Copper-Catalyzed Domino Halide Exchange-Cyanation of Aryl Bromides

Jacopo Zanon, Artis Klapars and Stephen L. Buchwald*

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Supporting Information

General Considerations

Reagents: Sodium cyanide (CAUTION: HIGHLY TOXIC)[1] was purchased from Aldrich (97% pure). Copper(I) iodide (fine powder) was purchased from Strem (98% pure). If granulated CuI, available from other sources, is used instead, it may be necessary to grind it. CuI is air-stable and does not require any special precautions other than storage in an amber vial. *N,N'*-Dimethylethylenediamine was purchased from Aldrich. It forms a carbonate salt if exposed to air although we did not encounter any reproducibility problems even when using old samples of the diamine that had turned light brown and contained some precipitate. Potassium iodide (99.9% pure, powder) was purchased from Alfa Aesar and stored in a dessicator. Although KI and NaCN were weighed out in the air, care was taken to minimize exposure to air due to the hygroscopicity of the salts, particularly during very humid periods of the year. Toluene was purchased from J. T. Baker in CYCLE-TAINER[2] solvent delivery kegs, which were purged with argon for 2 h and purified by passing the toluene through two packed columns of neutral alumina and copper (II) oxide under argon pressure. All other reagents were commercially available and used without further purification. Flash column chromatography was performed with J. T. Baker silica gel 60 (230-400 mesh).

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[1] Cyanide containing waste can be decontaminated using a solution of NaOCl in water (CLOROX bleach). See: Lunn, G.; Sansone, E. B. *Destruction of Hazardous Chemicals in the Laboratory*, 2nd ed., Wiley & Sons: New York, 1994; pp 133-138.

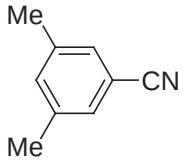
[2] (a) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520. (b) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.

Techniques: The copper-catalyzed cyanation reactions are sensitive to oxygen and moisture. Nevertheless, neither glovebox techniques nor purification of the commercially available reagents are required. The following procedure was used for the reactions that were performed in Schlenk tubes. After a 15 mL Schlenk tube with a screw thread (Kontes) was dried in an oven at 120 °C overnight, it was equipped with a 10×3 mm Teflon-coated stirring bar and a Teflon valve, evacuated, then backfilled with argon. The solid reagents were weighed out in the air by adding them directly to the Schlenk tube with the Teflon valve removed. The Schlenk tube was again fitted with the Teflon valve, evacuated and backfilled with argon. Under a positive pressure of argon, the Teflon valve was replaced with a rubber septum, and the liquid reagents were added to the Schlenk tube using Hamilton mycrosyringes (if <500 μL) or all polypropylene/polyethylene disposable syringes (if >500 μL). The rubber septum was replaced with a Teflon valve under positive pressure of argon. The Schlenk tube was sealed and heated in an oil bath for the specified time while stirring at the appropriate stirring rate. The stirring rate must be set carefully to avoid deposition of the solid on the walls of the Schlenk tube and to ensure at the same time an effective mixing.

Analytical methods: IR spectra were recorded on a Perkin-Elmer FT-IR 2000. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument with chemical shifts reported relative to residual deuterated solvent peaks or tetramethylsilane internal standard. Gas chromatographic analysis was performed on an Agilent 6890 instrument with an FID detector and an Agilent 10 m × 0.10 μm i.d. HP-1 capillary column. Mass spectra (GC/MS) were recorded on a Hewlett Packard model GCD. All yields reported in Table 1 and Tale 2 refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H NMR and GC. The procedures described in this section are representative, and thus the yields for the individual reactions may differ slightly from the average yields reported in Table 1 and Table 2.

Copper-Catalyzed Conversion of Aryl Bromides into the Corresponding Cyanides

General Procedure. A Schlenk tube was charged with NaCN (102 mg, 2.08 mmol), CuI (33 mg, 0.17 mmol, 10 mol%), aryl bromide (if it is a solid at room temperature; 1.74 mmol), and KI (57 mg, 0.34 mmol, 20 mol%). The tube was then briefly evacuated and backfilled with argon three times. Anhydrous toluene (1.2 mL), *N,N*-dimethylethylenediamine (185 μL, 1.74 mmol), and aryl bromide (if it is a liquid at room temperature; 1.74 mmol) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 110 °C for 22-24 h. The resulting suspension was allowed to reach room temperature, diluted with 30% aq ammonia (3 mL), and extracted with ethyl acetate (4×2 mL). The combined organic phases were dried ($MgSO_4$ or Na_2SO_4), concentrated, and the residue was purified by flash chromatography on silica gel to provide the desired product.



3,5-Dimethylbenzonitrile (Table 1, Entry 1)

An oven dried 100 mL three necked round bottom flask was charged, under positive pressure of argon, with NaCN (2.04 g, 41.6 mmol) CuI (660 mg, 3.47 mmol, 10 mol%), KI (1.14 g, 6.87 mmol, 20 mol%), and anhydrous toluene (25 mL). *N,N'*-Dimethylethylenediamine (3.7 mL, 35 mmol) and 5-bromo-*m*-xylene (4.7 mL, 35 mmol) were added dropwise under mechanical stirring. The reaction mixture was stirred at 110 °C for 24 h. The resulting suspension was allowed to reach room temperature, diluted with 30% aq ammonia (20 mL) and extracted with toluene (2×10 mL). The combined organic phases were dried over $MgSO_4$, concentrated, and the residue was purified by distillation under reduced pressure (bp 100 °C @ 10 Torr) to provide the desired product as a white crystalline solid (4.08 g, 90% yield). Mp 42-43 °C (lit.,[3] 42.9 °C). ^{1}H NMR (lit.;[4] 400 MHz, $CDCl_3$): δ 7.27 (s, 2H), 7.23 (s, 1H), 2.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 139.4, 135.0, 130.1, 119.7, 112.4, 21.5; IR (neat, cm^{-1}): 2230, 1605, 1378, 907, 854, 682. Anal. Calcd. for C_9H_9N: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.11; H, 6.88, N, 10.52.

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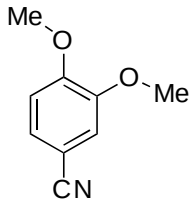
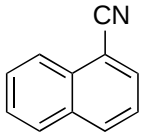
[3] Birch, S. F.; Dean, R. A.; Fidler, F. A.; Lowry, R. A. *J. Am. Chem. Soc.* **1949**, *71*, 1362.
[4] Nomura, Y.; Takeuchi, Y. *Tetrahedron* **1969**, *25*, 3825.



3,4-Dimethoxy-benzonitrile (Table 1, Entry 2)

A Schlenk tube was charged with NaCN (204 mg, 4.16 mmol), CuI (66 mg, 0.35 mmol, 10 mol%), and KI (114 mg, 0.687 mmol, 20 mol%), briefly evacuated and backfilled with argon three times. Anhydrous toluene (2.4 mL), *N,N'*-dimethylethylenediamine (370 µL, 3.48 mmol), and 4-bromoveratrole (500 µL, 3.46 mmol) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 110 °C for 24 h. The resulting suspension was allowed to reach room temperature, diluted with 30% aq ammonia (2 mL), and extracted with ethyl acetate (4×4 mL). The combined organic phases were dried over $MgSO_4$, concentrated, and the residue was purified by distillation at reduced pressure (bp 160 °C @ 1 Torr) to provide the desired product as pale yellow solid (500 mg, 91% yield). Mp 60-62 °C (lit.,[5] 63.0-63.5 °C). ^{1}H NMR (lit.;[5] 400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 7.29 (dd, *J* = 8.3, *J* = 2.0, 1H), 7.08 (d, *J* = 2.0, 1H), 6.91 (d, *J* = 8.3, 1H), 3.94 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 149.6, 126.9, 119.7, 114.3, 111.6, 104.3, 56.54, 56.51; IR (neat, cm^{-1}): 2225, 1598, 1583, 1519, 1245, 1158, 1139, 1018, 876, 811, 617. Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.02; H, 5.72; N, 8.69.

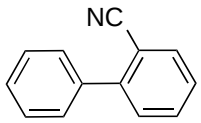


Naphthalene-1-carbonitrile (Table 1, Entry 3)

A Schlenk tube was charged with NaCN (95 mg, 1.94 mmol), CuI (31 mg, 0.16 mmol, 10 mol%), and KI (54 mg, 0.33 mmol, 20 mol%), briefly evacuated and backfilled with argon three times. Anhydrous toluene (1.2 mL), *N,N'*-dimethylethylenediamine (175 µL, 1.64 mmol), and 1-bromonaphthalene (225 µL, 1.62 mmol) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 130 °C for 24 h. The resulting suspension was allowed to reach room temperature, diluted with 30% aqueous ammonia (2 mL) and extracted with ethyl acetate (4×2 mL). The combined organic phases were dried over

[5] Murahashi, S.-I.; Naota, T.; Nakajima, N. *J. Org. Chem*. **1986**, *51*, 898.

$MgSO_4$, concentrated, and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 20:1) to provide the desired product as a pale yellow solid (234 mg, 94% yield). Mp 35-36 °C (lit.,[6] 37 °C). ^{1}H NMR (lit.;[7] 400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 8.27 (d, *J* = 8.4, 1H), 8.11 (d, *J* = 8.3, 1H), 7.96 (d, *J* = 8.1, 1H), 7.94 (dd, *J* = 7.2, *J* = 1.1, 1H), 7.73 (ddd, *J* = 8.3, *J* = 6.9, *J* = 1.34, 1H), 7.65 (ddd, *J* = 8.3, *J* = 7.1, *J* = 1.2, 1H), 7.55 (dd, *J* = 8.3, *J* = 7.1, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 133.7, 133.2, 133.1, 132.8, 129.1, 129.0, 128.0, 125.6, 125.4, 118.3, 110.6; IR (neat, cm^{-1}): 2222, 1604, 1513, 1376, 855, 802, 772, 684, 451. Anal. Calcd. for $C_{11}H_7N$: C, 86.25; H, 4.61; N, 9.14. Found: C, 86.04; H 4.61; N 9.05.



Biphenyl-2-carbonitrile (Table 1, Entry 4)

A Schlenk tube was charged with NaCN (98 mg, 2.0 mmol), CuI (31 mg, 0.16 mmol, 10 mol%), and KI (55 mg, 0.33 mmol, 20 mol%), briefly evacuated and backfilled with argon three times. Anhydrous toluene (1.2 mL), *N,N'*-dimethylethylenediamine (175 μL, 1.64 mmol), and 2-bromobiphenyl (285 μL, 1.65 mmol) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 130 °C for 24 h. The resulting suspension was allowed to reach room temperature, diluted with 30% aq ammonia (2 mL), and extracted with ethyl acetate (4×2 mL). The combined organic phases were dried over $MgSO_4$, concentrated, and the residue was purified by flash chromatography on silica gel (hexane-ethyl acetate 20:1) to provide the desired product as a light yellow oil which crystallized upon storing in a refrigerator (289 mg, 98% yield). Mp 34-37 °C (lit.,[8] 35-37 °C). ^{1}H NMR (lit.;[9] 400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 7.80 (ddd, *J* = 7.8, *J* = 1.5, *J* = 0.5, 1H), 7.68 (td, *J* = 7.8, *J* = 1.3, 1H), 7.61-7.44 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): 145.9, 138.6, 138.5, 134.2, 133.3, 130.5, 129.2, 129.1, 128.0, 119.2, 111.7; IR (neat, cm^{-1}): 2224, 1597, 1500, 1477, 1451, 1433, 759, 735, 700. Anal. Calcd. for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.82. Found: C 86.84; H 5.22; N 7.94.

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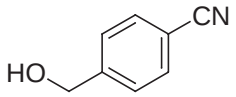
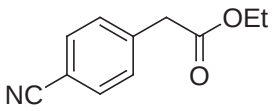
[6] Blum, J.; Oppenheimer, E.; Bergmann, E. *J. Am. Chem. Soc.* **1967**, *89*, 2338.
[7] Abraham, R. J.; Reid, M. *Magn. Reson. Chem.* **2000**, *38*, 570.
[8] Sain, B.; Sandhu, J. S. *J. Org. Chem.* **1990**, *55*, 2545.
[9] Hassan, J.; Hathroubi, C.; Gozzi, C.; Lemaire, M. *Tetrahedron* **2001**, *57*, 7845.



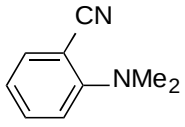
4-Hydroxymethylbenzonitrile (Table 1, Entry 5)

Following the general procedure, 4-bromophenylmethanol (325 mg, 1.74 mmol) was converted into 4-hydroxymethylbenzonitrile in 20 h at 110 °C. Purification of the crude product by column chromatography on silica gel (hexane/ethyl acetate 2:1) provided the desired product as a white crystalline solid (190 mg, 83% yield). Mp 39-40 °C (lit.,[10] 39-41 °C). ^{1}H NMR (lit.;[10] 400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 7.66 (dt, *J* = 8.1, *J* = 1.8, 2H), 7.49 (d, *J* = 8.1, 2H), 4.80 (s, 2H), 2.15 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 146.6, 132.7, 127.4, 119.3, 111.5, 64.6; IR (neat, cm^{-1}): 3484, 2233, 1609, 1428, 1208, 1030, 847, 820, 566. Anal. Calcd. for C_8H_7NO: C, 72.16; H, 5.30; N, 10.52. Found: C 72.15; H 5.33; N 10.44



Ethyl 4-Cyanophenylacetate (Table 1, Entry 6)

Following the general procedure, ethyl 4-bromophenylacetate (417 mg, 1.72 mmol) was converted into ethyl 4-cyanophenylacetate in 24 h at 130 °C. Purification of the crude product by column chromatography on silica gel (hexane/ethyl acetate 10:1) provided the desired product as a fine white powder (230 mg, 70% yield). Mp 86-87 °C (lit.,[11] 87-88 °C). ^{1}H NMR (lit.;[12] 400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 7.63 (dt, *J* = 8.2, *J* = 1.8, 2H), 7.42 (d, *J* = 8.2, 2H), 4.18 (q, *J* = 7.0, 2H), 3.69 (s, 2H), 1.27 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 139.9, 132.7, 130.6, 119.2, 111.5, 61.7, 41.7, 14.6; IR (neat, cm^{-1}): 2231, 1734, 1421, 1222, 1176, 1028. Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C 69.69; H 5.93; N 7.24.



2-Dimethylaminobenzonitrile (Table 1, Entry 7)

Following the general procedure, *N,N*-dimethyl-2-bromoaniline (250 μL, 1.75 mmol) was converted into 2-dimethylaminobenzonitrile in 24 h at 130 °C. Purification of the crude product

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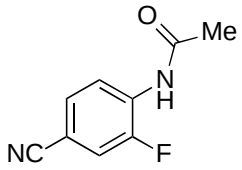
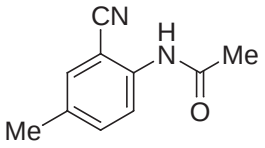
[10] Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786.
[11] Norman, R. O. C.; Ralph, P. D. *J. Chem. Soc.* **1963**, 5431.
[12] Beugelmans, R.; Bois-Choussy, M.; Boudet, B. *Tetrahedron*, **1982**, *38*, 3479.

by column chromatography on silica gel (hexane/ethyl acetate 10:1) provided the desired product as a pale yellow oil (225 mg, 88% yield). ^{1}H NMR (lit.;[13] 400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 7.54 (ddd, *J* = 7.7, *J* = 1.7, *J* = 1.0, 1H), 7.44 (ddd, *J* = 9.00, *J* = 7.3, *J* = 1.7, 1H), 6.93 (bd, *J* = 8.5, 1H), 6.87 (td, *J* = 7.3, *J* = 1.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 135.4, 133.9, 120.1, 119.6, 117.2, 101.7, 43.5; IR (neat, cm^{-1}): 2215, 1599, 1499, 1433, 948, 756.



***N*-(4-Cyano-2-fluorophenyl)acetamide (Table 1, Entry 8)**

A Schlenk tube was charged with NaCN (137 mg, 2.80 mmol), CuI (44 mg, 0.23 mmol, 10 mol%), KI (77 mg, 0.46 mmol, 20 mol%), and *N*-(4-bromo-2-fluorophenyl)acetamide (540 mg, 2.33 mmol), briefly evacuated and backfilled with argon three times. Anhydrous toluene (1.2 mL) and *N,N'*-dimethylethylenediamine (250 μL, 2.35 mmol) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 110 °C for 24 h. The resulting suspension was allowed to reach room temperature, diluted with 30% aq ammonia (2 mL), and extracted with ethyl acetate (4×2 mL). The combined organic phases were dried over $MgSO_4$, concentrated, and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 1:1) to provide the desired product as a fine white powder (337 mg, 87% yield). Mp 169.5-171.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 8.59 (t, *J* = 8.4, 1H), 7.63 (bs, 1H), 7.48 (d, *J* = 8.4, 1H), 7.41 (dd, *J* = 10.6, *J* = 1.8, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 169.0, 151.3 (d, *J* = 244 Hz), 131.6 (d, *J* = 9.6 Hz), 129.9 (d, *J* = 3.5 Hz), 121.9, 118.7 (d, *J* = 22.8 Hz), 118.1 (d, *J* = 2.9 Hz), 107.1 (d, *J* = 9.3 Hz), 25.3; IR (neat, cm^{-1}): 3317, 2235, 1699, 1593, 1515, 834, 707. Anal. Calcd. for $C_9H_7FN_2O$: C, 60.67; H, 3.96; N, 15.72. Found: C 60.42; H 3.94; N 15.63.

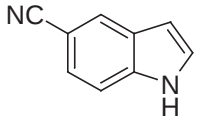


***N*-(2-Cyano-4-methylphenyl)acetamide (Table 1, Entry 9)**

Following the general procedure, 2-bromo-4-methylacetanilide (395 mg, 1.74 mmol) was converted into *N*-(2-cyano-4-methylphenyl)acetamide in 24 h at 130 °C. Purification of the crude

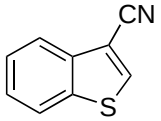
[13] Gupton, J. T.; Idoux, J. P.; Baker, G.; Colon, C.; Crews, A.D.; Jurss, C.D.; Rampi, R. C. *J. Org. Chem.*

product by column chromatography on silica gel (hexane/ethyl acetate 1:1) provided the desired product as a pale yellow crystalline powder (200 mg, 70% yield). Mp 133-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 8.24 (d, *J* = 8.3, 1H), 7.65 (bs, 1H), 7.40 (d, *J* = 8.3, 1H), 7.39 (s, 1H), 2.34 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 169.0, 138.5, 135.4, 134.7, 132.6, 122.0, 117.0, 102.4, 25.1, 20.9; IR (neat, cm^{-1}): 3253, 2225, 1665, 1589, 1535, 1304, 1275, 1157, 828, 678, 497. Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.10; H, 5.90; N, 15.97.



1*H*-Indole-5-carbonitrile (Table 2, Entry 1)

Following the general procedure, 5-bromoindole (340 mg, 1.74 mmol) was converted into 1*H*-indole-5-carbonitrile in 24 h at 110 °C. Purification of the crude product by column chromatography on silica gel (hexane/ethyl acetate 6:1) provided the desired product as a light brown solid (190 mg, 80% yield). Mp 104-105 °C (lit.,[14] 104-106 °C). ^{1}H NMR (lit.;[15] 400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 8.72 (bs, 1H), 8.03 (s, 1H), 7.50 (d, *J* = 8.4, 1H), 7.45 (dd, *J* = 8.4, *J* = 1.5, 1H), 7.38 (t, *J* = 2.8, 1H), 6.68-6.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 128.1, 126.9, 126.8, 125.3, 121.3, 112.4, 103.9, 103.2; IR (neat, cm^{-1}): 3399, 2226, 1612, 1470, 1418, 1347, 1089, 894. Anal. Calcd. for $C_9H_6N_2$: C, 76.04; H, 4.25; N, 19.71. Found: C, 76.21; H, 4.28; N, 19.52.



Benzo[*b*]thiophene-3-carbonitrile (Table 2, Entry 2)

Following the general procedure, 3-bromothianaphthene (225 μL, 1.72 mmol) was converted into benzo[*b*]thiophene-3-carbonitrile in 24 h at 110 °C. Purification of the crude product by column chromatography on silica gel (hexane/ethyl acetate 8:1) provided the desired product as a pale yellow solid (200 mg, 73% yield). Mp 67-69 °C (lit.,[16] 70-71 °C). ^{1}H NMR (lit.;[16] 400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 8.15 (s, 1H), 8.03 (d, *J* = 7.8, 1H), 7.94 (d, *J* = 7.8, 1H), 7.58 (td, *J* = 8.1, *J* = 1.0, 1H), 7.52 (dt, *J* = 7.1, *J* = 1.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9,

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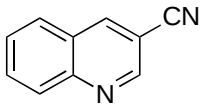
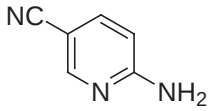
[15] Morales-Rios, M. S.; del Rio, R. E.; Joseph-Nathan, P. *Magn. Reson. Chem*. **1989**, *27*, 1039.
[16] Yoshida, K.; Miyoshi, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 333.

138.0, 137.7, 126.6, 126.4, 123.3, 122.9, 114.8, 107.5; IR (neat, cm^{-1}): 3108, 2224, 1462, 1426, 1256, 857, 814, 755, 729, 445. Anal. Calcd. for C_9H_5NS: C, 67.90; H, 3.17; N, 8.80. Found: C, 67.69; H, 3.11; N, 8.62.



Quinoline-3-carbonitrile (Table 2, Entry 3)

Following the general procedure, 3-bromoquinoline (235 μL, 1.73 mmol) was converted into quinoline-3-carbonitrile in 24 h at 110 °C. Purification of the crude product by column chromatography on silica gel (hexane/ethyl acetate 6:1) provided the desired product as a white crystalline powder (205 mg, 75% yield). Mp 105-107 °C (lit.,[17] 105-107 °C). ^{1}H NMR (lit.;[17] 400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 9.07 (d, *J* = 2.0, 1H), 8.57 (dd, *J* = 2.0, *J* = 0.5, 1H), 8.20 (d, *J* = 9.1, 1H), 7.95-7.90 (m, 2H), 7.73 (t, *J* = 7.6, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 149.2, 141.9, 133.2, 130.3, 128.9, 128.7, 126.6, 117.5, 107.0; IR (neat, cm^{-1}): 2229, 1619, 1597, 1489, 1370, 1130, 982, 961, 923, 739, 747, 638, 474. Anal. Calcd. for $C_{10}H_6N_2$: C, 77.91; H, 3.92; N, 18.17. Found: C, 77.96; H, 3.97; N, 18.32.



6-Aminonicotinonitrile (Table 2, Entry 4)

Following the general procedure, 2-amino-5-bromopyridine (294 mg, 1.70 mmol) was converted into 6-aminonicotinonitrile in 20 h at 110 °C. Purification of the crude product by column chromatography on silica gel (hexane/ethyl acetate 2:5) provided the desired product as a white crystalline powder (180 mg, 90% yield). Mp 160-162 °C (lit.,[18] 161-162 °C). ^{1}H NMR (lit.;[19] 400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 8.41-8.36 (m, 1H), 7.64 (dd, *J* = 8.6, *J* = 2.2, 1H), 6.53 (dd, *J* = 8.6, *J* = 0.9, 1H), 5.08 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 160.5, 153.6, 140.7, 118.6, 108.4, 98.8; IR (neat, cm^{-1}): 3414, 3136, 2211, 1654, 1601, 1509, 1410, 832, 546. Anal. Calcd. for $C_6H_5N_3$: C, 60.50; H, 4.23; N, 35.27. Found: C 60.37; H 4.28; N 35.31.

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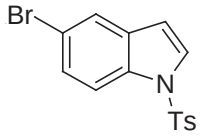
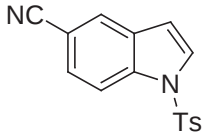


5-Bromo-1-(*p*-toluenesulfonyl)-1*H*-indole

A 100 mL round bottom flask was sequentially charged with 5-bromoindole (1.96 g, 10 mmol), *p*-toluenesulfonyl chloride (2.30 g, 12 mmol), tetrabutylammonium hydrogen sulfate (240 mg, 0.70 mmol) and toluene (40 mL). An aqueous solution of potassium hydroxide (13 mL, 50%) was added dropwise and the mixture was stirred at room temperature overnight. At this point the organic layer was separated, diluted with ethyl ether (40 mL), washed with two portions of dilute potassium hydroxide solution (2×20 mL, 2M) and dried over $MgSO_4$. The solvent was removed at reduced pressure and the product was purified by flash chromatography on silica gel (hexane/ethyl acetate 1:1) to provide the desired product as a light yellow solid (3.50 g, 99% yield). Mp 135 °C (lit.,[20] 139-140 °C). ^{1}H NMR (lit.;[20] 400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 7.88 (d, *J* = 8.8, 1H), 7.76 (d, *J* = 8.6, 2H), 7.68 (d, *J* = 1.8, 1H), 7.59 (d, *J* = 3.5, 1H), 7.42 (dd, *J* = 8.8, *J* = 2.0, 1H), 7.25 (d, *J* = 8.6, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 135.3, 133.9, 132.9, 130.4, 128.0, 127.9, 127.2, 124.5, 117.2, 115.4, 108.7, 22.0.



1-(*p*-Toluenesulfonyl)-1*H*-indole-5-carbonitrile (Table 2, Entry 5)

Following the general procedure, 5-bromo-1-(*p*-toluenesulfonyl)-1*H*-indole (607 mg, 1.73 mmol) was converted into 1-(*p*-toluenesulfonyl)-1*H*-indole-5-carbonitrile in 24 h at 110 °C. Purification of the crude product by column chromatography on silica gel (hexane/ethyl acetate 6:1) provided the desired product as a white crystalline powder (475 mg, 93% yield). Mp 130-131 °C. ^{1}H NMR (400 MHz, $CDCl_3$, *J* values are reported in Hz): δ 8.09 (dt, *J* = 8.7, *J* = 0.8, 1H), 7.90 (d, *J* = 1.6, 1H), 7.80 (dt, *J* = 8.3, *J* = 1.8, 2H), 7.72 (d, *J* = 3.7, 1H), 7.58 (dd, *J* = 8.7, *J* = 1.7, 1H), 7.29 (d, *J* = 8.3, 2H), 6.73 (dd, *J* = 3.7, *J* = 0.8, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 136.8, 135.1, 131.1, 130.6, 128.8, 128.0, 127.3, 126.8, 119.8, 114.7, 108.9, 107.3, 22.1; IR (neat, cm^{-1}): 2226, 1597, 1456, 1373, 1269, 1174, 1138, 672, 593, 540. Anal. Calcd. for $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45. Found: C, 65.04; H, 4.11; N, 9.47.

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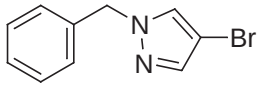
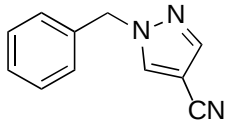
[20] Fresneda, M. P.; Molina, P.; Bleda, A. J. *Tetrahedron* **2001**, *57*, 2355.



1-Benzyl-4-bromo-1*H*-pyrazole[21]

A 100 mL round bottom flask was charged with 4-bromopyrazole (4.41 g, 30 mmol), tetrabutylammonium bromide (484 mg, 1.5 mmol) and potassium hydroxide pellets (3.37 g, 60 mmol). After the mixture was sonicated for 15 min, benzyl chloride (5.2 mL, 45 mmol) was added dropwise and the resulting mixture was stirred overnight. Ethyl ether (20 mL), water (20 mL), and diluted hydrochloric acid (1 mL, 10%) were added under stirring. The organic layer was washed with water (2×20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was purified by flash chromatography on silica gel (hexane/ethyl acetate 10:1) to provide the desired product as a white solid (6.74 g, 95% yield). Mp 51-52 °C (lit.,[22] 44-45 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.42-7.33 (m, 4H), 7.28-7.22 (m, 2H), 5.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 136.2, 129.8, 129.4, 128.8, 128.3, 93.9, 57.1.



1-Benzyl-1*H*-pyrazole-4-carbonitrile (Table 2, Entry 6)

Following the general procedure, 1-benzyl-4-bromo-1*H*-pyrazole (308 mg, 1.74 mmol) was converted into 1-benzyl-1*H*-pyrazole-4-carbonitrile in 24 h at 110 °C. Purification of the crude product by column chromatography on silica gel (hexane/ethyl acetate 5:1) provided the desired product as a light yellow solid (252 mg, 80% yield). Mp 61-63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.78 (s, 1H), 7.45-7.36 (m, 2H), 7.31-7.24 (m, 2H), 5.35 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 143.1, 134.8, 134.6, 129.6, 129.3, 128.5, 113.8, 93.1, 51.2; IR (neat, cm^{-1}): 3109, 2231, 1543, 1455, 1440, 1383, 1354, 1152, 1004, 991, 718, 693. Anal. Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C 72.00; H 4.92, N 23.01.

[21] We are grateful to Michele C. Harris for performing this reaction.
[22] Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 3994.

Conversion of 5-Iodo-*m*-xylene into 3,5-Dimethylbenzonitrile Using Different Copper Precatalysts

Three Schlenk tubes were charged with sodium cyanide (102 mg, 2.08 mmol) and either CuI (33 mg, 0.17 mmol, 10 mol%), CuBr (25 mg, 0.17 mmol, 10 mol%), or CuCN (15.5 mg, 0.173 mmol, 10 mol%). The Schlenk tubes were evacuated and backfilled with argon. Toluene (1.2 mL), *N,N'*-dimethylethylenediamine (185 μL, 1.74 mmol), and 5-iodo-*m*-xylene (250 μL, 1.73 mmol) were added to each Schlenk tube. The Schlenk tubes were sealed with Teflon valves, and the reaction mixtures were stirred at 90 °C in an oil bath for 24 h. The resulting suspensions were allowed to reach room temperature. Ethyl acetate (2 mL) and dodecane (internal GC standard, 200 μL) were added to the reaction mixtures. A 50 μL sample of the supernatant solution was diluted with ethyl acetate (1 mL) and analyzed by GC to provide the following results:
CuI, 99.9% conversion of 5-iodo-*m*-xylene and 96% yield of 3,5-dimethylbenzonitrile;
CuBr, 99.7% conversion of 5-iodo-*m*-xylene and 97% yield of 3,5-dimethylbenzonitrile;
CuCN, >99.9% conversion of 5-iodo-*m*-xylene and 98% yield of 3,5-dimethylbenzonitrile.

Conversion of 5-Bromo-*m*-xylene into 3,5-Dimethylbenzonitrile Using Different Copper Precatalysts

Three Schlenk tubes were charged with sodium cyanide (102 mg, 2.08 mmol) and either CuI (33 mg, 0.17 mmol, 10 mol%), CuBr (25 mg, 0.17 mmol, 10 mol%), or CuCN (15.5 mg, 0.173 mmol, 10 mol%). The Schlenk tubes were evacuated and backfilled with argon. Toluene (1.2 mL), *N,N'*-dimethylethylenediamine (185 μL, 1.74 mmol), and 5-bromo-*m*-xylene (235 μL, 1.73 mmol) were added to each Schlenk tube. The Schlenk tubes were sealed with Teflon valves, and the reaction mixtures were stirred at 110 °C in an oil bath for 24 h. The resulting suspensions were allowed to reach room temperature. Ethyl acetate (2 mL) and dodecane (internal GC standard, 200 μL) were added to the reaction mixtures. A 50 μL sample of the supernatant solution was diluted with ethyl acetate (1 mL) and analyzed by GC to provide the following results:
CuI, 91% conversion of 5-bromo-*m*-xylene, 82% yield of 3,5-dimethylbenzonitrile, and 3% yield of 5-iodo-*m*-xylene;

CuBr, 10% conversion of 5-bromo-*m*-xylene and 2% yield of 3,5-dimethylbenzonitrile; CuCN, 5% conversion of 5-bromo-*m*-xylene and 1% yield of 3,5-dimethylbenzonitrile.