Cu-Mediated C-H Cyanation of Arenes Using

*N,N*-Dimethylformamide (DMF) as the “CN” Source

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**General Remarks.**

All manipulations were conducted with Schlenk tube. $^1$H-NMR spectra were recorded on a Bruker AVANCE III-400 spectrometers. Chemical shifts (in ppm) were referenced to tetramethylsilane ($\delta = 0$ ppm) in CDCl$_3$ as an internal standard. $^{13}$C-NMR spectra were obtained by using the same NMR spectrometers and were calibrated with CDCl$_3$ ($\delta = 77.00$ ppm). High Resolution Mass spectra were recorded using a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (APEX IV, Bruker). Mass spectra were recorded using a PE SCLEX QSTAR spectrometer. The 2-phenylpyridine substrates were prepared according to the literature.\(^1\) Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

**Analytical data for compounds 2**

**2-(Pyridin-2-yl)benzonitrile (2a)**

*Typical procedure:* CuBr (114.8 mg, 0.8 mmol), substrate 2-phenylpyridine 1a (62.1 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) were added to a 25 mL Schlenk tube under O$_2$ (1 atm), followed by addition of 3 mL DMF. The reaction mixture was vigorously stirred at 135 °C for 48h as monitored by TLC. After cooling down to room temperature, 10 mL brine was added in the solution and extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over anhydrous MgSO$_4$. The solvent was concentrated *in vacuo* and the residue was purified by flash chromatography on a short silica gel (eluent: petroleum ether/ethyl acetate = 5:1) to afford 44.0 mg (61%) of 2a. 2a: $^1$H NMR (CDCl$_3$, 400 MHz): $\delta =$ 8.78 (d, $J = 4.4$ Hz, 1H), 7.86-7.78 (m, 4H), 7.72-7.68 (m, 1H), 7.53-7.49 (m, 1H), 7.38-7.34 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta =$ 155.2, 149.9, 143.5, 136.8, 134.1, 132.8, 130.0, 128.7, 123.3, 123.2, 118.7, 111.1 ppm; IR (neat): $\nu =$ 3064.0, 2224.3, 1585.4, 1300.6, 761.2 cm$^{-1}$; MS (EI) $m/z$ 181.3 (100) [M]$^+$.  

**5-Methyl-2-(pyridin-2-yl)benzonitrile (2b)**
The reaction of CuBr (114.8 mg, 0.8 mmol), 2-(p-tolyl)pyridine 1b (67.7 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 56.0 mg (70%) of 2b. 2b: ¹H NMR (CDCl₃, 400 MHz): δ = 8.77-8.75 (m, 1H), 7.82-7.73 (m, 3H), 7.60 (s, 1H), 7.50-7.48 (m, 1H), 7.35-7.31 (m, 1H), 2.44 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 155.2, 149.8, 140.7, 139.1, 136.7, 134.4, 133.7, 129.8, 123.0, 118.9, 110.7, 20.8 ppm; IR (neat): ν = 3065.3, 2224.6, 1585.7, 1562.7, 1462.9, 1439.2, 1152.9, 761.6 cm⁻¹; MS (EI) m/z 194.2 (100) [M⁺].

4-(Pyridin-2-yl)-[1,1′-biphenyl]-3-carbonitrile (2c)²

The reaction of CuBr (114.8 mg, 0.8 mmol), 2-([1,1′-biphenyl]-4-yl)pyridine 1c (92.5 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 59.8 mg (59%) of 2c. 2c: ¹H NMR (CDCl₃, 400 MHz): δ = 8.79 (d, J = 4.4 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.95-7.88 (m, 2H), 7.84 (d, J = 3.6 Hz, 2H), 7.63-7.61 (m, 2H), 7.51-7.48 (m, 2H) 7.45-7.42 (m, 1H) 7.37-7.34 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ = 154.8, 149.9, 141.9, 138.3, 136.8, 132.5, 131.3, 130.4, 129.1, 128.5, 127.0, 123.3, 123.1, 118.7, 111.4 ppm; IR (neat): ν = 2225.2, 1763.2, 1585.3, 1464.4, 1242.7, 762.0 cm⁻¹; MS (EI) m/z 256.1 (100) [M⁺].

5-Bromo-2-(pyridin-2-yl)benzonitrile (2d)³

The reaction of CuBr (114.8 mg, 0.8 mmol), 2-(4-bromophenyl)pyridine 1d (93.6 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 52.5 mg (51%) of 2d. 2d: ¹H NMR (CDCl₃, 400 MHz): δ = 8.74 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.84-7.71 (m, 4H), 7.36-7.33 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ = 154.1, 149.9, 142.1, 136.9, 136.3, 136.0, 131.3, 123.5, 122.9, 122.5, 117.2, 112.6 ppm; MS (EI) m/z 258.0 (100) [M⁺].

5-Chloro-2-(pyridin-2-yl)benzonitrile (2e)²
The reaction of CuBr (114.8 mg, 0.8 mmol), 2-(4-chlorophenyl)pyridine 1e (75.6 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 44.0 mg (52%) of 2e. 2e: ¹H NMR (CDCl₃, 400 MHz): δ = 8.77 (d, J = 4.8 Hz, 1H), 7.86-7.77 (m, 4H), 7.66 (dd, J = 8.4 Hz, J = 2.0, 1H), 7.39-7.36 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ = 154.1, 150.0, 141.8, 136.9, 134.9, 133.6, 133.1, 131.3, 123.6, 123.0, 117.4, 112.4 ppm; IR (neat): ν = 2228.1, 1591.1, 1460.8, 1430.2, 1097.9, 860.0, 783.7 cm⁻¹; MS (EI) m/z 214.0 (100) [M⁺].

5-Fluoro-2-(pyridin-2-yl)benzonitrile (2f)

The reaction of CuBr (114.8 mg, 0.8 mmol), 2-(4-fluorophenyl)pyridine 1f (69.3 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 54.1 mg (43%) of 2f. 2f: ¹H NMR (CDCl₃, 400 MHz): δ = 8.76 (s, 1H), 7.87-7.75 (m, 3H), 7.49 (dd, J = 8.0 Hz, J = 2.0 Hz, 1H), 7.43-7.34 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ = 161.9 (d, J₉,F = 250.3 Hz), 154.1, 149.8, 139.8, 136.8, 132.0 (d, J₉,F = 8.1 Hz), 123.3, 122.9, 120.6 (d, J₉,F = 24.7 Hz), 120.4 (d, J₉,F = 20.4 Hz), 117.4, 112.3 (d, J₉,F = 9.1 Hz) ppm; IR (neat): ν = 3737.0, 3069.0, 2230.5, 1609.0, 1583.0, 1428.0, 1275.9, 1263.2, 1152.2, 884.4, 784.6 cm⁻¹; MS (EI) m/z 198.3 (100) [M⁺].

Methyl 3-cyano-4-(pyridin-2-yl)benzoate (2g)

The reaction of CuBr (114.8 mg, 0.8 mmol), methyl 4-(pyridin-2-yl)benzoate 1g (85.3 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 16.4 mg (17%) of 2g. 2g: ¹H NMR (CDCl₃, 400 MHz): δ = 8.80 (d, J = 4.8 Hz, 1H), 8.46 (d, J = 2.0 Hz, 1H), 8.31 (dd, J = 4.0, 1.6 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.89-7.82 (m, 2H), 7.41-7.38 (m, 1H), 3.98 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 165.0, 154.2, 150.11, 146.9, 137.0, 135.3, 133.5, 130.7, 130.2, 123.9, 123.4, 117.8, 111.4, 52.7 ppm; MS (EI) m/z 238.1 (100) [M⁺].
5-Ethoxy-2-(pyridin-2-yl)benzonitrile (2h)

The reaction of CuBr (114.8 mg, 0.8 mmol), 2-(4-ethoxyphenyl)pyridine 1h (79.7 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 49.0 mg (58%) of 2h. 2h: ¹H NMR (CDCl₃, 400 MHz): δ = 8.73 (d, J = 4.0 Hz, 1H), 7.81-7.73 (m, 3H), 7.31-7.25 (m, 2H), 7.20-7.18 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 158.8, 154.9, 149.6, 136.6, 135.7, 131.2, 122.64, 122.61, 119.6, 118.9, 118.6, 111.5, 64.0, 14.4 ppm; IR (neat): ν = 2982.4, 2225.0, 1769.4, 1603.6, 1464.4, 1241.9, 1045.9, 786.5 cm⁻¹; HRMS m/z (ESI) calcd. for C₁₄H₁₃N₂O (M + H)⁺ 225.1028, found 225.1018.

4-Ethoxy-2-(pyridin-2-yl)benzonitrile (2i)

The reaction of CuBr (114.8 mg, 0.8 mmol), 2-(3-ethoxyphenyl)pyridine 1i (79.7 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 46.6 mg (52%) of 2i. 2i: ¹H NMR (CDCl₃, 400 MHz): δ = 8.75 (d, J = 3.2 Hz, 1H), 7.84-7.80 (m, 2H), 7.69 (d, J = 8.8 Hz, 1H), 7.34 (s, 2H), 6.98 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 6.4 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 162.2, 155.2, 149.8, 145.4, 136.7, 135.6, 123.3, 123.2, 119.1, 115.6, 115.2, 102.3, 64.0, 14.5 ppm; IR (neat): ν = 2982.9, 2219.3, 1796.4, 1603.7, 1463.0, 1307.2, 1239.7, 1404.6, 762.0 cm⁻¹; HRMS m/z (ESI) calcd. for C₁₄H₁₃N₂O (M + H)⁺ 225.1028, found 225.1019.

3-Ethoxy-2-(pyridin-2-yl)benzonitrile (2j)

The reaction of CuBr (114.8 mg, 0.8 mmol), 2-(2-ethoxyphenyl)pyridine 1j (79.7 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 52.9 mg (59%) of 2j. 2j: ¹H NMR (CDCl₃, 400 MHz): δ = 8.77 (d, J = 4.4 Hz, 1H), 7.93-7.75 (m, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.43-7.30 (m, 3H), 7.19 (d, J = 8.4 Hz, 1H), 4.04 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 156.4, 153.1, 149.4, 135.8, 133.3, 129.9, 125.5, 125.4, 122.9, 118.0, 116.7, 114.0, 64.7, 14.4 ppm; IR (neat): ν = 2982.2,
The reaction of CuBr (114.8 mg, 0.8 mmol), 2-(4-(tert-butyl)phenyl)pyridine 1k (84.5 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 48.2 mg (51 %) of 2k. 2k: ¹H NMR (CDCl₃, 400 MHz): δ = 8.76 (d, J = 4.0 Hz, 1H), 7.83-7.77 (m, 4H), 7.72-7.70 (m, 1H), 7.34-7.31 (m, 1H), 1.37 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz): δ = 155.2, 152.3, 149.8, 140.6, 136.7, 131.0, 129.7, 123.01, 122.97, 119.2, 110.6, 34.7, 30.9 ppm; IR (neat): ν = 2964.2, 2868.0, 2222.8, 1584.7, 1461.8, 1364.6, 1272.5, 842.3, 790.5 cm⁻¹; HRMS m/z (ESI) calcd. for C₁₄H₁₃N₂O (M + H)+ 237.1392, found 237.1381.

The reaction of CuBr (114.8 mg, 0.8 mmol), 5-methyl-2-phenylpyridine 1l (67.7 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 44.3 mg (57 %) of 2l. 2l: ¹H NMR (CDCl₃, 400 MHz): δ = 8.60 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.69-7.62 (m, 3H), 7.50-7.46 (m, 1H), 2.41 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 152.5, 150.4, 143.5, 137.2, 134.0, 133.1, 132.7, 129.8, 128.4, 122.6, 118.8, 110.9, 18.2 ppm; IR (neat): ν = 2224.7, 1764.9, 1471.6, 1377.2, 1243.0, 775.9, 758.0 cm⁻¹; MS (EI) m/z 194.0 (100) [M]+.

The reaction of CuBr (114.8 mg, 0.8 mmol), 3-methyl-2-phenylpyridine 1m (67.7 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 39.6 mg (51 %) of 2m. 2m: ¹H NMR (CDCl₃, 400 MHz): δ = 8.57 (d, J = 4.4 Hz, 1H), 7.79-7.77 (m, 1H), 7.70-7.64
(m, 2H), 7.53-7.49 (m, 2H), 7.28 (dd, $J = 8.0$ Hz, $J = 4.8$ Hz, 1H), 2.27 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 155.5$, 147.2, 144.4, 138.5, 133.0, 132.6, 131.6, 130.0, 128.4, 123.5, 117.8, 112.5, 19.0 ppm; IR (neat): $\nu = 2925.1$, 2226.5, 1763.8, 1440.2, 1424.7, 1736.5, 1443.1, 1051.7, 762.8 cm$^{-1}$; MS (El) $m/z$ 193.2 (100) [M]$^+$. 

1-(Pyridin-2-yl)-2-naphthonitrile (2n)$^2$

The reaction of CuBr (114.8 mg, 0.8 mmol), 2-(naphthalen-1-yl)pyridine 1n (82.1 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (1 mL) under O$_2$ (1 atm) afforded 41.4 mg (45%) of 2n. 2n: $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 8.86$ (d, $J = 4.8$ Hz, 1H), 7.98-7.90 (m, 3H), 7.71 (d, $J = 8.4$ Hz, 2H), 7.65-7.59 (m, 2H), 7.54-7.50 (m, 1H), 7.47-7.44 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 155.2$, 150.0, 144.4, 136.7, 135.0, 131.1, 129.4, 128.7, 128.3, 127.9, 126.8, 126.7, 125.6, 123.5, 118.5, 109.7 ppm; IR (neat): $\nu = 2994.3$, 2228.0, 1769.4, 1585.7, 1469.7, 1383.1, 1243.2, 811.7, 745.6 cm$^{-1}$; MS (El) $m/z$ 229.0 (100) [M]$^+$. 

2-(Isoquinolin-1-yl)benzonitrile (2o)$^4$

The reaction of CuBr (114.8 mg, 0.8 mmol), 1-phenylisoquinoline 1o (82.1 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O$_2$ (1 atm) afforded 32.2 mg (35%) of 2o. 2o: $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 8.67$ (d, $J = 5.6$ Hz, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 7.6$ Hz, 1H), 7.76-7.70 (m, 4H), 7.66 (d, $J = 7.2$ Hz, 1H), 7.61-7.54 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 157.0$, 143.0, 142.2, 136.7, 133.4, 132.3, 130.9, 130.4, 128.8, 127.8, 127.2, 126.8, 126.4, 121.3, 117.7, 113.2 ppm; IR (neat): $\nu = 2225.6$, 1585.3, 1570.0, 1449.5, 1029.0, 792.5, 730.2 cm$^{-1}$; MS (El) $m/z$ 230.0 (100) [M]$^+$. 

Benzo[h]quinoline-10-carbonitrile (2p)$^2$
The reaction of CuBr (114.8 mg, 0.8 mmol), benzo[h]quinoline 1p (71.7 mg, 0.4 mmol), 1,3-diphenyl-1,3-propanedione (44.9 mg, 0.2 mmol) in DMF (3 mL) under O₂ (1 atm), afforded 35.9 mg (44%) of 2p.

2p: ¹H NMR (CDCl₃, 400 MHz): δ = 9.14-9.13 (m, 1H), 8.21 (dd, J = 8 Hz, J = 1.6 Hz, 1H), 8.16-8.10 (m, 2H), 7.83-7.70 (m, 3H), 7.62 (dd, J = 8.0 Hz, J = 4.4 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ = 148.4, 144.5, 136.2, 135.7, 134.0, 132.7, 130.7, 127.4, 127.2, 127.0, 126.9, 123.0, 120.7, 108.9 ppm; IR (neat): ν = 3434.9, 2210.6, 1619.2, 1511.0, 1424.0, 832.2, 717.0 cm⁻¹; MS (EI) m/z 204.3 (100) [M⁺].

3-(Pyridin-2-yl)-2-naphthonitrile (2q)² and 2-(pyridin-2-yl)-1-naphthonitrile (2q')²

The reaction of CuBr (114.8 mg, 0.8 mmol), 2-(naphthalen-2-yl)pyridine 1q (82.1 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 58.0 mg (63%) 2q and 2q’ as a mixture (2q:2q’ = 2.7:1).

2-(Pyridin-2-yl)naphthalene-1,3-dicarbonitrile (2r)²

The reaction of CuBr (114.8 mg, 0.8 mmol), 2-(naphthalen-2-yl)pyridine 1r (82.1 mg, 0.4 mmol), benzil (21.0 mg, 0.1 mmol) in DMF (3 mL) under O₂ (1 atm) afforded 12.7 mg (12%) of 2r. 2r: ¹H NMR (CDCl₃, 400 MHz): δ = 8.89 (d, J = 4.4 Hz, 1H), 8.57 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.98-7.90 (m, 2H), 7.83-7.78 (m, 2H), 7.5045 (dd, J = 7.2, 5.2 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ = 152.9, 150.3, 144.1, 139.7, 137.0, 133.7, 132.1, 131.4, 129.4, 129.0, 126.1, 124.9, 124.5, 116.8, 115.4, 111.7, 110.5; MS (EI) m/z 255.1 (100) [M⁺].
References:
