, 32.7, 31.6, 28.8, 27.8, 27.6, 21.6; HRMS (ESI) m/z: 446.1766 (Calcd for C25H29NaO3S [M+Na]+: 446.1766).

2-(5-Methoxy-1-tosyl-1H-indol-3-yl)cyclopentan-1-one (7bb)

236.6 mg, 62% yield. colorless oil; 1H NMR (500 MHz, CDCl3) δ: 7.83 (d, J = 9.8 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H),
7.37 (s, 1H), 7.20 (d, J = 8.6 Hz, 2H), 6.90–6.92 (m, 2H), 3.80 (s, 3H), 3.46 (dd, J = 9.2, 8.0 Hz, 1H), 2.44–2.57 (m, 2H), 2.30–2.38 (m, 1H), 2.33 (s, 3H), 2.14–2.20 (m, 1H), 2.04–2.13 (m, 1H), 1.95–2.03 (m, 1H); 13C NMR (125 MHz, CDCl3) δ: 216.8, 156.4, 145.0, 135.2, 131.5, 130.0, 129.9, 126.8, 123.9, 119.9, 114.6, 113.7, 55.8, 46.6, 38.1, 30.5, 21.6, 21.1; HRMS (ESI) m/z: 406.1090 (Calcd for C21H21NNaO4S [M+Na]+: 406.1089).

2-(5-Methoxy-1-tosyl-1H-indol-3-yl)cyclododecan-1-one (7bd)

380.0 mg, 79% yield. colorless solid; 1H NMR (500 MHz, CDCl3) δ: 7.84 (d, J = 9.2 Hz, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.47 (s, 1H), 7.19 (d, J = 8.9 Hz, 2H), 6.90 (dd, J = 9.2, 2.3 Hz, 1H), 6.86 (d, J = 2.3 Hz, 1H), 3.87 (dd, J = 12.0, 2.9 Hz, 1H), 3.79 (s, 3H), 2.52 (ddd, J = 16.6, 11.5, 2.9 Hz, 1H), 2.32 (s, 3H), 2.24–2.32 (m, 1H), 1.85–1.97 (m, 1H), 1.24–1.50 (m, 16H); 13C NMR (125 MHz, CDCl3) δ: 211.2, 156.7, 145.0, 135.1, 131.1, 130.0, 129.9, 126.8, 124.4, 121.4, 114.8, 114.1, 102.1, 55.7, 49.4, 36.2, 29.2, 25.8, 25.5, 24.1, 24.0, 23.8, 23.5, 22.4, 22.2, 21.6; HRMS (ESI) m/z: 504.2185 (Calcd for C28H35NNaO4S [M+Na]+: 504.2185).

1-phenyl-2-(1-tosyl-1H-indol-3-yl)ethan-1-one (7af)

315.5 mg, 81% yield. colorless oil; 1H NMR (500 MHz, CDCl3) δ: 8.01 (d, J = 6.9 Hz, 2H), 7.96 (d, J = 8.6 Hz, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.54 (s, 1H), 7.45–7.49 (m, 3H), 7.31 (t, J = 7.4 Hz, 1H), 7.23 (t, J = 6.9 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 4.32 (s, 2H), 2.31 (s, 3H); 13C NMR (125 MHz, CDCl3) δ: 196.3, 144.9, 136.3, 135.3, 135.2, 133.5, 130.8, 129.9, 128.8, 128.6, 126.9, 125.1, 125.0, 123.4, 119.7, 115.9, 113.8, 35.3, 21.6; HRMS (ESI) m/z: 412.0984 (Calcd for C23H19NNaO3S [M+Na]+: 412.0983).

1-(4-Methoxyphenyl)-2-(1-tosyl-1H-indol-3-yl)ethan-1-one (7ag)

328.1 mg, 78% yield. colorless oil; 1H NMR (500 MHz, CDCl3) δ: 7.98 (d, J = 9.2 Hz, 2H), 7.96 (d, J = 8.6 Hz, H), 7.69 (d, J = 8.6 Hz, 2H), 7.51 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 9.2 Hz, 2H), 4.26 (s, 2H), 3.86 (s, 3H), 2.30 (s, 3H); 13C NMR (125 MHz, CDCl3) δ:
1-(4-Bromophenyl)-2-(1-tosyl-1H-indol-3-yl)ethan-1-one (7ah)

352.2 mg, 75% yield. colorless oil; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.96 (d, $J = 8.6$ Hz, 1H), 7.84 (d, $J = 8.6$ Hz, 2H), 7.68 (d, $J = 8.6$ Hz, 2H), 7.57 (d, $J = 8.6$ Hz, 2H), 7.51 (s, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.31 (t, $J = 8.1$ Hz, 1H), 7.23 (t, $J = 7.4$ Hz, 1H), 7.16 (d, $J = 8.6$ Hz, 2H), 4.27 (s, 2H), 2.32 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 195.4, 145.0, 135.2, 135.1, 132.1, 130.6, 130.1, 129.9, 128.7, 126.8, 125.1, 125.0, 123.5, 119.6, 115.6, 113.9, 35.4, 21.7; HRMS (ESI) $m/z$: 490.0089, 492.0067 (Calcd for C$_{23}$H$_{18}$BrNaO$_3$ [M+Na]$^+$: 490.0088, 492.0068).

1-(3-Methoxyphenyl)-2-(1-tosyl-1H-indol-3-yl)ethan-1-one (7ai)

184.6 mg, 44% yield. colorless oil; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.96 (d, $J = 8.1$ Hz, 1H), 7.69 (d, $J = 8.0$ Hz, 2H), 7.59 (dd, $J = 8.6$, 1.2 Hz, 1H), 7.53 (s, 1H), 7.51 (dd, $J = 2.9$, 1.7 Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.37 (t, $J = 8.6$ Hz, 1H), 7.31 (td, $J = 7.5$, 1.2 Hz, 1H), 7.23 (t, $J = 7.4$ Hz, 1H), 7.16 (d, $J = 8.1$ Hz, 2H), 7.12 (dd, $J = 8.0$, 3.4 Hz, 1H), 4.30 (s, 2H), 3.82 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 196.2, 160.0, 144.9, 137.7, 135.3, 135.2, 130.8, 129.9, 129.8, 126.9, 125.1, 125.0, 123.4, 121.2, 120.0, 119.6, 115.9, 113.8, 112.7, 55.5, 35.4, 21.6; HRMS (ESI) $m/z$: 442.1089 (Calcd for C$_{24}$H$_{21}$NNaO$_4$S [M+Na]$^+$: 442.1089).

1-(2-Methoxyphenyl)-2-(1-tosyl-1H-indol-3-yl)ethan-1-one (7aj)

288.2 mg, 69% yield. colorless oil; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.94 (d, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 8.6$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.49 (s, 1H), 7.45 (d, $J = 8.6$ Hz, 2H), 7.28 (t, $J = 7.5$ Hz, 1H), 7.21 (t, $J = 6.9$ Hz, 1H), 7.15 (d, $J = 8.6$ Hz, 2H), 6.98 (t, $J = 7.5$ Hz, 1H), 6.95 (d, $J = 8.6$ Hz, 1H), 4.34 (s, 2H), 3.86 (s, 3H), 2.30 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 198.7, 158.5, 144.8, 135.4, 135.1, 133.9, 131.2, 130.8, 129.9, 127.7, 126.8, 124.8, 124.7, 123.3, 120.9, 119.8, 116.6, 113.7, 111.6, 55.6, 40.0, 21.6; HRMS (ESI) $m/z$: 442.1089 (Calcd for C$_{24}$H$_{21}$NNaO$_4$S [M+Na]$^+$: 442.1089).
1-(4-Iodophenyl)-2-(1-tosyl-1H-indol-3-yl)ethan-1-one (7ak)

313.3 mg, 61% yield. colorless oil; $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.96 (d, $J = 8.6$ Hz, 1H), 7.80 (d, $J = 8.6$ Hz, 2H), 7.69 (d, $J = 1.7$ Hz, 2H), 7.67 (d, $J = 1.7$ Hz, 2H), 7.51 (s, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.31 (t, $J = 7.5$ Hz, 1H), 7.23 (t, $J = 7.5$ Hz, 1H), 7.16 (d, $J = 8.0$ Hz, 2H), 4.26 (s, 2H), 2.32 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 195.7, 145.0, 138.1, 138.0, 135.5, 135.2, 135.1, 130.6, 129.9, 126.8, 125.1, 125.0, 123.5, 119.6, 115.6, 113.9, 101.5, 35.3, 21.7; HRMS (ESI) m/z: 537.9950 (Calcd for C$_{23}$H$_{18}$INaO$_3$ $^{[M+Na]}$: 537.9950).

Procedure for Gram-Scale Synthesis of 7aa (Scheme 4)

A mixture of 3a (4.69 g, 10 mmol), 6a (1.84 g, 11 mmol) and Et$_3$N (2.8 mL, 20 mmol) in AcOEt (100 mL) was heated at 80 °C with stirring for 4 h. After cooling to room temperature, 10% aq. HCl (50 mL) was added to the mixture. Then the mixture was heated at 80 °C for 1 h. After cooling to room temperature, the whole was extracted with AcOEt (3 x 100 mL), washed with brine (50 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt:hexane = 1:5–1:2 then CHCl$_3$:hexane = 1:1) to give 7aa (3.30 g, 90%).

Procedure for Gram-Scale Synthesis of 7ab (Scheme 4)

A mixture of 3a (4.69 g, 10 mmol), 6b (1.69 g, 11 mmol) and Et$_3$N (2.8 mL, 20 mmol) in AcOEt (100 mL) was
heated at 80 °C with stirring for 16 h. After cooling to room temperature, 10% aq. HCl (50 mL) was added to the mixture. Then the mixture was heated at 80 °C for 1 h. After cooling to room temperature, the whole was extracted with AcOEt (3 x 100 mL), washed with brine (50 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt:hexane = 1:5–1:2 then CHCl$_3$:hexane = 1:1) to give 7ab (2.50 g, 71%).

**General Procedure for Synthesis of Bisindoles using In(OTf)$_3$ (Scheme 5)**

To a solution of 7aa (367.5 mg, 1.0 mmol) or 7ab (353.4 mg, 1.0 mmol) and 2-methylindole (262.2 mg, 2.0 mmol) or indole (234.1 mg, 2.0 mmol) in MeCN (10 mL) was added In(OTf)$_3$ (56.2 mg, 0.1 mmol) at room temperature and the mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the whole was extracted with AcOEt (3 x 20 mL), washed with brine (20 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (CHCl$_3$:hexane = 1:1) to give bisindoles.

2-Methyl-3-(2-(1-tosyl-1H-indol-3-yl)cyclohex-1-en-1-yl)-1H-indole (8)

268.2 mg, 56% yield. colorless oil; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.75 (d, $J$ = 8.6 Hz, 1H), 7.48 (dd, $J$ = 1.7, 6.9 Hz, 1H), 7.37 (br s, 1H), 7.33 (d, $J$ = 8.6 Hz, 2H), 7.17 (d, $J$ = 7.5 Hz, 2H), 7.13 (dd, $J$ = 1.8, 5.8 Hz, 1H), 7.02–7.09 (m, 5H), 6.87 (t, $J$ = 7.4 Hz, 1H), 2.72–2.76 (m, 1H), 2.56–2.65 (m, 1H), 2.37–2.50 (m, 1H), 2.31 (s, 3H), 2.20–2.33 (m, 1H), 1.86–1.98 (m, 4H), 1.79 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 144.5, 135.3, 135.2, 134.7, 131.4, 130.7, 130.1, 129.8, 128.4, 128.1, 126.6, 126.2, 124.0, 123.5, 122.6, 121.1, 120.9, 119.5, 119.0, 115.9, 113.3, 110.2, 32.0, 31.9, 23.6, 23.4, 21.7, 12.4; HRMS (ESI) $m/z$: 503.1768 (Calcd for C$_{30}$H$_{28}$N$_2$NaO$_2$S [M+Na]$^+$: 503.1769).

2-Methyl-3-(2-(1-tosyl-1H-indol-3-yl)cyclopent-1-en-1-yl)-1H-indole (9)

318.2 mg, 68% yield. colorless oil; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.90 (d, $J$ = 8.6 Hz, 1H), 7.64 (br s, 1H), 7.57 (d, $J$ = 8.6 Hz, 2H), 7.48 (d, $J$ = 8.0 Hz, 1H), 7.38 (s, 1H), 7.22 (d, $J$ = 8.0 Hz, 1H), 7.11–7.16 (m, 4H), 7.03 (t, $J$ = 8.1 Hz, 1H), 6.93 (d, $J$ = 8.0 Hz, 1H), 6.83 (t, $J$ = 8.0 Hz, 1H), 3.06 (t, $J$ = 7.5 Hz, 4H), 2.32 (s, 3H), 2.17 (quint, $J$ = 7.4 Hz, 2H), 1.67 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 144.7, 135.6, 135.1, 135.0, 134.1, 132.1, 129.8, 129.6, 129.5, 127.9, 126.8, 124.2, 124.1, 122.8, 122.2, 121.9, 121.2, 119.7, 119.6, 113.5, 111.5, 110.4, 38.8, 38.0, 23.3, 21.6, 12.7; HRMS (ESI) $m/z$: 489.1612 (Calcd for C$_{29}$H$_{26}$N$_2$NaO$_2$S [M+Na]$^+$: 489.1613).
3-(2-(1H-Indol-3-yl)cyclopent-1-en-1-yl)-1-tosyl-1H-indole (10)

234.0 mg, 52% yield. colorless oil; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.95 (br s, 1H), 7.88 (d, \(J = 8.6\) Hz, 1H), 7.59 (d, \(J = 8.6\) Hz, 2H), 7.40 (s, 1H), 7.28 (d, \(J = 8.0\) Hz, 2H), 7.16–7.17 (m, 3H), 7.07–7.10 (m, 2H), 6.91 (t, \(J = 7.5\) Hz, 1H), 6.87 (d, \(J = 2.3\) Hz, 1H), 6.76 (t, \(J = 8.5\) Hz, 1H), 3.04–3.08 (m, 2H), 2.93–2.99 (m, 2H), 2.35 (s, 3H), 2.14 (quint, \(J = 7.4\) Hz, 2H); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 144.7, 136.0, 135.3, 135.0, 133.6, 129.9, 129.6, 127.1, 126.9, 125.9, 124.2, 123.6, 122.8, 122.1, 121.9, 121.7, 121.1, 119.7, 114.6, 113.4, 111.1, 39.0, 38.9, 22.8, 21.7; HRMS (ESI) \(m/z\): 475.1457 (Calcd for C\(_{28}\)H\(_{24}\)N\(_2\)NaO\(_2\)S [M+Na]\(^+\): 475.1456).

General Procedure for Synthesis of Enamines (Scheme 6a)

A mixture of 3d (548.3 mg, 1.0 mmol), 6a (184 mg, 1.1 mmol) and Et\(_3\)N (0.28 mL, 2.0 mmol) in AcOEt (10 mL) was heated at 80 °C with stirring for 16 h. After cooling to room temperature, H\(_2\)O (10 mL) was added to the mixture. The whole was extracted with AcOEt (3 x 20 mL), washed with brine (20 mL). The organic layer was dried over MgSO\(_4\) and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt:hexane = 1:5–1:2 then CHCl\(_3\)::hexane = 1:1) to give 12a (425.2 mg, 80% yield) and 12b (86.4 mg, 16% yield).

Rel-(2S,3S)-5-bromo-3-((R)-2-morpholinocyclohex-2-en-1-yl)-1-tosylindolin-2-ol (12a)

425.2 mg, 80% yield. colorless solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.82 (d, \(J = 8.6\) Hz, 2H), 7.23–7.28 (m, 5H), 7.11 (s, 1H), 5.99 (d, \(J = 7.5\) Hz, 1H), 4.14 (t, \(J = 8.0\) Hz, 1H), 3.64–3.72 (m, 4H), 2.79–2.80 (m, 2H), 2.54–2.58 (m, 2H), 2.45 (dt, \(J = 7.4, 6.3\) Hz, 1H), 2.38 (s, 3H), 1.40–1.52 (m, 2H), 1.10–1.17 (m, 2H), 0.94–1.00 (m, 1H), 0.40–
0.47 (m, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta:\) 144.3, 141.6, 136.2, 132.1, 131.1, 129.7, 128.9, 127.6, 115.5, 114.8, 99.0, 94.8, 67.8, 49.8, 45.7, 40.7, 27.0, 24.3, 24.2, 21.7, 21.5; HRMS (ESI) \(m/z:\) 555.0929, 557.0908 (Caled for C\textsubscript{25}H\textsubscript{29}BrN\textsubscript{2}NaO\textsubscript{4}S [M+Na]\textsuperscript{+}\: 555.0929, 557.0909).

**Rel-(2S,3S)-5-bromo-3-(2-morpholinocyclohex-1-en-1-yl)-1-tosylindolin-2-ol (12b)**

86.4 mg, 16% yield. colorless solid; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta:\) 7.74 (d, \(J = 8.6\) Hz, 2H), 7.34 (d, \(J = 9.2\) Hz, 1H), 7.23–7.27 (m, 4H), 7.11 (s, 1H), 6.18 (d, \(J = 7.4\) Hz, 1H), 3.32 (d, \(J = 6.9\) Hz, 1H), 3.08 (m, 2H), 2.54 (m, 2H), 2.47 (dd, \(J = 11.5, 6.3\) Hz, 1H), 2.37 (s, 3H), 2.12–2.16 (m, 2H), 1.89–1.96 (m, 2H), 1.58–1.64 (m, 3H), 1.32–1.42 (m, 2H), 1.05–1.08 (m, 2H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta:\) 144.3, 141.3, 136.8, 136.2, 130.2, 129.9, 127.1, 126.0, 115.6, 115.1, 98.9, 95.3, 66.5, 53.2, 45.9, 43.6, 31.9, 24.4, 23.8, 21.8, 21.6; HRMS (ESI) \(m/z:\) 555.0928, 557.0909 (Caled for C\textsubscript{25}H\textsubscript{29}BrN\textsubscript{2}NaO\textsubscript{4}S [M+Na]\textsuperscript{+}\: 555.0929, 557.0909).

**Conversion of 12a into 7da (Scheme 6b)**

To a solution of 12a (53.4 mg, 0.1 mmol) in AcOEt (2 mL) was added BF\textsubscript{3}•Et\textsubscript{2}O (0.06 mL, 0.5 mmol) and heated at 90 \(^\circ\)C (oil bath) with stirring for 3 h. After cooling to room temperature, saturated aq. NaHCO\textsubscript{3} was added to the mixture. The whole was extracted with AcOEt (3 x 10 mL), washed with brine (10 mL). The organic layer was dried over MgSO\textsubscript{4} and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CHCl\textsubscript{3}:hexane = 1:1) to give 7da (32.3 mg, 72% yield).
Conversion of 12b into 7da (Scheme 6c)

![Diagram of conversion of 12b into 7da]

To a solution of 12a (53.4 mg, 0.1 mmol) in AcOEt (2 mL) was added BF$_3$•Et$_2$O (0.06 mL, 0.5 mmol) and heated at 90 °C (oil bath) with stirring for 16 h. After cooling to room temperature, saturated aq. NaHCO$_3$ was added to the mixture. The whole was extracted with AcOEt (3 x 10 mL), washed with brine (10 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (CHCl$_3$:hexane = 1:1) to give 7da (30.4 mg, 57% yield).

3. Supplementary References

NMe

Ts

N