The Copper-Catalyzed *N*-Arylation of Indoles

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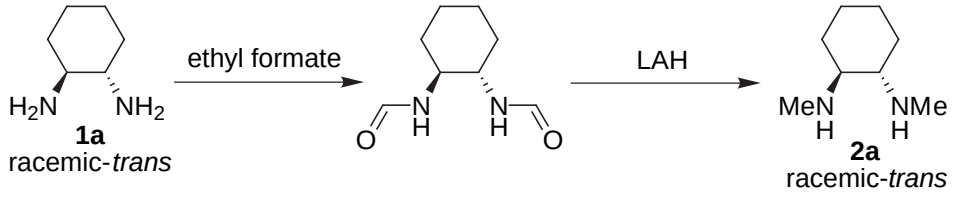
Supporting Information

General Considerations: All reactions were carried out in resealable Schlenk flasks or test tubes and run under a dry argon or nitrogen atmosphere. Toluene was purchased from J. T. Baker in CYCLE-TAINER® solvent delivery kegs, was vigorously purged with argon for 2 h, and further purified by passing through two packed columns of neutral alumina and copper (II) oxide under argon pressure. The K_3PO_4 base was purchased from Fluka and used without further purification. Alternatively, the use of K_3PO_4 from Alfa Aesar, that was sufficiently ground to a fine powder, provided comparable results in the several reactions where it was used. Copper (I) iodide was purchased from Strem company (98% purity, off-white) and was a fine powder. Aryl halides and indoles were purchased from commercial sources and used without further purification. Flash column chromatography was performed with Silicycle ultra pure silica gel (230-400 mesh) or Merck silica gel (230-400 mesh). IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR instrument for all previously unknown compounds (neat, thin film). Elemental analysis was performed by Atlantic Microlabs, Inc., Norcross, GA. ^{1}H NMR and ^{13}C NMR were recorded on a

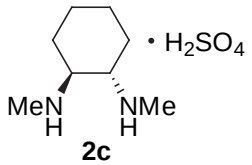
Bruker 400 MHz instrument with chemical shifts reported relative to tetramethylsilane (TMS). Gas chromatographic analysis were performed on a Hewlett Packard 6890 instrument with an FID detector and a Hewlett Packard 10 m x 0.2 mm i.d. HP-1 capillary column. Mass spectra (GC/MS) were recorded on a Hewlett Packard model GCD. All yields reported in the publication represent an average of at least two independent runs. Previously unknown compounds were synthesized, purified and analyzed from a single run and were then repeated for an average yield to be determined. Compounds described in the literature were characterized by comparing their ^{1}H NMR, melting point (mp) and GC/MS to the previously reported data; their purity was confirmed by GC.



***trans*-*N*,*N'*-Dimethyl-1,2-cyclohexanediamine (2a)** The synthesis of **2a** followed a procedure by Seebach[1] modified and detailed below: Ethyl formate (210 mL, 2.60 mol) and *trans*-1,2-cyclohexanediamine (52 mL, 0.42 mol) were combined to form a solution in a 500 mL RB flask with a stir bar. The flask, open to air, was lowered into an oil bath heated to 50 °C, and stirred for a period of 6 h. During this time a white precipitate formed, which thickened as the reaction progressed. The reaction mixture was allowed to reach ambient temperature and the solid was filtered through a frit and the crystals were washed with ethyl acetate (3x100 mL) to provide 59.2 g of the bis-amide. The filtrate was concentrated by the aid of a rotary evaporator to 100 mL, cooled to 4 °C for 24 h, and the resulting solid was isolated by filtration to give a second crop of the bis-amide (2.97 g). The combined yield of the bis-amide was 62.1 g (86% yield). This product was used in the next step without further purification.

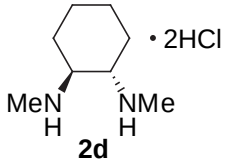
Lithium aluminum hydride (6.1 g, 160 mmol) (a new bottle purchased from Alfa Aesar) was added to a flame-dried 500 mL 2-necked flask, charged with a stir bar. The flask was then fitted with a rubber septum, evacuated through the side-arm, and back-filled with argon. To this flask, under a stream of argon, was canula transferred THF (150 mL) from a round-bottom flask. The flask was lowered into an ice bath and allowed to equilibrate, with stirring, for 20 min. The septum was removed under a stream of argon and the bis-amide (10.0 g, 59 mmol) was added in eight portions over 10 min. After 30 min the cooling bath was removed and the mixture was allowed to attain ambient temperature. Under a stream of argon a reflux condenser was quickly attached and the flask was heated, using an oil bath to 65 °C for 16 h. The flask was removed from heating, a septum was attached, and the reaction mixture was allowed to reach ambient temperature. The flask was lowered into an ice bath and allowed to equilibrate for 20 min. The septum was removed and, sequentially, water (5 mL), then 20% NaOH (50 mL) were added dropwise (exothermic reaction!), with stirring; the resulting mixture was stirred for an additional 2 h. Celite (25 g) was added to the mixture and the flask was swirled by hand and its contents were poured on to a frit. The solid was washed with THF (2x75 mL) and the resulting filtrate was concentrated to give a colorless residue. The residue was taken up in 1 M HCl (75 mL) and water (150 mL) and extracted with CH_2Cl_2 (3x100 mL). The *aqueous* layer was treated carefully with 20% NaOH solution (75 mL) and extracted with CH_2Cl_2 (3x100 mL). The resulting *organic* layer was transferred to an Erlenmeyer flask, dried over K_2CO_3, gravity filtered through filter paper, and concentrated to give 8.04 g (96% yield) of product **2a**. Further purification was found to not be necessary, but can be performed by distillation at 51 °C (20 mm Hg) to give a colorless oil that converts to a white solid if cooled to 4 °C (refrigerator). The ^{1}H NMR spectrum was in accord with that reported by Seebach.[1]

Using an identical procedure as above, *cis*-1,2-cyclohexanediamine (1.00 mL, 8.3 mmol) was converted to the bis-amide, and reduced with LAH to provide 0.84 g (71% yield over two steps) of **2b** as a light yellow oil. The ^{1}H NMR spectrum was in accord with that reported by Seebach.[1]



2c
racemic-*trans*

***trans*-*N*,*N'*-Dimethyl-1,2-cyclohexanediamine • H_2SO_4 salt (2c)** The *trans*-*N*,*N'*-Dimethyl-1,2-cyclohexanediamine (1.40 mL, 8.91 mmol) was dissolved in 10.0 mL of 0.89 M H_2SO_4 solution over 30 min. The solution was concentrated to a residue and was dried under vacuum to provide a white solid. The solid was dried under vacuum and then washed with of ethyl acetate (2x5 mL). The solid was collected and dried under vacuum to provide 1.65 g (77% yield) of **2c**. Mp: >250 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42 (m, 2H), 2.73 (s, 6H), 2.19 (d, 2H, J = 3.2 Hz), 1.75 (bs, 2H), 1.55 (m, 2H), 1.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.7, 30.5, 25.4, 22.0.



2d
racemic-*trans*

***trans*-*N*,*N'*-Dimethyl-1,2-cyclohexanediamine • 2 HCl salt (2d)**[2] *trans*-*N*,*N'*-Dimethyl-1,2-cyclohexanediamine (96 μL, 0.61 mmol) was dissolved in 1.22 M HCl solution (1.00 mL) over 30 min. The solution was concentrated to a residue and was dried under vacuum to slowly provide a crystalline white solid. The solid was dissolved in hot ethanol (5 mL) with 5 drops of water. Ethyl acetate (10 mL) was quickly added to induce crystal formation. After 1 h the solution was filtered to provide 113 mg (86% yield) of off-white crystals of **2d**. Mp: >250 °C. The ^{1}H NMR spectrum was in accord with that reported in the literature.[2]

A general procedure for the *N*-arylation of indoles.

To a resealable Schlenk tube or alternatively, a screw-cap test tube, was added CuI, the indole (1.00 equiv), K_3PO_4 (2.1 mmol), a stir bar, and the reaction vessel was fitted with a rubber septum. The vessel was evacuated and back-filled with argon, and this sequence was repeated an additional time. The aryl halide (1.20 equiv), diamine (1-20 mol%) and toluene (1 mL) were then added successively under a stream of argon. The reaction tube was sealed and the contents were stirred with heating from an oil bath at 110 °C for 24 h. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (2-3 mL), filtered through a plug of silica gel, eluting with additional ethyl acetate (10-20 mL). The filtrate was concentrated and the resulting residue was purified by column chromatography to provide the desired product.

Procedure for the screening of potential diamine ligands (Table 1).

Using the general procedure above, in 14 separate experiments, indole (0.117 g, 1.00 mmol) was coupled with 2-bromotoluene (144 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and 20 mol% of the ligands listed in Table 1. Gas Chromatographic (GC) analysis (dodecane as an internal standard) indicated the conversion of indole and the GC yield by comparison to previously synthesized product.[3]

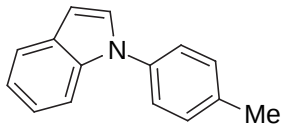
Procedure for the screening of copper sources (Table 2).

Using the general procedure above, in five separate experiments, indole (0.117 g, 1.00 mmol) was coupled with 4-bromotoluene (148 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), 5 mol% of the copper sources listed in Table 2 (column 1), and 10 mol% **2a (**16 μL, 0.10 mmol). Gas Chromatographic analysis with dodecane as an internal standard indicated the conversion of indole and the GC yield by comparison to previously synthesized product.[4]

Using the general procedure above, in two separate experiments, indole (0.117 g, 1.00 mmol) was coupled with 2-bromotoluene (144 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), 5 mol% of the copper sources listed in Table 2 (column 2), and 10 mol% **2a (**16 μL, 0.10 mmol).

Gas Chromatographic analysis with dodecane as an internal standard indicated the conversion of indole and the GC yield by comparison to previously synthesized product.[3]

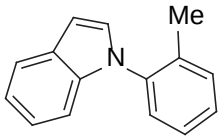
Experimental procedures for the comparison of ligands 1a and 2a (Table 3).



1-(4-Methylphenyl)indole[4] Following the general procedure, indole (0.141 g, 1.00 mmol) was coupled with 4-bromotoluene (123 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.002 g, 0.01 mmol), and **1a (**6 μL, 0.05 mmol, 5 mol%). The reaction provided a 57% GC yield of the title compound.

Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 4-bromotoluene (148 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **1a** (24 μL, 0.20 mmol, 20 mol%). The reaction provided 0.197 g (95% yield) of the title compound as an oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[4]

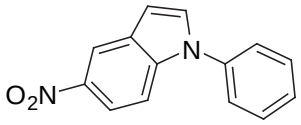
Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 4-bromotoluene (148 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.002 g, 0.001 mmol), and **2a** (8 μL, 0.05 mmol, 5 mol%). The reaction provided 0.199 g (96% yield) of the title compound as an oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[4]



1-(2-Methylphenyl)indole[3] Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 2-bromotoluene (144 μL, 1.00 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **1a** (24 μL, 0.20 mmol, 20 mol%). Flash chromatography on

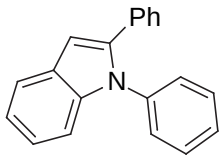
silica gel (2x15 cm; hexane:ethyl acetate 10:1) provided 0.182 g (88% yield) of the desired product as a colorless oil**.** The ^{1}H NMR spectrum was in accord with that reported in the literature.[3]

Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 2-bromotoluene (148 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2a** (32 μL, 0.20 mmol, 20 mol%). Flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 10:1) provided 0.189 g (91% yield) of the desired product as a colorless oil**.** The ^{1}H NMR spectrum was in accord with that reported in the literature.[3]



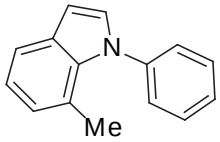
1-Phenyl-5-nitroindole Following the general procedure, 5-nitroindole (0.162 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **1a** (24 μL, 0.20 mmol, 20 mol%). The GC of the crude reaction mixture after 24 h showed a 38% yield of the desired product.

Following the general procedure, 5-nitroindole (0.162 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2a** (16 μL, 0.10 mmol, 10 mol%). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 10:1) to provide 0.229 g (96% yield) of the desired product as a yellow solid. Mp: 84-85 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.03 (d, 1H, J = 8.9 Hz), 7.54 (m, 2H), 7.44 (m, 5H), 6.80 (d, 1H, J = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 138.4, 138.3, 131.2, 129.8, 128.3, 127.6, 124.4, 118.0, 117.6, 110.3, 105.4. IR (neat, cm^{-1}): 1599, 1553, 1461, 1388, 1324, 1274, 1224, 774, 746, 701. Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23. Found: C, 70.30; H, 4.34.



1,2-Diphenylindole[5] Following the general procedure, 2-phenylindole (0.203 g, 1.00 mmol, 95% tech grade) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **1a** (24 μL, 0.20 mmol, 20 mol%). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 20:1) to provide 0.199 g (74% yield) of the title compound as a white solid. Mp 81-82 °C (chloroform). The ^{1}H NMR spectrum was in accord with that reported in the literature.[5]

Following the general procedure, 2-phenylindole (0.203 g, 1.00 mmol, 95% tech grade) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2a** (16 μL, 0.10 mmol, 10 mol%). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 20:1) to provide 0.249 g (92% yield) of the title compound as a white solid. Mp 81-82 °C (chloroform). The ^{1}H NMR spectrum was in accord with that reported in the literature.[5]

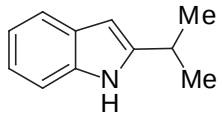


1-Phenyl-7-methylindole Following the general procedure, 7-phenylindole (0.131 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **1a** (24 μL, 0.20 mmol, 20 mol%). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 20:1) to provide 0.155 g (75% yield) of the title compound as a white solid (Characterization found in next paragraph).

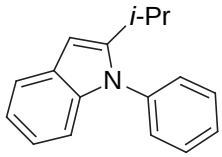
Following the general procedure, 7-phenylindole (0.131 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), and **2a** (16 μL, 0.10 mmol, 10 mol%). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 20:1) to provide 0.180 g (87% yield) of the title compound

as a white solid. Mp: 41-42 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, 1H, J = 7.9 Hz), 7.35 (m, 5H), 7.08 (d, 1H, J = 3.2 Hz), 7.05 (t, 1H, J = 7.6 Hz), 6.92 (d, 1H, J = 7.1 Hz), 6.59 (d, 1H, J = 3.2 Hz), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 135.6, 130.5, 129.4, 128.5, 127.9, 127.7, 124.7, 121.6, 120.2, 118.9, 102.7, 19.7. IR (neat, cm^{-1}): 3044, 1595, 1498, 1334, 1223, 783, 696, 559. Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32. Found: C, 86.81; H, 6.36.

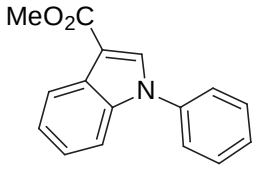
Experimental procedures for all compounds contained in Tables 4 and 5.



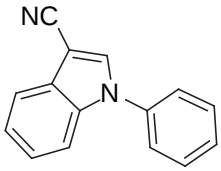
2-Isopropylindole The title compound can be synthesized through the known procedure by A. B. Smith.[6] The synthesis of 2-isopropylindole was accomplished through the use of unpublished chemistry from our laboratory.[7] The ^{1}H NMR spectrum was in accord with that reported by Smith, et al.[6]



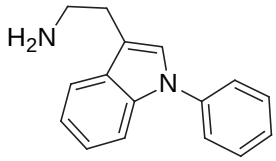
1-Phenyl-2-isopropylindole Following the general procedure, 2-isopropylindole (0.070 g, 0.38 mmol) was coupled with iodobenzene (63 μL, 0.57 mmol) using K_3PO_4 (0.169 g, 0.80 mmol), CuI (0.0072 g, 0.038 mmol, 10 mol%), **2a** (12 μL, 0.075 mmol, 20 mol%), and toluene (0.5 mL) for 48 h. The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 50:1) to provide 0.063 g (70% yield) of the desired product as a thick colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (m, 1H), 7.50 (m, 2H), 7.42 (m, 1H), 7.33 (m, 2H), 7.08 (m, 2H), 6.99 (m, 1H), 6.43 (s, 1H), 2.95 (septet, 1H, J = 7 Hz), 1.15 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 138.4, 138.1, 129.4, 128.5, 127.9, 127.9, 121.1, 119.9, 119.7, 110.0, 97.7, 25.8, 22.9. IR (neat, cm^{-1}): 3027, 2959, 2867, 1490, 1468, 1210, 745. Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28. Found: C, 86.52; H, 7.28.



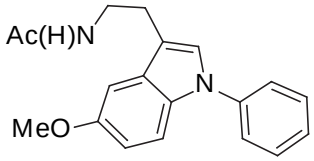
Methyl-1-phenylindole-3-carboxylate Following the general procedure, indole-3-methylbenzoate (0.175 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (16 μL, 0.010 mmol, 10 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 10:1) to provide 0.242 g (96% yield) of the desired product as a white solid. Mp: 75-76 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, 1H, J = 15 Hz), 7.99 (s, 1H), 7.45 (m, 6H), 7.28 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 138.3, 136.5, 134.0, 129.7, 127.6, 126.8, 124.6, 123.3, 122.4, 121.7, 110.9, 108.9, 51.0. IR (neat, cm^{-1}): 3056, 2948, 1705, 1538, 1503, 1213, 1052, 777, 748, 696. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21. Found: C, 76.49; H, 5.31.



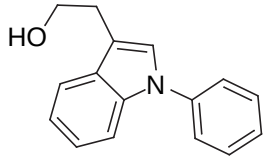
1-Phenyl-3-cyanoindole Following the general procedure, 3-cyanoindole (0.142 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 10:1) to provide 0.201 g (92% yield) of the desired product as a white solid. Mp: 119-120 °C (chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (m, 1H), 7.75 (s, 1H), 7.56 (m, 2H), 7.47 (m, 4H), 7.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 135.4, 134.5, 129.9, 128.3, 127.8, 124.7, 124.4, 122.7, 119.9, 115.5, 111.4, 87.9. IR (neat, cm^{-1}): 3123, 2224, 1599, 1501, 1458, 1225, 735, 694. Anal. Calcd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62. Found: C, 82.15; H, 4.76.



1-Phenyltryptamine[8] Following the general procedure, tryptamine (0.160 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.20 mmol, 20 mol%), and toluene (1.0 mL). The crude mixture was taken up in ethyl acetate (as in procedure B) and filtered through celite. The crude product was purified by flash chromatography on silica gel (2x15 cm; CH_2Cl_2(NH_3 saturated):MeOH 50:1) to provide 0.217 g (92% yield) of the title compound as a light yellow oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[8]

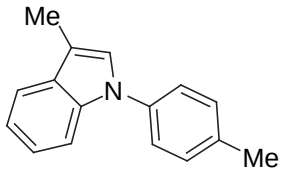


1-Phenylmelatonin[9] Following the general procedure, melatonin (0.232 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.20 mmol, 20 mol%), and toluene (1.0 mL). The crude mixture was taken up in ethyl acetate (as in procedure B) and filtered through celite. The crude product was purified by flash chromatography on silica gel (2x15 cm; hexanes:ethyl acetate 10:1) to provide 0.230 g (74% yield) of the title compound as a white solid. Mp 119-120 °C (chloroform). The ^{1}H NMR spectrum was in accord with that reported in the literature.[9]

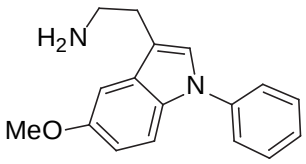


1-Phenyltryptophol[8] Following the general procedure, tryptophol (0.161 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI

(0.0095 g, 0.050 mmol), **2a** (16 μL, 0.10 mmol, 10 mol%), and toluene (1.0 mL). Crude GC/MS indicated up to 7% of the bis-arylated product (*N*- and *O*-arylated). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexanes:ethyl acetate 10:1 then hexanes:ethyl acetate 1:1) to provide 0.213 g (90% yield) of the title compound as a colorless oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[8]

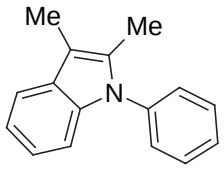


1-Phenyl-3-methylindole[10] Following the general procedure, 3-methylindole (0.131 g, 1.00 mmol) was coupled with 4-bromotoluene (148 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.002 g, 0.001 mmol), **2a** (8 μL, 0.05 mmol, 5 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexanes:ethyl acetate 50:1) to provide 0.188 g (85% yield) of the title compound as a white solid. Mp 43-44 °C (chloroform). The ^{1}H NMR spectrum was in accord with that reported in the literature.[10]

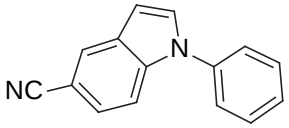


1-Phenyl-5-methoxytryptamine Following the general procedure, 5-methoxytryptamine (0.190 g, 1.00 mmol) was coupled with bromobenzene (126 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (16 μL, 0.010 mmol, 10 mol%), and toluene (0.5 mL). The crude mixture was taken up in ethyl acetate (as in procedure B) and filtered through celite. The crude product was purified by flash chromatography on silica gel (2x15 cm; CH_2Cl_2(NH_3 saturated):MeOH 50:1) to provide 0.194 g (77% yield) of the title compound as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (m, 5H), 7.24 (m, 1H), 7.12 (s, 1H), 7.08 (d, 1H, J = 6 Hz), 6.87 (dd, 1H, J = 6 Hz and J = 14 Hz), 3.85 (s, 3H), 3.05 (t, 2H, J = 7 Hz), 2.90 (t, 2H, J = 7 Hz) 1.18 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 139.6, 131.0, 129.3, 125.9, 125.6, 123.3,

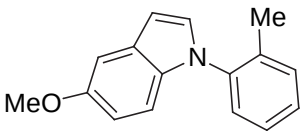
114.3, 112.1, 111.2, 100.8, 55.6, 42.1, 29.2. IR (neat, cm^{-1}): 2934, 1596, 1501, 1480, 1251, 758, 697. Anal. Calcd for $C_{17}H_{118}N_2O$: C, 76.67; H, 6.81. Found: C, 76.37; H, 6.89.



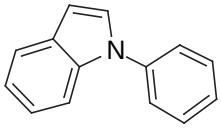
1-Phenyl-2,3-dimethylindole[11] Following the general procedure, 2,3-dimethylindole (0.145 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.010 mmol, 10 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexanes:ethyl acetate 50:1) to provide 0.215 g (97% yield) of the title compound as a colorless oil. The ^1H NMR spectrum was in accord with that reported in the literature.[11]



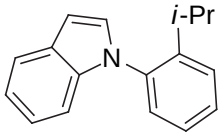
1-Phenyl-5-cyanoindole Following the general procedure, 5-cyanoindole (0.142 g, 1.00 mmol) was coupled with iodobenzene (134 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 20:1) to provide 0.214 g (98% yield) of the desired product as a viscous oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.52 (m, 3H), 7.41 (m, 5H), 6.72 (d, 1H, J = 4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 137.2, 130.3, 129.8, 128.8, 127.4, 126.5, 125.0, 124.5, 120.5, 111.2, 104.0, 103.2. IR (neat, cm^{-1}): 3108, 2221(s), 1596, 1499, 1339, 1221, 762, 725, 697. Anal. Calcd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62. Found: C, 82.75; H, 4.76. Alternatively, the above procedure can be accomplished using **3** (22 μL, 0.020 mmol, 20 mol%) as the ligand to provide 0.215 g (99% yield) of the above product.



1-(2-Methylphenyl)-5-methoxyindole Following the general procedure, 5-methoxyindole (0.177 g, 1.20 mmol) was coupled with 2-iodotoluene (127 μL, 1.00 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 20:1) to provide 0.199 g (84% yield) of the desired product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (m, 2H), 7.18 (m, 2H), 7.02 (d, 1H, J = 4 Hz), 7.00 (d, 1H, J = 6 Hz), 6.81 (d, 1H, J = 13 Hz), 6.72 (dd, 1H, J = 4 Hz and J = 13 Hz), 6.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 138.3, 135.6, 132.2, 131.1, 129.1, 128.6, 128.0, 128.0, 126.7, 112.2, 111.2, 102.3, 102.0, 55.7, 17.6. IR (neat, cm^{-1}): 3070, 2963, 1590, 1505, 1475, 1253, 778, 746. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37. Found: C, 81.11; H, 6.55.

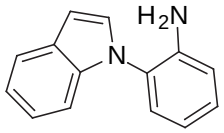


1-Phenylindole[12] Following the general procedure, indole (0.293 g, 2.50 mmol) was coupled with iodobenzene (335 μL, 3.00 mmol) using K_3PO_4 (1.06 g, 5.00 mmol), CuI (0.001 g, 0.005 mmol, 0.2 mol%), **2a** (4 μL, 0.025 mmol, 1 mol%), and toluene (2.5 mL) for 48 h. The crude product was purified by flash chromatography on silica gel (2x15 cm; hexanes:ethyl acetate 50:1) to provide 0.473 g (98% yield) of the title compound as a colorless oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[12]



1-(2-Isopropylphenyl)indole Following the general procedure, indole (0.177 g, 1.00 mmol) was coupled with 1-bromo-2-isopropylbenzene (185 μL, 1.20 mmol) using K_3PO_4 (0.446 g,

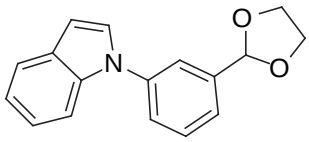
2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (0.5 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 100:1) to provide 0.205 g (87% yield) of the desired product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (m, 1H), 7.42 (m, 2H), 7.22 (m, 2H), 7.13 (m, 3H), 7.01 (m, 1H), 6.63 (m, 1H), 2.62 (septet, 1H, J = 7 Hz), 1.10 (d, 3H, J = 7 Hz), 1.07 (d, 3H, J = 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 137.8, 136.8, 129.2, 128.9, 128.6, 128.0, 126.7, 126.5, 122.0, 120.7, 119.8, 110.4, 102.3, 27.7, 24.6, 23.5. IR (neat, cm^{-1}): 3056, 3029, 2964, 2868, 1493, 1460, 1307, 1215, 779, 741. Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28. Found: C, 86.48; H, 7.38.



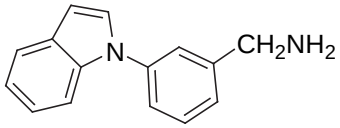
1-(2-Aminophenyl)indole Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 2-iodoaniline (0.263 g, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL) at 80 ^{0}C. The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 5:1) to provide 0.187 g (90% yield) of the desired product as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (m, 1H), 7.18 (m, 6H), 6.82 (m, 2H), 6.67 (d, 1H, J = 6 Hz), 3.52 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 136.3, 129.1, 128.6, 128.5, 124.8, 122.2, 120.9, 120.1, 118.5, 116.2, 110.7, 103.2, 102.0. IR (neat, cm^{-1}): 3380, 1600, 1582, 1464, 1332, 1212, 780, 740. Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81. Found: C, 80.68; H, 6.06.

Alternatively, 2-bromoaniline (0.206 g, 1.20 mmol) may be used as the aryl halide to provide, using the above conditions, 0.148 g (71% yield) of the desired product.

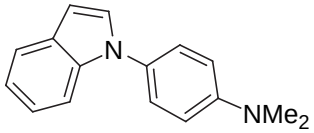
Use of ligand **3** (22 μL, 0.020 mmol, 20 mol%), in the above conditions with 2-bromoaniline (0.206 g, 1.20 mmol) provided 0.133 g (64% yield) of the desired product.



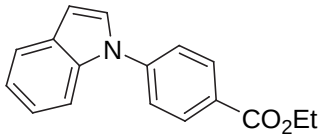
1-[3-(1,3-Dioxalane)phenyl]indole Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 3-(bromophenyl)-1,3-dioxalane (180 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 10:1) to provide 0.228 g (86% yield) of the desired product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (m, 1H), 7.61 (m, 1H), 7.56 (d, 1H, J = 8.3 Hz), 7.42 (m, 3H), 7.28 (d, 1H, J = 3.3 Hz), 7.16 (m, 2H), 6.63 (dd, 1H, J = 3.3 Hz and J = 0.6 Hz), 5.78 (s, 1H), 4.05 (m, 2H), 3.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 139.6, 135.5, 129.5, 129.1, 127.7, 124.7, 124.4, 122.2, 122.1, 121.0, 120.2, 110.3, 103.5, 102.9, 65.1. IR (neat, cm^{-1}): 2886, 1493, 1460, 1335, 1213, 1097, 942, 743. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70. Found: C, 76.81; H, 5.74.



1-(3-Aminomethylphenyl)indole[13] Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 3-iodobenzylamine (160 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL) at 80 ^{0}C. The crude product was purified by flash chromatography on silica gel (2x15 cm; CH_2Cl_2(NH_3 saturated):MeOH 100:1) to provide 0.201 g (90% yield) of the desired product as a colorless oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[13]



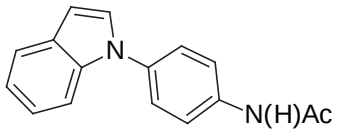
1-(4-Dimethylaminophenyl)indole[14] Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with *N*,*N*-dimethyl-4-bromoaniline (0.240 g, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 20:1) to provide 0.220 g (93% yield) of the desired product as a white viscous oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[14]



1-(Ethyl-4-benzoate)indole[15] Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with ethyl-4-iodobenzoate (185 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL) at 80 ^{0}C. The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 20:1) to provide 0.237 g (90% yield) of the desired product as a colorless oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[15]

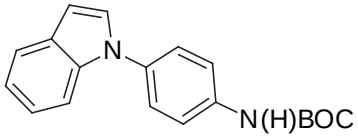
Alternatively, ethyl-4-bromobenzoate (200 μL, 1.20 mmol) may be used as the aryl halide to provide, using the above conditions, 0.239 g (90% yield) of the desired product.[15]

Use of ligand **3** (22 μL, 0.020 mmol, 20 mol%), in the above conditions with ethyl-4-bromobenzoate (200 μL, 1.20 mmol) provided 0.244 g (92% yield) of the desired product.[15]

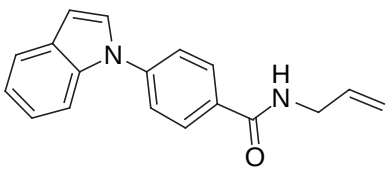


1-(4-*N*-Acetylaminophenyl)indole Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 4-iodo-*N*-acetylaminobenzene[16] (0.313 g, 1.20 mmol) using K_3PO_4

(0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 2:1) to provide 0.180 g (72% yield) of the desired product as a white solid. Mp: 158-160 °C (chloroform) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (m, 2H), 7.66 (d, 1H, J = 11 Hz), 7.50 (m, 3H), 7.38 (d, 1H, J = 3 Hz), 7.19 (m, 1H), 7.14 (m, 1H), 6.66 (d, 1H, J = 3 Hz), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 138.2, 137.2, 136.9, 130.6, 128.9, 125.6, 123.2, 122.1, 121.9, 121.1, 111.2, 104.2, 24.0. IR (neat, cm^{-1}): 3304, 1657, 1519, 1456, 1314, 1213, 840, 741. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.72; H, 5.64. Found: C, 76.32; H, 5.84.

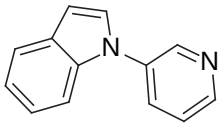


1-(4-*N*-*tert*-Butoxycarbonylamino)indole Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 4-iodo-*N*-*tert*-butoxycarbonylamino-benzene[17] (0.382 g, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 2:1) to provide 0.231 g (75% yield) of the desired product as a white solid. Mp: 135-137 °C (chloroform) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (m, 2H), 7.45 (m, 3H), 7.37 (m, 2H), 7.25 (d, 1H, J = 6 Hz), 7.15 (m, 1H), 6.63 (m, 2H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 136.8, 136.0, 134.7, 129.0, 128.0, 125.0, 122.2, 121.0, 120.1, 119.5, 110.3, 103.1, 28.3. IR (neat, cm^{-1}): 3321, 2983, 1713, 1522, 1368, 1234, 1158, 762, 738. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54. Found: C, 73.84; H, 6.58.

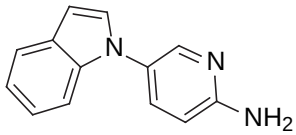


1-(4-*N*-Allylaminocarbonylphenyl)indole Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 4-iodo-*N*-allylaminocarbonylbenzene[18] (0.382 g, 1.20

mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 2:1) to provide 0.231 g (75% yield) of the desired product as a white solid. Mp: 117-118 °C (chloroform) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, 2H, J = 8.5 Hz), 7.64 (m, 1H), 7.51 (m, 1H), 7.47 (d, 2H, J = 8.5 Hz), 7.43 (d, 1H, J = 3.3 Hz), 7.15 (m, 2H), 7.05 (t, 1H, J = 5.6 Hz), 6.65 (d, 1H, J = 3.0 Hz), 5.90 (m, 1H), 5.23 (dd, 1H, J = 1.4 Hz and J = 12.8 Hz), 5.14 (dd, 1H, J = 1.4 Hz and J = 10.3 Hz), 4.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 142.2, 135.2, 134.0, 131.7, 129.5, 128.5, 127.3, 123.2, 122.6, 121.2, 120.7, 116.3, 110.3, 104.5, 42.4. IR (neat, cm^{-1}): 3312, 3079, 1638, 1604, 1506, 1456, 1301, 1235, 1211, 759, 742. Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84. Found: C, 77.87; H, 5.83.

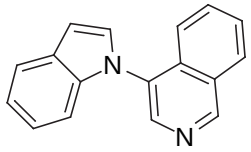


1-(3-Pyridyl)indole[15] Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 3-bromopyridine (116 μL, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 10:1) to provide 0.177 g (91% yield) of the desired product as a colorless oil. The ^{1}H NMR spectrum was in accord with that reported in the literature.[15]



1-(3-Pyridyl-6-amino)indole Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 2-amino-5-bromopyridine (0.208 g, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 1:2) to provide 0.169 g (81% yield) of the desired product as a thick colorless oil. ^{1}H NMR

(400 MHz, $CDCl_3$): δ 8.20 (d, 1H, J = 1.3 Hz), 7.68 (d, 1H, J = 10 Hz), 7.50 (dd, 1H, J = 2.0 Hz and J = 10 Hz), 7.34 (d, 1H, J = 9 Hz), 7.16 (m, 3H), 6.63 (d, 1H, J = 2.0 Hz), 6.53 (d, 1H, J = 8 Hz), 4.78 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 144.5, 136.5, 134.9, 128.7, 128.1, 127.5, 122.2, 121.0, 120.1, 110.0, 108.7, 103.0. IR (neat, cm^{-1}): 3380, 1624, 1500, 1458, 1409, 1213, 741. Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30. Found: C, 74.83; H, 5.24.



1-(4-Isoquinolino)indole Following the general procedure, indole (0.117 g, 1.00 mmol) was coupled with 4-bromoisoquinoline (0.250 g, 1.20 mmol) using K_3PO_4 (0.446 g, 2.1 mmol), CuI (0.0095 g, 0.050 mmol), **2a** (32 μL, 0.020 mmol, 20 mol%), and toluene (1.0 mL). The crude product was purified by flash chromatography on silica gel (2x15 cm; hexane:ethyl acetate 3:1) to provide 0.173 g (71% yield) of the desired product as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 9.33 (d, 1H, J = 0.4 Hz), 8.62 (s, 1H), 8.07 (m, 1H), 7.74 (m, 1H), 7.62 (m, 2H), 7.51 (m, 1H), 7.32 (d, 1H, J = 3.2 Hz), 7.16 (m, 2H), 7.04 (m, 1H), 6.80 (dd, 1H, J = 0.8 Hz and J = 3.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 141.5, 137.8, 133.0, 131.2, 131.1, 129.4, 129.1, 128.6, 128.0, 127.8, 122.4, 122.3, 121.0, 120.4, 110.5, 103.8. IR (neat, cm^{-1}): 3050, 1583, 1463, 1403, 1332, 1212, 934, 783, 742, 604. Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.59; H, 4.95. Found: C, 83.36; H, 5.07.

Reference Section:

(1) Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta.* **1988**, *71*, 1999.

(2) Akester, J.; Jingji, C.; Gideon, F. *J. Org. Chem.* **1997**, *62*, 431.

(3) Maiorana, S.; Baldoli, C.; Buttero, P. D.; Michela, D.; Papagni, A. *Synthesis* **1998**, *5*, 735.

(4) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

(5) Aldrich Chemical Spectra FT-NMR **1**(3),125A.

(6) Smith, A. B. (III); Visnick, M.; Hseltine, J. N.; Sprengler, P. A. *Tetrahedron* **1986**, *42*, 2957.

(7) Unpublished results from the laboratory of S. L. Buchwald.

(8) Grandberg, B. *Chem. Heterocycl. Compd. (Eng.)* **1973**, *9*, 196. *Khim. Geterotskl. Soedin.* **1973**, *9*, 213.

(9) Mori, M.; Rivara, S.; Silva, C.; Bordi, F.; Plazzi, P. V.; *J. Med. Chem.* **1998**, *41*, 3831.

(10) Lopez-Alvarado, P.; Avendano, C.; Menendez, J. C. *J. Org. Chem.* **1995**, *60*, 5678.

(11) Tokmakov, G. P.; Grandberg, I. I. *Tetrahedron*, **1995**, *51*, 2091.

(12) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403.

(13) Glamkowski, E. J.; Fortunato, J. M.; Spaulding, T. C.; Winkler, J. C.; Ellis, D. B. *J. Med. Chem.* **1985**, *28*, 66.

(14) Old, D. W.; Harris, M. C.; Buchwald, S. L.; *Org. Lett.* **2000**, *2*, 1403.

(15) Smith, W. J. (III); Sawyer, J. S. *Tetrahedron Lett.* **1996**, *37*, 299.

(16) Brazdi, L. C.; Fitch, J. L.; Cutler, C. J.; Haynik, D. M.; Ace, E. R. *J. Chem. Soc. Perkin Trans. 2* **1998**, *4*, 933.

(17) Hu, L.,-Y.; Ryder, T. R.; Rafferty, M. F.; Taylor, C. P.; Feng, M. R.; Kuo, B.,-S.; Lotarski, S. M.; Miljanich, G. P.; Millerman, E.; Siebers, K. M.; Szoke, B. G. *Bioorg. Med. Chem.* **2000**, 1203.

(18) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.