P(*i*-BuNCH₂CH₂)₃N: An Effective Ligand for Direct α -Arylation of Nitriles with Aryl Bromides

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Supporting information

General Methods

¹H NMR spectra were recorded at 400 or 300 MHz, and ¹³C NMR spectra were recorded at 100.6 or 75.5 MHz. Melting points were determined in unsealed capillary tubes and are uncorrected. All reactions were performed under an argon atmosphere. All solvents were dried over P₄O₁₀ (dichloromethane) or sodium/benzophenone (*n*-hexane, diethyl ether, THF, dioxane and toluene) and were freshly distilled prior to use. All aryl halides, nitriles, bases and palladium catalyst precursors were purchased from Aldrich Chemical Co. and used without further purification. The yields reported are isolated yields and are the averages of two runs. Ligands **1a-1d** were prepared according to our previously reported procedures¹ (although ligands **1a**, **1b**, and **1c** are commercially available – see ref. 12 in the ms). All the cross coupling products are known and their ¹H and ¹³C NMR spectra agreed with those in the literature cited below, or if such spectra were not reported, these spectra were consistent with the formulation of the products as shown in Table 2 (entries 11 and 14).

Ethyl 2-phenylcyanoacetate (Table 2, entry 1).² Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/5) to give the desired product (185 mg, 98 %) as a colorless oil. ¹H NMR (CDCl₃, 299.94 MHz) δ 1.22 (t, J = 7.1 Hz, 3H, CH₃), 4.18 (m, 2H, CH₂), 4.73 (s, 1H, NCCH), 7.39-7.47 (m, 5H, Ph-H); ¹³C {¹H} NMR (CDCl₃, 75.43 MHz) δ 14.10, 43.94, 63.52, 115.99, 128.14, 129.43, 129.56, 130.28, 165.25.

Ethyl 2-(2-methylphenyl)cyanoacetate (Table 2, entry 4).² Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/3) to give the desired product (191 mg, 94 %) as a colorless oil. ¹H NMR (CDCl₃, 299.94 MHz) δ 1.25 (t, J = 7.2 Hz, 3H, CH₂CH₃), 2.41 (s, 3H, Ph-CH₃), 4.23 (m, 2H,

CH₂), 4.89 (s, 1H, NCCH), 7.23-7.48 (m, 4H, Ph-H); ¹³C{¹H} NMR (CDCl₃, 75.43 MHz) δ 14.15 19.65, 41.31, 63.46, 116.14, 127.27, 128.85, 129.18, 129.56, 131.47, 136.48, 165.26.

Ethyl 2-(4-methylphenyl)cyanoacetate (Table 2, entry 5).³ Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/3) to give the desired product (193 mg, 95 %) as a colorless oil. ¹H NMR (CDCl₃, 299.94 MHz) δ 1.25 (t, J = 7.2 Hz, 3H, CH₂CH₃), 2.36 (s, 3H, Ph-CH₃), 4.22 (m, 2H, CH₂), 4.69 (s, 1H, NCCH), 7.20 (d, J = 8.0 Hz, 2H, 2Ph-H), 7.33 (d, J = 8.1 Hz, 2H, Ph-H); ¹³C{¹H} NMR (CDCl₃, 75.43 MHz) δ 14.12, 21.37, 43.60, 63.44, 116.10, 127.27, 127.99, 130.22, 139.44, 165.41.

Ethyl 2-(4-*tert*-butylphenyl)cyanoacetate (Table 2, entry 6).⁴ Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/3) to give the desired product (230 mg, 94 %) as a colorless oil. ¹H NMR (CDCl₃, 299.94 MHz) δ 1.26 (t, J = 7.2 Hz, 3H, CH₂CH₃), 1.32 (s, 9H, Ph-C(CH₃)₃), 4.22 (m, 2H, CH₂), 4.71 (s, 1H, NCCH), 7.37-7.46 (m, 4H, Ph-H); ¹³C{¹H} NMR (CDCl₃, 75.43 MHz) δ 14.15, 31.44, 34.89, 43.51, 63.42, 116.11, 126.53, 127.22, 127.83, 152.55, 165.40.

Ethyl 2-(2,5-dimethylphenyl)cyanoacetate (Table 2, entry 7).² Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/3) to give the desired product (200 mg, 92 %) as a pale yellow oil. ¹H NMR (CDCl₃, 299.94 MHz) δ 1.26 (t, J = 7.2 Hz, 3H, CH₂CH₃), 2.33 (s, 3H, Ph-CH₃), 2.35 (s, 3H, Ph-CH₃), 4.23 (m, 2H, CH₂), 4.87 (s, 1H, NCCH), 7.10 (s, 2H, 2Ph-H), 7.28 (s, 1H, Ph-H); ¹³C{¹H} NMR (CDCl₃, 75.43 MHz) δ 14.15, 19.14, 21.10, 41.23, 63.40, 116.31, 128.93, 129.37, 130.29, 131.34, 133.27, 136.94, 165.41.

Ethyl 2-(2,4,6-trimethylphenyl)cyanoacetate (Table 2, entry 8).⁵ Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/3) to give the desired product (206 mg, 89 %) as a white solid, mp 64-66 °C. ¹H NMR (CDCl₃, 299.94 MHz) δ 1.27 (t, J = 7.2 Hz, 3H, CH₂CH₃), 2.28 (s, 3H, Ph-CH₃), 2.39 (s, 6H, Ph-CH₃), 4.25 (m, 2H, CH₂), 5.14 (s, 1H, NCCH), 6.92 (s, 2H, Ph-H); ¹³C{¹H} NMR (CDCl₃, 75.43 MHz) δ 14.21, 20.46, 21.13, 38.10, 63.33, 115.72, 125.35, 130.32, 137.11, 139.04, 165.76.

Ethyl 2-(1-naphthyl)cyanoacetate (Table 2, entry 9).³ Dioxane as a solvent. Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/3) to give the desired product (236 mg, 99 %) as a slightly yellow oil. ¹H NMR (CDCl₃, 400.15 MHz) δ 1.21 (t, J = 7.2 Hz, 3H, CH₃), 4.23 (m, 2H, CH₂), 5.40 (s, 1H, NCCH), 7.50-8.04 (m, 7H, Nap-H); ¹³C{¹H} NMR (CDCl₃, 100.63 MHz) δ 14.17, 41.79, 63.67, 116.26, 122.88, 125.71, 126.51, 126.71, 127.64, 127.83, 129.43, 130.48, 130.56, 134.24, 165.35.

Ethyl 2-(4-methoxyphenyl)cyanoacetate (Table 2, entry 10).² Purified by column chromatography on silica gel (dichloromethane/hexanes = 1/2) to give the desired product (205 mg, 94 %) as a colorless oil. ¹H NMR (CDCl₃, 299.94 MHz) δ 1.26 (t, J = 7.2 Hz, 3H, CH₂CH₃), 3.81 (s, 3H, OCH₃), 4.22 (m, 2H, CH₂), 4.65 (s, 1H, NCCH), 6.91 (d, J = 8.8 Hz, 2H, 2Ph-H), 7.35 (d, J = 8.8 Hz, 2H, Ph-H); ¹³C{¹H} NMR (CDCl₃, 75.43 MHz) δ 14.14, 43.19, 55.61, 63.44, 114.92, 116.13, 122.11, 129.35, 160.42, 165.49.

Ethyl 2-(4-dimethylaminophenyl)cyanoacetate (Table 2, entry 11).⁶ Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/3) to give the desired product (220 mg, 95 %) as a pale yellow solid, mp 182-183 °C. ¹H NMR (CDCl₃, 400.15 MHz) δ 1.30 (t, J = 7.2 Hz, 3H, CH₂CH₃), 2.96 (s, 6H, 2NCH₃), 4.35 (m, 2H, CH₂), 6.57 (d, J = 6.8 Hz, 2H, 2Ph-H), 6.94 (d, J = 6.8 Hz, 2H, Ph-H); ¹³C{¹H} NMR (CDCl₃, 100.63 MHz) δ 14.09, 40.34, 60.61, 64.16, 111.49, 115.81, 116.41, 129.81, 151.16, 167.06.

Ethyl 2-(3-trifluoromethylphenyl)cyanoacetate (Table 2, entry 12).² Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/3) to give the desired product (248 mg, 96 %) as a colorless oil. ¹H NMR (CDCl₃, 299.94 MHz) δ 1.26 (t, J = 7.2 Hz, 3H, CH₂CH₃), 4.23 (m, 2H, CH₂), 4.81 (s, 1H, NCCH), 7.57-7.72 (m, 4H, Ph-H); ¹³C{¹H} NMR (CDCl₃, 100.63 MHz) δ 14.06, 43.64, 63.96, 115.26, 122.38, 125.11, 126.39, 130.19, 131.20, 131.61, 132.12, 164.50.

Ethyl 2-(4-cyanophenyl)cyanoacetate (Table 2, entry 13).⁷ Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/3) to give the desired product (210 mg, 98 %) as a pale yellow oil. ¹H NMR (CDCl₃, 299.94 MHz) δ 1.24 (t, J = 7.2 Hz, 3H, CH₃), 4.20 (m, 2H, CH₂), 4.82 (s, 1H, NCCH), 7.58 (d, J = 8.3 Hz, 2H, 2Ph-H), 7.58 (d, J = 8.6 Hz, 2H, Ph-H); ¹³C{¹H} NMR (CDCl₃, 75.43 MHz); δ 14.08, 43.80, 64.13, 113.67, 114.93, 118.10, 129.15, 133.27, 135.07, 164.12.

(4-Cyano-ethoxycarbonyl-methyl)-benzoic acid methyl ester (Table 2, entry 14).⁸ Purified by column chromatography on silica gel (dichloromethane/hexanes = 1/1) to give the desired product (232 mg, 94 %) as a pale yellow solid, mp 93-95 °C. ¹H NMR (CDCl₃, 400.15 MHz) δ 1.26 (t, J = 7.2 Hz, 3H, CH₃), 3.93 (s, 3H, OCH₃), 4.23 (m, 2H, CH₂), 4.78 (s, 1H, NCCH), 7.54 (d, J = 8.4 Hz, 2H, 2Ph-H), 8.08 (d, J = 8.4 Hz, 2H, Ph-H); ¹³C{¹H} NMR (CDCl₃, 100.63 MHz); δ 14.14, 43.91, 52.65, 63.89, 115.31, 128.27, 130.75, 131.32, 134.69, 164.53, 166.37.

Ethyl 2-(2-pyridyl)cyanoacetate (Table 2, entry 16).⁹ Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/1) to give the desired product (178 mg, 94 %) as a pale yellow solid, mp 107-108 °C. ¹H NMR (CDCl₃, 299.94 MHz) δ 1.25 (m, 3H, CH₂CH₃), 4.15 (m, 2H, CH₂), 6.62-7.65 (m,

4H, Py-H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75.43 MHz) δ 14.77, 60.40, 62.73, 112.78, 119.52, 120.52, 134.26, 139.96, 155.75, 170.58.

Cyano-[4-(cyano-ethoxycarbonyl-methyl)-phenyl]-acetic acid ethyl ester (Table 2, entry 17).¹⁰ Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/5) to give the desired product (138 mg, 92 %) as a white solid, mp 77-80 °C. ^1H NMR (CDCl_3 , 400.15 MHz) δ 1.25 (t, J = 7.2 Hz, 6H, 2CH₃), 4.23 (m, 4H, 2CH₂), 4.76 (s, 2H, 2NCCH), 7.52 (s, 4H, Ph-H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100.63 MHz) δ 14.13, 43.53, 63.86, 115.51, 129.20, 131.39, 164.72.

2-Phenyl-2-methyl-propionitrile (Table 3, entry 1).¹¹ Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/10) to give the desired product (138 mg, 95 %) as a colorless oil. ^1H NMR (CDCl_3 , 400.15 MHz) δ 1.74 (s, 6H, 2CH₃), 7.32-7.51 (m, 5H, Ph-H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100.63 MHz) δ 29.42, 37.44, 124.81, 125.30, 128.05, 129.18, 141.64.

2-(4-*tert*-Butyl-phenyl)-2-methyl-propionitrile (Table 3, entry 2).¹² Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/9) to give the desired product (185 mg, 92 %) as a pale yellow solid, mp 56-57 °C. ^1H NMR (CDCl_3 , 400.15 MHz) δ 1.33 (s, 9H, PhC(CH₃)₃), 1.73 (s, 6H, NCC(CH₃)₂), 7.42 (m, 4H, Ph-H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100.63 MHz) δ 29.41, 31.54, 34.75, 36.99, 124.94, 125.01, 126.04, 138.62, 150.98.

2-(2-methylphenyl)-2-methyl-propionitrile (Table 3, entry 3).¹² Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/9) to give the desired product (142 mg, 89 %) as a colorless oil. ^1H NMR (CDCl_3 , 299.95 MHz) δ 1.80 (s, 6H, NCC(CH₃)₂), 2.68 (s, 3H, Ph-CH₃), 7.23-7.33 (m, 4H, Ph-H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75.43 MHz) δ 21.37, 28.45, 35.22, 124.80, 124.96, 126.74, 128.26, 132.97, 136.51, 138.26.

2-(1-Cyano-1-methyl-ethyl)-benzonitrile (Table 3, entry 4).¹² Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/1) to give the desired product (167 mg, 98 %) as a white solid, mp 86-88 °C. ^1H NMR (CDCl_3 , 299.95 MHz) δ 1.73 (s, 6H, 2CH₃), 7.58 (d, J = 8.6 Hz, 2H, Ph-H), 7.67 (d, J = 8.6 Hz, 2H, Ph-H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75.43 MHz) δ 29.06, 37.71, 112.23, 118.42, 123.58, 126.33, 133.05, 146.74.

2-(4-Methoxy-phenyl)-2-methyl-propionitrile (Table 3, entry 5).¹² Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/9) to give the desired product (154 mg, 88 %) as a lightly yellow oil. ^1H NMR (CDCl_3 , 299.94 MHz) δ 1.70 (s, 6H, NCC(CH₃)₂), 3.81 (s, 3H, OCH₃), 6.89 (d, J = 8.9 Hz, 2H, Ph-H), 7.37 (d, J = 8.9 Hz, 2H, Ph-H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75.43 MHz) δ 29.49, 36.66, 55.56, 114.41, 125.02, 126.47, 133.73, 159.25.

Diphenyl acetonitrile (Table 3, entry 6).¹² Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/10) to give the desired product (179 mg, 93 %) as a pale yellow solid, mp 74-75 °C. ¹H NMR (CDCl₃, 299.95 MHz) δ 5.17 (s, 1H, CHCN), 7.34-7.41 (m, 10H, 2Ph-H); ¹³C{¹H} NMR (CDCl₃, 75.43 MHz); δ 42.84, 120.07, 128.02, 128.54, 129.50, 136.24.

Diphenyl acetonitrile (Table 3, entry 7).¹² Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/10) to give the desired product (78.5 mg, 81 %) as a pale yellow solid, mp 74-75 °C. ¹H NMR (CDCl₃, 299.95 MHz) δ 5.17 (s, 1H, CHCN), 7.34-7.41 (m, 10H, 2Ph-H); ¹³C{¹H} NMR (CDCl₃, 75.43 MHz); δ 42.84, 120.07, 128.02, 128.54, 129.50, 136.24.

2-Phenyl-butyronitrile (Table 3, entry 9).¹² Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/9) to give the desired product (123 mg, 85 %) as a colorless oil. ¹H NMR (CDCl₃, 299.95 MHz) δ 1.05 (t, J = 7.3 Hz, 3H, CH₃), 1.89 (m, 2H, CH₂), 5.17 (t, J = 7.2 Hz, 1H, CHCN), 7.32-7.38 (m, 5H, Ph-H); ¹³C{¹H} NMR (CDCl₃, 75.43 MHz); δ 11.71, 29.45, 39.12, 121.01, 127.53, 128.23, 129.25, 135.99.

2-Diphenyl-butyronitrile (Table 3, entry 10).¹² Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/9) to give the desired product (201 mg, 91 %) as a pale yellow oil. ¹H NMR (CDCl₃, 299.95 MHz) δ 1.07 (t, J = 7.4 Hz, 3H, CH₃), 2.43 (q, J = 7.2 Hz, 2H, CH₂), 7.31-7.46 (m, 10H, 2Ph-H); ¹³C{¹H} NMR (CDCl₃, 75.43 MHz); δ 10.40, 33.08, 52.86, 122.55, 127.23, 128.10, 129.12, 140.43.

2-Phenyl-2-phenylsulfonyl-acetonitrile (Table 3, entry 11).¹³ Purified by column chromatography on silica gel (ethyl acetate/hexanes = 1/3) to give the desired product (247 mg, 96 %) as a white solid, mp 147-148 °C. ¹H NMR (CDCl₃, 299.95 MHz) δ 5.15 (s, 1H, CHCN), 7.26-7.73 (m, 10H, 2Ph-H); ¹³C{¹H} NMR (CDCl₃, 75.43 MHz); δ 63.31, 113.65, 125.57, 129.29, 129.44, 129.97, 130.32, 130.78, 134.50, 135.52.

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