SUPPORTING INFORMATION

2-Aryl and 2-Heteroaryl Indoles from 1-Alkynes and *o*-Iodotrifluoroacetanilide through a Domino Copper-Catalyzed Coupling-Cyclization Process

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Melting points were determined with a Büchi apparatus and are uncorrected. 1-Alkynes containing aryl and heteroaryl groups were prepared through the Sonogashira coupling of aryl and heteroaryl halides with trimethylsilylacetylene.¹ Cu(1,10-phenanthroline)(PPh₃)Cl, [Cu(1,10-phenanthroline)(PPh₃)₂]NO₃, and Cu(PPh₃)₂NO₃ were prepared according to the procedure described by Venkataraman and co-workers.² *o*-Iodotrifluoroacetanilide was prepared according to our procedure.³ All of the other reagents, catalysts, ligands, and solvents are commercially available and were used as purchased, without further purification. Reaction products were purified on axially compressed columns, packed with SiO₂ 25-40 µm (Macherey Nagel), connected to a Gilson solvent delivery system and to a Gilson refractive index detector, and eluting with *n*-hexane/ethyl acetate mixtures. ¹H NMR spectra (400 MHz) and ¹³C NMR spectra (100.6 MHz) were recorded with a Bruker Avance 400 spectrometer. IR spectra were recorded with a Jasco FT/IR 430 spectrometer.

Typical Procedure for the Synthesis of 2-Substituted Indoles (4) from Coupling Products (3) (Table 1, entry 6): in a Carusel Tube Reactor (Radely Discovery Technology), to a solution of *o*-(heptyn-1-yl)trifluoroacetanilide (0.141 g, 0.50 mmol) in 2.0 mL of 1,4-dioxane, CuI (0.0048 g, 0.025 mmol), (±)-1,2-*trans*-cyclohexanediamine (0.050 mmol, 6 µL), and K₃PO₄ (0.212 g, 1.00 mmol) were added. The mixture was stirred for 1.5 h at 110 °C under an argon atmosphere. After cooling, the reaction mixture was diluted with ethyl acetate, washed with water, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; *n*-hexane/EtOAc 95/5 v/v) to give 0.0782 g of the 2-pentylindole product (84 % yield): mp: 41-42 °C; IR (KBr): 3394, 3053, 2925, 2858, 1456 cm⁻¹; ¹H NMR (CDCl₃) δ 7.84 (s, 1 H), 7.58 (d, *J* = 7.6 Hz, 2 H), 7.32 (dd, *J*₁ = 7.7 Hz, *J*₂ = 0.6 Hz, 1 H), 7.18-7.11 (m, 2 H), 7.28 (bs, 1 H), 2.78 (t, *J* = 7.6 Hz, 2 H), 1.80-1.73 (m, 2 H), 1.46-1.39 (m, 4 H), 1.00-0.94 (m, 3 H); ¹³C NMR (CDCl₃) δ 140.1, 135.9, 129.0, 121.0, 119.8, 119.7, 110.4, 99.5, 31.6, 29.0, 28.3, 22.6, 14.1. Anal calcd for C₁₃H₁₇N. C, 83.37; H, 9.15; N, 7.48. Found: C, 83.43; H, 9.13; N, 7.45.

Typical Procedure A for the Synthesis of 2-Substituted Indoles (4) from *o*-Iodotrifluoroacetanilide (1b) and 1-Alkynes (2) (Table 3, entry 5): in a Carusel Tube Reactor (Radely Discovery Technology), to a solution of *o*-iodotrifluoroacetanilide (0.157 g, 0.50 mmol) and 1-chloro-4-ethynyl-benzene (0.068 g, 0.50 mmol) in 2.0 mL of toluene, [Cu(phen)(PPh₃)]NO₃ (0.050 mmol, 0.041 g), and K₃PO₄ (0.212 g, 1.00 mmol) were added. The mixture was stirred for 6

¹ (a) Sonogashira, K. in *Metal-Catalyzed Cross-Coupling Reactions*, Eds. F. Diederich and P. J. Stang, Wiley-WCH, Weinheim **1998**, 203; (b) Sonogashira, K. in *Handbook of Organopalladium Chemistry for Organic Synthesis*, Ed. Negishi, E. John Wiley & Sons, New York, **2002**, 1, 493.

² Bates, C. G., Saejueng, P., Murphy, J. M., Venkataraman, D. *Org. Lett.* **2002**, 4, 4727.

³ Arcadi, A., Cacchi, S., Marinelli, F. *Tetrahedron Lett.* **1989**, 30, 2581.

h at 110 °C under an argon atmosphere. After cooling, the reaction mixture was diluted with ethyl acetate, washed with water, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; *n*-hexane/EtOAc 85/15 v/v) to give 0.0900 g of the 2-(*p*-chlorophenyl)indole product (80 % yield).

Table 2. Ligands, Bases, and Solvents in the Copper-Catalyzed Synthesis of 2-Phenyl Indole **4a** from *o*-Iodotrifluoroacetanilide **1b** and Phenylacetylene.^a

entry	catalyst system (Cu %)	base	solvent	t (h)	4a (%) ^b	3c (%) ^b
1	CuI/CHDA ^{c,d} (5)	K ₃ PO ₄	dioxane	24	30	traces
2	CuI/PPh ₃ ^d (5)	K ₃ PO ₄	dioxane	24	34	23
3	CuI/PPh ₃ ^d (10)	K ₃ PO ₄	dioxane	24	61	34
4	CuI/PPh ₃ ^d (15)	K ₃ PO ₄	dioxane	24	88	-
5	CuI/PPh ₃ ^d (15)	K ₃ PO ₄	DMSO	24	43	-
6	CuI/PPh ₃ ^d (15)	K ₃ PO ₄	DMA	24	31	35 ^e
7	CuI/PPh ₃ ^d (15)	K ₃ PO ₄	toluene	24	71	9
8	Cu(PPh ₃) ₂ NO ₃ (10)	K ₃ PO ₄	dioxane	24	48	41
9	Cu(PPh ₃) ₂ NO ₃ (10)	K ₃ PO ₄	DMSO	24	65	-
10	Cu(PTPP)Cl ^f (10)	K ₃ PO ₄	toluene	12	68	2
11	Cu(PBTTP)NO ₃ ^g (10)	K ₃ PO ₄	dioxane	24	75	21
12	Cu(PBTTP)NO ₃ ^g (10)	K ₃ PO ₄	toluene	12	78	-
13	Cu(PBTTP)NO ₃ ^g (10)	Cs ₂ CO ₃	dioxane	12	41	-
14	Cu(PBTTP)NO ₃ ^g (10)	Cs ₂ CO ₃	toluene	2	49	- ^h

^a Unless otherwise stated, reactions were carried out on a 0.5 mmol scale in 2 mL of solvent by using 1 equiv of *o*-iodotrifluoroacetanilide **1b**, 1 equiv of phenylacetylene, 2 equiv of K₃PO₄ in the presence copper(I) salts and ligands or copper(I) complexes (see Table) at 110 °C. ^b Yields are given for isolated products. ^c CHDA = (±)-1,2-*trans*-cyclohexanediamine. ^d Cu:ligand = 1:2. ^e **1b** was recovered in 11% yield. ^f Cu(PTPP)Cl = Cu(1,10-phenanthroline)(PPh₃)Cl. ^g Cu(PBTTP)NO₃ = [Cu(1,10-phenanthroline)(PPh₃)₂]NO₃. ^h **1b** was recovered in 10% yield.

Typical Procedure B for the Synthesis of 2-Substituted Indoles (4) from *o*-Iodotrifluoroacetanilide (1b) and 1-Alkynes (2) (Table 3, entry 6): in a Carousel Tube Reactor (Radely Discovery Technology), to a solution of *o*-iodotrifluoroacetanilide (0.157 g, 0.50 mmol) and 1-chloro-4-ethynyl-benzene ((0.068 g, 0.50 mmol) in 2.0 mL of 1,4-dioxane, CuI (0.075 mmol, 0.014 g), PPh₃ (0.150 mmol, 0.039 g), and K₃PO₄ (0.212 g, 1.00 mmol) were added. The mixture was stirred for 24 h at 110 °C under an argon atmosphere. After cooling, the reaction mixture was diluted with ethyl acetate, washed with water, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; *n*-hexane/EtOAc 85/15 v/v) to give 0.075 g of 2-(*p*-chlorophenyl)indole (66 % yield; mp: 203-205 °C, lit. mp 206-207)⁴ and 0.050 g of *o*-(*p*-chlorophenylethynyl)trifluoroacetanilide (31 % yield): mp: 138 °C; IR (KBr): 3300, 1708 cm⁻¹; ¹H NMR (CDCl₃) δ 8.84 (s, 1 H), 8.39 (d, *J* = 8.3 Hz, 1 H), 7.58 (dd, *J*₁ = 7.7 Hz, *J*₂ = 1.5 Hz, 1 H), 7.50-7.23 (m, 6 H); ¹³CNMR (CDCl₃) δ 154.5 (q, *J* = 37.4 Hz), 136.2, 135.6, 132.7, 131.8, 130.2, 129.2, 125.7, 120.2, 119.8, 115.8 (q, *J* = 292.1 Hz), 113.3, 96.9, 83.9; ¹⁹F NMR {H} (CDCl₃) δ -76.27. Anal calcd for C₁₆H₉F₃ClNO C, 59.37; H, 2.80; N, 4.33. Found C, 59.30; H, 2.78; N, 4.31.

2-Phenylindole (Table 3, entry 1): mp: 186-187 °C lit. mp : 188-190 °C¹

2-(*p*-Acetylphenyl)indole (Table 3, entry 3): mp. 201-204 °C; IR (KBr): 3355, 3056, 1670 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 11.72 (s, 1 H), 8.06-7.98 (m, 4 H), 7.58 (d, *J* = 7.9 Hz, 1 H), 7.45 (dd, *J*₁ = 8.1 Hz, *J*₂ = 0.6 Hz, 1 H), 7.16 (dt, *J*₁ = 7.1 Hz, *J*₂ = 1.1 Hz, 1 H), 7.10-7.08 (m, 1 H), 7.04 (dt, *J*₁ = 7.1 Hz, *J*₂ = 0.9 Hz, 1 H), 2.61 (s, 3 H); ¹³CNMR (DMSO-*d*₆) δ 199.7, 138.1, 137.0, 136.8, 135.8, 129.5, 129.0, 125.3, 123.0, 121.0, 120.2, 112.1, 101.4, 27.2. Anal calcd for C₁₆H₁₃NO C, 81.68; H, 5.57; N, 5.95. Found C, 81.59; H, 5.55; N, 5.92.

2-(*o*-Methoxyphenyl)indole (Table 1, entry 5): mp: 72-74 °C, lit. 75-77 °C⁵; IR (KBr) 3386, 3053 cm⁻¹; ¹H NMR (CDCl₃) δ 8.64 (bs, 1 H), 7.75-7.71 (m, 2 H), 7.64 (d, *J* = 7.7 Hz, 1 H), 7.48-7.40 (m, 2 H), 7.31-7.17 (m, 3 H), 6.87 (d, *J* = 1.1 Hz, 1 H); ¹³C NMR (CDCl₃) δ 136.4, 134.1, 133.6, 131.6, 129.3, 128.3, 127.8, 122.7, 121.5, 120.9, 120.3, 111.2, 103.8. Anal calcd for C₁₄H₁₀BrN C, 61.79; H, 3.70; N, 5.15. Found C, 61.70; H, 3.69; N, 5.13.

2-(*p*-Acetamidophenyl)indole (Table 3, entry 7): mp: 279-280 °C; IR (KBr): 3426, 3330, 3048, 2924, 1634 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 11.43 (s, 1 H), 10.05 (s, 1 H), 7.80 (d, *J* = 8.7 Hz, 2 H), 7.68 (d, *J* = 8.7 Hz, 2 H), 7.51 (d, *J* = 7.9 Hz, 1 H), 7.39 (dd, *J*₁ = 7.9 Hz, *J*₂ = 0.7 Hz, 1 H), 7.08 (dt, *J*₁ = 7.0 Hz, *J*₂ = 1.1 Hz, 1 H), 6.99 (dt, *J*₁ = 7.0 Hz, *J*₂ = 1.1 Hz, 1 H), 6.80 (d, *J* = 1.4 Hz, 1 H), 2.08 (s, 1 H); ¹³CNMR (DMSO-*d*₆) δ 168.9, 139.2, 138.2, 137.6, 129.3, 127.6, 126.0, 121.8, 120.3, 119.8, 119.7, 111.7, 98.4, 24.6. Anal calcd for C₁₆H₁₄N₂O C, 76.78; H, 5.64; N, 11.19. Found C, 76.69; H, 5.63; N, 11.17.

2-(*o*-Methoxyphenyl)indole (Table 3, entry 12): mp: wax; IR (neat): 3408, 3039, 2973 cm⁻¹; ¹H NMR (CDCl₃) δ 7.88 (dd, *J*₁ = 7.4 Hz, *J*₂ = 1.7 Hz, 1 H), 7.68 (dd, *J*₁ = 7.8 Hz, *J*₂ = 0.7 Hz, 1 H), 7.46 (d, *J* = 8.1 Hz, 1 H), 7.35-7.04 (m, 4 H), 6.96 (d, *J* = 1.1 Hz, 1 H), 4.05 (s, 3 H); ¹³CNMR (CDCl₃) δ 155.9, 136.2, 136.1, 134.5, 128.6, 128.4, 121.9, 121.6, 120.6, 120.3, 119.9, 112.0, 111.4, 99.9, 55.9. Anal calcd for C₁₅H₁₃NO C, 80.69; H, 5.87; N, 6.27. Found C, 80.60; H, 5.85; N, 6.29.

⁴ Blades, C. E., Wilds A. L., *J. Org. Chem.*, **1956**, 21, 1013.

⁵ Dalton, L.; Humphrey, G.L., Cooper, M.M., Joule, J.A., *J. Chem. Soc., Perkin Trans. 1 Organic and Bio-Organic Chemistry (1972-1999)*, **1983**,10, 2417.

2-(3,5-Dimethylphenyl)indole (Table 3, entry 13): mp: 146-147 °C; IR (KBr): 3385, 3049, 2916, 1351 cm⁻¹; ¹H NMR (CDCl₃) δ 8.35 (bs, 1 H), 7.73 (d, *J* = 8.1 Hz, 1 H), 7.46-7.20 (m, 5 H), 7.06 (s, 1 H), 6.90-6.87 (m, 1 H), 2.47 (s, 6 H); ¹³C NMR (CDCl₃) δ 138.6, 138.3, 136.8, 132.3, 129.6, 129.4, 123.1, 122.2, 120.7, 120.2, 111.0, 99.8, 21.5. Anal calcd for C₁₆H₁₅N C, 86.84; H, 6.83; N, 6.33. Found C, 86.75; H, 6.81; N, 6.35.

2-(2-Pyridyl)indole (Table 3, entry 19): mp: 148 °C, lit mp: 150-152 °C⁶

2-(*p*-Methoxyphenyl)indole (Table 3, entry 10): mp °C: 228-229 °C, lit. mp. 230-231 °C¹.

2-(*p*-Nitrophenyl)indole (Table 3, entry 17): mp: 230-231 °C, lit. mp: 251-252 °C¹.

2-(3-Quinolyl)indole (Table 3, entry 20): mp: 250-252 °C; IR (KBr) 3371, 3068 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 11.83 (s, 1 H), 9.46 (s, 1 H), 8.73 (s, 1 H), 8.04 (d, *J* = 8.3 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 7.75 (t, *J* = 6.9 Hz, 1 H), 7.66-7.59 (m, 2 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 7.21 (s, 1 H), 7.16 (t, *J* = 7.1 Hz, 1 H), 7.04 (t, *J* 7.1 Hz, 1 H); ¹³C NMR (DMSO-*d*₆) δ 149.1, 147.1, 138.1, 135.3, 130.3, 129.8, 129.4, 129.1, 128.6, 128.2, 127.9, 126.1, 122.9, 120.9, 120.2, 112.0, 101.0. Anal calcd for C₁₇H₁₂N₂ C, 83.58; H, 4.95; N, 11.47. Found C, 83.50; H, 4.93; N, 11.46.

4-(*p*-Methoxycarbonylphenyl)indole (Table 3, entry 14): mp. 201-202 °C; IR (KBr): 3348, 3058, 2949, 1692 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 11.7 (s, 1 H), 8.06-7.98 (m, 4 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 7.40 (d, *J* = 8.2 Hz, 1 H), 7.15 (dt, *J*₁ = 7.5 Hz, *J*₂ = 0.8 Hz, 1 H), 7.08-7.00 (m, 2 H), 3.88 (s, 3 H); ¹³C NMR (DMSO-*d*₆) δ 166.5, 138.1, 137.2, 136.8, 130.4, 129.0, 128.4, 125.4, 123.0, 121.0, 120.2, 112.1, 101.4, 52.6. Anal calcd for C₁₆H₁₃NO₂ C, 76.48; H, 5.21; N, 5.57. Found C, 76.40; H, 5.22; N, 5.55.

2-(*p*-Formylphenyl)indole (Table 3, entry 16): mp: 160-162 °C; IR (KBr): 3421, 1685 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 11.76 (s, 1 H), 10.01 (s, 1 H), 8.09 (d, *J* = 8.4 Hz, 2 H), 7.98 (d, *J* = 8.4 Hz, 2 H), 7.59 (d, *J* = 7.9 Hz, 1 H), 7.45 (d, *J* = 8.1 Hz, 1 H), 7.20-7.13 (m, 2 H), 7.06 (t, *J* = 7.5 1 H); ¹³C NMR (DMSO-*d*₆) δ 193.1, 138.6, 138.5, 137.0, 135.5, 131.1, 129.3, 126.0, 123.5, 121.5, 120.6, 112.5, 102.3. Anal calcd for C₁₅H₁₁NO C, 81.43; H, 5.01; N, 6.33. Found C, 81.35; H, 4.99; N, 6.31.

2-(*m*-Methoxyphenyl)indole (Table 3, entry 11): mp 136-137 °C; IR (KBr): 3433 cm⁻¹; ¹H NMR (CDCl₃) δ 8.39, (s, 1 H), 7.67 (d, *J* = 7.9 Hz, 1 H), 7.44-7.36 (m, 2 H), 7.30-7.20 (m, 3 H), 7.17 (dt, *J*₁ = 8.0 Hz, *J*₂ = 1.1 Hz, 1 H), 6.93-6.90 (m, 1 H), 6.87-6.86 (m, 1 H), 3.91 (s, 3 H); ¹³C NMR (CDCl₃) δ 160.2, 137.9, 136.9, 133.9, 130.2, 129.3, 122.5, 120.8, 120.3, 117.8, 113.2, 111.1, 111.0, 100.3, 55.5. Anal calcd for C₁₅H₁₃NO C, 80.69; H, 5.87; N, 6.27. Found C, 80.59; H, 5.88; N, 6.26.

***N*-(Indol-2-ylmethyl)propionamide (Table 1, entry 3):** mp: 278-279 °C; IR (KBr) 3339, 3287, 3091, 3050, 2978, 2923, 1649, 1376 cm⁻¹; ¹H NMR (CDCl₃) δ 9.05 (bs, 1 H), 7.57 (dd, *J*₁ = 7.8 Hz, *J*₂ = 1.1 Hz, 1 H), 7.35 (dd, *J*₁ = 8.1 Hz, *J*₂ = 0.9 Hz, 1 H), 7.19-7.08 (m, 2 H), 6.34 (s, 1 H), 6.09 (bs, 1 H), 4.50 (d, *J* = 6.0 Hz, 2 H), 2.28 (q, *J* = 7.5 Hz, 2 H), 1.21 (t, *J* = 7.5 Hz, 3 H); ¹³C NMR (CDCl₃) δ 175.5, 136.7, 136.5, 127.7, 122.1, 120.4, 119.8, 111.2, 100.6, 34.5, 29.6, 9.7. Anal calcd for C₁₆H₁₄N₂O C, 71.26; H, 6.98; N, 13.85. Found C, 71.17; H, 6.97; N, 13.82.

⁶ Barolo, S. M., Lukach, A. E., Rossi, R. A., *J. Org. Chem.* **2003**, 68, 2807.