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Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles: Facile Access to C(3) All-Carbon Quaternary Stereocenters

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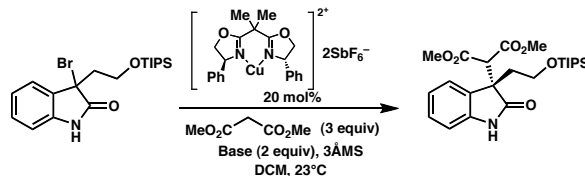
*The Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, USA***Table of Contents**

Materials and Methods	S2
Base Optimization for Enantioselective Malonate Alkylation	S3
Lewis Acid Metal Screen for Enantioselective Malonate Alkylation	S3
General Synthesis of 3-Alkyl Bromooxindoles Substrates from Corresponding 3-Alkyl Indoles	S3
General Synthesis of 3-Aryl Halooxindoles Substrates from Isatin	S10
General Synthesis of [Cu((<i>R</i>)-Ph-BOX)(SbF₆)₂]	S13
General Procedures of Enantioselective Malonate Alkylation	S13
Synthesis of Pyrrolidinone-spirooxindole	S20
Synthesis of Other Pyrrolidinone-spirooxindole: Further Confirmation of Absolute Stereochemistry	S24
Synthesis of Fused Indolinopyrrolidinone	S27
References	S28

Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKA mag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or ceric ammonium molybdate staining. SiliaFlash P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm and flow rate of 1 mL/min, unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 126 MHz, respectively) and a Varian Mercury 300 spectrometer (at 300 MHz and 75 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were either obtained from the Caltech Mass Spectral Facility or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode. Optical rotations were measured on either a Jasco P-1010 using a 50 mm path-length cell or Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. Melting points were determined using a Thomas capillary melting point apparatus and the values reported are uncorrected. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.

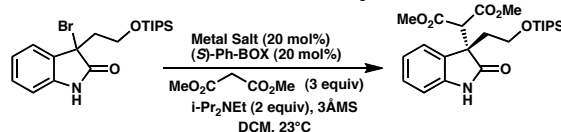
Base Optimization for Enantioselective Malonate Alkylation



Entry	Base	Yield [%] ^b	ee[%] ^c	Entry	Base	Yield [%] ^b	ee[%] ^c
1 ^a	Pyridine	--	--	7 ^a	Imidazole	--	--
2 ^a	2,6-di-tert-butylpyridine	--	--	8 ^a	TEA	74	82
3 ^a	<i>N</i> -Methylmorpholine	--	--	9 ^a	DABCO	--	--
4 ^a	DMAP	--	--	10 ^a	<i>N,N</i> -Dimethylcyclohexylamine	40	81
5	<i>N</i> -Methyl-dicyclohexylamine	46	80	11	<i>i</i> -Pr ₂ NEt	60	83
6	CS ₂ CO ₃	30	60	12	NaH	73	32

a. No product observed. b. Isolated yield. c. Measured by chiral HPLC.

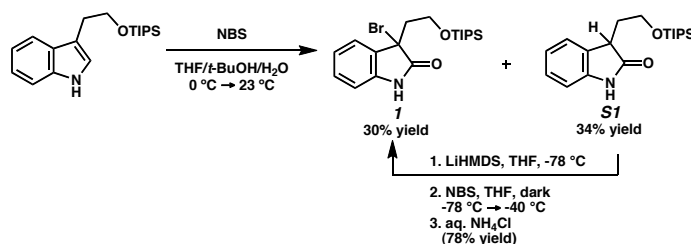
Lewis Metal Screen for Enantioselective Malonate Alkylation



Entry	Metal Salt	Yield[%] ^b	ee[%] ^c
1	Cu(OTf) ₂	63	77
2	Mg(OTf) ₂	41	0
3 ^a	La(OTf) ₃	93	0
4	NiCl ₂	59	25

a. Performed with (*R*)-Ph-BOX. b. Isolated yield. c. Measured by chiral HPLC.

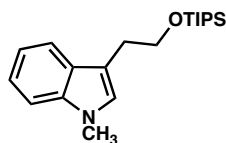
General Synthesis of 3-Alkyl Bromooxindoles From Corresponding 3-Alkyl Indoles.



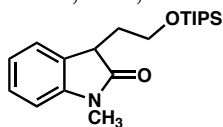
3-(2-(triisopropylsilyloxy)ethyl)-1*H*-indole (2.01 g, 6.33 mmol, 1.0 equiv) was dissolved in a mixture of THF (63 mL), *t*-BuOH (63 mL), and H₂O (1.3 mL). The solution was cooled to 0–5 °C and solid *N*-bromosuccinimide (1.58 g, 8.86 mmol, 1.4 equiv) was added in small portions over 60 minutes. The reaction mixture was then allowed to warm to ambient temperature and concentrated under reduced pressure. The residue obtained was purified by column chromatography (SiO₂, 6% ethyl acetate in hexanes → 10% ethyl acetate in hexanes) to afford bromooxindole **1** as an off-white solid (790.6 mg, 30% yield) and oxindole **S1** as a colorless oil (711.8 mg, 34% yield). TIPS oxindole **S1**: R_f = 0.30 (SiO₂, 25% ethyl acetate in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.31 (br s, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.20 (tt, *J* = 8.0, 1.0 Hz, 1H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 3.92 (m, 2H), 3.66 (app. t, *J* = 6.5 Hz, 1H), 2.25 (m, 1H), 2.07 (m, 1H), 1.04 (m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 180.5, 141.5, 129.7, 127.8, 124.6, 122.2, 109.6, 60.1, 42.8, 33.7, 18.1, 12.1; IR (neat film, NaCl) 3215,

2941, 2863, 1711, 1620, 1471, 1109, 747 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{19}\text{H}_{32}\text{NO}_2\text{Si}[\text{M}+\text{H}]^+$: 334.2202, found 334.2202.

Oxindole **S1** could be brominated to give bromooxindole **1** as follows: To a solution of oxindole **S1** (485.3 mg, 1.455 mmol, 1.0 equiv) in THF (15 mL) that had been pre-cooled to $-78\text{ }^\circ\text{C}$ was added a freshly prepared solution of LiHMDS (535.6 mg, 3.201 mmol, 2.2 equiv) in THF (4 mL) dropwise. The reaction mixture was then maintained at $-78\text{ }^\circ\text{C}$ for 30 minutes, and then transferred via cannula to a solution of NBS (517.9 mg, 2.91 mmol, 2.0 equiv) in THF (10 mL) that had been pre-cooled to $-78\text{ }^\circ\text{C}$ and wrapped in aluminum foil to protect from light. The reaction mixture was allowed to warm to $-40\text{ }^\circ\text{C}$ and maintained at this temperature for 2 hours. The reaction mixture was then poured into saturated aqueous NH_4Cl (60 mL). 1M aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (40 mL) was then added and the mixture was stirred for 10 minutes to reduce any excess NBS. The mixture was then extracted with EtOAc ($3 \times 100\text{ mL}$). The combined EtOAc extracts were washed with brine (100 mL), dried (MgSO_4) and concentrated under reduced pressure to afford a pale yellow solid. Purification by column chromatography (SiO_2 , 10% ethyl acetate in hexanes) afforded bromooxindole **1** as a pale yellow solid (467.7 mg, 78% yield). $R_f = 0.35$ (SiO_2 , 25% ethyl acetate in hexanes); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.56 (s, 1H), 7.37 (dd, $J = 7.5, 0.5$ Hz, 1H), 7.26 (app. t, $J = 5.0$ Hz, 1H), 7.07 (app. dt, $J = 7.5, 1.0$ Hz, 1H), 6.94 (d, $J = 7.5$ Hz, 1H), 3.62 (m, 2H), 2.89 (m, 1H), 2.61 (m, 1H), 0.91 (m, 21H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 177.4, 140.2, 130.1, 129.7, 124.8, 123.0, 111.0, 60.1, 55.8, 41.7, 17.8, 11.9; IR (neat film, NaCl) 3202, 2946, 2866, 1725, 1619, 1474, 1115 cm^{-1} ; HMRS (FAB+) m/z calc'd for $\text{C}_{19}\text{H}_{31}\text{BrNO}_2\text{Si} [\text{M}+\text{H}]^+$: 412.1307, found 412.1290.

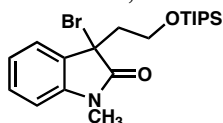


To NaH (53 mg, 60%, 1.326 mmol, 1.2 equiv) in DMF (1 mL) was added a solution of 3-(2-(triisopropylsilyloxy)ethyl)-1H-indole (0.351 g, 1.105 mmol, 1.0 equiv) in DMF (4 mL) at ambient temperature. The reaction solution was stirred for 20 min and then MeI (103 μL , 1.606 mmol, 1.5 equiv) was added dropwise. The reaction solution was stirred for additional 30 min at ambient temperature. Water (5 mL) and brine (5 mL) were added, and the mixture was extracted with a mixture of hexanes/EtOAc (1:2) ($2 \times 15\text{ mL}$). The combined extracts were dried with magnesium sulfate prior to concentration. The residue obtained was purified by column chromatography (SiO_2 , 2% ethyl acetate in hexanes) to afford 1-methyl-3-(2-(triisopropylsilyloxy)ethyl)-1H-indole as a pale yellow viscous oil (303 mg, 83% yield). $R_f = 0.66$ (22% ethyl acetate in hexanes); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.61 (d, $J = 8.1$ Hz, 1H), 7.30 (d, $J = 8.1$ Hz, 1H), 7.23 (td, $J = 7.2, 1.2$ Hz, 1H), 7.11 (ddd, $J = 6.9, 6.6, 1.2$ Hz, 1H), 6.91 (s, 1H), 3.94 (t, $J = 7.2$ Hz, 2H), 3.75 (s, 3H), 3.04 (t, $J = 7.2$ Hz, 2H), 1.15-1.05 (comp. m, 21H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 137.0, 128.2, 127.1, 121.5, 119.1, 118.8, 111.6, 109.2, 64.5, 32.7, 29.2, 18.2, 12.2; IR (neat film, NaCl) 3056, 2942, 2865, 1616, 1470, 1382, 1328, 1248, 1100, 1069, 1013, 918, 883 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{20}\text{H}_{33}\text{NSi} [\text{M}]^+$: 331.2331, found 331.2320.

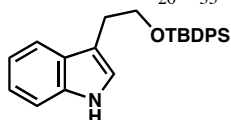


Prepared according to the procedure used for oxindole **S1** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2 , 2% ethyl acetate in hexanes \rightarrow 5% ethyl acetate in hexanes). Isolated as a colorless viscous oil. 43% yield. $R_f = 0.41$ (17% ethyl acetate in hexanes); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.30-7.24 (comp. m, 2H), 7.07-7.01 (m, 1H), 6.81 (d, $J = 7.5$ Hz, 1H), 4.00-3.86 (comp.

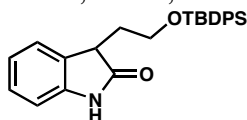
m, 2H), 3.63 (t, $J = 6.6$ Hz, 1H), 3.19 (s, 3H), 2.23 (dq, $J = 13.8, 6.6$ Hz, 1H), 2.02 (dq, $J = 13.8, 6.6$ Hz, 1H), 1.08-1.01 (comp. m, 21H); ^{13}C NMR (75 MHz, CDCl_3) δ 178.3, 144.5, 129.3, 127.8, 124.2, 122.3, 108.0, 60.3, 42.4, 33.9, 26.2, 18.1, 12.1; IR (neat film, NaCl) 3056, 2941, 2865, 1712, 1613, 1494, 1468, 1375, 1344, 1263, 1263, 1193, 1095, 1019, 921 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{20}\text{H}_{33}\text{NSi}$ [$\text{M}+\text{H}$] $^+$: 348.2359, found 348.2376.



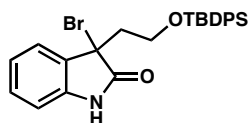
Prepared according to the procedure used for bromoindole **1** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2 , 2% ethyl acetate in hexanes \rightarrow 5% ethyl acetate in hexanes). Isolated as a pale yellow viscous oil. 28% yield. $R_f = 0.56$ (17% ethyl acetate in hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.39 (dd, $J = 7.5, 1.2$ Hz, 1H), 7.31 (td, $J = 7.8, 1.2$ Hz, 1H), 7.08 (td, $J = 7.5, 1.2$ Hz, 1H), 6.80 (d, $J = 7.8$ Hz, 1H), 3.67-3.54 (m, 2H), 3.21 (s, 3H), 2.84 (ddd, $J = 14.1, 7.2, 6.6$ Hz, 1H), 2.60 (ddd, $J = 13.8, 5.4, 4.5$ Hz, 1H), 0.91 (s, 21H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.2, 142.7, 130.1, 129.7, 124.8, 123.1, 108.8, 60.3, 55.3, 41.8, 26.8, 17.9, 11.9; IR (neat film, NaCl) 2943, 2891, 2866, 1732, 1614, 1494, 1471, 1422, 1372, 1344, 1244, 1137, 1104, 1071, 1018, 958 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{20}\text{H}_{33}\text{NO}_2\text{Si}^{81}\text{Br}$ [M] $^+$: 428.1443, found 428.1447.



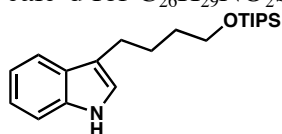
To a solution of tryptophol (1.069 g, 6.632 mmol, 1 equiv) and imidazole (0.993 g, 14.59 mmol, 2.2 equiv) in DMF (25 mL) was added TIPSCl (1.90 mL, 7.295 mmol, 1.1 equiv) dropwise at ambient temperature. The reaction solution was stirred for 18 hours. Saturated aqueous NaHCO_3 (50 mL) was added and the mixture was extracted with EtOAc (2 x 50 mL). The combined extracts were dried with magnesium sulfate prior to concentration. The residue obtained was purified by column chromatography (SiO_2 , 9% ethyl acetate in hexanes) to afford 3-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-1*H*-indole as a yellow viscous oil (2.60 g, 98% yield). $R_f = 0.60$ (22% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.89 (br s, 1H), 7.67 (dd, $J = 7.5, 1.5$ Hz, 4H), 7.44-7.40 (m, 3H), 7.38-7.32 (m, 5H), 7.18 (td, $J = 7.5, 1.0$ Hz, 1H), 7.06 (td, $J = 7.5, 1.0$ Hz, 1H), 7.00 (d, $J = 2.5$ Hz, 1H), 3.95 (t, $J = 7.5$ Hz, 2H), 3.05 (t, $J = 7.5$ Hz, 2H), 1.08 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 135.7, 134.1, 129.7, 127.8, 127.7, 122.3, 122.0, 119.3, 119.0, 113.1, 111.1, 64.6, 28.8, 27.0, 19.3.



Prepared according to the procedure used for oxindole **S1** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2 , 9% ethyl acetate in hexanes \rightarrow 17% ethyl acetate in hexanes). Isolated as a white solid. 57% yield. $R_f = 0.30$ (22% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 8.08 (br s, 1H), 7.66 (dt, $J = 6.5, 1.5$ Hz, 2H), 7.52 (dt, $J = 6.5, 1.5$ Hz, 2H), 7.44-7.36 (comp. m, 4H), 7.33 (tt, $J = 7.5, 1.0$ Hz, 2H), 7.22 (tt, $J = 8.0, 1.0$ Hz, 1H), 7.11 (d, $J = 7.5$ Hz, 1H), 6.98 (td, $J = 7.5, 1.0$ Hz, 1H), 6.87 (d, $J = 7.5$ Hz, 1H), 3.86 (ddd, $J = 12.5, 7.0, 5.5$ Hz, 1H), 3.78 (dt, $J = 10.5, 6.0$ Hz, 1H), 3.69 (t, $J = 7.5$ Hz, 1H), 2.27 (dq, $J = 14.0, 6.0$ Hz, 1H), 2.19-2.12 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 180.3, 141.6, 135.8, 135.6, 133.64, 133.60, 129.8, 129.7, 129.4, 127.92, 127.84, 127.78, 124.7, 122.3, 109.7, 60.6, 42.9, 32.9, 26.9, 19.2; IR (neat film, NaCl) 3198, 3071, 2956, 2930, 2889, 2857, 1709, 1621, 1472, 1428, 1390, 1335, 1307, 1235, 1111, 1073, 953 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{26}\text{H}_{30}\text{NO}_2\text{Si}$ [$\text{M}+\text{H}$] $^+$: 416.2046, found 416.2033.

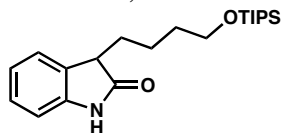


Prepared according to the procedure used for bromooxindole **1** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO₂, 9% ethyl acetate in hexanes→17% ethyl acetate in hexanes). Isolated as a white solid. 13% yield. R_f = 0.46 (22% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.48 (br s, 1H), 7.50 (dt, J = 6.5, 1.5 Hz, 2H), 7.41 (tt, J = 7.5, 1.5 Hz, 1H), 7.37-7.30 (comp. m, 5H), 7.28-7.23 (comp. m, 4 H), 7.10 (td, J = 8.0, 1.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 3.54-3.46 (m, 2H), 3.01 (ddd, J = 15.5, 9.0, 6.5 Hz, 1H), 2.60 (dt, J = 14.0, 4.0 Hz, 1H), 0.92 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 176.4, 140.1, 135.7, 135.4, 133.1, 132.9, 130.3, 129.9, 129.7, 129.7, 127.8, 127.7, 125.2, 123.2, 110.8, 60.7, 55.4, 41.2, 26.6, 19.0; IR (neat film, NaCl) 3209, 3175, 3107, 2930, 2879, 2857, 1731, 1614, 1470, 1427, 1388, 1332, 1195, 1107, 1084, 824, 758, 748 cm⁻¹; HRMS (FAB+) m/z calc'd for C₂₆H₂₉NO₂Si⁸¹Br [M+H]⁺: 496.1118, found 496.1130.



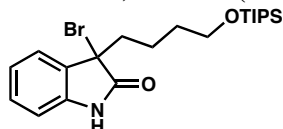
To a solution of indole-3-butyric acid (1.500 g, 7.380 mmol, 1.0 equiv) in THF (20 mL) at 0 °C was added a solution of LAH (5.5 mL, 11.07 mmol, 2.0 M in THF, 1.5 equiv) dropwise. The reaction mixture was then allowed to warm to ambient temperature and stirred for 6 hours. Water (2 mL), 10 % aqueous NaOH (2 mL), and water (6 mL) were added in order and the mixture was stirred at ambient temperature for additional 30 min, filtered through celite, concentrated under vacuum to get indole-3-butanol as pale yellow viscous oil (1.40 g). Crude product was used for next step without further purification.

To a solution of above crude alcohol (1.395 g, 7.371 mmol) and imidazole (1.103 g, 16.216 mmol, 2.2 equiv) in DMF (20 mL) was added TIPSCl (1.74 mL, 8.108 mmol, 1.1 equiv) dropwise at ambient temperature. The reaction solution was stirred for 18 hours. Saturated aqueous NaHCO₃ (30 mL) was added and the mixture was extracted with EtOAc (4 x 30 mL). The combined extracts were dried with magnesium sulfate prior to concentration. The residue obtained was purified by column chromatography (SiO₂, 5% ethyl acetate in hexanes) to afford 3-(4-(triisopropylsilyloxy)butyl)-1*H*-indole as a pale yellow viscous oil (2.50 g, 98% yield). R_f = 0.45 (22% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.90 (br s, 1 H), 7.62 (dd, J = 7.5, 1.0 Hz, 1 H), 7.35 (dt, J = 8.0, 1.0 Hz, 1 H), 7.19 (td, J = 7.5, 1.0 Hz, 1 H), 7.11 (td, J = 7.5, 1.0 Hz, 1 H), 6.98 (t, J = 1.0 Hz, 1 H), 3.74 (t, J = 6.5 Hz, 2 H), 2.79 (t, J = 7.5 Hz, 2 H), 1.84-1.78 (m, 2 H), 1.70-1.64 (m, 2 H), 1.14-1.01 (comp. m, 21 H); ¹³C NMR (126 MHz, CDCl₃) δ 136.5, 127.8, 121.9, 121.2, 119.18, 119.15, 117.1, 111.1, 63.5, 33.1, 26.5, 25.1, 18.2, 12.2; IR (neat film, NaCl) 3420, 3057, 2941, 2864, 1458, 1420, 1382, 1351, 1336, 1246, 1228, 1105, 1070, 1012, 995, 969, 882, 796, 739 cm⁻¹; HRMS (FAB+) m/z calc'd for C₂₁H₃₅NOSi [M+H]⁺: 345.2488, found 345.2483.

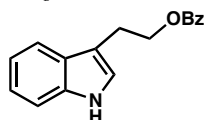


Prepared according to the procedure used for oxindole **S1** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO₂, 9% ethyl acetate in hexanes→17% ethyl acetate in hexanes). Isolated as a white solid. 15% yield. R_f = 0.11 (29% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.80 (br s, 1H), 7.24 (d, J = 7.0 Hz, 1H), 7.20 (t, J = 7.0 Hz, 1H), 7.01 (td, J = 7.5, 1.0 Hz,

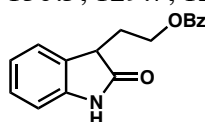
1H), 6.90 (d, $J = 7.5$ Hz, 1H), 3.70-3.61 (m, 2H), 3.48 (t, $J = 6.5$ Hz, 1H), 2.07-2.00 (m, 1H), 1.98-1.90 (m, 1H), 1.61-1.53 (m, 2H), 1.52-1.43 (m, 2H), 1.09-0.97 (m, 21H); ^{13}C NMR (126 MHz, CDCl_3) δ 180.8, 141.7, 129.9, 127.9, 124.4, 122.4, 109.8, 63.2, 46.2, 33.0, 30.6, 22.4, 18.1, 12.1; IR (neat film, NaCl) 3209, 3091, 2942, 2892, 2866, 1711, 1621, 1486, 1472, 1383, 1338, 1233, 1106, 1070, 1015, 996, 883 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{21}\text{H}_{36}\text{NO}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 362.2515, found 362.2498.



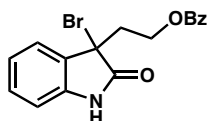
Prepared according to the procedure used for bromooxindole **1** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2 , 9% ethyl acetate in hexanes \rightarrow 17% ethyl acetate in hexanes). Isolated as a pale yellow viscous oil. 15% yield. $R_f = 0.34$ (22% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 9.03 (br s, 1H), 7.37 (d, $J = 7.0$ Hz, 1H), 7.26 (td, $J = 7.0, 1.0$ Hz, 1H), 7.08 (td, $J = 7.5, 0.5$ Hz, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 3.65-3.56 (m, 2H), 2.42 (t, $J = 8.0$ Hz, 2H), 1.56-1.47 (m, 2H), 1.31-1.22 (m, 2H), 1.04-0.93 (m, 21H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.0, 139.8, 130.5, 130.1, 124.9, 123.5, 110.8, 62.8, 56.9, 39.4, 32.6, 22.1, 18.1, 12.1; IR (neat film, NaCl) 3239, 2943, 2865, 2732, 1619, 1472, 1383, 1331, 1246, 1208, 1180, 1112, 1069, 1014, 996, 882, 749 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{21}\text{H}_{35}\text{NO}_2\text{Si}^{81}\text{Br}$ $[\text{M}+\text{H}]^+$: 442.1600, found 442.1583.



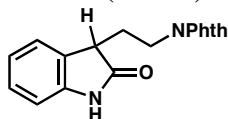
To a solution of benzoic acid (0.970 g, 7.946 mmol, 1.0 equiv) and EDCI (1.675 g, 8.741 mmol, 1.1 equiv) in CH_2Cl_2 (15 mL) was added DMAP (0.107 g, 0.874 mmol, 0.11 equiv) and tryptophol (1.409 g, 8.741 mmol, 1.1 equiv) at 23 $^\circ\text{C}$. The reaction mixture was stirred at 23 $^\circ\text{C}$ for 14 hours. Saturated aqueous NaHCO_3 solution (30 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 30 mL). The combined extracts were dried with magnesium sulfate prior to concentration. Purification by flash chromatography (SiO_2 , 9% ethyl acetate in hexanes \rightarrow 17% ethyl acetate in hexanes) afforded 2-(1*H*-indol-3-yl)ethyl benzoate as a yellow solid (1.05 g, 50% yield). ^1H NMR (300 MHz, CDCl_3) δ 8.09-8.03 (comp. m, 3H), 7.72-7.69 (m, 1H), 7.57 (tt, $J = 7.5, 1.2$ Hz, 1H), 7.48-7.41 (comp. m, 2H), 7.40-7.37 (m, 1H), 7.23 (td, $J = 6.9, 1.5$ Hz, 1H), 7.17 (td, $J = 7.5, 1.5$ Hz, 1H), 7.11 (d, $J = 2.4$ Hz, 1H), 4.63 (t, $J = 7.5$ Hz, 2H), 3.26 (td, $J = 6.9, 0.9$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 166.8, 136.3, 133.1, 130.5, 129.7, 128.5, 127.6, 122.3, 122.2, 119.6, 118.9, 112.2, 111.3, 65.2, 25.0.



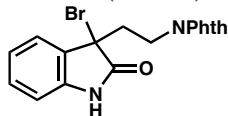
Prepared according to the procedure used for oxindole **S1** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO_2 , 5% ethyl acetate in hexanes \rightarrow 25% ethyl acetate in hexanes). Isolated as a white solid. 47% yield. $R_f = 0.21$ (33% ethyl acetate in hexanes); ^1H NMR (300 MHz, CDCl_3) δ 8.99 (br s, 1H), 7.96-7.92 (comp. m, 2H), 7.50 (t, $J = 7.2$ Hz, 1H), 7.39 (t, $J = 7.8$ Hz, 2H), 7.27 (d, $J = 7.5$ Hz, 1H), 7.20 (t, $J = 7.5$ Hz, 1H), 7.02 (td, $J = 7.5, 0.9$ Hz, 1H), 6.89 (d, $J = 7.8$ Hz, 1H), 4.52 (dt, $J = 11.4, 7.2$ Hz, 1H), 4.41 (dt, $J = 11.1, 6.8$ Hz, 1H), 3.66 (t, $J = 6.0$ Hz, 1H), 2.48 (q, $J = 6.3$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.1, 166.5, 141.6, 133.1, 130.1, 129.7, 128.6, 128.4, 128.3, 124.4, 122.6, 110.2, 61.8, 43.4, 29.2; IR (neat film, NaCl) 3207, 3059, 2961, 1715, 1620, 1471, 1452, 1335, 1314, 1272, 1176, 1116, 1070, 1026 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{17}\text{H}_{16}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 282.1130, found 282.1126.



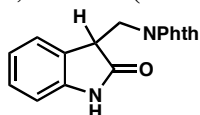
Prepared according to the procedure used for bromooxindole **1** using *N*-bromosuccinimide (1.0 equiv). Purified by flash chromatography (SiO₂, 5% ethyl acetate in hexanes→25% ethyl acetate in hexanes). Isolated as a pale yellow solid. 23% yield. $R_f = 0.48$ (33% ethyl acetate in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.64 (br s, 1H), 7.86-7.81 (comp. m, 2H), 7.48 (td, $J = 7.8, 1.2$ Hz, 1H), 7.42 (d, $J = 7.8$ Hz, 1H), 7.35 (t, $J = 7.5$ Hz, 2H), 7.25 (td, $J = 7.5, 1.6$ Hz, 1H), 7.07 (td, $J = 7.5, 1.2$ Hz, 1H), 6.85 (t, $J = 7.1, 1$ Hz), 4.34 (dt, $J = 11.7, 5.7$ Hz, 1H), 4.16 (ddd, $J = 11.4, 8.1, 4.8$ Hz, 1H), 3.06 (ddd, $J = 14.4, 8.4, 6.0$ Hz, 1H), 2.89 (dt, $J = 14.4, 5.4$ Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 176.4, 166.2, 139.8, 133.3, 130.6, 129.6, 129.6, 129.5, 128.4, 125.0, 123.7, 111.2, 61.4, 54.5, 38.2; IR (neat film, NaCl) 3256, 3090, 3064, 3033, 2961, 1723, 1619, 1602, 1473, 1451, 1329, 1316, 1273, 1192, 1114, 1071, 1028, 752 cm⁻¹; HRMS (FAB+) m/z calc'd for C₁₇H₁₅N₂O₂⁸¹Br [M+H]⁺: 360.0296, found 360.0287.



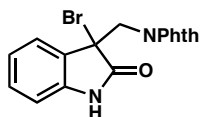
Prepared from *N*-phthalimidotryptamine according to the procedure used for oxindole **S1**. 54% yield. $R_f = 0.12$ (SiO₂, 50% ethyl acetate in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.82 (bs, 1H), 7.75 (m, 2H), 7.66 (m, 2H), 7.29 (d, $J = 7.7$ Hz, 1H), 7.08 (d, $J = 7.7$ Hz, 1H), 6.87 (t, $J = 7.7$ Hz, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 3.97 (m, 1H), 3.80 (m, 1H), 3.53 (t, $J = 6.0$ Hz, 1H), 2.51 (m, 1H), 2.32 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 178.7, 168.2, 141.3, 133.9, 132.1, 128.6, 128.0, 124.1, 123.2, 122.4, 109.7, 43.9, 35.2, 28.5; IR (Neat film, NaCl) 3271, 1772, 1711, 1621, 1471, 1398, 1220, 1022, 718 cm⁻¹; HRMS (FAB+) m/z calc'd for C₁₈H₁₅N₂O₃ [M+H]⁺: 307.1083, found 307.1076.



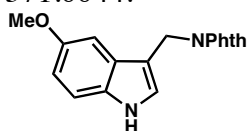
Prepared from *N*-phthalimidotryptamine according to the procedure used for bromooxindole **1**. 9% yield. $R_f = 0.31$ (SiO₂, 50% ethyl acetate in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.71 (s, 1H), 7.71 (m, 2H), 7.62 (m, 2H), 7.28 (m, 1H), 7.06 (m, 1H), 6.80 (m, 2H), 3.81 (m, 1H), 3.65 (m, 1H), 3.01 (m, 1H), 2.86 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 175.5, 167.8, 139.8, 134.0, 131.8, 130.2, 129.5, 124.4, 123.2, 123.1, 111.1, 54.2, 36.5, 34.6; IR (Neat film, NaCl) 3256, 1711, 1615, 1471, 1398, 1184, 716 cm⁻¹; HRMS (FAB+) m/z calc'd for C₁₈H₁₄BrN₂O₃ [M+H]⁺: 385.0188, found 385.0178.



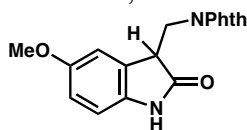
Prepared from *N*-(indol-3-yl)methyl]phthalimide according to procedure used for oxindole **S1** using *N*-bromosuccinimide (1.0 equiv).² Purified by flash chromatography (SiO₂, 25% ethyl acetate in hexanes→50% ethyl acetate in hexanes; then 9% ethyl acetate in methylene chloride). Isolated as a pale yellow solid with 35% (w/w) of succinimide. 23% yield (corrected for succinimide). $R_f = 0.17$ (9% ethyl acetate in methylene chloride); ¹H NMR (500 MHz, CDCl₃) δ 8.15 (br s, 1H), 7.90-7.86 (m, 2H), 7.76-7.71 (m, 2H), 7.22 (td, $J = 7.5, 1.0$ Hz, 1H), 7.19 (d, $J = 7.0$ Hz, 1H), 6.99 (td, $J = 7.5, 1.0$ Hz, 1H), 6.87 (d, $J = 8.0$ Hz, 1H), 4.20 (dd, $J = 14.0, 9.0$ Hz, 1H), 4.14 (dd, $J = 14.0, 6.0$ Hz, 1H), 3.99 (dd, $J = 9.0, 6.0$ Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 177.5, 168.3, 141.6, 134.2, 132.1, 128.8, 126.6, 124.6, 123.7, 122.6, 110.1, 43.5, 38.2; HRMS (FAB+) m/z calc'd for C₁₇H₁₃N₂O₃ [M+H]⁺: 293.0926, found 293.0915.



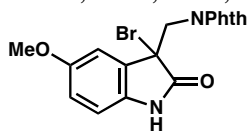
Prepared from *N*-(indol-3-yl)methylphthalimide according to procedure used for bromooxindole **1** using *N*-bromosuccinimide (1.0 equiv).² Purified by flash chromatography (SiO₂, 25% ethyl acetate in hexanes → 50% ethyl acetate in hexanes; then 9% ethyl acetate in methylene chloride). Isolated as a white solid. 22% yield. *R_f* = 0.30 (9% ethyl acetate in methylene chloride); ¹H NMR (500 MHz, CDCl₃) δ 8.13 (br s, 1H), 7.76-7.72 (comp. m, 2H), 7.68-7.64 (comp. m, 2H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.20 (td, *J* = 8.0, 1.5 Hz, 1H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.64 (ABq, *J* = 14.5 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 174.6, 167.4, 140.3, 134.4, 131.5, 130.9, 127.4, 126.3, 123.8, 123.3, 110.8, 53.7, 43.9; IR (neat film, NaCl) 3268, 1778, 1734, 1719, 1617, 1472, 1389, 1335, 1192, 1142, 986, 967, 876 cm⁻¹; HRMS (FAB+) *m/z* calc'd for C₁₇H₁₂N₂O₃Br [M+H]⁺: 371.0031, found 371.0044.



CH₃I (0.89 mL, 14.20 mmol, 5 equiv) was added to a solution of 5-methoxy-gramine (0.580 g, 2.839 mmol, 1 equiv) in THF (25 mL) at 0 °C over 30 min. After stirring of the reaction mixture at ambient temperature for 1 hour, the solvent was removed in vacuo. The residue was heated with potassium phthalimide (0.526 g, 2.839 mmol, 1 equiv) at 140 °C for 6 hours. Upon cooling to ambient temperature, reaction mixture was then diluted with water (20 mL) and brine (20 mL) and then extracted with ethyl acetate (3 x 50 mL). Organic layers were collected and dried with magnesium sulfate. Purification by column chromatography (SiO₂, 33% ethyl acetate in hexanes) afforded *N*-(5-methoxyindol-3-yl)methylphthalimide as a yellow solid (0.441 g, 51% yield). *R_f* = 0.23 (33% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.06 (br s, 1H), 7.81-7.78 (comp. m, 2H), 7.67-7.64 (comp. m, 2H), 7.44 (d, *J* = 2.5 Hz, 1H), 7.38 (d, *J* = 2.5 Hz, 1H), 7.22 (dd, *J* = 9.0, 0.5 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.99 (s, 2H), 3.91 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 168.4, 154.5, 133.9, 132.4, 131.1, 127.1, 125.9, 123.3, 113.0, 111.9, 111.3, 101.0, 55.9, 32.8; IR (neat film, NaCl) 3401, 2938, 1767, 1708, 1488, 1432, 1394, 1334, 1216, 1178, 1056 cm⁻¹; HRMS (FAB+) *m/z* calc'd for C₁₈H₁₄N₂O₃ [M]⁺: 306.1005, found 306.1007.

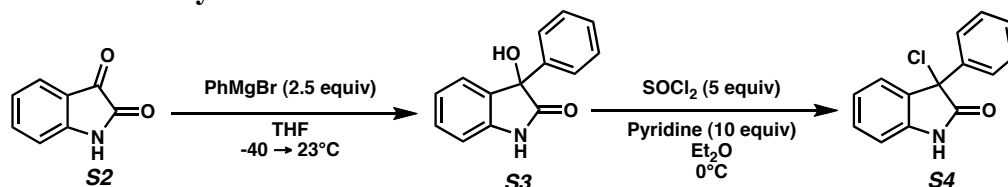


Prepared according to the procedure similar to that used to synthesize oxindole **S1** using *N*-bromosuccinimide (1.6 equiv). Purified by column chromatography (SiO₂, 9% ethyl acetate in CH₂Cl₂ → 17% ethyl acetate in CH₂Cl₂). Isolated as a white solid. 33% yield. *R_f* = 0.06 (9% ethyl acetate in methylene chloride); ¹H NMR (500 MHz, CDCl₃) δ 7.89-7.85 (comp. m, 2H), 7.75-7.71 (comp. m with broad singlet at δ 7.73, 3H), 6.80 (s, 1H), 6.77 (d, *J* = 8.0, 1H), 6.74 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.19 (dd, *J* = 14.0, 9.5 Hz, 1H), 4.12 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.95 (dd, *J* = 9.0, 7.0 Hz, 1H), 3.72 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 176.9, 168.3, 155.9, 134.8, 134.3, 132.1, 127.8, 123.7, 113.6, 111.7, 110.3, 55.9, 43.8, 38.2; HRMS (FAB+) *m/z* calc'd for C₁₈H₁₅N₂O₄ [M+H]⁺: 323.1032, found 323.1024.



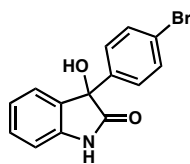
Prepared according to the procedure similar to that used to synthesize bromooxindole **1** using *N*-bromosuccinimide (1.6 equiv). Purified by column chromatography (SiO₂, 9% ethyl acetate in methylene chloride) and then recrystallized from methylene chloride. Isolated as a yellow solid. 78% yield. $R_f = 0.18$ (9% ethyl acetate in methylene chloride); ¹H NMR (500 MHz, CDCl₃) δ 7.78-7.74 (comp. m, 2H), 7.69-7.65 (comp. m, 2H), 7.61 (br s, 1H), 7.07, (d, $J = 2.5$ Hz, 1H), 6.75 (dd, $J = 7.5, 2.5$ Hz, 1H), 6.70 (d, $J = 7.5$, 1H), 4.62 (ABq, $J = 150$ Hz, 2H), 3.77 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 174.2, 167.4, 156.1, 134.4, 133.3, 131.6, 128.3, 123.8, 117.1, 111.9, 111.2, 56.0, 53.9, 43.9; IR (neat film, NaCl) 3271, 2997, 1777, 1721, 1492, 1389, 1299, 1205, 719 cm⁻¹; HRMS (FAB+) m/z calc'd for C₁₈H₁₄N₂O₄Br [M+H]⁺: 401.0137, found 401.0142.

General Synthesis of 3-Aryl Halooxindoles from Isatin



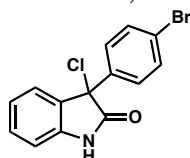
To a solution of isatin (**S2**, 1.0 g, 6.8 mmol, 1.0 equiv) in THF (60 mL) cooled to -40 °C was added PhMgBr (3M in Et₂O, 5.7 mL, 17 mmol, 2.5 equiv). The reaction mixture was allowed to warm to ambient temperature. After 6 hours, 1N hydrochloric acid (30 mL) was added dropwise to quench the reaction, and the phases were separated. The aqueous phase was extracted with ether (2 x 50 mL), dried with sodium sulfate and concentrated to afford **S3** as a yellow solid in 99% yield.³ No further purification necessary. $R_f = 0.18$ (20% ethyl acetate in methylene chloride); ¹H NMR (500 MHz, MeOD) δ 7.39-7.37 (comp. m, 2H), 7.33-7.26 (comp. m, 4H), 7.17 (d, $J = 7.5$ Hz, 1H), 7.06 (ddd, $J = 8.5, 8.5, 0.97$ Hz, 1H), 6.97 (d, $J = 7.8$ Hz, 1H); ¹³C NMR (126 MHz, MeOD) δ 181.8, 143.2, 142.2, 135.0, 130.8, 129.4, 129.1, 126.8, 126.2, 124.2, 111.5, 79.5; IR (neat film, NaCl) 3312, 1711, 1622, 1473, 1183 cm⁻¹; HRMS (FAB+) m/z calc'd for C₁₄H₁₁O₂N [M⁺] 225.0790, found 255.0796.

To solution of hydroxyoxindole **S3** (321.9 mg, 1.429 mmol, 1.0 equiv) and pyridine (1.2 mL, 14.29 mmol, 3.0 equiv) in THF (10 mL) cooled to 0 °C in a round bottom flask equipped with a stirbar, thionyl chloride (522 μL, 850.1 mg, 5.0 equiv) added dropwise. The reaction solution was stirred at 0 °C for one hour or when complete by TLC. Water (60 mL) then added and the mixture was extracted with EtOAc (3 x 100 mL). The combined extracts washed with brine (1 x 100 mL), and then dried with magnesium sulfate prior to concentration. Purification by flash chromatography (SiO₂, 10% ethyl acetate in hexanes) afforded chlorooxindole **S4** as a white powder (83% yield). $R_f = 0.27$ (25% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.20 (bs, 1H), 7.56-7.54 (comp. m, 2H), 7.39-7.32 (comp. m, 5H), 7.14 (ddd, $J = 7.6, 7.6, 0.9$ Hz, 1H), 6.97 (d, $J = 7.8$ Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 175.2, 139.9, 136.5, 131.0, 130.6, 129.1, 128.7, 127.6, 126.5, 123.9, 110.8, 66.8; IR (neat film, NaCl) 3247, 1729, 1619, 1472, 1322, 1211 cm⁻¹; HRMS (FAB+) m/z calc'd for C₁₄H₁₁ONCl [M+H]⁺: 244.0529, found 244.0539.

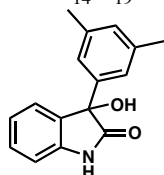


Prepared according to procedure used for hydroxyoxindole **S3**. Purified by flash chromatography (SiO₂, 50% ethyl acetate in hexanes). Isolated as a white powder. 80% yield. $R_f = 0.33$ (50% ethyl acetate in hexanes); ¹H NMR (500 MHz, MeOD) δ 7.38 (app. d, $J = 8.5$ Hz, 2H), 7.23-7.19 (comp. m, 3H), 7.08

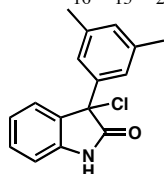
(d, $J = 7.3$ Hz, 1H), 6.96 (dd, $J = 7.6, 7.6$ Hz, 1H), 6.88 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (126 MHz, MeOD) δ 179.9, 141.9, 140.2, 133.2, 131.2, 129.8, 127.6, 124.9, 123.0, 121.7, 110.3, 77.8; IR (neat film, NaCl) 3234, 1718, 1621, 1472, 1184 cm^{-1} ; HRMS (EI⁺) m/z calc'd for $\text{C}_{14}\text{H}_{10}\text{BrNO}_2$ [M]⁺: 302.9895, found 302.9896.



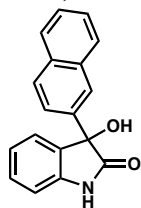
Prepared according to procedure used for chlorooxindole **S4**. Purified by flash chromatography (SiO_2 , 20% ethyl acetate in hexanes). Isolated as a white solid. 63% yield. $R_f = 0.67$ (50% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 8.59 (s, 1H), 7.49 (app. d, $J = 8.8$ Hz, 2H), 7.42 (app. d, $J = 8.8$ Hz, 2H), 7.53 (dd, $J = 6.1, 6.1$ Hz, 2H), 7.16 (dd, $J = 7.6, 7.6$ Hz, 1H), 6.98 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.2, 140.0, 135.6, 131.9, 130.9, 130.4, 129.4, 127.6, 126.3, 124.0, 111.2, 66.2; IR (neat film, NaCl) 3247, 1728, 1619, 1472, 1395, 1322, 1211, 1011 cm^{-1} ; HRMS (EI⁺) m/z calc'd for $\text{C}_{14}\text{H}_9\text{ONCl}^{81}\text{Br}$ [M]⁺: 322.9536, found 322.9521.



Prepared according to procedure used for hydroxyoxindole **S3**. Purified by flash chromatography (SiO_2 , 20% ethyl acetate in methylene chloride). Isolated as a pale yellow solid. 46% yield. $R_f = 0.50$ (50% ethyl acetate in hexanes); ^1H NMR (500 MHz, MeOD) δ 7.29 (ddd, $J = 7.8, 7.8, 1.2$ Hz, 1H), 7.16 (d, $J = 7.6$ Hz, 1H), 7.04 (ddd, $J = 7.6, 7.6, 1.0$ Hz, 1H), 6.98-6.96 (comp. m, 3H), 6.92 (s, 1H), 2.26 (s, 6H); ^{13}C NMR (126 MHz, MeOD) δ 182.0, 143.2, 142.0, 139.2, 135.3, 130.8, 130.6, 126.2, 124.5, 124.2, 111.5, 79.5, 21.6; IR (neat film, NaCl) 3270, 1720, 1620, 1472, 1186, 1109 cm^{-1} ; MS (EI⁺) m/z calc'd for $\text{C}_{16}\text{H}_{15}\text{O}_2\text{N}$ [M]⁺: 253.1103, found 253.1112.

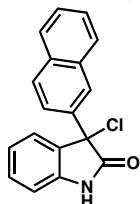


Prepared according to procedure used for chlorooxindole **S4**. Purified by flash chromatography (SiO_2 , 20% ethyl acetate in hexanes). Isolated as a light yellow solid. 85% yield. $R_f = 0.40$ (25% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.36-7.30 (comp. m, 2H), 7.14-7.11 (comp. m, 3H), 6.98-6.97 (comp. m, 2H), 2.30 (s, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.7, 140.0, 138.4, 136.2, 131.5, 130.9, 130.4, 126.3, 125.2, 123.8, 110.9, 67.0, 21.5; IR (neat film, NaCl) 3247, 1729, 1619, 1473, 1192 cm^{-1} ; HRMS (FAB⁺) m/z calc'd for $\text{C}_{16}\text{H}_{15}\text{ClNO}$ [M+H]⁺: 272.0842, found 272.0847.

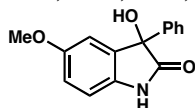


Prepared according to procedure used for hydroxyoxindole **S3**. Purified by flash chromatography (SiO_2 , 50% ethyl acetate in hexanes). Isolated as a yellow solid. 86% yield. $R_f = 0.46$ (50% ethyl acetate in hexanes); ^1H NMR (500 MHz, MeOD) δ 7.84 (d, $J = 1.5$ Hz, 1H), 7.73-7.71 (comp. m, 2H), 7.69 (d, $J =$

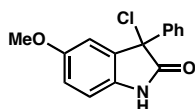
8.5 Hz, 1H), 7.38-7.36 (comp. m, 2H), 7.31 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.22 (ddd, $J = 7.8, 7.8, 1.2$ Hz, 1H), 7.12 (d, $J = 7.6$ Hz, 1H), 6.96 (dd, $J = 8.0, 8.0$ Hz, 1H), 6.92 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (126 MHz, MeOD) δ 181.5, 143.2, 139.3, 134.8, 134.5, 134.5, 130.8, 129.2, 129.0, 128.6, 127.3, 127.2, 126.2, 125.6, 124.7, 124.1, 111.5, 79.5; IR (Neat Film, NaCl) 3235, 1727, 1711, 1619, 1471, 1339, 1180, 1109, 1074, 893, 929, 859, 811, 754, 740 cm^{-1} ; HRMS (EI⁺) m/z calc'd for $\text{C}_{18}\text{H}_{13}\text{O}_2\text{N}$ [M]⁺: 275.0946, found 275.0936.



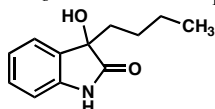
Prepared according to procedure used for chlorooxindole **S4**. Purified by flash chromatography (SiO_2 , 0% ethyl acetate in hexanes→40% ethyl acetate in hexanes). Isolated as a pale yellow solid. 67% yield. $R_f = 0.30$ (50% ethyl acetate in hexanes); ^1H NMR (500 MHz, MeOD) δ 7.83 (s, 1H), 7.72-7.68 (comp. m, 3H), 7.38 (comp. m, 2H), 7.29 (dd, $J = 8.5, 1.7$ Hz, 1H), 7.22 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.11 (d, $J = 7.6$ Hz, 1H), 6.96 (dd, $J = 7.6, 7.6$ Hz, 1H), 6.91 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (126 MHz, MeOD) δ 180.4, 142.0, 138.2, 133.6, 133.4, 133.3, 129.6, 128.0, 127.9, 127.4, 126.1, 126.0, 125.0, 124.4, 123.5, 122.9, 110.3, 78.4; IR (neat film, NaCl) 3261, 1726, 1679, 1622, 1474, 1342, 1268, 1180, 1126, 1111, 933, 894, 810, 752 cm^{-1} ; HRMS (EI⁺) m/z calc'd for $\text{C}_{18}\text{H}_{12}\text{ONCl}$ [M]⁺: 293.0607, found 293.0604.



Prepared according to procedure used for hydroxyoxindole **S3**. Purified by flash chromatography (SiO_2 , 20% ethyl acetate in hexanes→50% ethyl acetate in hexanes). Isolated as a pale pink solid. 86% yield. $R_f = 0.25$ (50% ethyl acetate in hexanes); ^1H NMR (500 MHz, MeOD) δ 7.39-7.36 (comp. m, 2H), 7.34-7.26 (comp. m, 3H), 6.91-6.85 (comp. m, 2H), 6.78 (d, $J = 1.4$ Hz, 1H); ^{13}C NMR (126 MHz, MeOD) δ 181.7, 157.8, 142.0, 136.1, 129.3, 129.0, 126.7, 115.6, 112.6, 111.9, 79.8, 56.2; IR (neat film, NaCl) 3271, 1708, 1489, 1203, 1026, 758, 733 cm^{-1} ; HRMS (EI⁺) m/z calc'd for $\text{C}_{15}\text{H}_{13}\text{NO}_3$ [M]⁺: 255.0895, found 255.0891.

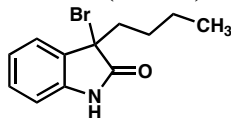


Prepared according to procedure used for chlorooxindole **S4**. Purified by flash chromatography (SiO_2 , 20% ethyl acetate in hexanes). Isolated as a white powder. 66% yield. $R_f = 0.70$ (50% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 8.20 (s, 1H), 7.56 (comp. m, 2H), 7.40-7.26 (comp. m, 3H), 6.95 (app. s, 1H), 6.90-6.86 (comp. m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 175.4, 156.8, 136.6, 133.2, 132.2, 129.2, 128.9, 127.6, 127.6, 116.0, 112.6, 111.5, 67.2, 56.0; IR (neat film, NaCl) 3206, 2961, 1726, 1613, 1492, 1440, 1300, 1206, 1146, 1104, 1031, 959, 846, 814, 750, 734, 695 cm^{-1} ; MS (FAB⁺) m/z calc'd for $\text{C}_{15}\text{H}_{12}\text{ClNO}_2$ [M]⁺: 273.0556, found 273.0557.



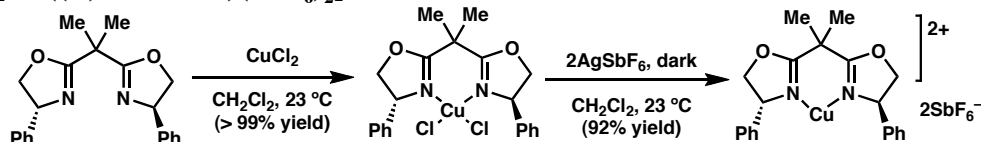
Prepared according to procedure used for hydroxyoxindole **S3**. Purified by flash chromatography (SiO_2 , 33% ethyl acetate in hexanes→50% ethyl acetate in hexanes) and recrystallized from ethyl acetate and hexanes. Isolated as a white solid. 29% yield. $R_f = 0.47$ (33% ethyl acetate in hexanes); ^1H NMR (300

MHz, CDCl₃) δ 7.82 (br s, 1H), 7.37 (dd, *J* = 7.2, 0.6 Hz, 1H), 7.27 (td, *J* = 7.5, 1.2 Hz, 1H), 7.09 (td, *J* = 7.5, 1.2 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 2.76 (s, 1H), 1.99-1.90 (comp. m, 2H), 1.31-1.16 (comp. m, 3H), 1.12-1.04 (comp. m, 1H), 0.82 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 181.0, 140.6, 130.7, 129.7, 124.4, 123.3, 110.5, 77.2, 38.4, 25.3, 22.9, 13.9; IR (neat film, NaCl) 3401, 3189, 2951, 2934, 2860, 1718, 1624, 1474, 1400, 1338, 1234, 1194, 1103, 1083, 1059, 1010, 961, 774, 748 cm⁻¹; HRMS (FAB+) *m/z* calc'd for C₁₂H₁₅NO₂ [M+H]⁺: 205.1103, found 205.1109.



To solution of 3-butyl-3-hydroxyindolin-2-one (188 mg, 0.916 mmol, 1.0 equiv) and pyridine (0.89 mL, 0.99 mmol, 12 equiv) in THF (8 mL) cooled to 0 °C in a round bottom flask equipped with a stirbar, a solution of POBr₃ (1.050g, 3.66 mg, 4.0 equiv) in THF (2 mL) was added dropwise. The reaction solution was stirred at 0 °C for 20 min. Water (20 mL) then added and the mixture was extracted with EtOAc (3 x 30 mL). The combined extracts were dried with magnesium sulfate prior to concentration. Purification by flash chromatography (SiO₂, 10% ethyl acetate in hexanes) afforded 3-bromo-3-butylindolin-2-one as a pale yellow viscous oil (31% yield). *R_f* = 0.48 (33% ethyl acetate in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 9.45 (br s, 1H), 7.38 (dd, *J* = 7.2, 0.6 Hz, 1H), 7.27 (td, *J* = 7.5, 1.2 Hz, 1H), 7.09 (td, *J* = 7.8, 1.2 Hz, 1H), 6.98 (d, *J* = 7.1 Hz, 1H), 2.47-2.32 (comp. m, 2H), 1.37-1.00 (comp. m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 177.3, 139.9, 130.6, 130.1, 124.8, 123.5, 111.0, 57.1, 39.3, 27.6, 22.6, 13.9; IR (neat film, NaCl) 3247, 2957, 2930, 2872, 1722, 1618, 1472, 13.81, 1331, 1223, 1193, 1139, 1118, 1102, 1018, 863, 837 cm⁻¹; HRMS (FAB+) *m/z* calcd. for C₁₂H₁₅BrNO [M+H]⁺: 268.0337, found 268.0328.

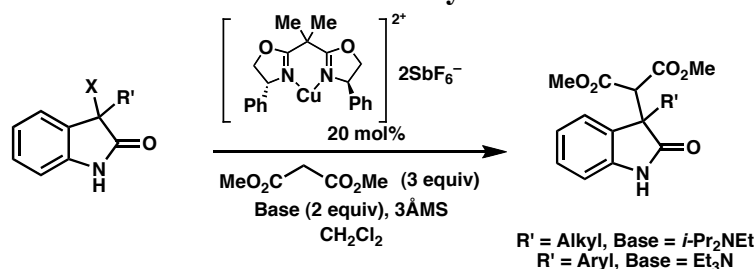
Synthesis of [Cu(*R*-Ph-BOX)(SbF₆)₂]



(*R*)-Ph-BOX (194.5 mg, 0.582 mmol, 1.0 equiv) was stirred along with copper(II) chloride (82.1 mg, 0.611 mmol, 1.05 equiv) in CH₂Cl₂ (8 mL) for 24 hours at ambient temperature in a glovebox. The reaction mixture was then filtered through celite, and the green solution was concentrated under reduced pressure to afford [Cu(*R*-Ph-BOX)Cl₂] as a light green powder (272.0 mg, >99% yield).

A 25 mL reaction flask equipped with a magnetic stir bar was charged with [Cu(*R*-PhBOX)Cl₂] (102.9 mg, 0.220 mmol, 1.0 equiv) and silver hexafluoroantimonate (150.2 mg, 2.0 equiv) in a glovebox. The flask was wrapped with aluminum foil to prevent exposure to light, and CH₂Cl₂ (11 mL) was added. The flask was capped and the reaction mixture stirred in the glovebox for 14 hours, then filtered through a pad of celite. The dark green filtrate was concentrated under reduced pressure to afford [Cu(*R*-PhBOX)(SbF₆)₂] as a dark green powder (174.0 mg, 92% yield).⁴

General Procedure for Enantioselective Malonate Alkylation



To 1 dram vial equipped with a stirbar, [Cu((*R*)-Ph-BOX)(SbF₆)₂] (17.4 mg, 0.02 mmol, 0.2 equiv) and 3 ÅMS (32.3 mg) were added in the glovebox. After the reaction vial was removed from the glove box, methylene chloride (0.25 mL of 0.5 mL added, 0.2 M solution) was added and allowed to stir for 15 minutes. Upon cooling to reaction temperature, malonate (34.3 μL, 0.3 mmol, 3.0 equiv) followed by halooxindole (0.1 mmol, 1.0 equiv) dissolved in remaining methylene chloride were added via syringe to give a dark blue-green solution.⁵ Base (0.2 mmol, 2.0 equiv) was then added to give a dark brown solution. Upon completion of reaction, saturated aqueous ammonium chloride solution (2 mL) added. Upon extraction with methylene chloride (3 x 2 mL), the collected organic layers were then dried with sodium sulfate and purified as stated.

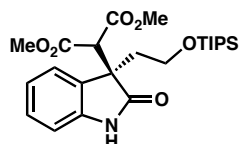


Table 2, Entry 1

Purified by flash chromatography (SiO₂, 5% acetonitrile in benzene). Isolated as a white solid. 77% yield. $R_f = 0.53$ (17% acetonitrile in benzene); ¹H NMR (300 MHz, CDCl₃) δ 7.54 (m, 2H), 7.21 (td, $J = 7.7, 1.0$ Hz, 1H), 7.01 (td, $J = 7.6, 1.0$ Hz, 1H), 6.84 (d, $J = 7.7$ Hz, 1H), 4.17 (s, 1H), 3.79 (s, 3H), 3.52 (s, 3H), 3.51 (m, 1H), 3.35 (m, 1H), 3.25 (m, 2H), 0.93 (s, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 179.3, 168.0, 167.1, 141.4, 129.4, 128.6, 125.4, 122.5, 109.5, 58.9, 57.1, 52.6, 52.5, 50.9, 38.5, 17.9, 11.9; IR (neat film, NaCl) 3251, 2941, 2863, 1747, 1721, 1687, 1471, 1321, 1197, 1114 cm⁻¹; HRMS (FAB+) m/z calc'd for C₂₄H₃₈NO₆Si [M+H]⁺: 464.2468, found 464.2468; [α]_D²⁵ -28.6 (*c* 0.43, CH₂Cl₂, 88% ee).

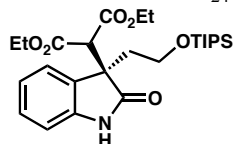
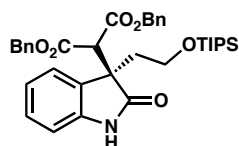
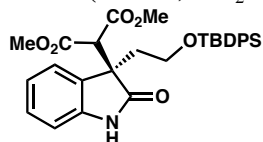


Table 2, Entry 2

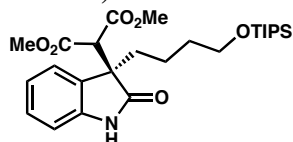
Purified by flash chromatography (SiO₂, 9% ethyl acetate in hexanes → 17% ethyl acetate in hexanes). Isolated as a white solid. 73% yield. $R_f = 0.24$ (33% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.80 (br s, 1H), 7.61 (d, $J = 7.5$ Hz, 1H), 7.20 (td, $J = 8.0, 1.0$ Hz, 1H), 7.00 (td, $J = 7.5, 1.0$ Hz, 1H), 6.83 (d, $J = 8.0$ Hz, 1H), 4.29-4.23 (m, 2H), 4.14 (s, 1H), 4.00-3.89 (m, 2H), 3.52 (ddd, $J = 12.0, 8.0, 7.0$ Hz, 1H), 3.36 (ddd, $J = 13.5, 8.5, 5.0$ Hz, 1H), 2.32-2.21 (m, 2H), 1.29 (t, $J = 7.0$ Hz, 3H), 0.99 (t, $J = 7.0$ Hz, 3H), 0.93 (s, 21H); ¹³C NMR (126 MHz, CDCl₃) δ 179.5, 167.8, 166.9, 141.6, 129.7, 128.7, 125.9, 122.7, 109.5, 61.82, 61.81, 59.1, 57.6, 51.0, 38.9, 18.1, 14.2, 13.8, 12.1; IR (neat film, NaCl) 3218, 2942, 2866, 1731, 1716, 1621, 1472, 1197 cm⁻¹; HRMS (FAB+) m/z calc'd for C₂₆H₄₂NO₆Si [M+H]⁺: 492.2781, found 492.2774; [α]_D²⁵ -16.4 (*c* 0.78, CH₂Cl₂, 84% ee).

**Table 2, Entry 3**

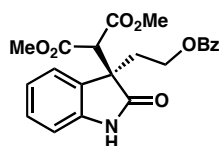
Purified by flash chromatography (SiO₂, 7% ethyl acetate in hexanes→17% ethyl acetate in hexanes). Isolated as a white solid. 78% yield. $R_f = 0.25$ (33% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.80 (br s, 1H), 7.52 (d, $J = 7.5$ Hz, 1H), 7.33-7.23 (comp. m, 8H), 7.16 (td, $J = 7.5$, 1.0 Hz, 1H), 7.07 (dd, $J = 8.0$, 1.5 Hz, 2H), 6.94 (td, $J = 7.5$, 0.5 Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 5.20 (ABq, $J = 17.0$ Hz, 2H), 4.91 (ABq, $J = 18.5$ Hz, 2H), 4.27 (s, 1H), 3.50 (dt, $J = 9.5$, 6.0 Hz, 1H), 3.50 (ddd, $J = 10.0$, 8.5, 5.0 Hz, 1H), 2.33-2.22 (m, 2H), 0.92 (s, 21H); ¹³C NMR (126 MHz, CDCl₃) δ 179.3, 167.5, 166.6, 141.5, 135.2, 135.1, 129.4, 128.8, 128.7, 128.6, 128.43, 128.39, 125.7, 122.7, 109.8, 67.7, 67.5, 59.1, 57.6, 51.1, 38.9, 18.1, 12.1; IR (neat film, NaCl) 3251, 2941, 2863, 1747, 1721, 1687, 1471, 1321, 1197, 1114 cm⁻¹; HRMS (FAB+) m/z calc'd for C₂₄H₃₈NO₆Si [M+H]⁺: 464.2468, found 464.2468; [α]_D²⁵ -17.7 (*c* 0.71, CH₂Cl₂, 88% ee).

**Table 2, Entry 4**

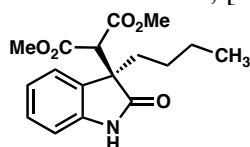
Purified by flash chromatography (SiO₂, 5% acetonitrile in benzene). Isolated as a white solid. 78% yield. $R_f = 0.48$ (17% acetonitrile in benzene); ¹H NMR (500 MHz, CDCl₃) δ 7.56 (br s, 1 H), 7.51 (dd, $J = 8.0$, 1.5 Hz, 2H), 7.42-7.39 (comp. m, 3H), 7.38-7.35 (comp. m, 2H), 7.33-7.28 (comp. m, 4H), 7.21 (td, $J = 7.5$, 1.5 Hz, 1H), 6.98 (td, $J = 7.5$, 1.0 Hz, 1H), 6.80 (d, $J = 7.5$ Hz, 1H), 4.13 (s, 1H), 3.73 (s, 3H), 3.51 (s, 3H), 3.46 (ddd, $J = 14.0$, 7.5, 6.5 Hz, 1H), 3.34 (ddd, $J = 12.0$, 7.5, 4.5 Hz, 1H), 2.38 (dt, $J = 13.5$, 8.0 Hz, 1H), 2.25 (ddd, $J = 13.5$, 6.5, 4.5 Hz, 1H), 0.94 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 179.1, 168.1, 167.1, 141.5, 135.6, 135.5, 133.5, 133.4, 129.7, 129.6, 129.1, 128.6, 127.74, 127.70, 125.6, 122.6, 109.6, 59.8, 57.5, 52.7, 52.6, 51.0, 38.2, 26.8, 19.1; IR (neat film, NaCl) 3369, 3071, 2953, 2930, 2857, 1736, 1717, 1620, 1472, 1429, 1325, 1237, 1198, 1156, 1112, 1088, 1022, 823, 740 cm⁻¹; HRMS (FAB+) m/z calc'd for C₃₁H₃₆NO₆Si [M+H]⁺: 546.2312, found 546.2320; [α]_D²⁵ -17.3 (*c* 0.94, CH₂Cl₂, 88% ee).

**Table 2, Entry 5**

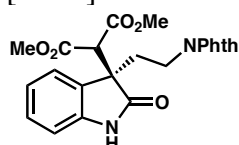
Purified by flash chromatography (SiO₂, 9% ethyl acetate in hexanes→17% ethyl acetate in hexanes). Isolated as a white solid. 47% yield. $R_f = 0.16$ (22% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.80 (br s, 1H), 7.53 (d, $J = 7.5$ Hz, 1H), 7.20 (td, $J = 7.5$, 1.0 Hz, 1H), 7.01 (td, $J = 7.5$, 1.0 Hz, 1H), 6.84 (d, $J = 7.5$ Hz, 1H), 4.15 (s, 1H), 3.79 (s, 3H), 3.56-3.46 (comp. m with a singlet at δ 3.51, 5H), 1.96-1.89 (comp. m, 2H), 1.46-1.31 (comp. m, 2H), 1.18-1.08 (comp. m, 1H), 1.02-0.88 (comp. m, 22H); ¹³C NMR (126 MHz, CDCl₃) δ 179.6, 168.2, 167.3, 141.5, 129.9, 128.5, 125.2, 122.8, 109.4, 63.0, 57.2, 52.9, 52.8, 52.7, 36.4, 33.0, 20.0, 18.1, 12.1; IR (neat film, NaCl) 3248, 2944, 2866, 1736, 1716, 1620, 1472, 1436, 1326, 1225, 1155, 1109, 1058, 995, 883, 752 cm⁻¹; HRMS (FAB+) m/z calc'd for C₂₆H₄₂NO₆Si [M+H]⁺: 492.2781, found 492.2775; [α]_D²⁵ -6.3 (*c* 0.58, CH₂Cl₂, 86% ee).

**Table 2, Entry 6**

Purified by flash chromatography (SiO₂, 9% acetonitrile in benzene). Isolated as a white solid. 51% yield. $R_f = 0.13$ (33% ethyl acetate in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.23 (br s, 1H), 7.85 (dd, $J = 8.1, 1.2$ Hz, 2H), 7.57 (d, $J = 7.5$ Hz, 1H), 7.51 (tt, $J = 7.5, 1.2$ Hz, 1H), 7.37 (t, $J = 7.5$ Hz, 2H), 7.19 (td, $J = 7.5, 1.2$ Hz, 1H), 7.01 (td, $J = 7.8, 1.2$ Hz, 1H), 6.84 (d, $J = 7.8$ Hz, 1H), 4.19 (s, 1H), 4.08 (comp. m, 2H), 3.78 (s, 3H), 3.51 (s, 3H), 2.53 (t, $J = 6.6$ Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 179.2, 167.8, 166.9, 166.2, 141.6, 133.0, 129.9, 129.7, 130.1, 128.8, 128.3, 125.5, 122.9, 110.1, 60.7, 57.3, 52.8, 52.7, 51.2, 34.6; IR (neat film, NaCl) 3307, 2955, 1723, 1620, 1473, 1452, 1436, 1318, 1274, 1199, 1158, 1117, 1026, 756, 714 cm⁻¹; HRMS (FAB+) m/z calc'd for C₂₂H₂₂NO₇ [M+H]⁺: 412.1396, found 412.1392; [α]_D²⁵ -52.5 (c 1.40, CH₂Cl₂, 83% ee).

**Table 2, Entry 7**

Purified by flash chromatography (SiO₂, 9% ethyl acetate in hexanes → 17% ethyl acetate in hexanes). Isolated as a pale yellow solid. 47% yield. $R_f = 0.22$ (33% ethyl acetate in hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.11 (br s, 1H), 7.54 (d, $J = 7.5$ Hz, 1H), 7.22 (td, $J = 7.8, 2.0$ Hz, 1H), 7.02 (td, $J = 7.5, 1.5$ Hz, 1H), 6.87 (d, $J = 7.8$ Hz, 1H), 4.15 (s, 1H), 3.79 (s, 3H), 3.50 (s, 3H), 1.93-1.87 (comp. m, 2H), 1.22-1.04 (comp. m, 3H), 0.81-0.72 (comp. m with a triplet at δ 0.75, $J = 7.5$ Hz, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 179.9, 168.2, 167.3, 141.6, 130.1, 128.5, 125.2, 122.7, 109.5, 57.3, 52.8, 52.7, 52.6, 36.2, 25.5, 22.8, 13.9; IR (neat film, NaCl) 3249, 2956, 2930, 2862, 1736, 1716, 1620, 1486, 1472, 1436, 1327, 1292, 1230, 1198, 1157, 1057, 1022, 755 cm⁻¹; HRMS (FAB+) m/z calc'd for C₁₇H₂₂NO₅ [M+H]⁺: 320.1498, found 320.1512; [α]_D²⁵ -10.6 (c 1.46, CH₂Cl₂, 84% ee).

**Table 2, Entry 8**

Purified by flash chromatography (SiO₂, 17% acetone in hexanes). Isolated as a white solid. 63% yield. $R_f = 0.22$ (33% acetone in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.07 (br s, 1H), 7.73-7.70 (comp. m, 2H), 7.66-7.63 (comp. m, 2H), 7.55 (d, $J = 7.5$ Hz, 1H), 7.07 (td, $J = 7.5, 1.0$ Hz, 1H), 6.88 (td, $J = 7.5, 1.0$ Hz, 1H), 6.84 (d, $J = 7.5$ Hz, 1H), 4.18 (s, 1H), 3.82 (s, 3H), 3.56 (t, $J = 7.5$ Hz, 2H), 3.50 (s, 3H), 2.52 (dt, $J = 13.5, 8.0$ Hz, 1H), 2.35 (pentet, $J = 7.0$ Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 178.5, 167.9, 167.8, 166.9, 141.4, 133.9, 132.1, 128.9, 128.8, 125.4, 123.2, 122.9, 110.0, 57.0, 52.9, 52.7, 51.3, 33.55, 33.49; IR (neat film, NaCl) 3261, 3034, 2935, 1755, 1724, 1698, 1473, 1398, 1347, 1272, 1153, 1060, 719 cm⁻¹; HRMS (FAB+) m/z calc'd for C₂₃H₂₁N₂O₇ [M+H]⁺: 437.1349, found 437.1342; [α]_D²⁵ -4.4 (c 0.56, MeOH, 94% ee).

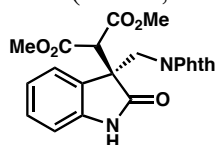
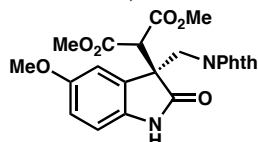
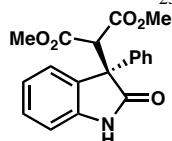


Table 2, Entry 9

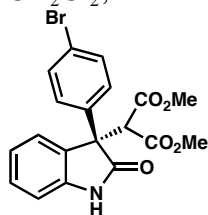
Purified by flash chromatography (SiO₂, 5% acetonitrile in benzene→25% acetonitrile in benzene). Isolated as a white solid. 42% yield. *R_f* = 0.48 (17% acetonitrile in benzene); ¹H NMR (500 MHz, CDCl₃) δ 7.79 (br s, 1H), 7.70-7.74 (m, 2H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.68-7.64 (m, 2H), 7.18 (td, *J* = 7.5, 1.5 Hz, 1H), 7.00 (td, *J* = 8.0, 1.0 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 4.62 (d, *J* = 14.5 Hz, 1H), 4.30 (s, 1H), 4.15 (d, *J* = 14.5 Hz, 1H), 3.90 (s, 3H), 3.50 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 177.2, 168.1, 168.0, 167.3, 141.2, 134.2, 131.8, 129.3, 127.8, 126.5, 123.6, 122.7, 109.9, 54.7, 52.95, 52.87, 52.4, 41.3; IR (neat film, NaCl) 3340, 2954, 2924, 2853, 1776, 1732, 1718, 1618, 1472, 1434, 1394, 1354, 1316, 1295, 1225, 1197, 1158, 1001, 905 cm⁻¹; HRMS (FAB+) *m/z* calc'd for C₂₂H₁₉N₂O₇ [M]⁺: 423.1192, found 423.1203; [α]_D²⁵ -3.3 (*c* 0.55, CH₂Cl₂, 81% ee).

**Table 2, Entry 10, Malonate Adduct 8**

Purified by flash chromatography (SiO₂, 33% ethyl acetate in hexanes→50% ethyl acetate in hexanes; then 9% acetonitrile in benzene→17% acetonitrile in benzene). Isolated as a white solid. 42% yield. *R_f* = 0.22 (17% acetonitrile in benzene); ¹H NMR (500 MHz, CDCl₃) δ 7.89-7.76 (m, 2H), 7.69-7.66 (m, 2H), 7.48 (br s, 1H), 7.41 (d, *J* = 2.0 Hz, 1H), 6.75-6.71 (comp. m, 2H), 4.62 (d, *J* = 14.5 Hz, 1H), 4.30 (s, 1H), 4.10 (d, *J* = 14.5 Hz, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 3.52 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 177.1, 168.1, 168.0, 167.2, 155.7, 134.6, 134.1, 131.8, 129.1, 123.6, 114.6, 113.2, 110.4, 55.9, 54.6, 53.0, 52.9, 52.8, 41.3; IR (neat film, NaCl) 3350, 3003, 2954, 2840, 1776, 1722, 1602, 1488, 1468, 1435, 1394, 1331, 1301, 1265, 1206, 1160, 1051, 1032, 1004, 909, 815, 720 cm⁻¹; HRMS (FAB+) *m/z* calc'd for C₂₃H₂₁N₂O₈ [M+H]⁺: 453.1298, found 453.1319; [α]_D²⁵ -2.3 (*c* 1.10, CHCl₃, 95% ee).

**Table 3, Entry 1; Malonate Adduct 12**

Purified by flash chromatography (SiO₂, 10% acetonitrile in toluene→15% acetonitrile in toluene). Isolated as a pale yellow solid. 76% yield. *R_f* = 0.22 (33% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.08 (bs, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.25-7.16 (comp. m, 5H), 7.06 (ddd, *J* = 7.6, 7.6, 0.9 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 4.85 (s, 1H), 3.50 (s, 3H), 3.32 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 178.7, 167.8, 167.3, 141.8, 137.3, 129.2, 128.7, 128.4, 128.0, 127.1, 122.8, 110.1, 58.5, 56.7, 52.7, 52.6; IR (neat film, NaCl) 3254, 2954, 1734, 1620, 1473, 1436, 1325, 1156, 1039, 912, 733 cm⁻¹; HRMS (FAB) *m/z* calc'd for C₁₉H₁₈NO₅ [M+H]⁺: 340.1185, found 340.1183; [α]_D²⁵ -66.6 (*c* 1.12, CH₂Cl₂, 76% ee).

**Table 3, Entry 2**

Purified by flash chromatography (SiO₂, 0% acetonitrile in toluene → 20% acetonitrile in toluene). Isolated as a 74% yield. Isolated as a pale yellow oil. 84% yield. *R_f* = 0.45 (20% acetonitrile in

toluene); ^1H NMR (500 MHz, CDCl_3) δ 7.97 (d, $J = 7.6$ Hz, 1H), 7.66 (s, 1H), 7.38 (app. d, $J = 8.5$ Hz, 2H), 7.33 (dd, $J = 8.8, 8.8$ Hz, 1H), 7.20 (app. d, $J = 6.8$ Hz, 2H), 7.15 (dd, $J = 7.8, 7.8$ Hz, 1H), 6.93 (d, $J = 7.6$ Hz), 4.85 (s, 1H), 3.61 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.0, 167.7, 167.2, 141.6, 136.5, 131.9, 129.6, 129.0, 128.4, 128.2, 123.2, 122.6, 110.2, 58.5, 56.3, 52.9, 52.8; IR (neat film, NaCl) 3307, 1736, 1619, 1472, 1435, 1323, 1158 cm^{-1} ; HRMS (EI^+) m/z calc'd for $\text{C}_{19}\text{H}_{16}\text{O}_5\text{NBr}$ $[\text{M}]^+$: 417.0212, found 417.0219; $[\alpha]_{\text{D}}^{25} +175.0$ (c 1.52, CH_2Cl_2 , 81% ee).

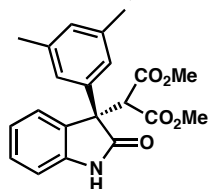


Table 3, Entry 3

Purified by flash chromatography (SiO_2 , 0% acetonitrile in toluene \rightarrow 10% acetonitrile in toluene). Isolated as a yellow oil. 69% yield. $R_f = 0.25$ (15% acetonitrile in toluene); ^1H NMR (500 MHz, CDCl_3) δ 8.24 (bs, 1H), 7.95 (d, $J = 7.1$ Hz, 1H), 7.29 (ddd, $J = 7.8, 7.8, 1.2$ Hz, 1H), 7.12 (ddd, $J = 7.6, 7.6, 1.0$ Hz, 1H), 6.91 (d, $J = 7.6$ Hz, 1H), 6.87-6.85 (comp. m, 3H), 4.90 (s, 1H), 3.60 (s, 3H), 3.38 (s, 3H), 2.21 (s, 6H); ^{13}C NMR (500 MHz, CDCl_3) δ 178.9, 167.9, 167.5, 141.8, 138.1, 137.3, 129.8, 129.1, 129.0, 128.3, 124.7, 122.8, 110.0, 58.4, 56.7, 52.6, 52.5, 21.6; IR (neat film, NaCl) 3248, 2956, 1737, 1718, 1618, 1473, 1324, 1199, 1155 cm^{-1} ; HRMS (FAB) m/z calc'd for $\text{C}_{21}\text{H}_{22}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 368.1498, found 368.1507; $[\alpha]_{\text{D}}^{25} +181.7$ (c 0.84, CH_2Cl_2 , 84% ee).

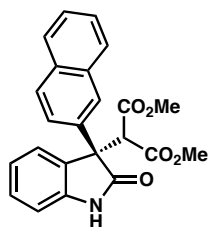


Table 3, Entry 4

Purified by flash chromatography (SiO_2 , 0% acetonitrile in toluene \rightarrow 20% acetonitrile in toluene). Isolated as a light yellow solid. 74% yield. $R_f = 0.65$ (50% ethyl acetate in hexanes); ^1H NMR (300 MHz, CDCl_3) δ 8.06 (d, $J = 7.8$ Hz, 1H), 8.01 (s, 1H), 7.77-7.76 (comp. m, 2H), 7.70-7.68 (comp. m, 1H), 7.23 (app. s, 1H), 7.58 (dd, $J = 8.5, 2.0$ Hz, 1H), 7.45-7.39 (comp. m, 2H), 7.33 (ddd, $J = 7.8, 7.8, 1.2$ Hz, 1H), 7.19 (ddd, $J = 7.8, 7.8, 1.0$ Hz, 1H), 6.94 (d, $J = 7.8$ Hz, 1H), 5.05 (s, 1H), 3.52 (s, 3H), 3.42 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.6, 167.9, 167.5, 141.9, 134.8, 133.3, 133.0, 129.4, 128.8, 128.6, 128.5, 127.7, 126.8, 126.6, 126.4, 124.6, 123.1, 110.2, 58.5, 56.9, 52.8, 52.7; IR (neat film, NaCl) 3256, 3059, 2953, 1732, 1619, 1597, 1472, 1435, 1323, 1294, 1198, 1157, 1037, 912, 732, 648 cm^{-1} ; HRMS (FAB $^+$) m/z calc'd for $\text{C}_{23}\text{H}_{20}\text{O}_5\text{N}$ $[\text{M}+\text{H}]^+$: 390.1341, found 390.1354; $[\alpha]_{\text{D}}^{25} +171.8$ (c 1.20, CH_2Cl_2 , 74% ee).

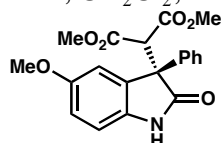
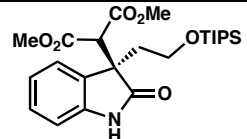
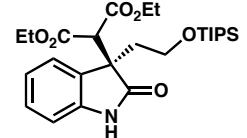
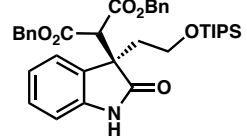
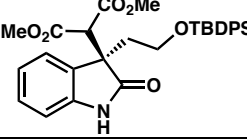
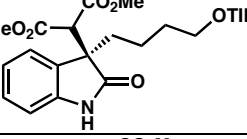
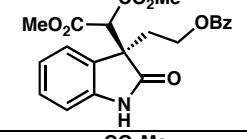
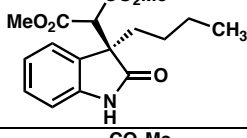
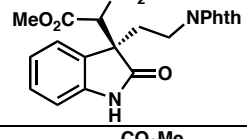
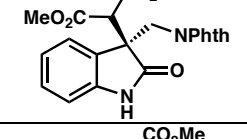
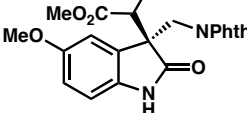


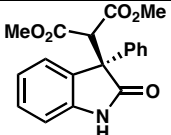
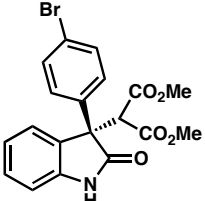
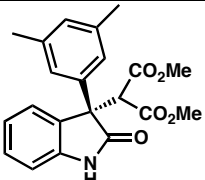
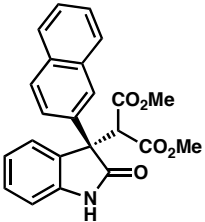
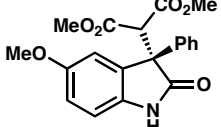
Table 3, Entry 5

Purified by flash chromatography (SiO_2 , 0% acetonitrile in toluene \rightarrow 10% acetonitrile in toluene). Isolated as an orange solid. 82% yield. $R_f = 0.23$ (15% acetonitrile in toluene); ^1H NMR (500 MHz, CDCl_3) δ 7.90 (s, 1H), 7.6 (app. s, 1H), 7.24-7.23 (app. d, $J = 6.6$ Hz, 2H), 7.20-6.74 (comp. m, 5H), 4.92 (s, 1H), 3.83 (s, 3H), 3.57 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.34, 167.82,

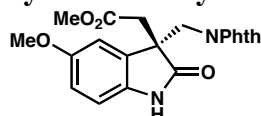
167.29, 155.95, 137.33, 135.00, 130.00, 128.70, 128.05, 127.05, 114.94, 114.36, 110.28, 58.39, 57.09, 55.97, 52.72, 52.59; IR (neat film, NaCl) 3271, 2953, 1733, 1600, 1487, 1437, 1301, 1266, 1207, 1156, 1058, 1033 cm^{-1} ; HRMS (FAB⁺) m/z calc'd for $\text{C}_{20}\text{H}_{19}\text{O}_6\text{N}[\text{M}]^+$: 369.1212, found 369.1204; $[\alpha]_{\text{D}}^{25}$ +168.1 (c 1.09, CH_2Cl_2 , 84% ee).

Table 1. Chiral HPLC Assay conditions

Malonate Adduct	Conditions	Time	ee
	5% IPA/Hexanes	28.9 min (major) 35.3 min (minor)	88%
	4% EtOH/Hexanes	16.4 min (major) 19.0 min (minor)	84%
	4% EtOH/Hexanes	24.4 min (major) 28.1 min (minor)	88%
	10% IPA/Hexanes	16.8 min (major) 24.4 min (minor)	88%
	5% IPA/Hexanes	17.7 min (major) 41.9 min (minor)	86%
	20% IPA/Hexanes	19.9 min (major) 33.1 min (minor)	83%
	10% IPA/Hexanes	19.5 min (major) 24.4 min (minor)	84%
	80% EtOH/Hexanes	17.2 min (major) 22.8 min (minor)	94%
	80% EtOH/Hexanes	18.6 min (major) 26.0 min (minor)	81%
	80% EtOH/Hexanes	21.7 min (major) 35.4 min (minor)	91%

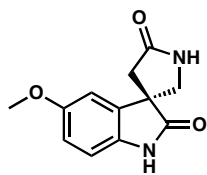
	20% IPA/Hexanes	7.6 min (major) 19.5 min (minor)	76%
	15% IPA/Hexanes	26.1 min (minor) 37.5 min (major)	-81%
	15% IPA/Hexanes	14.1 min (minor) 34.5 min (major)	-84%
	20 % IPA/Hexanes	29.2 min (minor) 41.2 min (major)	-74%
	15% IPA/Hexanes	21.4 min (minor) 40.5 min (major)	-84%

Synthesis of Pyrrolidinone-spirooxindole



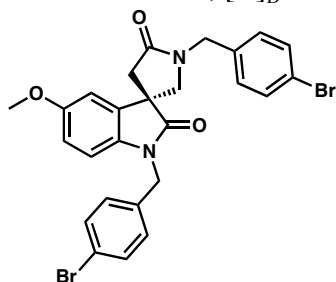
Phthalimidoester **9**

To a round bottom flask equipped with a stirbar, malonate adduct **8** (99% ee, 114.8 mg, 0.254 mmol, 1 equiv) and sodium chloride (29.7 mg, 0.508 mmol, 2 equiv) were dissolved in water (23 μ L, 1.27 mmol, 5 equiv) and DMSO (5 mL).⁶ The reaction flask was then heated to 150 °C for 5 hours. Upon cooling to ambient temperature, reaction mixture was then diluted with water (5 mL) and brine (5 mL) and then extracted with ethyl acetate (3 x 20 mL). Organic layers were collected and dried with magnesium sulfate. Purification by column chromatography (SiO₂, 9% acetonitrile in benzene \rightarrow 17% acetonitrile in benzene) afforded phthalimidoester **9** as a pale yellow solid (57.5 mg, 58% yield). R_f = 0.09 (17% acetonitrile in benzene); ¹H NMR (500 MHz, CDCl₃) δ 7.82 (dd, J = 5.0, 3.0 Hz, 2H), 7.71 (dd, J = 5.0, 3.0 Hz, 2H), 7.54 (br s, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.79 (d, J = 9.0 Hz, 1H), 6.74 (dd, J = 9.0, 2.5 Hz, 1H), 4.00 (ABq, J = 14.0 Hz, 2H), 3.74 (s, 3H), 3.51 (s, 3H), 3.15 (ABq, J = 17.0 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 178.4, 170.2, 168.2, 155.7, 134.5, 134.3, 131.9, 130.8, 123.7, 113.7, 110.9, 110.5, 55.9, 51.9, 50.4, 43.1, 38.6; IR (neat film, NaCl) 3306, 2997, 2952, 2838, 1776, 1719, 1604, 1490, 1468, 1437, 1395, 1363, 1302, 1207, 1140, 1027, 928, 908, 812 cm⁻¹; HRMS (FAB+) m/z calc'd for C₂₁H₁₉N₂O₆ [M+H]⁺: 395.1243, found 395.1243; [α]_D^{18.0} +26.1 (c 1.00, CH₂Cl₂).



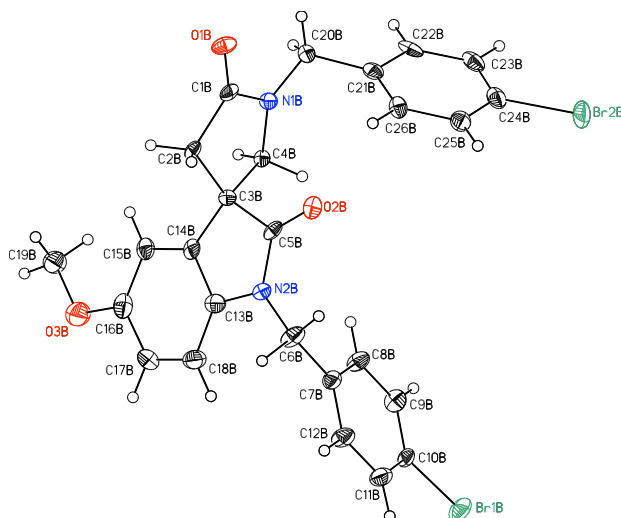
Spirocyclic Oxindole 10

To phthalimidoester **9** (12.5 mg, 0.0317 mmol, 1 equiv) in EtOH (3 mL), $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$ (16 μL , 0.317, 10 equiv) was added at 23 °C. The reaction flask was then heated to 95 °C for 13 hours. Upon cooling to ambient temperature, reaction mixture was filtered through a short plug of celite and concentrated. Purification by preparative TLC (SiO_2 , 9% MeOH in methylene chloride) afforded spirocyclic oxindole **10** as a white solid (6.5 mg, 88% yield). $R_f = 0.36$ (9% MeOH in methylene chloride); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.82 (br s, 1H), 6.95 (d, $J = 2.0$ Hz, 1H), 6.83 (d, $J = 7.5$ Hz, 1H), 6.80 (dd, $J = 7.5, 2.0$ Hz, 1H), 5.98 (br s, 1H), 3.87 (d, $J = 9.5$ Hz, 1H), 3.79 (s, 3H), 3.59 (dd, $J = 9.5, 0.5$ Hz, 1H), 2.98 (d, $J = 16.5$ Hz, 1H), 2.50 (d, $J = 17.0$ Hz, 1H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 179.0, 175.3, 156.7, 134.9, 132.9, 113.8, 110.7, 109.6, 56.1, 51.0, 50.4, 40.4; IR (neat film, NaCl) 3231, 2956, 2925, 2847, 1699, 1494, 1439, 1306, 1207, 1179, 1033 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 233.0926, found 233.0918; $[\alpha]_D^{23.0} +43.5$ (c 0.65, MeOH).



Bis(*p*-Br-benzyl)lactam 11

To NaH (3.4 mg, 60 %, 0.840 mmol, 3 equiv) in THF (1 mL) at 0 °C, a solution of spirocyclic oxindole **10** (6.5 mg, 0.0280 mmol, 1 equiv) in THF (2.0 mL) was added dropwise via syringe at 23 °C. The flask was rinsed with THF (1 mL) and the solutions were also added dropwise via syringe at 0 °C. The reaction was allowed to stir for 30 minutes at 23 °C before addition of 4-bromobenzyl bromide (21 mg, 0.840 mmol, 3 equiv). After stirring for 14 hours at 23 °C, the reaction was quenched with brine (3 mL) and extracted with CH_2Cl_2 (3 x 5 mL). Organic layers were collected and dried with magnesium sulfate. Purification by column chromatography (SiO_2 , 25% ethyl acetate in CH_2Cl_2) afforded bis(*p*-Br-benzyl)lactam **11** as a white solid (10.1 mg, 67% yield). M.p. 214.5-216 °C from CH_2Cl_2 /hexanes; $R_f = 0.66$ (50% ethyl acetate in CH_2Cl_2); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.48 (dt, $J = 8.5, 2.5$ Hz, 2H), 7.43 (dt, $J = 9.0, 2.5$ Hz, 2H), 7.22 (dt, $J = 8.5, 2.5$ Hz, 2H), 7.11 (dt, $J = 8.5, 2.5$ Hz, 2H), 6.71-6.68 (comp. m, 2H), 6.60 (d, $J = 9.5$ Hz, 1H), 4.80 (ABq, $J = 16.0$ Hz, 2H), 4.66 (d, $J = 14.5$ Hz, 1H), 4.41 (d, $J = 15.0$ Hz, 1H), 3.74 (d, $J = 9.5$ Hz, 1H), 3.69 (s, 3 H), 3.31 (d, $J = 9.5$ Hz, 1H), 3.12 (d, $J = 17.0$ Hz, 1H), 2.63 (d, $J = 17.0$ Hz, 1H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 177.4, 171.7, 156.9, 135.0, 134.9, 134.6, 134.4, 132.2, 130.2, 129.1, 122.1, 122.0, 113.5, 110.0, 109.4, 105.1, 55.9, 55.3, 47.1, 46.5, 43.7, 41.7; IR (neat film, NaCl) 2930, 1700, 1601, 1488, 1435, 1406, 1366, 1294, 1200, 1177, 1071, 1034, 1012, 798 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{26}\text{H}_{23}\text{N}_2\text{O}_3\text{Br}^{81}\text{Br}$ $[\text{M}+\text{H}]^+$: 571.0055, found 571.0048; $[\alpha]_D^{25.0} -46.7$ (c 0.39, CH_2Cl_2).



Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 730732.

Table 1. Crystal data and structure refinement for XQH02 (CCDC 730732).

Empirical formula	$C_{26}H_{22}N_2O_3Br_2$
Formula weight	570.28
Crystallization Solvent	Dichloromethane/hexanes
Crystal Habit	Blade
Crystal size	0.31 x 0.15 x 0.04 mm ³
Crystal color	Colorless



Data Collection

Type of diffractometer	Bruker KAPPA APEX II
Wavelength	0.71073 Å MoK α
Data Collection Temperature	100(2) K
θ range for 9806 reflections used in lattice determination	2.31 to 28.58°
Unit cell dimensions	a = 17.9356(10) Å b = 5.7243(3) Å c = 23.3899(14) Å $\beta = 101.021(3)^\circ$
Volume	2357.1(2) Å ³
Z	4
Crystal system	Monoclinic
Space group	P2 ₁
Density (calculated)	1.607 Mg/m ³
F(000)	1144
Data collection program	Bruker APEX2 v2.1-0
θ range for data collection	1.59 to 28.84°

Completeness to $\theta = 28.84^\circ$	90.2 %
Index ranges	$-23 \leq h \leq 23, -7 \leq k \leq 7, -31 \leq l \leq 29$
Data collection scan type	ω scans; 9 settings
Data reduction program	Bruker SAINT-Plus v7.34A
Reflections collected	34011
Independent reflections	10814 [$R_{\text{int}} = 0.0407$]
Absorption coefficient	3.470 mm^{-1}
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7458 and 0.5386
Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	10814 / 1 / 597
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	2.111
Final R indices [$I > 2\sigma(I)$, 9564 reflections]	$R1 = 0.0496, wR2 = 0.0966$
R indices (all data)	$R1 = 0.0583, wR2 = 0.0978$
Type of weighting scheme used	Sigma
Weighting scheme used	$w = 1/\sigma^2(F_o^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure determination	Anomalous differences
Absolute structure parameter	0.009(8)
Largest diff. peak and hole	2.847 and $-0.755 \text{ e.}\text{\AA}^{-3}$

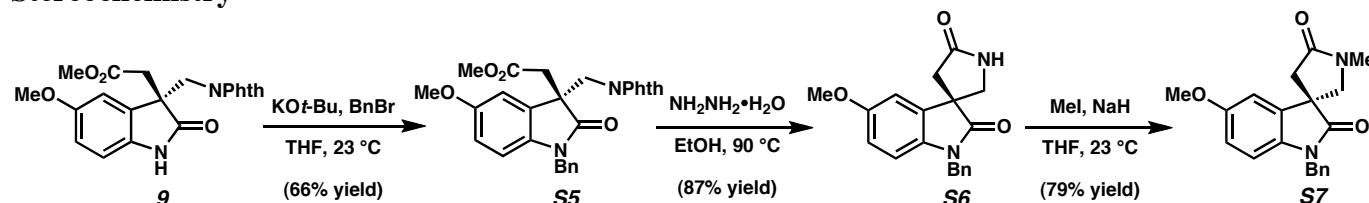
Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (wR) and goodness of fit (S) are based on F^2 , conventional R-factors (R) are based on F , with F set to zero for negative F^2 . The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F , and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Synthesis of Other Pyrrolidinone-spirooxindole: Further Confirmation of Absolute Stereochemistry

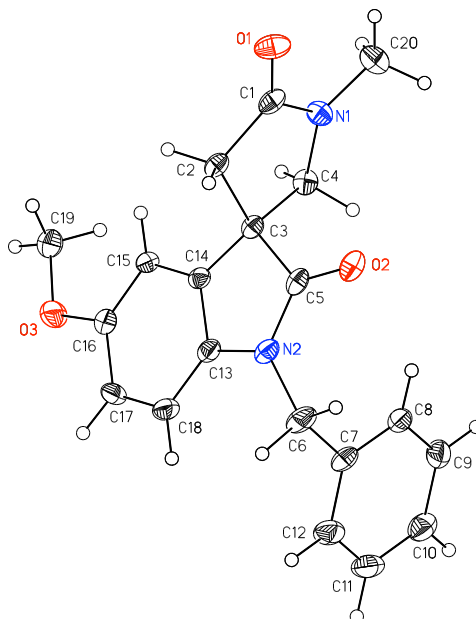


To pthalimidoester **9**⁷ (56.1 mg, 0.142 mmol, 1 equiv) in THF (2 mL), a solution of $\text{KO}^t\text{-Bu}$ (19.2 mg, 0.171 mmol, 1.2 equiv) in THF (1 mL) was added dropwise via syringe at 23 °C. The reaction was allowed to stir for 20 minutes before addition of BnBr (51 μL , 0.426 mmol, 3 equiv) via syringe. After stirring for 3 hours at 23 °C, the reaction was quenched with saturated brine solution (5 mL) and extracted with ethyl acetate (3 x 15 mL). Organic layers were collected and dried with magnesium sulfate. Purification by column chromatography (SiO_2 , 33% ethyl acetate in hexanes \rightarrow 50% ethyl acetate in hexanes) afforded **S5** as a pale yellow solid (45.5 mg, 66% yield). $R_f = 0.50$ (50% ethyl acetate in hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.86-7.82 (m, 2H), 7.73-7.69 (m, 2H), 7.43 (d, $J = 7.5$ Hz, 2H), 7.32 (t, $J = 7.5$ Hz, 2H), 7.25 (tt, $J = 7.5, 2.0$ Hz, 1H), 6.86 (d, $J = 2.0$ Hz, 1H), 6.65 (dd, $J = 8.5, 2.0$ Hz, 1H), 6.57 (d, $J = 8.5$ Hz, 1H), 4.93 (ABq, $J = 16.0$ Hz, 2H), 4.02 (ABq, $J = 14.0$ Hz, 2H), 3.70 (s, 3H), 3.45 (s, 3H), 3.20 (ABq, $J = 17.0$ Hz, 2H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 176.8, 170.1, 168.2, 155.8, 136.1, 135.8, 134.3, 131.9, 130.5, 128.8, 127.63, 127.59, 123.7, 113.3, 110.8, 110.0, 55.9, 51.9, 50.0, 44.5, 43.3, 38.7; IR (neat film, NaCl) 2951, 2930, 2858, 1776, 1717, 1602, 1496, 1456, 1435, 1394, 1333, 1298, 1206, 1178, 1144, 1077, 1029 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{28}\text{H}_{25}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$: 485.1713, found 485.1707; $[\alpha]_D^{19.0} -17.7$ (c 1.00, CH_2Cl_2).

To benzylated **S5** (45.5 mg, 0.0939 mmol, 1 equiv) in EtOH (5 mL), $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$ (46 μL , 0.939, 10 equiv) was added at 23 °C. The reaction flask was then heated to 95 °C for 18 hours. Upon cooling to ambient temperature, reaction mixture was filtered through a short plug of celite and concentrated. Purification by column chromatography (SiO_2 , 2% MeOH in methylene chloride \rightarrow 3% MeOH in methylene chloride) afforded spirocyclic lactam **S6** as a white solid (26.3 mg, 87% yield). $R_f = 0.59$ (9% MeOH in methylene chloride); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.34-7.31 (comp. m, 2 H), 7.29-7.25 (comp. m, 3 H), 6.99 (d, $J = 2.5$ Hz, 1 H), 6.72 (dd, $J = 7.5, 2.5$ Hz, 1 H), 6.66 (d, $J = 8.0$ Hz, 1 H), 6.35 (br s, 1 H), 4.90 (s, 2 H), 3.92 (d, $J = 9.0$ Hz, 1 H), 3.76 (s, 3 H), 3.50 (d, $J = 9.5$ Hz, 1 H), 3.03 (d, $J = 16.5$ Hz, 1 H), 2.51 (d, $J = 16.5$ Hz, 1 H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 177.2, 175.6, 156.8, 135.6, 135.2, 134.5, 129.0, 128.0, 127.4, 113.4, 110.1, 109.6, 56.0, 51.2, 50.0, 44.3, 40.6; IR (neat film, NaCl) 3271, 2925, 1705, 1602, 1496, 1455, 1436, 1368, 1298, 1200, 1178, 1032 cm^{-1} ; HRMS (ESI-APCI) m/z calc'd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 323.1390, found 323.1393; $[\alpha]_D^{23.0} +64.7$ (c 0.50, CH_2Cl_2).

To NaH (9.9 mg, 60 %, 0.248 mmol, 3 equiv) in THF (0.5 mL) at 23 °C, a solution of spirocyclic lactam **S6** (24.7 mg, 0.0825 mmol, 1 equiv) in THF (2.0 mL) was added dropwise via syringe at 23 °C. The flask was rinsed with THF (2 x 1 mL) and the solutions were also added dropwise via syringe at 23 °C. The reaction was allowed to stir for 30 minutes before addition of MeI (16 μL , 0.248 mmol, 3 equiv) via syringe. After stirring for 14 hours at 23 °C, the reaction was quenched with water (30 μL) and concentrated under reduced pressure. Purification by column chromatography (SiO_2 , 55% ethyl acetate in CH_2Cl_2) afforded **S7** as a white solid (19.6, 79% yield). M.p. 146.0-147.5 °C; $R_f = 0.18$ (33% ethyl acetate in CH_2Cl_2); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.32 (td, $J = 7.5, 1.5$ Hz, 2H), 7.28-7.24 (comp. m, 3H), 6.87 (d, $J = 3.0$ Hz, 1H), 6.71 (dd, $J = 7.5, 3.0$ Hz, 1H), 6.65 ($J = 7.5$ Hz, 1H), 4.89 (ABq, $J = 16.0$

Hz, 2H), 3.88 (d, $J = 9.5$ Hz, 1H), 3.74 (s, 3H), 3.45 (d, $J = 9.5$ Hz, 1H), 3.07 (dd, $J = 17.0, 0.5$ Hz, 1H), 2.99 (s, 3H), 2.58 (d, $J = 17.0$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 177.7, 171.9, 156.8, 135.6, 135.3, 134.9, 129.0, 127.9, 127.4, 113.1, 110.1, 109.5, 58.1, 56.0, 47.2, 44.3, 41.6, 29.0; IR (neat film, NaCl) 3033, 2929, 2879, 2837, 1704, 1602, 1496, 1456, 1436, 1368, 1348, 1298, 1200, 1178, 1033, 977 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 337.1552, found 337.1567; $[\alpha]_{\text{D}}^{22.0} +37.3$ (c 1.00, CH_2Cl_2).



Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 725334.

Table 1. Crystal data and structure refinement for XQH01 (CCDC 725334).

Empirical formula	$\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_3$
Formula weight	336.38
Crystallization Solvent	Dichloromethane/ethylacetate/hexanes
Crystal Habit	Blade
Crystal size	0.33 x 0.14 x 0.07 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker SMART 1000
Wavelength	1.54178 Å $\text{CuK}\alpha$
Data Collection Temperature	100(2) K
θ range for 11578 reflections used in lattice determination	3.58 to 69.41°
Unit cell dimensions	a = 5.50060(10) Å b = 15.6733(3) Å c = 19.9921(3) Å
Volume	1723.57(5) Å ³

Z	4
Crystal system	Orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
Density (calculated)	1.296 Mg/m ³
F(000)	712
Data collection program	Bruker SMART v5.630
θ range for data collection	3.58 to 69.47°
Completeness to $\theta = 69.47^\circ$	98.8 %
Index ranges	-5 \leq h \leq 6, -19 \leq k \leq 18, -23 \leq l \leq 24
Data collection scan type	ω scans at 16 ϕ settings
Data reduction program	Bruker SAINT v6.45A
Reflections collected	23652
Independent reflections	3194 [R _{int} = 0.0979]
Absorption coefficient	0.712 mm ⁻¹
Absorption correction	None
Max. and min. transmission	0.9518 and 0.7989
Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F ²
Data / restraints / parameters	3194 / 0 / 229
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F ²	1.599
Final R indices [I > 2 σ (I), 2906 reflections]	R1 = 0.0349, wR2 = 0.0684
R indices (all data)	R1 = 0.0394, wR2 = 0.0697
Type of weighting scheme used	Sigma
Weighting scheme used	w=1/ σ^2 (Fo ²)
Max shift/error	0.000
Average shift/error	0.000
Absolute structure determination	Anomalous differences
Absolute structure parameter	-0.1(2)
Largest diff. peak and hole	0.148 and -0.215 e. \AA^{-3}

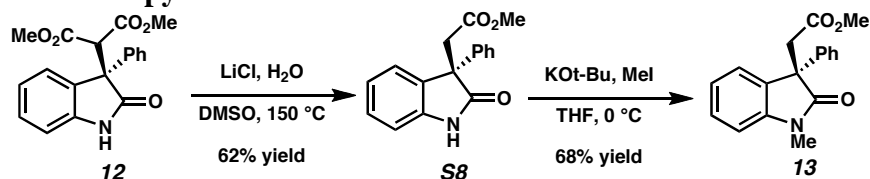
Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (wR) and goodness of fit (S) are based on F^2 , conventional R-factors (R) are based on F , with F set to zero for negative F^2 . The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F , and R-factors based on ALL data will be even larger.

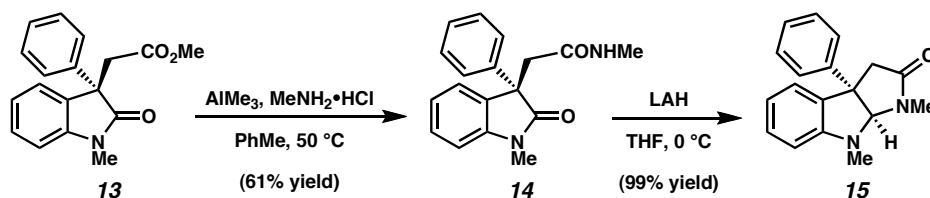
All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Synthesis of Fused Indolinopyrrolidinone



To a round bottom flask equipped with a stirbar, malonate adduct **12** (50.5 mg, 0.137 mmol, 1 equiv) and lithium chloride (115.7 mg, 0.273 mmol, 2 equiv) were dissolved in water (12.3 μ L, 0.685 mmol, 5 equiv) and DMSO (2 mL). The reaction flask was then heated at 150 $^{\circ}$ C for 12 hours. Upon cooling to ambient temperature, reaction mixture was then diluted with water (10 mL) and then extracted with ethyl acetate (5 x 5 mL). Organic layers were collected and dried with magnesium sulfate. Purification by flash chromatography (SiO_2 , 50 % ethyl acetate in hexanes) afforded **8** as a colorless oil (62% yield). $R_f = 0.41$ (50% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 8.87 (br s, 1H), 7.31-7.21 (comp. m, 7H), 7.04 (ddd, $J = 7.6, 7.6, 1.0$ Hz, 1H), 6.92 (dd, $J = 7.8, .5$ Hz, 1H), 3.54 (d, $J = 16.1$ Hz, 1H), 3.44 (s, 3H), 3.26 (d, $J = 16.1$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 180.2, 170.3, 141.8, 139.1, 131.8, 128.9, 128.8, 127.8, 126.7, 124.9, 122.6, 110.3, 53.9, 51.9, 41.7; IR (neat film, NaCl) 3248, 1721, 1619, 1472, 1203 cm^{-1} ; HRMS (FAB $^+$) m/z calc'd for $\text{C}_{17}\text{H}_{16}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 282.1130, found 282.1138; $[\alpha]_D^{27.4} -90.6$ (c 1.05, CHCl_3 , from 76% ee of malonate adduct **12**).

To unmethylated methyl ester **8** (14.3 mg, 0.051 mmol, 1 equiv) in THF (5mL), KO t -Bu from a freshly prepared stock solution in THF (6.8 mg, 0.061 mmol, 1.2 equiv) was added dropwise via syringe at 0 $^{\circ}$ C. The reaction was allowed to stir for 15 minutes before addition of MeI (9.5 μ L, 0.153 mmol, 3 equiv) via syringe. After stirring for one hour at 0 $^{\circ}$ C, the reaction was quenched with saturated brine solution (2 mL) and extracted with ethyl acetate (3 x 5 mL). Organic layers were collected and dried with magnesium sulfate. Purification by column chromatography (SiO_2 , 20 % ethyl acetate in hexanes) afforded methyl ester **13** as a light yellow oil (68% yield. 56% yield over two steps). $R_f = 0.57$ (50% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.37-7.24 (comp. m, 7H), 7.11 (ddd, $J = 7.6, 7.6, 1.0$ Hz, 1H), 6.92 (d, $J = 7.8$ Hz, 1H), 3.55 (d, $J = 16.4$ Hz, 1H), 3.45 (s, 3H), 3.27 (d, $J = 16.4$ Hz, 1H), 3.25 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 178.2, 170.3, 144.8, 139.2, 131.2, 128.8, 127.8, 126.8, 124.6, 122.6, 108.6, 53.4, 51.8, 42.0, 26.8; IR (neat film, NaCl) 3065, 2951, 1744, 1716, 1612, 1494, 1470, 1349, 1200 cm^{-1} ; HRMS (FAB $^+$) m/z calc'd for $\text{C}_{18}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 296.128730, found 296.1282; $[\alpha]_D^{27.6} -81.8$ (c 0.64, CHCl_3).



A freshly prepared stock solution of trimethylaluminum amine complex was prepared by adding trimethylaluminum (0.5 mL, 2M in toluene) to methyl amine hydrochloride (67.5 mg, 1 mmol) in toluene (4.5 mL) at 0 °C and allowed to warm to ambient temperature. After the methane evolution had ceased (about 1 hour), the aluminum amine complex solution (0.9 mL, 0.18 mmol, 3 equiv) was then added to methyl ester **13** (18 mg, 0.061 mmol, 1 equiv) in toluene (2 mL) at ambient temperature and immediately heated to 50 °C. Reaction was maintained at 50 °C for five days, where additional freshly prepared trimethylaluminum amine complex (0.9 mL, 0.18 mmol, 3 equiv) was added after initial 72 hours. Reaction was then cooled to room temperature and quenched with aqueous solution of saturated Rochelle's salt (5 mL) and extracted with ethyl acetate (3 x 10 mL). Organic layers were collected and dried with magnesium sulfate. Purification by flash chromatography (SiO₂, 10% toluene in acetonitrile) afforded amide **14** isolated as a white solid (71% yield). $R_f = 0.62$ (10% toluene in acetonitrile); ¹H NMR (500 MHz, CDCl₃) δ 7.36-7.24 (comp. m, 7H), 7.10 (ddd, $J = 7.3, 7.3, 1.0$ Hz, 1H), 6.90 (d, $J = 7.6$ Hz, 1H), 6.17 (br s, 1H), 3.38 (d, $J = 15.4$ Hz, 1H), 3.28 (s, 3H), 3.03 (d, $J = 15.4$ Hz, 1H), 2.59 (d, $J = 4.9$, 3H), ¹³C NMR (126 MHz, CDCl₃) δ 179.0, 169.3, 143.6, 139.4, 132.0, 128.9, 128.7, 127.7, 126.6, 124.6, 123.0, 108.7, 54.3, 44.2, 26.8, 26.4; IR (neat film, NaCl) 3326, 2933, 1711, 1653, 1615, 1495, 1470, 1375, 1349 cm⁻¹; HRMS (FAB⁺) m/z calc'd for C₁₈H₁₉O₂N₂ [M+H]⁺: 295.1447, found 295.1436; $[\alpha]_D^{25.0} +11.7$ (c 0.25, CHCl₃).

To methyl amide **14** (5.0 mg, 0.017 mmol, 1 equiv) in THF at 0°C, lithium aluminum hydride (2.0 M in hexanes, 12 equiv) was added dropwise via syringe. Reaction stirred for 1 hour and then quenched with saturated brine solution. Following extraction with ethyl acetate (3 x 10 mL), organic layers were collected and dried with magnesium sulfate. Purification by flash chromatography (SiO₂, 50% ethyl acetate in hexanes) afforded fused tricycle **15** as a white solid (92% yield). $R_f = 0.24$ (50% ethyl acetate in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.30 (comp. m, 2H), 7.26-7.18 (comp. m, 4H), 7.05 (d, $J = 7.3$ Hz, 1H), 6.79 (ddd, $J = 7.6, 7.6, 1.0$ Hz, 1H), 6.55 (d, $J = 7.8$ Hz, 1H), 4.96 (s, 1H), 3.26 (d, $J = 17.3$ Hz, 1H), 3.11 (d, $J = 17.3$ Hz, 1H), 3.10 (s, 3H), 2.98 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 173.0, 149.6, 144.5, 134.0, 129.3, 129.0, 127.3, 126.2, 125.0, 119.2, 108.1, 93.2, 53.9, 44.5, 35.4, 28.8; IR (neat film, NaCl) 3054, 2925, 1692, 1606, 1494 cm⁻¹; HRMS (FAB⁺) m/z calc'd for C₁₈H₁₉ON₂ [M+H]⁺: 279.1497, found 279.1509; $[\alpha]_D^{25.0} +52.0$ (c 0.20, CHCl₃).

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- 5 For compounds in Table 2, Entries 8–10, the bromooxindole was added in one portion as a solid due to low solubility in CH₂Cl₂.
- 6 Malonate adduct **8** was recrystallized to 99% ee from CH₂Cl₂–hexanes (3.5:1).
- 7 Malonate adduct **8** was recrystallized to 97% ee from CH₂Cl₂–hexanes (3.5:1).

