Supplemental Materials for:

Catalytic C-H Bond Functionalization with Palladium(II): Aerobic Oxidative Annulations of Indoles

Eric M. Ferreira and Brian M. Stoltz*

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

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Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized via UV, anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical GC was carried out using a DB-1701 column (30.0 m x 0.25 mm) from Agilent Technologies. ^{1}H spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C spectra were recorded on a Varian Mercury 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. Unless otherwise noted, compounds that are mixtures of *E* and *Z* olefin isomers are reported as the mixture as seen by ^{1}H NMR. 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 obtained from the California Institute of Technology Mass Spectral Facility. $Pd(OAc)_2$ was purchased from Strem Chemicals, Inc., Newburyport, MA. Titanium(III) chloride solution in 3% HCl was purchased from Alfa Aesar, Ward Hill, MA. All other chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

Additional References:

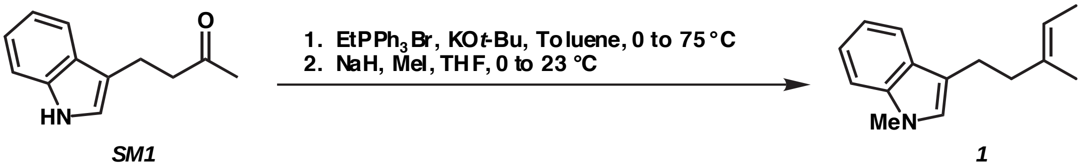
pK_a references (footnote 8):

(a) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1965; pp 141-183. (b) Rogne, O. *J. Chem. Soc., Perkin Trans. 2* **1972**, 489-492. (c) Ramsey, B. G.; Walker, F. A. *J. Am. Chem. Soc.* **1974**, *96*, 3314-3316.

Oxidation and oligomerization of indoles (footnote 13):

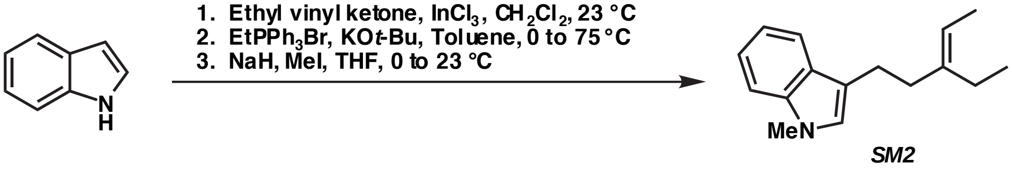
(a) Szabo-Pusztay, K.; Szabo, L. *Synthesis* **1979**, 276-277. (b) Dave, V.; Warnhoff, E. W. *Can. J. Chem.* **1971**, *49*, 1911-1920. (c) Hino, T.; Nakagawa, M. *Heterocycles* **1977**, *8*, 743-782. (d) Kunapuli, S. P.; Khan, N. U.; Divakar, N. G.; Vaidyanathan, C. S. *J. Indian. Inst. Sci.* **1981**, *63*, 167-202. (e) Trost, B. M.; Fortunak, J. M. D. *Organometallics* **1982**, *1*, 7-13.

Synthesis of Indole Substrates:



Indole 1. To a suspension of potassium *tert*-butoxide (7.50 g, 66.8 mmol) in toluene (267 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (24.8 g, 66.8 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, indolyl ketone **SM1**[1] (5.00 g, 26.7 mmol) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (250 mL, 1:1), and extracted with EtOAc (2 x 250 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin (4.31 g, 81% yield, $R_F = 0.67$ in 4:1 hexanes/EtOAc) as a clear oil.

To a solution of the olefin (4.31 g, 21.6 mmol) in THF (86.4 mL) at 0 °C was added NaH (1.73 g, 60% dispersion in mineral oil, 43.2 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (2.02 mL, 32.4 mmol), and allowed to warm to 23 °C. After 30 min, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (100 mL), and extracted with ether (2 x 250 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **1** (3.67 g, 80% yield, $R_F = 0.48$ in 9:1 hexanes/EtOAc, 59:41 mixture of olefin isomers) as a clear oil. **Indole 1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.1 Hz, 1H), 7.33 (app.t, *J* = 7.7 Hz, 1H), 7.33 (app.t, *J* = 7.7 Hz, 1H), 7.31-7.25 (m, 1H), 7.31-7.25 (m, 1H), 7.20-7.13 (comp m, 1H), 7.20-7.13 (comp m, 1H), 6.90 (s, 1H), 6.88 (s, 1H), 5.37 (app.q, *J* = 6.6 Hz, 1H), 5.33 (app.q, *J* = 6.6 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.90 (t, *J* = 8.8 Hz, 2H), 2.88 (t, *J* = 8.5 Hz, 2H), 2.52-2.42 (comp m, 2H), 2.52-2.42 (comp m, 2H), 1.84 (s, 3H), 1.77 (s, 3H), 1.67 (d, *J* = 6.6 Hz, 3H), 1.63 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 136.3, 136.2, 128.1, 126.1, 121.6, 119.5, 119.2, 118.7, 115.6, 109.3, 40.7, 32.8, 32.7, 24.2, 23.6, 16.0, 13.6, 13.5; IR (film) 2916, 1473, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{19}N]^+$: 213.1517, found 213.1514.



Indole SM2. Indium-catalyzed conjugate additions of indoles were done according to the procedure of Yadav et al.[1] To a solution of indole (1.61 g, 13.7 mmol) in CH_2Cl_2 (27.4 mL) at 23 °C was added ethyl vinyl ketone (1.36 mL, 13.7 mmol) and $InCl_3$ (303 mg, 1.37 mmol). The reaction mixture was stirred at 23 °C for 4 h, quenched with water (50 mL), and extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The resulting solid was purified by flash chromatography (2:1 to 4:1 CH_2Cl_2/hexanes eluent) to provide the ketone (2.25 g, 82% yield, $R_F = 0.38$ in CH_2Cl_2) as a white solid.

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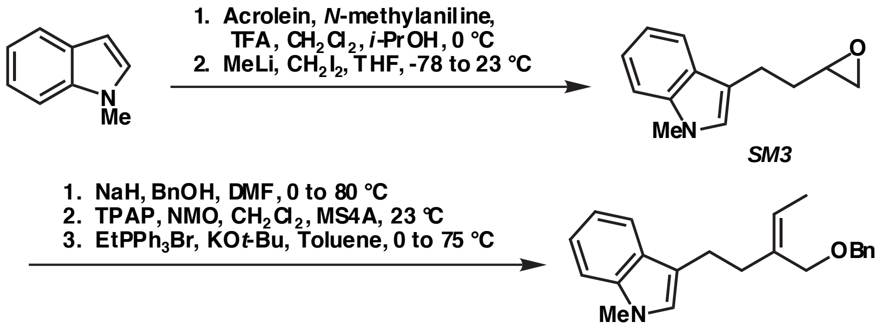
[1] Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165-2169.

To a suspension of potassium *tert*-butoxide (1.39 g, 12.4 mmol) in toluene (49.7 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (4.60 g, 12.4 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the ketone (1.00 g, 4.97 mmol) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (50 mL, 1:1), and extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin (990 mg, 93% yield, $R_F = 0.32$ in 9:1 hexanes/EtOAc) as a clear oil.

To a solution of the olefin (990 mg, 4.64 mmol) in THF (18.6 mL) at 0 °C was added NaH (297 mg, 60% dispersion in mineral oil, 7.42 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (375 μl, 6.03 mmol), and allowed to warm to 23 °C. After 30 min, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (50 mL), and extracted with ether (2 x 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **SM2** (830 mg, 79% yield, $R_F = 0.69$ in 4:1 hexanes/EtOAc, 56:44 mixture of olefin isomers) as a clear oil. **Indole SM2**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.31 (app.t, *J* = 8.2 Hz, 1H), 7.31 (app.t, *J* = 8.2 Hz, 1H), 7.25 (m, 1H), 7.25 (m, 1H), 7.17-7.11 (comp m, 1H), 7.17-7.11 (comp m, 1H), 6.89 (s, 1H), 6.87 (s, 1H), 5.33 (app.q, *J* = 6.6 Hz, 1H), 5.31 (app.q, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.90-2.80 (comp m, 2H), 2.90-2.80 (comp m, 2H), 2.50-2.40 (comp m, 2H), 2.50-2.40 (comp m, 2H), 2.22-2.11 (comp m, 2H), 2.22-2.11 (comp m, 2H), 1.66 (app.d, *J* = 6.6 Hz, 3H), 1.65 (app.d, *J* = 6.6 Hz, 3H), 1.09 (app.t, *J* = 7.7 Hz, 3H), 1.06 (app.t, *J* = 7.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 142.0, 137.2, 128.0, 126.1, 121.6, 119.2, 118.7, 118.1, 117.8, 115.7, 109.3, 37.7, 32.7, 31.3, 30.0, 24.4, 24.1, 23.2, 13.4, 13.2, 13.1; IR (film) 2964, 2930, 1472, 736 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{21}N]^+$: 227.1674, found 227.1678.



SM3

SM4

Indole SM4. To a solution of acrolein (4.62 mL, 70.5 mmol) in 85:15 CH_2Cl_2/*i*-PrOH (47 mL) at 23 °C was added *N*-methylaniline (179 μl, 1.65 mmol) and trifluoroacetic acid (127 μl, 1.65 mmol). The resulting solution was cooled to 0 °C, and *N*-methylindole (3.00 mL, 23.5 mmol) was added dropwise. The reaction was stirred at 0 °C for 4 h, then filtered through a pad of silica gel (5 x 6 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) provided aldehyde (3.54 g, 80% yield, $R_F = 0.34$ in 4:1 hexanes/EtOAc) as a yellow oil.

The epoxide was synthesized according to a modified procedure of Cainelli et al.[2] To a solution of the aldehyde (500 μl, 2.91 mmol) and diiodomethane (422 μl, 5.24 mmol) in THF (11.6 mL) at -78 °C was added methyllithium (3.28 mL, 1.6 M in Et_2O, 5.24 mmol) dropwise over 3 min. The reaction was stirred for 30 min at -78 °C and 2 h at 23 °C. It was then cooled to 0 °C and quenched by slow addition of saturated NH_4Cl (40 mL). Et_2O (50 mL) was added, the phases separated, and the aqueous layer extracted with Et_2O (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (5:1 hexanes/EtOAc eluent) afforded epoxide **SM3** (314 mg, 54% yield, R_F = 0.54 in 2:1 hexanes/EtOAc) as a yellow oil.

To a solution of benzyl alcohol (475 μl, 4.59 mmol) in DMF (8.5 mL) at 0 °C was added NaH (184 mg, 60% dispersion in mineral oil, 4.59 mmol). The solution was stirred at 0 °C for 10 min and 23 °C for 1 h. The resulting solution of sodium benzyloxide was added to a solution of epoxide **SM3** (308 mg, 1.53 mmol) in DMF (2.13 mL) at 0 °C. The reaction mixture was then heated to 80 °C and stirred 3 h. The reaction was cooled to 0 °C and quenched with saturated NH_4Cl (50 mL). Et_2O (75 mL) was added, the phases separated, and the aqueous layer extracted with Et_2O (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to an oil. Purification by flash chromatography (1:1 hexanes/Et_2O eluent) afforded alcohol (304 mg, 64% yield, R_F = 0.30 in 2:1 hexanes/EtOAc) as a yellow oil.

To a solution of the alcohol (304 mg, 0.981 mmol) in CH_2Cl_2 (1.96 mL) at 23 °C was added 4Å molecular sieves (491 mg, 500 mg/mmol substrate), then NMO (172 mg, 1.47 mmol). The suspension was stirred for 15 min, at which point TPAP (17.2 mg, 0.0491 mmol) was added. After stirring 15 min, the reaction mixture was filtered through a pad of silica gel (2 x 7 cm, CH_2Cl_2 eluent), and the filtrate was concentrated to an oil. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) afforded α-benzyloxyketone (265 mg, 86% yield, R_F = 0.50 in 2:1 hexanes/EtOAc) as a clear oil.

To a suspension of potassium *tert*-butoxide (230 mg, 2.05 mmol) in toluene (8 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (761 mg, 2.05 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the ketone (294 mg, 0.956 mmol) in toluene (1.56 mL) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (30 mL, 1:1), and extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (2:1 hexanes/CH_2Cl_2 eluent) to provide indole **SM4** (243 mg, 80% yield, R_F = 0.48 in 4:1 hexanes/EtOAc, 88:12 mixture of olefin isomers) as a clear oil. **Indole SM4**: (Major isomer only) ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3 Hz, 1H), 7.40-7.26 (comp m, 6H), 7.22 (app.t, J = 7.4 Hz, 1H), 7.09 (app.t, J = 7.4 Hz, 1H), 6.83 (s, 1H), 5.58 (q, J = 6.8 Hz, 1H), 4.52 (s, 2H), 4.14 (s, 2H), 3.73 (s, 3H), 2.89 (t, J = 8.1 Hz, 2H), 2.53 (t, J = 8.1 Hz, 2H), 1.68 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 137.2, 136.9, 128.6, 128.1, 128.0, 127.7, 126.2, 124.1, 121.6, 119.3, 118.7, 115.4, 109.3, 72.2, 67.2, 36.5, 32.7, 24.3, 13.6; IR (film) 1472, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{22}H_{25}NO]^+$: 319.1936, found 319.1938.

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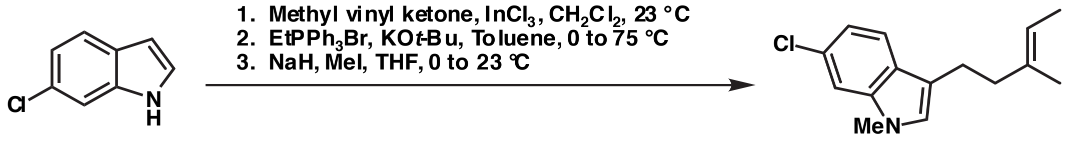
[2] Cainelli, G.; Tangari, N.; Umani, R. A. *Tetrahedron* **1972**, *28*, 3009-3013.

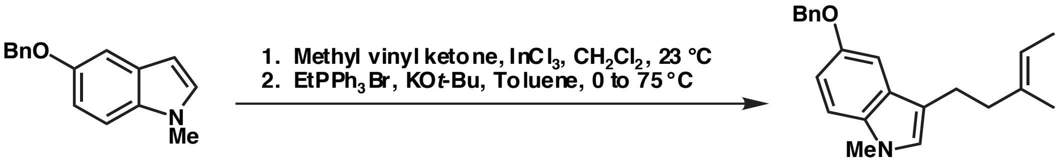


SM5

Indole SM5. To a solution of 6-chloroindole (400 mg, 2.64 mmol) in CH_2Cl_2 (5.28 mL) at 23 °C was added methyl vinyl ketone (220 μl, 2.64 mmol) and $InCl_3$ (58.4 mg, 0.264 mmol). The reaction mixture was stirred at 23 °C for 2 h, quenched with water (30 mL), and extracted with CH_2Cl_2 (2 x 40 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to a brown solid. Purification by flash chromatography (4:1 CH_2Cl_2/hexanes eluent) provided the ketone (309 mg, 53% yield, R_F = 0.33 in 2:1 hexanes/EtOAc) as a yellow solid.

To a suspension of potassium *tert*-butoxide (230 mg, 2.05 mmol) in toluene (8.21 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (761 mg, 2.05 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the ketone (182 mg, 0.821 mmol) was added, and the solution was heated to 75 °C. After stirring for 4 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (20 mL, 1:1), and extracted with EtOAc (2 x 35 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin (128 mg, 67% yield, R_F = 0.50 in 4:! hexanes/EtOAc) as a clear oil.

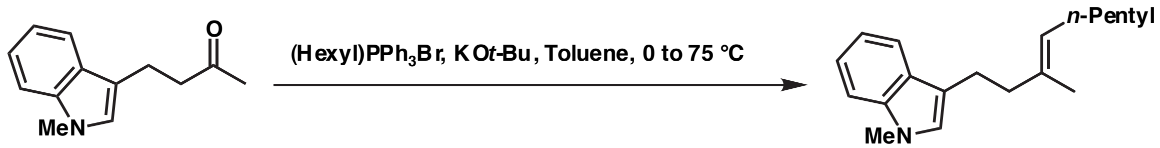
To a solution of the olefin (74.0 mg, 0.317 mmol) in THF (1.27 mL) at 0 °C was added NaH (25.4 mg, 60% dispersion in mineral oil, 0.634 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (29.6 μl, 0.476 mmol), and allowed to warm to 23 °C. After 30 min, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (20 mL), and extracted with ether (2 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **SM5** (70.3 mg, 90% yield, R_F = 0.47 in 9:1 hexanes/EtOAc, 57:43 mixture of olefin isomers) as a clear oil. **Indole SM5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.27 (s, 1H), 7.26 (s, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.83 (s, 1H), 6.81 (s, 1H), 5.29 (app.q, *J* = 6.6 Hz, 1H), 5.26 (app.q, *J* = 6.6 Hz, 1H), 3.70 (s, 3H), 3.70 (s, 3H), 2.80 (t, *J* = 8.2 Hz, 2H), 2.78 (t, *J* = 8.2 Hz, 2H), 2.42-2.32 (comp m, 2H), 2.42-2.32 (comp m, 2H), 1.76 (s, 3H), 1.69 (s, 3H), 1.60 (d, *J* = 6.6 Hz, 3H), 1.53 (d, *J* = 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 136.0, 135.9, 127.7, 126.8, 120.1, 120.0, 119.7, 119.4, 118.9, 115.8, 109.3, 40.6, 32.8, 32.6, 24.0, 23.6, 23.5, 16.0, 13.6, 13.5; IR (film) 2917, 1477, 799 cm^{-1}; HRMS (EI$^+$) *m*/*z* calc'd for $[C_{15}H_{18}NCl]^+$: 247.1128, found 247.1123.



SM6 *SM7*

Indole SM7. To a solution of 5-benzyloxy-*N*-methyl indole (**SM6**)[3] (493 mg, 2.08 mmol) in CH_2Cl_2 (4.16 mL) at 23 °C was added methyl vinyl ketone (173 μl, 2.08 mmol) and $InCl_3$ (46.0 mg, 0.208 mmol). The reaction mixture was stirred at 23 °C for 2.5 h, quenched with water (25 mL), and extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The resulting solid was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to provide the ketone (450 mg, 70% yield, $R_F = 0.42$ in 2:1 hexanes/EtOAc) as a white solid.

To a suspension of potassium *tert*-butoxide (328 mg, 2.92 mmol) in toluene (14.6 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (1.08 g, 2.92 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the ketone (450 mg, 1.46 mmol) was added, and the solution was heated to 75 °C. After stirring for 4 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (50 mL, 1:1), and extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (3:1 hexanes/CH_2Cl_2 eluent) to provide indole **SM7** (418 mg, 90% yield, $R_F = 0.64$ in 4:1 hexanes/EtOAc, 59:41 mixture of olefin isomers) as a clear oil. **Indole SM7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (app.d, *J* = 7.7 Hz, 2H), 7.51 (app.d, 7.7 Hz, 2H), 7.43-7.31 (comp m, 3H), 7.43-7.31 (comp m, 3H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 5.0 Hz, 1H), 7.15 (d, *J* = 5.5 Hz, 1H), 7.00 (s, 1H), 6.97 (s, 1H), 6.85 (s, 1H), 6.82 (s, 1H), 5.32 (app.q, *J* = 6.6 Hz, 1H), 5.27 (app.q, *J* = 6.6 Hz, 1H), 5.14 (s, 2H), 5.14 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.83-2.75 (comp m, 2H), 2.83-2.75 (comp m, 2H), 2.44-2.34 (comp m, 2H), 2.44-2.34 (comp m, 2H), 1.79 (s, 3H), 1.72 (s, 3H), 1.63 (d, *J* = 6.6 Hz, 3H), 1.57 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 138.1, 136.3, 136.2, 132.9, 128.7, 128.4, 127.9, 127.8, 126.8, 119.5, 118.7, 115.1, 112.5, 110.0, 103.2, 103.1, 71.4, 40.6, 32.9, 32.6, 24.2, 23.7, 16.0, 13.6, 13.5; IR (film) 1489, 1208 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{22}H_{25}NO]^+$: 319.1936, found 319.1947.



SM8 *SM9*

Indole SM9. To a suspension of potassium *tert*-butoxide (1.63 g, 14.5 mmol) in toluene (53.7 mL) at 0 °C was added (hexyl)triphenylphosphonium bromide (6.20 g, 14.5 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, indolyl ketone **SM8**[4] (1.08 g, 5.37

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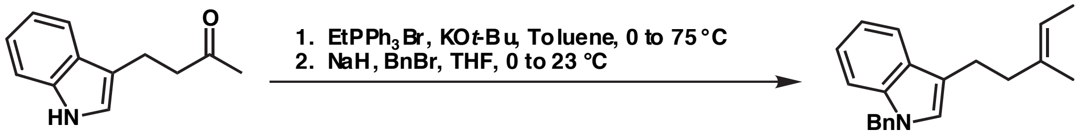
[3] Gwaltney, S. L.; Imade, H. M.; Barr, K. J.; Li, Q.; Gehrke, L.; Credo, R. B.; Warner, R. B.; Lee, J. Y.; Kovar, P.; Wang, J.; Nukkala, M. A.; Zielinski, N. A.; Frost, D.; Ng, S.-C.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2001,** *11*, 871-874.

[4] (a) Majchrzak, M. W.; Simchen, G. *Synthesis* **1986**, 956-958. (b) Harrington, P.; Kerr, M. A. *Can. J. Chem.* **1998**, *76*, 1256-1265.

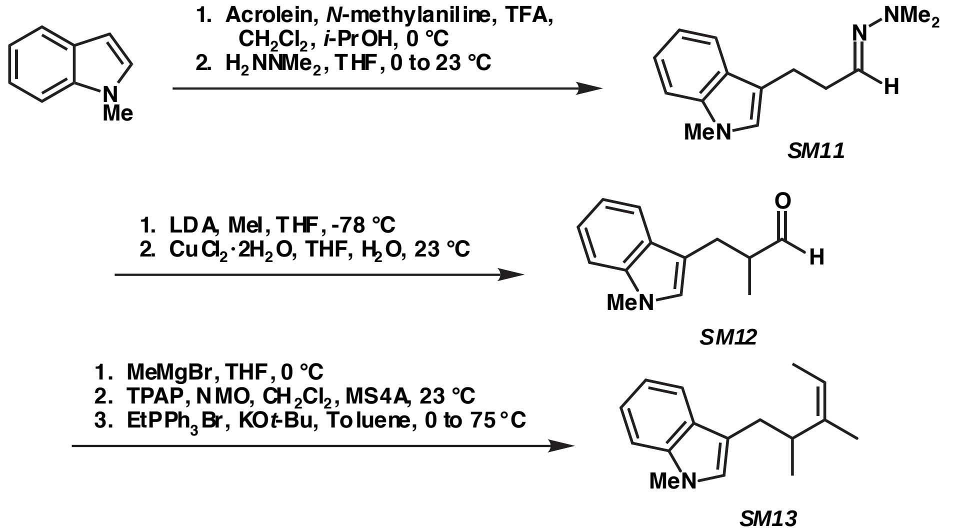
mmol) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (50 mL, 1:1), and extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (6:1 hexanes/CH_2Cl_2 eluent) to provide indole **SM9** (666 mg, 46% yield, R_F = 0.50 in 9:1 hexanes/EtOAc, 60:40 mixture of olefin isomers) as a clear oil. **Indole SM9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.31 (app.t, *J* = 8.2 Hz, 1H), 7.31 (app.t, *J* = 8.2 Hz, 1H), 7.29-7.23 (m, 1H), 7.29-7.23 (m, 1H), 7.18-7.11 (comp m, 1H), 7.18-7.11 (comp m, 1H), 6.88 (s, 1H), 6.86 (s, 1H), 5.24 (app.q, *J* = 7.1 Hz, 1H), 5.24 (app.q, *J* = 7.1 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.89 (app.t, *J* = 8.5 Hz, 2H), 2.85 (app.t, *J* = 8.0 Hz, 2H), 2.48-2.39 (comp m, 2H), 2.48-2.39 (comp m, 2H), 2.05 (app.q, *J* = 6.9 Hz, 2H), 2.00 (app.q, *J* = 6.9 Hz, 2H), 1.83 (s, 3H), 1.74 (s, 3H), 1.40-1.23 (comp m, 6H), 1.43-1.23 (comp m, 6H), 0.94 (t, *J* = 6.6 Hz, 3H), 0.92 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 135.1, 128.1, 126.2, 125.3, 121.6, 119.2, 118.7, 115.5, 109.3, 40.7, 33.1, 32.7, 31.8, 30.0, 29.8, 28.1, 24.2, 24.0, 23.7, 22.9, 16.3, 14.3; IR (film) 2924, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{19}H_{27}N]^+$: 269.2143, found 269.2136.



SM1 *SM10*

Indole SM10. To a suspension of potassium *tert*-butoxide (7.50 g, 66.8 mmol) in toluene (267 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (24.8 g, 66.8 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, indolyl ketone **SM1**[1] (5.00 g, 26.7 mmol) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (250 mL, 1:1), and extracted with EtOAc (2 x 250 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin (4.31 g, 81% yield, R_F = 0.67 in 4:1 hexanes/EtOAc) as a clear oil.

To a solution of the olefin (982 mg, 4.93 mmol) in THF (19.7 mL) at 0 °C was added NaH (394 mg, 60% dispersion in mineral oil, 9.86 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with benzyl bromide (880 μl, 7.40 mmol), and allowed to warm to 23 °C. After 4 h, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (100 mL), and extracted with ether (2 x 250 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide benzyl indole **SM10** (872 mg, 61% yield, R_F = 0.42 in 9:1 hexanes/EtOAc, 57:43 mixture of olefin isomers) as a clear oil. **Indole SM10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 6.6 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.33-7.26 (comp m, 4H), 7.33-7.26 (comp m, 4H), 7.22-7.11 (comp m, 4H), 7.22-7.11 (comp m, 4H), 6.95 (s, 1H), 6.92 (s, 1H), 5.34-5.24 (m, 1H), 5.34-5.24 (m, 1H), 5.30 (s, 2H), 5.30 (s, 2H), 2.89 (t, *J* = 8.2 Hz, 2H), 2.86 (t, *J* = 8.2 Hz, 2H), 2.49-2.39 (comp m, 2H), 2.49-2.39 (comp m, 2H), 1.80 (s, 3H), 1.72 (s, 3H), 1.61 (d, *J* = 7.1 Hz, 3H), 1.56 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 136.9, 136.2, 136.0, 128.9, 128.4, 127.7, 127.0, 125.5, 121.8, 119.5, 119.3, 119.0, 116.2, 109.8, 50.0, 40.5, 32.6, 24.2, 23.6, 16.0, 13.6, 13.5; IR (film) 2917, 1467, 1453, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{21}H_{23}N]^+$: 289.1830, found 289.1820.



Indole SM13. To a solution of acrolein (4.62 mL, 70.5 mmol) in 85:15 CH_2Cl_2/*i*-PrOH (47 mL) at 23 °C was added *N*-methylaniline (179 μl, 1.65 mmol) and trifluoroacetic acid (127 μl, 1.65 mmol). The resulting solution was cooled to 0 °C, and *N*-methylindole (3.00 mL, 23.5 mmol) was added dropwise. The reaction was stirred at 0 °C for 4 h, then filtered through a pad of silica gel (5 x 6 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) provided aldehyde (3.54 g, 80% yield, $R_F = 0.34$ in 4:1 hexanes/EtOAc) as a yellow oil.

Aldehyde alkylation was accomplished using dimethylhydrazone chemistry according to the procedure of Corey and Enders.[5] To a solution of the aldehyde (2.00 mL, 11.6 mmol) in THF (58 mL) at 0 °C was added 1,1-dimethylhydrazine (973 μl, 12.8 mmol) dropwise. The resulting solution was stirred at 0 °C for 30 min, then allowed to 23 °C and stirred overnight (12 h). The solution was concentrated to an oil, which was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide hydrazone **SM11** (1.84 g, 69% yield, $R_F = 0.41$ in 1:1 hexanes/EtOAc) as a yellow oil.

To a solution of LDA (26.0 mmol) in THF (13.7 mL) at -78 °C was added the hydrazone (5.43 g, 23.7 mmol) in THF (10 mL) dropwise via cannula. The reaction mixture was alllowed to warm to 0 °C and stirred 2.5 h. The mixture was then cooled to -78 °C, and methyl iodide (2.30 mL, 37.0 mmol) was added. After 1 h, the reaction was quenched by quick addition of saturated NH_4Cl (75 mL) and Et_2O (75 mL). The mixture was allowed to warm to 23 °C, the phases were separated, and the aqueous phase extracted with Et_2O (2 x 75 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) afforded α-methylhydrazone (3.64 g, 63% yield, $R_F = 0.52$ in 1:1 hexanes/EtOAc) as a yellow oil.

The dimethylhydrazone was converted to the aldehyde by the procedure outlined by Yamashita et al.[6] To a solution of copper(II) chloride dihydrate (2.81 g, 16.5 mmol) in water (150 mL) at 23 °C was added the α-methylhydrazone (3.64 g, 15.0 mmol) in THF (224 mL). The reaction was stirred vigorously for 16 h, then quenched with 3.0 M NH_4OH. EtOAc (200 mL) was added, the phases were separated, and the aqueous layer was

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[5] Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, *1*, 3-6.

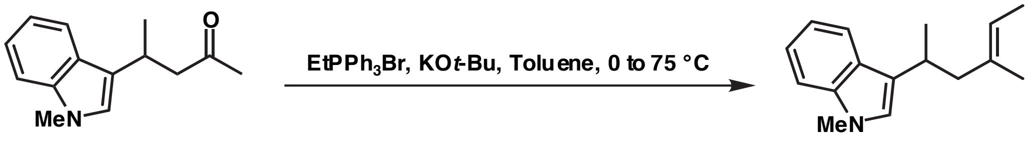
[6] Mino, T.; Fukui, S.; Yamashita, M. *J. Org. Chem.* **1997**, *62*, 734-735.

extracted with EtOAc (1 x 150 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (2:1 to 1:1 hexanes/EtOAc eluent) afforded aldehyde **SM12** (1.85 g, 61% yield, $R_F = 0.67$ in 2:1 hexanes/EtOAc) as a clear oil.

To a solution of **SM12** (1.85 g, 9.19 mmol) in THF (18.4 mL) at 0 °C was added methylmagnesium bromide (3.67 mL, 3.0 M in Et_2O, 11.0 mmol) dropwise over 5 min. The reaction was stirred for 30 min, and then quenched with saturated NH_4Cl (30 mL). The reaction mixture was partitioned between Et_2O (100 mL) and water (75 mL), and the aqueous phase was extracted with Et_2O (2 x 75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) afforded alcohol (1.50 g, 75% yield, $R_F = 0.36$ in 2:1 hexanes/EtOAc) as a colorless oil.

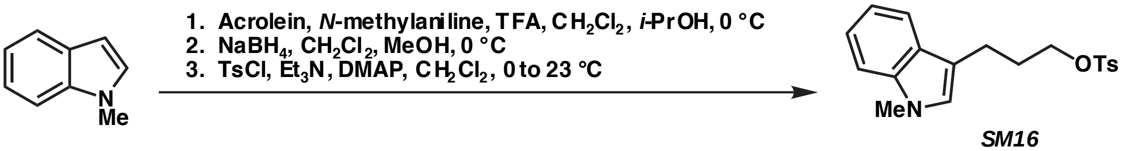
To a solution of the alcohol (593 mg, 2.73 mmol) in CH_2Cl_2 (5.46 mL) at 23 °C was added 4Å molecular sieves (1.36 g, 500 mg/mmol substrate), then NMO (479 mg, 4.09 mmol). The suspension was stirred for 15 min, at which point TPAP (47.8 mg, 0.136 mmol) was added. After stirring 15 min, the reaction mixture was filtered through a pad of silica gel (3 x 7 cm, CH_2Cl_2 eluent), and the filtrate was concentrated to an oil. The resulting ketone (374 mg) was used without further purification ($R_F = 0.59$ in 2:1 hexanes/EtOAc).

To a suspension of potassium *tert*-butoxide (526 mg, 4.69 mmol) in toluene (12.4 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (1.74 g, 4.69 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, ketone (from above) in toluene (5.00 mL) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (50 mL, 1:1), and extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil (indole contaminated with PPh_3) was dissolved in THF (10 mL), and to the solution was added methyl iodide (292 μl, 4.69 mmol). After stirring 2 h, the mixture was filtered through a pad of celite (2 x 7 cm, Et_2O eluent), and the filtrate was concentrated to an oil. This oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **SM13** (290 mg, 47% yield over 2 steps, $R_F = 0.61$ in 9:1 hexanes/EtOAc, 73:27 mixture of olefin isomers) as a clear oil. **Indole SM13**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.23 (app.t, *J* = 7.2 Hz, 1H), 7.23 (app.t, *J* = 7.2 Hz, 1H), 7.12 (app.t, *J* = 7.2 Hz, 1H), 7.12 (app.t, *J* = 7.2 Hz, 1H), 6.83 (s, 1H), 6.82 (s, 1H), 5.31 (q, *J* = 6.8 Hz, 1H), 5.22 (q, *J* = 6.8 Hz, 1H), 3.75 (s, 3H), 3.75 (s, 3H), 3.12 (m, 1H), 2.94-2.59 (comp m, 2H), 2.94-2.59 (comp m, 2H), 2.52 (m, 1H), 1.69 (s, 3H), 1.67 (s, 3H), 1.61 (d, *J* = 6.6 Hz, 3H), 1.55 (d, *J* = 8.2 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 140.5, 137.1, 128.4, 126.9, 126.8, 121.5, 119.3, 119.2, 118.9, 118.6, 117.6, 114.4, 114.2, 109.2, 43.6, 34.5, 32.8, 31.4, 30.6, 19.5, 18.8, 18.6, 13.5, 13.2, 13.0; IR (film) 2960, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{21}N]^+$: 227.1674, found 227.1675.

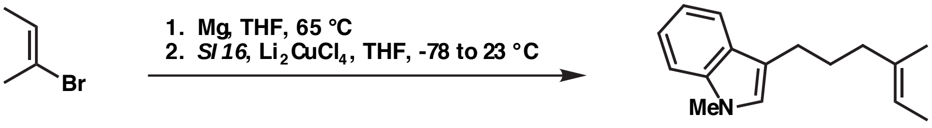


SM14 *SM15*

Indole SM15. To a suspension of potassium *tert*-butoxide (1.81 g, 16.1 mmol) in toluene (49.5 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (5.98 g, 16.1 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, indolyl ketone **SM14**^{4b} (1.28 g, 5.95 mmol) in toluene (10 mL) was added, and the solution was heated to 75 °C. After stirring for 9 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (150 mL, 1:1), and extracted with EtOAc (3 x 150 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil (indole contaminated with PPh_3) was dissolved in THF (32 mL), and to the solution was added methyl iodide (1.00 mL, 16.1 mmol). After stirring 2 h, the mixture was filtered through a pad of celite (3 x 7 cm, Et_2O eluent), and the filtrate was concentrated to an oil. This oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **SM15** (1.35 g, 99% yield, R_F = 0.65 in 4:1 hexanes/EtOAc, 53:47 mixture of olefin isomers) as a clear oil. **Indole SM15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.1 Hz, 1H), 7.69 (d, *J* = 7.1 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.25 (app.t, *J* = 7.7 Hz, 1H), 7.25 (app.t, *J* = 7.7 Hz, 1H), 7.13 (app.t, *J* = 7.4 Hz, 1H), 7.13 (app.t, *J* = 7.4 Hz, 1H), 6.88 (s, 1H), 6.84 (s, 1H), 5.35 (q, *J* = 6.6 Hz, 1H), 5.30 (q, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.27 (m, 1H), 3.27 (m, 1H), 2.59 (br dd, *J* = 4.7, 13.4 Hz, 1H), 2.47 (app.d, *J* = 7.2 Hz, 1H), 2.47 (app.d, *J* = 7.2 Hz, 1H), 2.20 (app.dd, *J* = 9.9, 13.2 Hz, 1H), 1.79 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.30 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 135.3, 134.8, 127.4, 124.9, 124.8, 121.6, 120.6, 120.4, 120.3, 119.6, 118.6, 109.4, 48.5, 39.9, 32.8, 29.3, 28.9, 23.9, 20.7, 15.8, 13.8, 13.6; IR (film) 2960, 1473, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{21}N]^+$: 227.1674, found 227.1676.



SM16



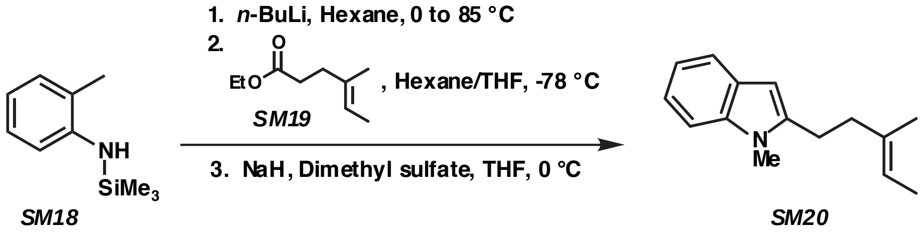
SM17

Indole SM17. To a solution of acrolein (4.62 mL, 70.5 mmol) in 85:15 CH_2Cl_2/*i*-PrOH (47 mL) at 23 °C was added *N*-methylaniline (179 μl, 1.65 mmol) and trifluoroacetic acid (127 μl, 1.65 mmol). The resulting solution was cooled to 0 °C, and *N*-methylindole (3.00 mL, 23.5 mmol) was added dropwise. The reaction was stirred at 0 °C for 4 h, then filtered through a pad of silica gel (5 x 6 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) provided aldehyde (3.54 g, 80% yield, R_F = 0.34 in 4:1 hexanes/EtOAc) as a yellow oil.

To a solution of the aldehyde (2.00 mL, 11.6 mmol) in 1:1 CH_2Cl_2/MeOH (11.6 mL) at 0 °C was added $NaBH_4$ (526 mg, 13.9 mmol) in four portions over 10 minutes. The resulting solution was quenched at 0 °C with 1.0 M HCl and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to an oil, which was used immediately without further purification (R_F = 0.28 in 2:1 hexanes/EtOAc).

The oil was dissolved in CH_2Cl_2 (58 mL), cooled to 0 °C, and treated with tosyl chloride (3.32 g, 17.4 mmol), triethylamine (3.23 mL, 23.2 mmol), and DMAP (142 mg, 1.16 mmol) sequentially. The solution was allowed to warm to 23 °C and stirred 10 h. The mixture was cooled to 0 °C and quenched with saturated NH_4Cl (75 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 75 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (1:1 hexanes/CH_2Cl_2 eluent) afforded tosylate **SM16** (2.62 g, 66% yield over 2 steps, R_F = 0.59 in 2:1 hexanes/EtOAc) as a colorless oil.

Copper-catalyzed coupling of vinyl Grignard reagents with alkyl sulfonates was accomplished using the procedure outlined by Foquet and Schlosser.[7] To a stirring suspension of magnesium turnings (260 mg, 10.7 mmol) in THF (21.4 mL) at 23 °C was added 2-bromo-2-butene (1.09 mL, 10.7 mmol). The mixture was heated to 65 °C and stirred 1 h, at which point the Grignard reagent had been fully generated. The solution was cooled to 23 °C, and then added via syringe to a solution of **SM16** (2.62 g, 7.63 mmol) in THF (7.63 mL) at -78 °C. Lithium tetrachlorocuprate (763 μl, 0.1 M in THF, 0.0763 mmol) was then added, and the reaction mixture was allowed to warm to 23 °C. After stirring for 32 h, the reaction was cooled to 0 °C and quenched by slow addition of 1.0 N HCl. The mixture was partitioned between 150 mL Et_2O and 150 mL H_2O. The organic phase was washed with H_2O (100 mL), and the aqueous layers were combined and extracted with Et_2O (150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (30:1 hexanes/Et_2O eluent) provided indole **SM17** (1.35 g, 78% yield, R_F = 0.63 in 4:1 hexanes/Et_2O, single olefin isomer of undetermined geometry) as a clear oil. **Indole SM17**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.24 (app.t, *J* = 7.3 Hz, 1H), 7.12 (app.t, *J* = 7.7 Hz, 1H), 6.86 (s, 1H), 5.27 (q, *J* = 6.4 Hz, 1H), 3.76 (s, 3H), 2.77 (t, *J* = 8.0 Hz, 2H), 2.18 (t, *J* = 7.7 Hz, 2H), 1.83 (comp m, 2H), 1.74 (s, 3H), 1.60 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 136.3, 128.2, 126.1, 121.6, 119.3, 119.2, 118.7, 115.6, 109.3, 32.7, 31.6, 28.7, 25.2, 23.6, 13.5; IR (film) 2930, 1473, 737 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{21}N]^+$: 227.1674, found 227.1680.



Indole SM20. 2-substituted indoles were synthesized according to the procedure of Smith et al.[8] To a solution of trimethylsilylaniline **SM18** (757 μl, 3.88 mmol) in hexane (34.6 mL) at 0 °C was added *n*-butyllithium (3.71 mL, 2.3 M solution in hexane, 8.54 mmol) dropwise. The orange solution was heated to 85 °C and stirred for 6 h. The resulting heterogeneous mixture was cooled to -78 °C and treated with ester **SM19**[9] (709 mg, 4.54 mmol) in THF (45.4 mL) quickly. The solution was allowed to warm to 23 °C, stirred 1 h, and quenched with brine. The layers were separated, and the aqueous phase was extracted with 2 x 150 mL Et_2O, 2 x 150 mL EtOAc, and 150 mL Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (2 columns: 9:1 hexanes/Et_2O eluent, then 3:1 hexanes/CH_2Cl_2 eluent) provided indole (372 mg, 48% yield, R_F = 0.52 in 4:1 hexanes/EtOAc) as a yellow solid.

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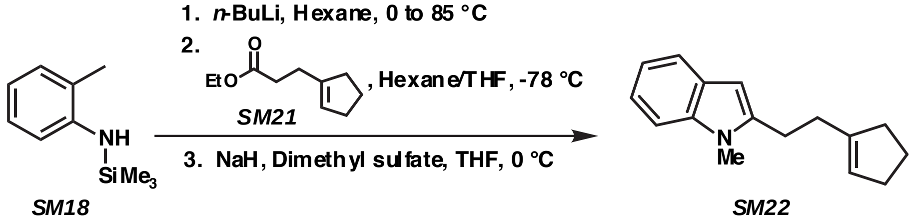
[7] Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82-83.

[8] Smith, A. B.; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957-2969.

[9] Kobayashi, Y.; Yoshida, S.; Nakayama, Y. *Eur. J. Org. Chem.* **2001**, 1873-1881.

To a solution of indole (116 mg, 0.582 mmol) in THF (2.33 mL) at 0 °C was added NaH (46.4 mg, 60% dispersion in mineral oil, 1.16 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C and treated with dimethyl sulfate (83.1 μl, 0.873 mmol). After 30 min, the reaction mixture was quenched with saturated NH_4Cl (20 mL) and extracted with ether (2 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was purified by flash chromatography (15:1 hexanes/Et_2O eluent) to provide indole **SM20** (106 mg, 85% yield, R_F = 0.50 in 9:1 hexanes/EtOAc) as a clear oil. **Indole SM20**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.17 (app.t, *J* = 7.4 Hz, 1H), 7.08 (app.t, *J* = 7.7 Hz, 1H), 6.28 (s, 1H), 5.35 (app.q, *J* = 6.6 Hz, 1H), 3.69 (s, 3H), 2.84 (app.t, *J* = 8.2 Hz, 2H), 2.42 (app.t, *J* = 8.2 Hz, 2H), 1.72 (s, 3H), 1.63 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 137.6, 135.1, 128.2, 120.7, 120.0, 119.5, 119.4, 108.9, 98.8, 38.9, 29.6, 26.0, 16.0, 13.6; IR (film) 2917, 1468, 745 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{19}N]^+$: 213.1517, found 213.1514.



Indole SM22. To a solution of trimethylsilylaniline **SM18** (408 μl, 2.09 mmol) in hexane (18.7 mL) at 0 °C was added *n*-butyllithium (2.00 mL, 2.3 M solution in hexane, 4.60 mmol) dropwise. The orange solution was heated to 85 °C and stirred for 6 h. The resulting heterogeneous mixture was cooled to -78 °C and treated with ester **SM21**[10] (412 mg, 2.45 mmol) in THF (24.5 mL) quickly. The solution was allowed to warm to 23 °C, stirred 1 h, and quenched with brine. The layers were separated, and the aqueous phase was extracted with 2 x 100 mL Et_2O, 2 x 100 mL EtOAc, and 100 mL Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (2 columns: 4:1 hexanes/CH_2Cl_2 eluent, then 9:1 hexanes/Et_2O eluent) provided indole (172 mg, 39% yield, R_F = 0.56 in 4:1 hexanes/EtOAc) as a white solid.

To a solution of indole (139 mg, 0.658 mmol) in THF (2.63 mL) at 0 °C was added NaH (52.8 mg, 60% dispersion in mineral oil, 1.32 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C and treated with dimethyl sulfate (94.0 μl, 0.987 mmol). After 30 min, the reaction mixture was quenched with saturated NH_4Cl (20 mL) and extracted with ether (2 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was purified by flash chromatography (6:1 hexanes/CH_2Cl_2 eluent) to provide indole **SM22** (127 mg, 86% yield, R_F = 0.57 in 4:1 hexanes/EtOAc) as a white solid. **Indole SM22**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.16 (app.t, *J* = 7.4 Hz, 1H), 7.07 (app.t, *J* = 7.4 Hz, 1H), 6.28 (s, 1H), 5.47 (m, 1H), 3.69 (s, 3H), 2.93-2.88 (comp m, 2H), 2.54-2.49 (comp m, 2H), 2.37 (comp m, 4H), 1.91 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 141.4, 137.5, 128.1, 124.3, 120.7, 120.0, 119.4, 108.9, 98.8, 35.5, 32.7, 30.5,

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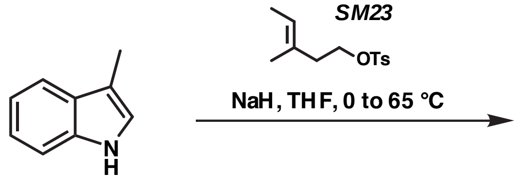
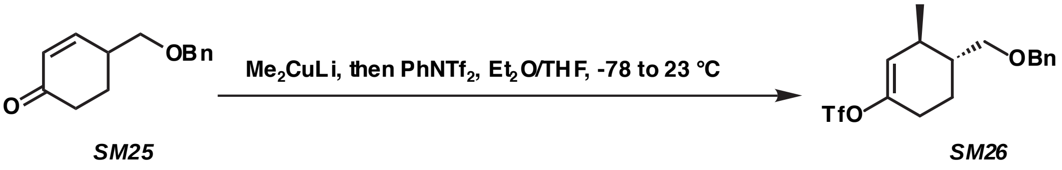
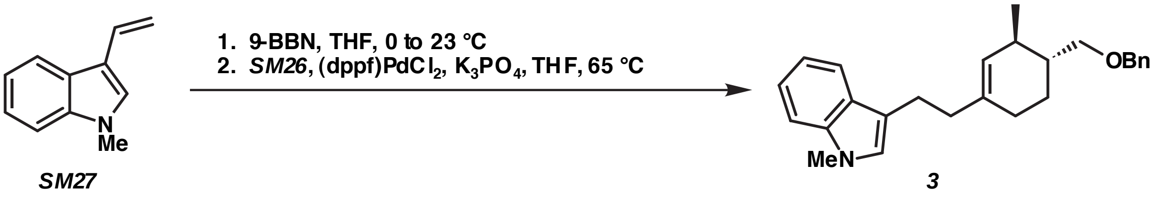
[10] Pitteloud, R.; Petrzilka, M. *Helv. Chim. Acta* **1979**, *62*, 1319-1325.

29.6, 25.6, 23.7; IR (film) 2842, 1468, 744 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1513.



Indole SM24. To a solution of 3-methylindole (227 mg, 1.73 mmol) in THF (5.00 mL) at 0 °C was added NaH (138 mg, 60% dispersion in mineral oil, 3.46 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C and treated with alkyl tosylate **SM23**[11] (483 mg, 1.90 mmol) in THF (1.92 mL). The reaction was heated to 65 °C and stirred 8 h. The reaction was cooled to 0 °C, quenched with saturated NH_4Cl (50 mL) and extracted with ether (2 x 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **SM24** (259 mg, 70% yield, R_F = 0.82 in 4:1 hexanes/EtOAc, single olefin isomer of undetermined geometry) as a clear oil. **Indole SM24**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.25 (app.t, *J* = 7.7 Hz, 1H), 7.14 (app.t, *J* = 7.7 Hz, 1H), 5.35 (q, *J* = 6.6 Hz, 1H), 4.12 (t, *J* = 7.7 Hz, 2H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.37 (s, 3H), 1.77 (s, 3H), 1.46 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 132.5, 129.0, 125.6, 122.1, 121.5, 119.2, 118.6, 110.3, 109.2, 44.5, 32.8, 23.8, 13.4, 9.8; IR (film) 2918, 1468, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{19}N]^+$: 213.1517, found 213.1513.





Indole 3. Enol triflate **SM26** was generated regioselectively by the procedure of McMurry and Scott.[12] To a stirring suspension of copper(I) iodide (159 mg, 0.833 mmol) in Et_2O (14.1 mL) at 0 °C was added methyllithium (1.04 mL, 1.6 M in Et_2O, 1.67 mmol) dropwise over 1 min. The pale yellow solution was stirred 30 min, then cooled to -78 °C. Enone **SM25**[13] (120 mg, 0.555 mmol) in THF (12.3 mL) was added dropwise over 3 min, and the resulting solution was stirred at -78 °C for 45 min and 0 °C for 45 min. $PhNTf_2$ (208 mg, 0.583 mmol) in THF (9 mL) was added via cannula, and the reaction mixture was stirred at 0 °C for 2 h, then 90 min at 23 °C. The

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[11] Parr, W. J. E. *J. Chem. Res., Miniprint* **1981**, *11*, 4101-4130.

[12] McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979-982.

[13] Smith, A. B.,; Haseltine, J. N.; Visnick, M. *Tetrahedron* **1989**, *45*, 2431-2449.

reaction was quenched with saturated NH_4OH (50 mL, saturated with NH_4Cl), and eluted with Et_2O (50 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/EtOAc eluent) afforded vinyl triflate (**SM26**) (146 mg, 72% yield, $R_F = 0.43$ in 9:1 hexanes/EtOAc) as a clear oil. Absolute stereochemistry was determined based on similar dimethyl cuprate conjugate additions to 4-substituted enones.[14]

Suzuki cross-coupling was carried out according to the procedure of Suzuki et al.[15] 9-BBN dimer (203 mg, 0.830 mmol) was dissolved in THF (1.66 mL) at 23 °C under an argon atmosphere. Once fully in solution, it was cooled to 0 °C, and to the solution was added 3-vinyl-*N*-methyl indole (**SM27**)[16] (261 mg, 1.66 mmol) in THF (1.66 mL). The reaction mixture was warmed to 23 °C and stirred for 3 h. To the solution was then added triflate **SM26** (552 mg, 1.51 mmol) in THF (7.55 mL), (dppf)$PdCl_2$ (30.8 mg, 0.0378 mmol), and K_3PO_4 (482 mg, 2.27 mmol), and the reaction was heated to 65 °C. After 5 h, the reaction was cooled to 23 °C and quenched with 1 mL NaOH (3.0 M aq.) and 1 mL 30% H_2O_2, and the resulting mixture was stirred 1 h. The mixture was then partitioned between Et_2O (50 mL) and water (40 mL), and the aqueous phase was extracted with Et_2O (1 x 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography afforded Suzuki product **3** (467 mg, 75% yield, $R_F = 0.20$ in 4:1 hexanes/CH_2Cl_2) as a clear oil. **Indole 3**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.34 (app.d, *J* = 4.4 Hz, 4H), 7.36-7.30 (comp m, 2H), 7.25 (app.t, *J* = 7.4 Hz, 1H), 7.13 (app.t, *J* = 7.4 Hz, 1H), 6.85 (s, 1H), 5.29 (s, 1H), 4.56 (ABq, *J* = 12.1 Hz, $\Delta\nu$ = 17.7 Hz, 2H), 3.75 (s, 3H), 3.59 (dd, *J* = 4.4, 9.3 Hz, 1H), 3.38 (dd, *J* = 7.2, 9.3 Hz, 1H), 2.88 (app.t, *J* = 8.0 Hz, 2H), 2.37 (app.t, *J* = 7.7 Hz, 2H), 2.10-1.98 (comp m, 3H), 1.58-1.46 (comp m, 2H), 1.03 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 137.2, 137.1, 128.5, 128.2, 127.7, 127.6, 127.2, 126.1, 121.6, 119.2, 118.7, 115.5, 109.3, 73.8, 73.3, 41.2, 38.6, 32.7, 32.5, 27.7, 25.5, 23.9, 21.0; IR (film) 2921, 1453, 1114, 737 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{26}H_{31}NO]^+$: 373.2406, found 373.2410.

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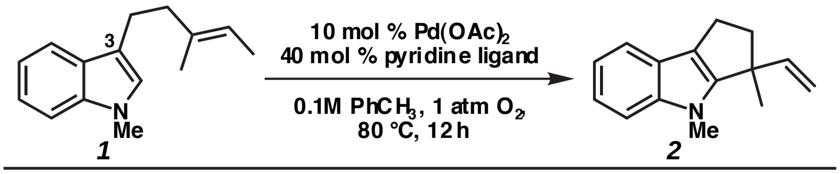
[14] Breit, B.; Demel, P. Copper-mediated Diastereoselective Conjugate Addition and Allylic Substitution Reactions. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley: Weinheim, 2002. Ch. 6, pp 188-223, and references therein.

[15] Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201-2208.

[16] Zhang, X.; Khan, S. I.; Foote, C. S. *J. Org. Chem.* **1993**, *58*, 7839-7847.

Table 1. The Effect of Pyridine Substitution on the Aerobic Indole Annulation.



entry	pyridine ligand	pK_a (PyrH$^+$)	conversion (%)[a]
1.	4-MeO	6.47	3
2.	4-*t*-Bu	5.99	1
3.	unsubstituted	5.25	23
4.	4-CO_2Et	3.45	52
5.	*3-CO_2Et*	*3.35*	*76*
6.	3-$COCH_3$	3.18	58
7.	3-F	2.97	64
8.	3-CN	1.39	55
9.	3,5-di-Cl	0.90	22

[a] Measured using GC by consumption of **1** relative to an internal standard (tridecane).

General procedure for the optimization of pyridine ligand: A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by toluene (1.63 mL) and ligand (0.0732 mmol, 0.40 equiv). The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **1** (40.0 μl, 0.183 mmol) in toluene (200 μl), and tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction was stirred under O_2 for 12 h. An aliquot (approx. 200 μl) was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR.

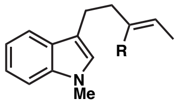
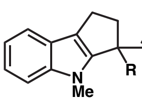
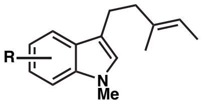
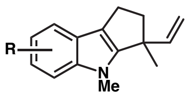
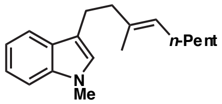
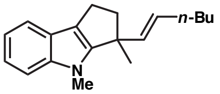
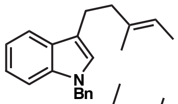
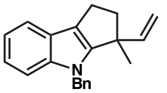
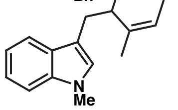
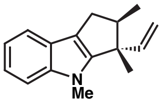
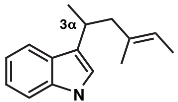
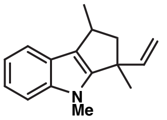
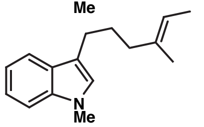
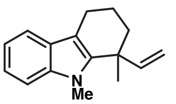
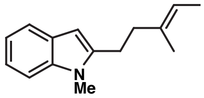
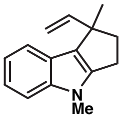
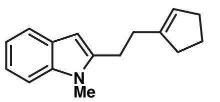
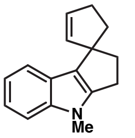
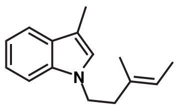
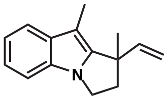
Table 2. Solvent Effects in the Reaction of 1 to 2.[a]

entry	solvent	% conversion	% yield (GC)
1.	toluene	88	33
2.	chlorobenzene	85	40
3.	butyl acetate	95	49
4.	*t*-amyl alcohol	94	53
5.	pinacolone	95	58
6.	AcOH	86	25
7.	pinacolone/AcOH (4:1)	91	76
8.	*t*-amyl alcohol/AcOH (4:1)	99	82[b]

[a] 10 mol% $Pd(OAc)_2$, 40 mol% ethyl nicotinate, 1 atm O_2, 80 °C, 0.1 M substrate **1** in solvent. [b] Isolated yield.

General procedure for the optimization of solvent: A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by solvent (1.63 mL) and ethyl nicotinate (10.0 μl, 0.0732 mmol). The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **1** (40.0 μl, 0.183 mmol) in solvent (200 μl), and tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction was stirred under O_2 for 24 h. An aliquot (approx. 200 μl) was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

Table 3. The Pd-Catalyzed Oxidative Indole Cyclization.[a]

entry	substrate[b]	product	time	% yield[c]
1.		 R = Me	24 h	82
2.		R = Et	18 h	74
3.		R = CH_2OBn	24 h	60
4.		 R = 6-Cl	32 h	62
5.		R = 5-OBn	20 h	73
6.			30 h	79[d]
7.			48 h	69
8.			18 h	76 (6:1 dr)
9.			53 h	64 (1:1 dr)
10.			39 h	66[e]
11.			6 h	73[f]
12.			5 h	68[f]
13.			18 h	74

[a] 10 mol% $Pd(OAc)_2$, 40 mol% ethyl nicotinate, 1 atm O_2, 80 °C, 0.1 M substrate in *t*-amyl alcohol:AcOH (4:1). [b] Typically used as a mixture of olefin isomers. [c] Isolated yields. [d] Product isolated as a 58:42 mixture of *E* and *Z* isomers. [e] 0.1 M in pinacolone. [f] 0.1 M in *t*-amyl alcohol.

General procedure for the oxidative annulation of indoles (Entry 1 is used as an example): A flame-dried 25 mL round bottom flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (17.2 mg, 0.0769 mmol, 0.100 equiv), *t*-amyl alcohol (5.15 mL), acetic acid (1.54 mL), and ethyl nicotinate (42.0 μl, 0.308 mmol, 0.400 equiv) sequentially. The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole (164 mg, 0.769 mmol) in *t*-amyl alcohol (1.00 ml) was then added via syringe, and the reaction was stirred under O_2 for the listed time. Filtration of the reaction mixture through a small pad of silica gel (1 x 5 cm, EtOAc eluent), concentration, and purification of the oil by flash chromatography afforded pure annulated indole.

Entry 1: 24 h. Purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (133 mg, 82% yield, $R_F = 0.76$ in 4:1 hexanes/acetone) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.1 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.16 (app.t, *J* = 8.2 Hz, 1H), 7.09 (app.t, *J* = 7.1 Hz, 1H), 6.09 (dd, *J* = 10.4, 17.0 Hz, 1H), 5.06 (dd, *J* = 1.7, 10.4 Hz, 1H), 4.98 (dd, *J* = 1.7, 17.0 Hz, 1H), 3.64 (s, 3H), 2.83 (app.t, *J* = 6.9 Hz, 2H), 2.57-2.48 (m, 1H), 2.40-2.32 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 145.3, 141.8, 124.1, 120.5, 119.2, 119.0, 117.6, 112.1, 109.5, 46.5, 46.2, 30.2, 24.0, 22.7; IR (film) 1468, 742 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{17}N]^+$: 211.1361, found 211.1363.

Entry 2: 18 h. Purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (123 mg, 74% yield, R_F = 0.80 in 4:1 hexanes/acetone) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.16 (app.t, *J* = 8.2 Hz, 1H), 7.08 (app.t, *J* = 7.7 Hz, 1H), 6.11 (dd, *J* = 10.5, 17.3 Hz, 1H), 5.03 (dd, *J* = 1.1, 10.5 Hz, 1H), 4.89 (dd, *J* = 1.1, 17.3 Hz, 1H), 3.63 (s, 3H), 2.80 (app.t, *J* = 7.2 Hz, 2H), 2.54-2.37 (comp m, 2H), 2.00-1.81 (comp m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.2, 144.8, 142.0, 124.2, 120.4, 119.1, 119.0, 118.9, 112.1, 109.4, 50.9, 42.8, 30.5, 30.4, 23.1, 9.4; IR (film) 2964, 2925, 1466, 738 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1510.

Entry 3: 24 h. Purification by flash chromatography (9:1 to 4:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (96.5 mg, 60% yield, R_F = 0.63 in 4:1 hexanes/Et_2O) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.7 Hz, 1H), 7.36-7.26 (comp m, 6H), 7.19 (app.t, *J* = 7.6 Hz, 1H), 7.11 (app.t, *J* = 7.3 Hz, 1H), 6.20 (dd, *J* = 10.7, 17.6 Hz, 1H), 5.17 (dd, *J* = 1.1, 10.7 Hz, 1H), 5.01 (dd, *J* = 1.1, 17.6 Hz, 1H), 4.54 (ABq, *J* = 12.1 Hz, Δν = 14.2 Hz, 2H), 3.74 (ABq, *J* = 9.1 Hz, Δν = 18.5 Hz, 2H), 3.66 (s, 3H), 2.85 (app.t, *J* = 6.9 Hz, 2H), 2.62-2.53 (m, 1H), 2.49-2.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 142.2, 142.0, 138.5, 128.5, 127.8, 127.7, 124.1, 120.6, 119.2, 119.1, 119.0, 114.2, 109.7, 75.6, 73.7, 51.9, 42.2, 31.3, 22.7; IR (film) 2855, 1467, 739 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{22}H_{23}NO]^+$: 317.1780, found 317.1774.

Entry 4: 32 h. Purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (61.2 mg, 62% yield, R_F = 0.72 in 4:1 hexanes/acetone) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.2 Hz, 1H), 7.24 (s, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.07 (dd, *J* = 10.4, 17.0 Hz, 1H), 5.08 (dd, *J* = 1.1, 10.4 Hz, 1H), 4.97 (dd, *J* = 1.1, 17.0 Hz, 1H), 3.60 (s, 3H), 2.80 (app.t, *J* = 6.9 Hz, 2H), 2.56-2.47 (m, 1H), 2.40-2.31 (m, 1H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 145.0, 142.2, 126.5, 122.7, 119.7, 117.7, 112.3, 109.6, 46.4, 46.3, 30.4, 23.9, 22.6; IR (film) 1471, 1375 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{16}NCl]^+$: 245.0971, found 245.0970.

Entry 5: 20 h. Purification by flash chromatography (3:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (118 mg, 73% yield, R_F = 0.62 in 4:1 hexanes/Et_2O) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (app.d, *J* = 6.6 Hz, 2H), 7.43-7.30 (comp m, 3H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 2.2 Hz, 1H), 6.90 (dd, *J* = 2.2, 8.8 Hz, 1H), 6.08 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.12 (s, 2H), 5.06 (dd, *J* = 1.1, 10.4 Hz, 1H), 4.98 (dd, *J* = 1.1, 17.6 Hz, 1H), 3.61 (s, 3H), 2.80 (app.t, *J* = 6.9 Hz, 2H), 2.55-2.46 (m, 1H), 2.38-2.30 (m, 1H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 149.8, 145.3, 138.2, 137.4, 128.7, 127.9, 127.7, 124.3, 117.2, 112.0, 111.1, 110.1, 103.2, 71.4, 46.4, 46.2, 30.3, 23.9, 22.7; IR (film) 1482, 1204 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{22}H_{23}NO]^+$: 317.1780, found 317.1774.

Entry 6: 30 h. Purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (133 mg, 79% yield, $R_F = 0.81$ in 4:1 hexanes/EtOAc) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.16 (app.t, *J* = 7.7 Hz, 1H), 7.15 (app.t, *J* = 7.7 Hz, 1H), 7.09 (app.t, *J* = 7.7 Hz, 1H), 7.08 (app.t, *J* = 7.7 Hz, 1H), 5.71 (s, 1H), 5.66 (s, 1H), 5.39 (t, *J* = 6.9 Hz, 1H), 5.33 (t, *J* = 6.9 Hz, 1H), 3.64 (s, 3H), 3.64 (s, 3H), 2.81 (app.t, *J* = 6.6 Hz, 2H), 2.81 (app.t, *J* = 6.6 Hz, 2H), 2.54-2.45 (m, 1H), 2.54-2.45 (m, 1H), 2.39-2.31 (m, 1H), 2.39-2.31 (m, 1H), 2.04 (app.q, *J* = 6.6 Hz, 2H), 2.04 (app.q, *J* = 6.6 Hz, 2H), 1.48 (s, 3H), 1.48 (s, 3H), 1.37-1.30 (comp m, 4H), 1.37-1.30 (comp m, 4H), 0.90 (app.t, *J* = 7.1 Hz, 3H), 0.90 (app.t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 141.8, 137.1, 128.2, 124.2, 120.3, 119.1, 118.9, 117.2, 109.4, 47.0, 45.4, 32.4, 32.0, 30.2, 24.8, 22.7, 22.4, 14.2; IR (film) 2927, 1466, 736 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{19}H_{25}N]^+$: 267.1987, found 267.1990.

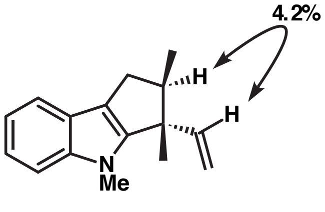
Entry 7: 48 h. Purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (132 mg, 68% yield, $R_F = 0.76$ in 4:1 hexanes/acetone) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.49 (m, 1H), 7.29-7.21 (comp m, 4H), 7.12-7.06 (comp m, 3H), 6.99 (app.d, *J* = 7.1 Hz, 2H), 6.04 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.28 (s, 2H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.98 (d, *J* = 17.6 Hz, 1H), 2.88 (app.t, *J* = 7.1 Hz, 2H), 2.59-2.50 (m, 1H), 2.40-2.31 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 145.0, 141.6, 138.5, 128.7, 127.2, 126.2, 124.4, 120.8, 119.5, 119.0, 118.1, 112.2, 110.5, 47.4, 46.5, 46.3, 23.9, 22.8; IR (film) 2930, 1453, 739 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{21}H_{21}N]^+$: 287.1674, found 287.1671.

Entry 8: 18 h. Purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (109 mg, 76% yield, $R_F = 0.78$ in 4:1 hexanes/acetone) as a clear oil.

Major diastereomer only: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.18 (app.t, *J* = 7.7 Hz, 1H), 7.11 (app.t, *J* = 7.7 Hz, 1H), 6.09 (dd, *J* = 11.0, 17.0 Hz, 1H), 5.25 (dd, *J* = 1.4, 11.0 Hz, 1H), 5.24 (dd, *J* = 1.4, 17.0 Hz, 1H), 3.66 (s, 3H), 3.02 (dd, *J* = 7.1, 13.7 Hz, 1H), 2.78 (m, 1H), 2.47 (dd, *J* = 9.3, 13.7 Hz, 1H), 1.22 (s, 3H), 1.12 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0, 145.2, 141.2, 124.2, 120.4, 119.2, 118.9, 115.9, 113.5, 109.5, 50.3, 48.2, 31.4, 30.0, 17.0, 13.9; IR (film) 2960, 2928, 1464, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1520.

NOE analysis of the major diastereomer:



Entry 9: 53 h. Purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (94.6 mg, 64% yield, $R_F = 0.76$ in 4:1 hexanes/acetone) as a clear oil. The indole was isolated as a 55:45 mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.18 (app.t, *J* = 7.4 Hz, 1H), 7.18 (app.t, *J* = 7.4 Hz, 1H), 7.11 (app.t, *J* = 6.6 Hz, 1H), 7.11 (app.t, *J* = 6.6 Hz, 1H), 6.16 (dd, *J* = 10.2, 17.9 Hz, 1H), 6.05 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.14 (dd, *J* = 1.1, 9.9 Hz, 1H), 5.14 (dd, *J* = 1.1, 17.6 Hz, 1H), 5.00 (dd, *J* = 1.1, 10.4 Hz, 1H), 4.86 (dd, *J* = 1.1, 17.6 Hz, 1H), 3.66 (s, 3H), 3.64 (s, 3H), 3.38 (m, 1H), 3.38 (m, 1H), 2.72 (dd, *J* = 7.7, 12.6 Hz, 1H), 2.55 (dd, *J* = 7.7, 12.6 Hz, 1H), 2.11 (dd, *J* = 6.6, 12.6 Hz, 1H), 1.98 (dd, *J* = 6.6, 12.6 Hz, 1H), 1.59 (s, 3H), 1.47 (s, 3H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.43 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 147.8, 146.5, 145.1, 141.8, 123.9, 122.6, 122.1, 120.5, 119.2, 119.1, 118.7, 112.3, 111.5, 109.6, 109.5, 55.9, 55.8, 46.3, 46.1, 31.8, 31.5, 30.2, 30.1, 25.7, 23.7, 21.9, 21.8; IR (film) 2955, 1466, 740 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1517.

Entry 10: 39 h. Purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (98.3 mg, 66% yield, $R_F = 0.84$ in 4:1 hexanes/acetone) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.20 (app.t, *J* = 7.4 Hz, 1H), 7.09 (app.t, *J* = 7.4 Hz, 1H), 6.01 (dd, *J* = 10.4, 17.0 Hz, 1H), 5.14 (dd, *J* = 1.1, 10.4 Hz, 1H), 4.89 (dd, *J* = 1.1, 17.6 Hz, 1H), 3.69 (s, 3H), 2.75 (app.t, *J* = 6.1 Hz, 2H), 1.88-1.70 (comp m, 4H), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 139.3, 137.7, 126.9, 121.2, 118.8, 118.3, 113.6, 110.5, 108.7, 41.2, 39.3, 31.7, 25.4, 22.0, 20.0; IR (film) 2929, 1471, 738 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1509.

Entry 11: 6 h. Purification by flash chromatography (6:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (88.8 mg, 73% yield, $R_F = 0.65$ in 4:1 hexanes/THF) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.14 (app.t, *J* = 7.7 Hz, 1H), 7.06 (app.t, *J* = 7.7 Hz, 1H), 6.15 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.02 (dd, *J* = 1.7, 17.6 Hz, 1H), 4.95 (dd, *J* = 1.7, 10.4 Hz, 1H), 3.68 (s, 3H), 2.89 (app.t, *J* = 6.9 Hz, 2H), 2.55-2.46 (m, 1H), 2.40-2.31 (m, 1H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 145.1, 141.6, 124.0, 122.8, 120.2, 119.1, 118.4, 110.5, 109.7, 46.6, 44.5, 30.9, 26.3, 23.8; IR (film) 2956, 740 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{17}N]^+$: 211.1361, found 211.1367.

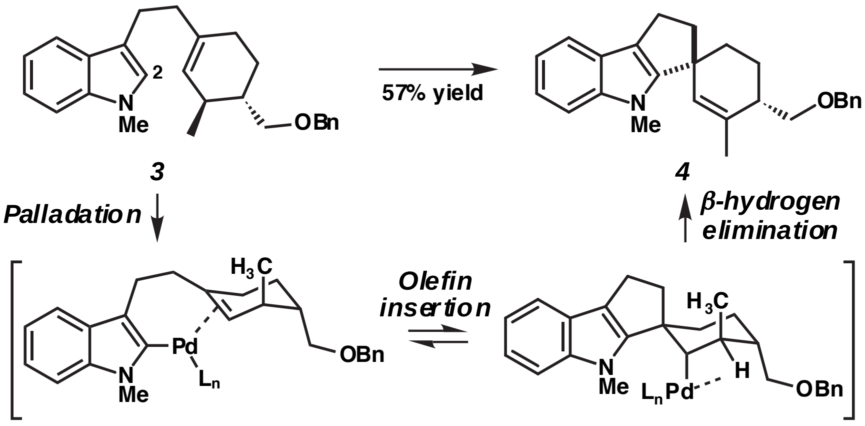
Entry 12: 5 h. Purification by flash chromatography (6:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (75.7 mg, 68% yield, $R_F = 0.62$ in 4:1 hexanes/THF) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.13 (app.t, *J* = 7.7 Hz, 1H), 7.05 (app.t, *J* = 7.4 Hz, 1H), 5.84-5.81 (m, 1H), 5.77-5.74 (m, 1H), 3.68 (s, 3H), 2.98-2.82 (comp m, 2H), 2.71-2.43 (comp m, 4H), 2.31-2.22 (m, 1H), 2.07-1.98 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 141.7, 139.1, 129.0, 123.8, 123.4, 120.2, 119.1, 118.3, 109.6, 56.2, 43.5, 38.0, 32.5, 30.8, 24.3; IR (film) 2942, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{17}N]^+$: 223.1361, found 223.1366.

Entry 13: 18 h. Purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided desired annulated indole (114 mg, 74% yield, $R_F = 0.45$ in 4:1 hexanes/benzene) as a clear oil.

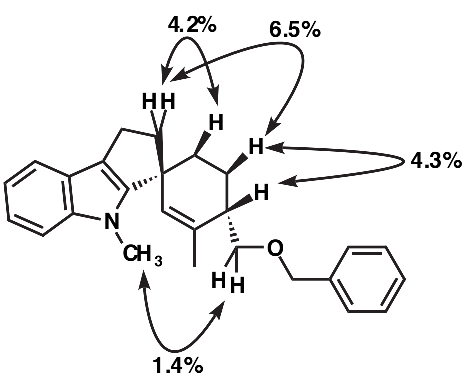
^{1}H NMR (300 MHz, CDCl$_3$) δ 7.54 (d, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.16 (app.t, *J* = 7.7 Hz, 1H), 7.10 (app.t, *J* = 7.7 Hz, 1H), 6.06 (dd, *J* = 10.4, 17.0 Hz, 1H), 5.09 (dd, *J* = 1.1, 10.4 Hz, 1H), 5.01 (dd, *J* = 1.1, 17.0 Hz, 1H), 4.10-3.98 (comp m, 2H), 2.61-2.53 (m, 1H), 2.48-2.39 (m, 1H), 2.27 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 144.6, 143.2, 133.4, 132.2, 120.6, 118.7, 118.6, 112.6, 109.4, 101.6, 44.8, 43.8, 42.0, 24.3, 8.2; IR (film) 2966, 2867, 1461, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{17}N]^+$: 211.1361, found 211.1360.

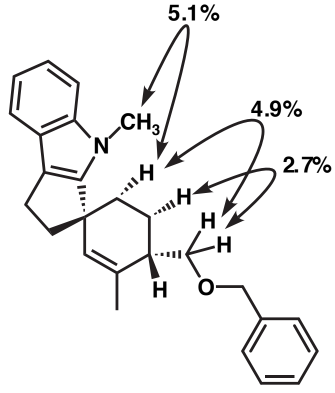
Procedure for the oxidative annulation of diastereomerically pure indole 3.



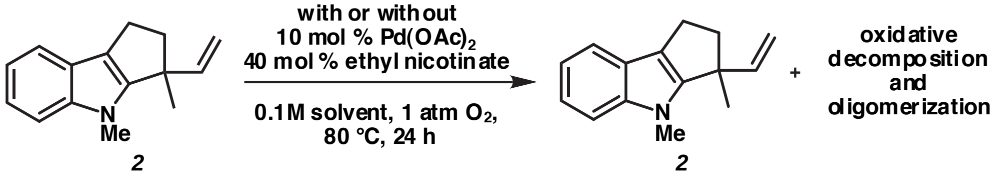
Indole 4. A flame-dried 25 mL round bottom flask equipped with magnetic stir bar was charged with Pd(OAc)$_2$ (4.5 mg, 0.0202 mmol) followed by *t*-amyl alcohol (1.52 mL) and ethyl nicotinate (11.0 μl, 0.0808 mmol) sequentially. The flask was evacuated and back-filled with O$_2$ (3 x, balloon), heated to 80 °C, and allowed to stir under O$_2$ (1 atm, balloon) for 10 min. A solution of indole **3** (75.5 mg, 0.202 mmol) in *t*-amyl alcohol (500 μl) was then added via syringe, and the reaction was stirred under O$_2$ for 24 h. The reaction mixture was filtered through a small pad of silica gel (1 x 5 cm, EtOAc eluent) and concentrated in vacuo. Purification of the oil by flash chromatography (1:1 hexane/PhH eluent) afforded diastereomerically pure annulated indole **4** (42.8 mg, 57% yield, R$_F$ = 0.59 in 4:1 hexanes/Et$_2$O) as a colorless oil. The absolute stereochemistry of the product was determined by NOE analysis. **Indole 4**: ^{1}H NMR (300 MHz, C$_6$D$_6$) δ 7.64-7.61 (m, 1H), 7.25-7.20 (comp m, 3H), 7.15-7.09 (comp m, 3H), 7.08-7.02 (comp m, 2H), 5.37 (s, 1H), 4.27 (ABq, *J* = 12.1 Hz, Δν = 22.2 Hz, 2H), 3.43-3.32 (comp m, 2H), 3.14 (s, 3H), 2.77 (dd, *J* = 5.2, 8.0 Hz, 2H), 2.33-2.21 (comp m, 2H), 2.16-2.09 (m, 1H), 1.99-1.91 (m, 1H), 1.83 (dd, *J* = 2.5, 13.5 Hz, 1H), 1.68 (ddd, *J* = 3.3, 5.5, 13.2 Hz, 1H), 1.61 (s, 3H), 1.53 (app.dt, *J* = 2.9, 12.6 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 150.5, 141.7, 138.6, 134.4, 130.8, 128.6, 128.0, 127.9, 124.2, 120.2, 119.1, 118.8, 117.1, 109.4, 73.4, 71.4, 44.8, 44.0, 39.0, 30.0, 28.5, 23.7, 23.0, 22.7; IR (film) 2929, 2855, 1466, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for [C$_{26}$H$_{29}$NO]$^+$: 371.2249, found 371.2241.

NOE measurements of annulated indole:

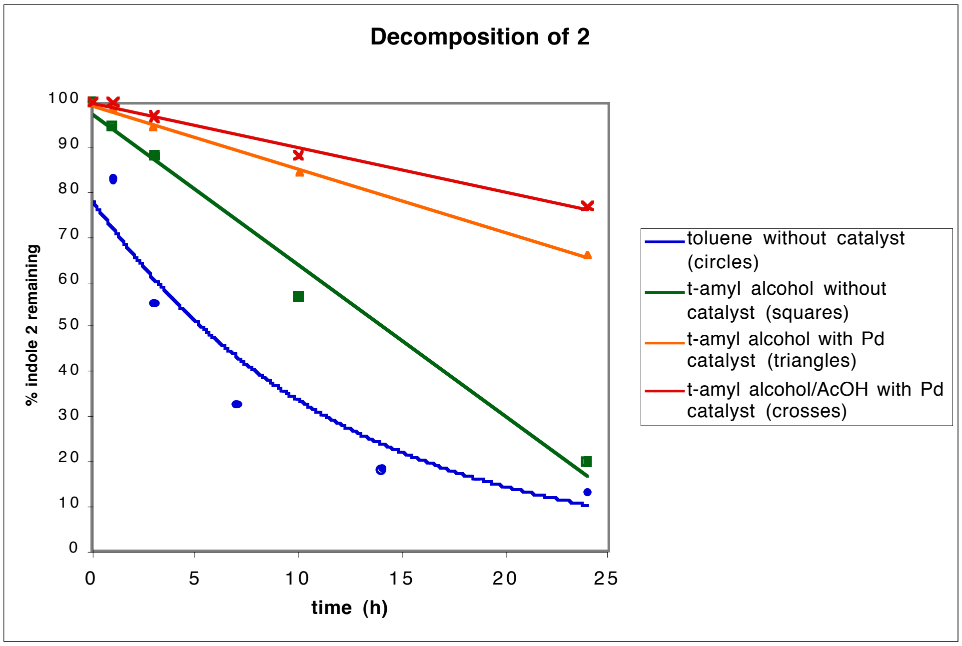




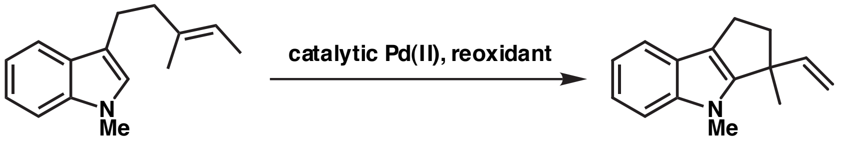
Control experiments to examine product stability:



General procedure for control experiments: A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with Pd(OAc)$_2$ (2.6 mg, 0.0118 mmol) if applicable, followed by solvent (918 μl) and ethyl nicotinate (6.4 μl, 0.0472 mmol) if applicable. The flask was evacuated and back-filled with O$_2$ (3 x, balloon), heated to 80 °C, and allowed to stir under O$_2$ (1 atm, balloon) for 10 min. A solution of indole **2** (25.0 mg, 0.118 mmol) in solvent (200 μl), and tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction was stirred under O$_2$ for 24 h. Aliquots (approx. 200 μl) were withdrawn periodically, filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.



Indole Annulation Comparison to Reported Pd(II) Oxidative Couplings



1 **2**

entry	conditions	ref	GC yield (%)
1.	$Pd(OAc)_2$, AgOAc, AcOH, air, 110 °C	1	4
2.	$Pd(OAc)_2$, $Cu(OAc)_2$, AcOH, air, 110 °C	1	0
3.	$Pd(OAc)_2$, $K_2S_2O_8$, AcOH, air, 110 °C	1	0
4.	$Pd(OAc)_2$, $NaNO_2$, AcOH, air, 110 °C	1	0
5.	$Pd(OAc)_2$, $Cu(OAc)_2$, Dioxane/AcOH (4:1), O_2, 100 °C	2	13
6.	$Pd(OAc)_2$, benzoquinone, $TsOH{\cdot}H_2O$, Toluene/AcOH (2:1), O_2, 23 °C	3	0
7.	$Pd(OAc)_2$, $H_6PMo_9V_3O_{40}$, acetylacetonate, NaOAc AcOH, O_2, 90 °C	4	0
8.	$Pd(OAc)_2$, cat. benzoquinone, TBHP AcOH/Ac_2O (4:1), 50 °C	5	5
9.	$Pd(OAc)_2$, ethyl nicotinate, t-amyl alcohol/AcOH (4:1), O_2, 80 °C		82

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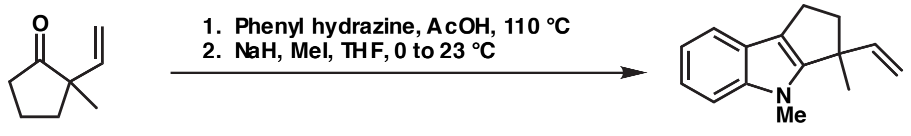
Independent Synthesis of Annulated Indole 2



SM27 ***2***

Indole 2. Phenylhydrazine (78.3 μl in 0.796 mmol) was dissolved in AcOH (174 μl) at 23 °C, and the solution was heated to 110 °C. Ketone **SM27**[17] (98.8 mg, 0.796 mmol) in AcOH (100 μl) was added dropwise, and the resulting mixture was stirred at 110 °C for 72 h. The dark mixture was cooled to 23 °C and eluted with Et_2O. The

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[17] Kuwajima, I.; Urabe, H. *Org. Synth.* **1988**, *66*, 87-94.

solution was then partitioned between Et_2O and 5% saturated $NaHCO_3$, and the aqueous layer was extracted with Et_2O. The organic phases were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (4:1 to 2:1 hexanes/CH_2Cl_2 eluent) afforded annulated indole (56.8 mg, 36% yield, $R_F = 0.66$ in 1:1 hexanes/CH_2Cl_2) as a pink oil.

To a solution of the annulated indole (17.9 mg, 0.0907 mmol) in THF (364 μl) at 0 °C was added NaH (7.2 mg, 60% dispersion in mineral oil, 0.181 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (8.5 μl, 0.136 mmol), and allowed to 23 °C. After 15 min, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (15 mL), and extracted with ether (2 x 20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide the indole **2** (5.6 mg, 29% yield, $R_F = 0.48$ in 4:1 hexanes/CH_2Cl_2) as a clear oil. This compound was identical to the product of Table 3, entry 1 in all respects.