

The First Regioselective Palladium-Catalyzed Indolization of 2-Bromo- or 2-Chloroanilines with Internal Alkynes: New Approach to 2,3-Disubstituted Indoles

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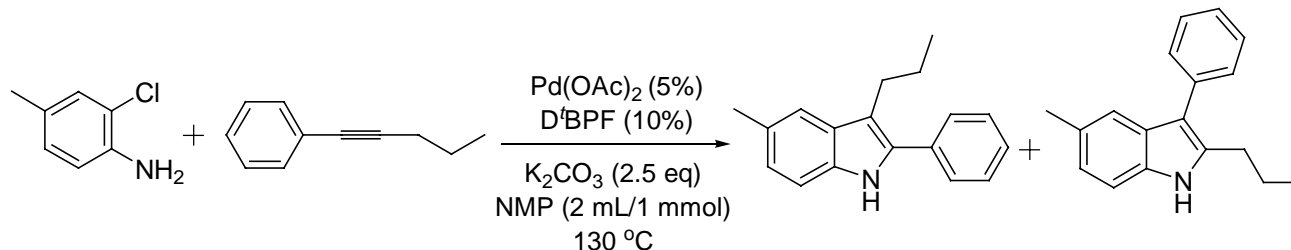
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Supporting Information

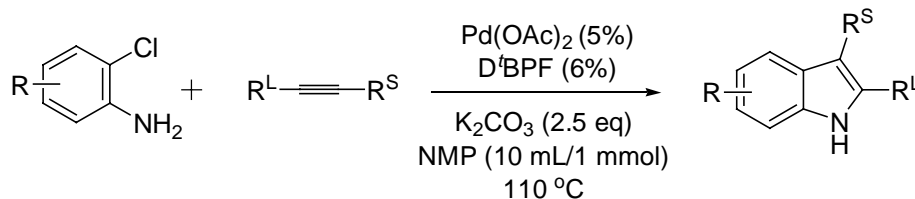
General: All reactions were carried out in oven-dried glassware sealed with rubber septa under an inert atmosphere of dry argon. All commercial materials were used without further purification. Analytical high performance liquid chromatography (HPLC) was performed on Agilent 1100 Series equipped with a UV detector and Eclipse XDB-C8 4.6 x 150 mm 5 μ m column. Analytical thin layer chromatography (TLC) was visualized by ultraviolet light (254 nm) and treatment with phosphomolybdic acid stain followed by gentle heating. Chemical yields refer to pure isolated substances. Purification of products was accomplished by flash chromatography using Isolute SPE columns pre-packed with Flash Si II purchased from Isolute. ¹H and ¹³C NMR were recorded using a Bruker 400. Chemical shifts are reported in ppm. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad. LC-MS was recorded on Agilent MSD spectrometer with VL API-ES positive scan. High resolution mass spectra were obtained on VG Fison AutoSpec mass spectrometer S/N M297 at 70 eV.

General Procedure for Condition Optimization:



Pd(OAc)₂ (11 mg, 0.05 mmol), 1,1'-bis(di-*t*-butylphosphino)ferrocene (47 mg, 0.1 mmol), potassium carbonate (346 mg, 2.5 mmol) were charged to an oven-dried reaction vial. The vial was purged with argon. 2-Chloro-4-methylaniline (123 μ L, 1 mmol), 1-pentyl-1-pentyne (192 μ L, 1.2 mmol) and NMP (2 mL) were added via syringe. The reaction was heated to 130 °C, stirred at the same temperature and monitored by HPLC. The reaction was complete after 4 h. The ratio of the regioisomer was 91:9. The mixture was filtered through a pad of celite. The cake was washed with ethyl acetate. The organic solvent was washed with water and brine, dried over MgSO₄, filtered and concentrated to give a brown residue. The product was purified via column chromatography.

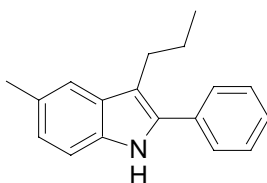
Representative Procedure for Palladium Catalyzed Indolization:



3-Ethyl-2-isopropenyl-5-methyl-1H-indole. A 100 mL reaction flask equipped with a stirring bar and thermocouple were charged with Pd(OAc)₂ (56 mg, 0.25 mmol), D'BPF (142 mg, 0.3 mmol), 2-chloro-4-methylaniline (0.71 g, 5 mmol), 2-methyl-1-hexen-3-yne (0.94 g, 10 mmol), K₂CO₃ (1.73 g, 12.5 mmol) and DMF (50 mL). The flask was purged with argon. The

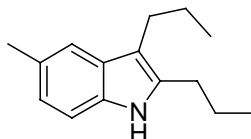
reaction was heated to 110 °C and stirred for overnight. The reaction was complete after 20 h at 110 °C. The mixture was filtered through a layer of celite and washed with ethyl acetate (10 mL). The filtrate was diluted with water (50 mL), extracted with EtOAc (100 mL x 3). The combined organic phase was washed with water (50 mL x 4) and brine, dried over MgSO₄, filtered and concentrated to give a dark brown residue. The product was purified via silica gel (hexane/EtOAc 50/1). The desired product was obtained as an off-white solid (0.6 g, 60%).

5-Methyl-2-phenyl-3-propyl-1H-indole:



Yield: 76%; off-white solid; m.p. 120-123 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.90 (s, 1H), 7.60-7.40 (m, 5H), 7.34-7.29 (m, 1H), 7.21-7.18 (m, 1H), 7.01-6.98 (m, 1H), 2.80 (t, *J* = 7.0 Hz, 2 H), 2.48 (s, 3H), 1.75-1.64 (m, 2H), 0.86 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 134.31, 134.27, 133.67, 129.62, 128.81, 128.67, 127.92, 127.38, 123.78, 119.05, 113.60, 110.48, 26.80, 24.30, 21.66, 14.53; LC-MSD (API-ES, positive) *m/z* = 250 (M + H⁺); HR-MS Calcd 249.1517, found 249.1515.

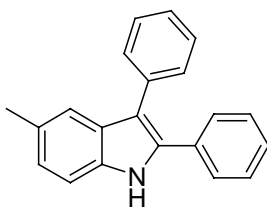
5-Methyl-2,3-dipropyl-1H-indole



Compound is easily decomposed after column; Yield: 82%; Yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 7.55 (s, 1H), 7.29 (d, *J* = 0.5 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.91 (dd, *J* = 8.5, 0.5

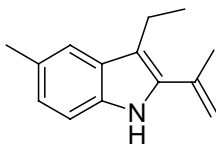
Hz, 1H), 2.65-2.61 (m, 4H), 2.44 (s, 3H), 1.64-1.62 (m, 4H), 0.97-0.93 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 134.16, 132.34, 127.79, 126.71, 120.95, 116.92, 110.38, 108.67, 26.93, 25.08, 22.90, 21.95, 20.33, 13.06, 12.74; LC-MSD (API-ES, positive) $m/z = 216.1$ (M + H); HR-MS Calcd 215.1672, found 215.1674.

5-Methyl-2,3-diphenyl-1H-indole (Baccolini, G.; Marotta, E. *Tetrahedron* **1985**, *41*, 4615-4620.)



Yield: 86%; Off-White solid; m.p. 153-155 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 7.48-7.28 (m, 12H), 7.12-7.09 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 135.22, 134.19, 134.18, 132.80, 130.19, 129.75, 129.00, 128.65, 128.50, 128.07, 127.57, 126.15, 124.30, 119.22, 114.57, 110.54, 21.54; LC-MSD (API-ES, positive) $m/z = 284.1$ (M + H); HR-MS Calcd 283.1361, found 283.1353.

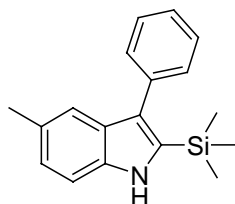
3-Ethyl-2-isopropenyl-5-methyl-1H-indole



Yield: 60%; Off-white solid; ^1H NMR (400 MHz, CDCl_3) δ 7.71 (s, 1H), 7.35 (s, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 5.23 (br s, 1H), 5.18-5.17 (m, 1H), 2.85 (q, $J = 7.5$ Hz, 2H), 2.45 (s, 3H), 2.20 (s, 3H), 1.26 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.34, 134.37, 133.56, 129.22, 128.47, 123.87, 118.56, 115.44, 113.83, 110.23, 22.46, 21.58, 18.10,

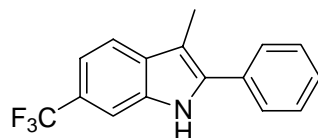
15.58; LC-MSD (API-ES, positive) $m/z = 200.2$ (M + H); HR-MS Calcd 199.1355, found 199.1361.

5-Methyl-3-phenyl-2-trimethylsilanyl-1H-indole



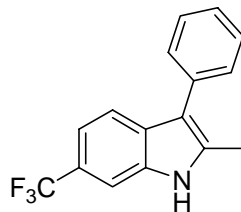
Yield: 63%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.03 (s, 1H), 7.47-7.27 (m, 7H), 7.05-7.02 (m, 1H), 2.40 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 137.10, 136.60, 134.51, 130.76, 129.54, 129.22, 128.43, 127.65, 126.87, 124.77, 119.36, 110.83, 21.85, 0.00; LC-MSD (API-ES, positive) $m/z = 280.1$ (M + H).

3-Methyl-2-phenyl-6-trifluoromethyl-1H-indole



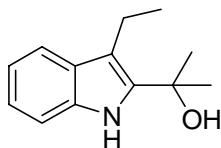
Yield: 65%; yellow solid; ^1H NMR (400 MHz, CDCl_3) δ 8.18 (s, 1H), 7.71 (d, $J = 8.5$ Hz, 1H), 7.60 (s, 1H), 7.48-7.47 (m, 4H), 7.36-7.31 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 135.69, 133.53, 131.49, 131.18, 127.94, 126.96, 126.80, 125.62, 123.23 (q, $J = 30$ Hz), 118.23, 115.20 (q, $J = 3$ Hz), 107.86, 107.15 (q, $J = 4$ Hz), 8.52; HR-MS Calcd 275.0931, found 275.0922.

2-Methyl-3-phenyl-6-trifluoromethyl-1H-indole



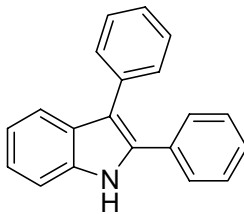
Yield: 9%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.18 (s, 1H), 7.71 (d, $J = 8.5$ Hz, 1H), 7.60 (s, 1H), 7.48-7.47 (m, 4H), 7.36-7.31 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 134.53, 134.34, 134.06, 130.18, 129.40, 128.66, 126.29, 125.26 (q, $J = 269$ Hz), 123.53 (q, $J = 32$ Hz), 119.03, 116.73 (q, $J = 3$ Hz), 114.99, 107.78 (q, $J = 5$ Hz), 12.66.

2-(3-Ethyl-1H-indol-2-yl)-propan-2-ol



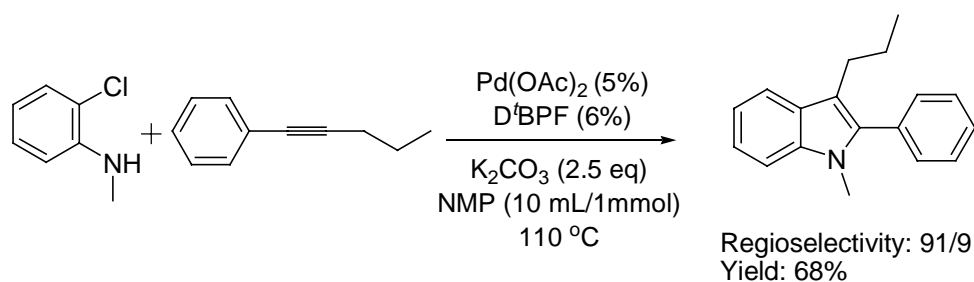
Yield: 60%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.44 (s, 1H), 7.54 (d, $J = 7.5$ Hz, 1H), 7.31 (d, $J = 8.5$ Hz, 1H), 7.16-7.06 (m, 2H), 2.83 (q, $J = 7.5$ Hz, 2H), 2.08 (s, 1H), 1.70 (s, 6H), 1.26 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 137.76, 132.16, 127.65, 119.73, 117.37, 116.87, 109.42, 109.13, 69.28, 29.49, 16.45, 14.32; HR-MS Calcd 203.1308, found 203.1310.

2,3-Diphenyl-1H-indole (Ackermann, L. *Organometallics* **2003**, 22, 4367-4368.)



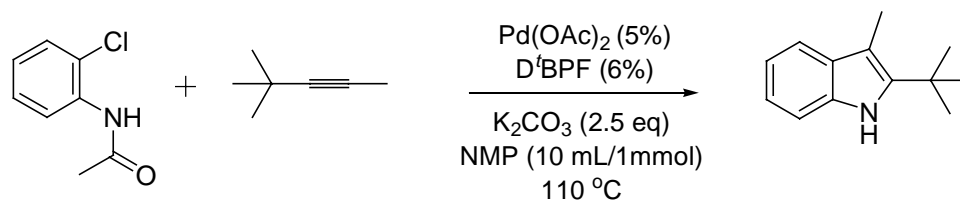
Yield: 97%; yellow solid; ^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.44-7.18 (m, 13H); ^{13}C NMR (100 MHz, CDCl_3) δ 135.70, 134.88, 133.92, 132.49, 129.99, 128.56, 128.52, 128.37, 128.02, 127.53, 126.07, 122.54, 120.27, 119.53, 114.85, 110.75; HR-MS Calcd 269.1205, found 269.1205.

1-Methyl-2-phenyl-3-propyl-1H-indole



Yield: 68%; Yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.67-7.62 (m, 1H), 7.48-7.10 (m, 8H), 3.54 (s, 3H), 2.66 (t, $J = 7.5$ Hz, 2H), 1.66-1.61 (m, 2H), 0.87 (t, $J = 7.0$ Hz, 3H); LC-MSD (API-ES, positive) $m/z = 250.1$ ($M + H$).

2-tert-Butyl-3-methyl-1H-indole (Smith, A. L.; Stevenson, G. I.; Swain, C. J.; Castro, J. L. *Tetrahedron Lett.* **1998**, 39, 8317-8320.)



Yield: 53%; Yellow solid; ^1H NMR (400 MHz, CDCl_3) δ 7.87 (br s, 1H), 7.50-7.47 (m, 1H), 7.26-7.23 (m, 1H), 7.12-7.06 (m, 2H), 2.39 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.73, 133.85, 130.52, 120.97, 119.04, 117.85, 110.29, 105.29, 32.82, 30.07, 10.34.