Supporting Information

Aerobic Ruthenium-Catalyzed Oxidative Cyanation of Tertiary Amines with Sodium Cyanide

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General. IR spectra were recorded on a Shimadzu FTIR-4100 spectrometer. ^{1}H and ^{13}C-{^{1}H} spectra were obtained on a JEOL JNM-GSX-270 (270 MHz) or a Varian Unity-Inova 500 (500 MHz) spectrometers. Chemical shifts of ^{1}H and ^{13}C-{^{1}H} NMR spectra were expressed in parts per million downfield from tetramethylsilane. Analytical GLC evaluations of product mixtures were carried out on a Shimadzu GC-17A series gas chromatograph. GC-MS analyses and mass spectra were performed on a Shimadzu QP-5000 mass spectrometer. HRMS analyses were performed on a JEOL JMS-700 mass spectrometer. Elemental analyses were performed on a Yanagimoto MT-3 CHN corder. Melting points were measured on a BÜCHI Melting Point B-545.

Materials. All tertiary amines were distilled over CaH_2 under argon. Methanol was distilled over Mg. Acetic acid was distilled with acetic anhydride. Unless otherwise stated, other starting materials were obtained from commercial suppliers and used without further purification. $RuCl_3 \cdot nH_2O$ was purchased from N.E. Chemcat Corporation. $RuCl_2(bpy)_2$ was purchased from STREM. $Ru_2(OAc)_4Cl$ was prepared according to the reported procedure.[1] *N*,*N*-Dimethyl-*p*-anisidine and *N*,*N*-dimethyl-4-phenoxyaniline were prepared according to the literature.[2] *N*-Phenyl-1,2,3,4-tetrahydroisoquinoline was prepared according to the literature.[3]

Cautionary note: All reactions and treatments must be carried out in a well

ventilated hood, because highly toxic HCN will be formed from NaCN in acidic media.

Aerobic Ruthenium-Catalyzed Oxidative Cyanation of *N*,*N*-Dimethylaniline with Sodium Cyanide. A 25 mL side-armed round-bottomed flask equipped with a magnetic stirring bar and a balloon filled with O_2 (1 atm) was charged with $RuCl_3 \cdot nH_2O$ (13 mg, 5.0×10^{-2} mmol), and sodium cyanide (59 mg, 1.2 mmol). Methanol (1.2 mL) and *N*,*N*-dimethylanline (121 mg, 1.0 mmol) were added into the flask, and then, acetic acid (0.4 mL) was added by sylinge technique. The reaction mixture was stirred under molecular oxygen at 60°C. After 2 hours, the mixture was poured into $NaHCO_3$ aqueous solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate. The yields of *N*-methyl-*N*-phenylacetonitrile, *N*-methylaniline, and *N*-methylformamide were determined to be 93%, < 3% and trace amount by GLC analysis using an internal standard as hexadecane. Chromatography on Silica gel (hexane-ethyl acetate, 20:1) gave pure *N*-methyl-*N*-phenylacetonitrile (130 mg, 88%).

***N*-Methyl-*N*-phenylaminoacetonitrile**: IR (neat) 3096, 2896, 2325 (CN), 1601, 1580, 1505, 1478, 1456, 1424, 1356, 1338, 1248, 1202, 1161, 1119, 1034, 999, 926, 870, 756, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.01 (s, 3 H), 4.16 (s, 2 H), 6.87 (dd, J = 8.7 Hz and 1.1 Hz, 2H), 6.93 (dd, J = 6.5 Hz and 0.86 Hz, 1H), 7.31 (ddd, J = 8.1 Hz, 8.1 Hz, and 1.1 Hz, 2H); ^{13}C-{^1H} NMR ($CDCl_3$, 68 MHz) δ 147.9, 129.5, 120.2, 115.4, 114.9, 42.3, 39.2; HRMS (EI) calcd for $C_9H_{10}N_2$ *m*/*z* 146.0844, found *m*/*z* 146.0807.

***N*-Methyl-*N*-(4-methylphenyl)aminoacetonitrile**: IR (neat) 3032, 2923, 2236(CN), 1615, 1577, 1520, 1474, 1453, 1429, 1350, 1337, 1246, 1194, 1115, 997, 926, 868, 810, 708 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.28 (s, 3 H), 2.95 (s, 3 H), 4.11 (s, 2 H), 6.79 (dm, J = 8.6 Hz, 2 H), 7.11 (dm, J = 8.6 Hz, 2 H); ^{13}C-{^1H} NMR ($CDCl_3$, 68 MHz) δ 145.8, 130.0, 129.9, 115.5, 115.4, 42.8, 39.5, 20.3; HRMS (EI) calcd for $C_{10}H_{12}N_2$ *m*/*z* 160.1001, found *m*/*z* 160.0988.

***N*-Methyl-*N*-(3-methylphenyl)aminoacetonitrile**: IR (neat) 3086, 2920, 2818, 2301 (CN), 1676, 1604, 1586, 1497, 1477, 1453, 1424, 1356, 1337, 1256, 1223, 1183, 1121, 1020, 939, 866, 774, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.34 (s, 3 H), 2.98 (s, 3 H), 4.14 (s, 2 H), 6.66 (dm, J = 9.0 Hz, 1 H), 6.68 (s, 1 H), 6.74 (dm, J = 7.4 Hz, 1 H), 7.18 (dd, J = 9.0 and 7.5 Hz, 1 H); ^{13}C-{^1H} NMR ($CDCl_3$, 68 MHz) δ 21.7, 39.2, 42.3, 112.1, 115.5, 115.7, 121.1, 129.3, 139.2, 147.9; HRMS (EI) calcd for $C_{10}H_{12}N_2$ *m*/*z* 160.1001 found *m*/*z* 160.1017.

***N*-Methyl-*N*-(4-phenoxyphenyl)aminoacetonitrile**: mp 65-66°C; IR (KBr) 3094, 2814, 2236 (CN), 1962, 1941, 1877, 1854, 1584, 1512, 1491, 1480, 1458, 1431, 1290, 1258, 1237, 1210, 1194, 1119, 1074, 995, 928, 874, 835, 758, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.97 (s, 3 H), 4.13 (s, 2 H), 6.87 (ddd, *J* = 9.0, 3.0, and 3.0 Hz), 6.96 (dddd, *J* = 8.7 and 1.0 Hz), 7.00, (ddd, *J* = 9.0, 3.0, and 3.0 Hz, 2 H), 7.05 (dddd, *J* = 7.3, 7.3, 1.0, and 1.0 Hz), 7.30 (dddd, *J* = 8.7 and 7.3 Hz); ^{13}C-{^1H} NMR ($CDCl_3$, 125 MHz) δ 39.7, 43.1, 115.3, 116.8, 117.8, 120.6, 122.6, 129.6, 144.2, 150.5, 158.1; Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found; C, 75.58; H, 5.94; N, 11.57.

***N*-Methyl-*N*-(4-methoxyphenyl)aminoacetonitrile**: IR (neat) 2996, 2836, 2236 (CN), 2058, 1736, 1686, 1616, 1584, 1514, 1466, 1420, 1333, 1298, 1252, 1186, 1115, 1036, 997, 926, 868, 824, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.92 (s, 3 H), 3.77 (s, 3 H), 4.07 (s, 2 H), 6.88 (4 H); ^{13}C-{^1H} NMR ($CDCl_3$, 68 MHz) δ 154.5, 142.2, 117.9, 115.4, 114.8, 55.6, 44.0, 40.0; HRMS calcd for $C_9H_{11}N_2O$ *m*/*z* 165.0790, found *m*/*z* 165.0771.

***N*-Methyl-*N*-(4-bromophenyl)aminoacetonitrile**: IR (neat) 3132, 2963, 2820, 2240 (CN), 1869, 1682, 1593, 1499, 1453, 1427, 1362, 1335, 1289, 1246, 1200, 1117, 1080, 997, 926, 871, 812, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.99 (s, 3 H), 4.13 (s, 2 H), 6.73 (dm, *J* = 9.0 Hz, 2 H), 7.37 (dm, *J* = 9.0 Hz, 2H); ^{13}C-{^1H} NMR ($CDCl_3$, 68 MHz) δ 146.8, 132.3, 116.5, 115.0, 112.6, 42.2, 39.3; HRMS (EI) calcd for $C_9H_9N_2Br$ *m*/*z* 223.9949, found *m*/*z* 223.9930.

***N*-Ethyl-*N*-phenylaminoacetonitrile**: IR (neat) 3063, 2997, 2240 (CN), 1601, 1578, 1503, 1458, 1431, 1379, 1350, 1275, 1244, 1186, 1130, 1076, 1040, 1013, 989, 976, 878, 797, 752, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.24 (t, *J* = 7.1 Hz, 3H), 3.43 (q, *J* = 7.1 Hz, 2H), 4.13 (s, 2H), 6.86 (dm, *J* = 7.8 Hz, 2H), 6.89 (dm, *J* = 7.8Hz, 1H), 7.31 (ddm, *J* = 7.3 Hz and 7.3 Hz, 2H); ^{13}C-{^1H} NMR ($CDCl_3$, 68 MHz) δ 146.9, 129.5, 119.9, 116.3, 115.0, 46.3, 39.5, 12.2; HRMS (EI) calcd for $C_{10}H_{12}N_2$ *m*/*z* 160.1001, found *m*/*z* 160.1020.

2-Cyano-1-phenyl-1,2,3,4-tetrahydrosioquinoline: mp 101-102°C; IR (KBr) 3108, 2990, 2824, 2222 (CN), 1595, 1497, 1460, 1424, 1373, 1356, 1339, 1309, 1273, 1221, 1206, 1142, 1026, 995, 938, 889, 779, 745, 693, 613 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.96 (dt, *J* = 16.1 and 3.7Hz, 1 H), 3.15, (ddd, *J* = 16.2, 10.5, and 5.9 Hz, 1H), 3.48 (ddd, *J* = 12.3, 10.5, and 4.3 Hz, 1H), 3.77 (ddd, *J* = 12.5, 6.1, 2.9, and 1.2 Hz, 1H), 5.50 (s, 1H), 7.01 (ddm, *J* = 7.3 and 2.2 Hz, 1H), 7.08 (ddm, *J* = 7.1 and 2.2 Hz, 2H), 7.19 (m, 6H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 148.4, 134.6, 129.7, 129.6, 129.3, 128.8, 127.1, 126.9, 121.9, 117.7, 117.6, 53.2, 44.2, 28.5. Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found; C, 82.04; H, 6.05; N, 11.91.

General Procedure for Hydrolysis of α-Aminonitriles.

Synthesis of *N*-Methyl-*N*-phenylglycine. A solution of *N*-methyl-*N*-phenylaminoacetonitrile (20 mg, 0.137 mmol) and NaOH (38 mg, 0.684 mmol) in ethanol (2 mL) was refluxed at 90°C for 5 h. The reaction mixture was acidified by adding 2M HCl aqueous solution and extracted with ether (10 mL × 2). The combined organic layer was dried over Na_2SO_4. Removal of the solvent gave *N*-methyl-*N*-phenylglycine (20 mg, 87%): IR (neat) 3030, 2928, 1721, 1601, 1509, 1456, 1418, 1368, 1346, 1254, 1211, 1123, 1036, 1013, 990, 947, 911, 864, 810, 750, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 270MHz) δ 3.04 (s, 3 H), 4.07 (s, 2 H), 6.71 (d, *J* = 7.7 Hz, 1 H), 6.78 (dd, *J* = 7.7 and 7.7 Hz, 2 H), 7.24 (dd, *J* = 7.7 and 7.7 Hz, 2 H), 8.90 (br, 1 H): ^{13}C-{^1H} NMR ($CDCl_3$, 68 MHz) δ 176.2, 148.7, 129.3, 118.0, 112.7, 54.5, 39.5; HRMS (EI) calcd for $C_9H_{11}NO_2$ *m*/*z* 165.0790, found *m*/*z* 165.0800.

***N*-(4-Methoxyphenyl)-*N*-methylglycine**: mp. 157-159°C; IR (KBr) 3304, 3167, 1653, 1601, 1514, 1397, 1327, 1257, 1242, 1211, 1184, 1122, 1099, 1039, 945, 806, 748, 721 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.96 (s, 3 H), 3.76 (s, 5 H), 659 (br, 1 H), 6.74 (dm, *J* = 9.0 Hz, 2 H), 6.86 (dm, *J* = 9.0Hz, 2 H); ^{13}C-{^1H} NMR ($CDCl_3$, 68 MHz) δ 173.7, 153.2, 143.8, 115.2, 114.9, 59.4, 55.7, 40.6.

General Procedure for Hydrogenation of α-Aminonitriles.

Synthesis of *N*-methyl-*N*-phenylethylenediamine. A solution of *N*-methyl-*N*-phenylaminoacetonitrile (145 mg, 1.0 mmol) in ether (2.0 mL) was added to a suspension of $LiAlH_4$ (190 mg, 5.0 mmol) in ether (4 mL) at 0°C, and the resulting suspension was stirred for 1h at room temperature. The reaction mixture was cooled to 0°C and quenched with water (*ca.* 5 mL). The resulting insoluble material was removed by filtration through Celite, and the filtrate was extracted with ether (30 mL × 3). The organic layer was dried over sodium sulfate. Filtration followed by evaporation of the solvent gave *N*-methyl-*N*-phenylethylenediamine (137 mg, 92%): IR (neat) 3875, 2986, 1921, 1603, 1597, 1591, 1576, 1509, 1501, 1480, 1451, 1431, 1370, 1356, 1308, 1223, 1194, 1132, 1121, 1100, 1082, 1033, 992, 953, 862, 820, 754, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.40 (br, 2 H), 2.92 (t, *J* = 6.4 Hz, 2 H), 2.95 (s, 3 H), 3.38 (t, *J* = 6.4 Hz, 2 H), 6.70 (dddd, *J* = 7.3, 7.3, 2.0, and 2.0 Hz, 1 H), 6.75 (ddm, *J* = 8.3 and 1.0 Hz, 2 H), 7.23 (dddd, *J* = 8.3, 7.3, 2.1, and 2.1 Hz, 2 H); ^{13}C-{^1H} NMR ($CDCl_3$, 125 MHz) δ 149.71, 129.13, 116.41, 112.33, 55.95, 39.66, 38.60; HRMS (EI) calcd for $C_9H_{14}N_2$ *m*/*z* 150.1157, found *m*/*z* 150.1144.

Hammett Treatment.

Competitive Reaction of Substituted *N*,*N*-Dimethylanilines (X-$C_6H_4N(CH_3)_2$, X= *p*-MeO, *p*-Me, H, *p*-Br) for the Ruthenium-Catalyzed Oxidative Cyanation with Molecular Oxygen in the Presence of Sodium Cyanide. A 25 mL side-armed round-bottomed flask equipped with a magnetic stirring bar and a balloon filled with molecular oxygen was charged with *N*,*N*-dimethylaniline (60 mg, 0.50 mmol), substituted *N*,*N*-dimethylaniline (0.5 mmol), $RuCl_3 \cdot nH_2O$ (13 mg, 0.05 mmol), sodium cyanide (59 mg, 1.2 mmol) and a mixture of methanol-acetic acid (3:1, 1.6 mL). The flask was immersed in an oil bath (60 °C), and the mixture was stirred under oxygen atmosphere for 15 min. The mixture was cooled to room temperature, and basified by adding a saturated $NaHCO_3$ aqueous solution. Extraction with ethyl acetate (10 mL × 3), and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and filtered. Removal of the solvent gave a mixture of *N*-cyanomethyl-*N*-methylaniline, the substituted *N*-cyanomethyl-*N*-methylaniline and the starting amines. The ratio of *N*-cyanomethyl-*N*-methylaniline to the substituted *N*-cyanomethyl-*N*-methylaniline (k_X/k_H) was determined by ^1H NMR analysis. The singlet signals of the methylene protones of NCH_2CN residue of the products are observed at 4.07 ppm (*p*-MeO), 4.11 ppm (*p*-Me), 4.17 ppm (H) and 4.13 ppm (*p*-Br), respectively. The ρ value for the oxidative cyanation reaction was determined to be -3.35 with $r^2 = 0.999$.

Kinetic Deuterium Isotope Effect Profile.

Intramolecular Deuterium Isotope Effect Profile for the Ruthenium-Catalyzed Oxidative Cyanation of *p*-Substituted *N*-Trideuteriomethyl-*N*-methylaniline (*p*-$XC_6H_4(CH_3)CD_3$, X = H, CH_3, CH_3O, Br) with Molecular Oxygen in the Presence of Sodium Cyanide. A 25 mL side-armed round-bottomed flask equipped with a magnetic stirring bar and a balloon filled with molecular oxygen was charged with *p*-substituted *N*-trideuteriomethyl-*N*-methylaniline (0.50 mmol), $RuCl_3 \cdot nH_2O$ (6.5 mg, 0.025 mmol), sodium cyanide (29.4 mg, 0.60 mmol) and methanol-acetic acid (3:1, 0.8 mL). The flask was immersed in an oil bath (60 °C), and the mixture was stirred under oxygen atmosphere for 10 minutes. The mixture was cooled to room temperature, and basified by adding a saturated $NaHCO_3$ aqueous solution. Extraction with ethyl acetate (5 mL × 3), and the combined organic layer was washed with brine (10 mL), dried over sodium sulfate, and filtered. Removal of the solvent gave a mixture of the corresponding

N-trideuterio-*N*-phenylaminoacetonitrile, 1,1-dideuterio-*N*-methyl-*N*-phenylamino-acetonitrile and starting amines. The relative reaction rates (k_H/k_D) were determined by the relative intensity of ^{1}H NMR singlet signals of the NCH_2CN residue (2 H, X = H as 4.16; CH_3 as 4.11: CH_3O as 4.13; Br as 4.13) and the NCH_3 residue (3 H, X = H as 3.01; CH_3 as 2.95; CH_3O as 3.00; Br as 2.99) of the corresponding products, respectively. The results were as follows. X = CH_3O (k_H/k_D = 4.1), CH_3 (3.2), H (2.4), Br (1.1).

Measurement of Oxygen Uptake for the Aerobic Ruthenium Catalyzed Oxidative Cyanation with Sodium Cyanide. A 25 mL side-armed round bottomed flask equipped with a magnetic stirring bar and a ball condenser connected to a gas burette with a balloon filled with molecular oxygen was charged with $RuCl_3 \cdot nH_2O$ (13 mg, 0.05 mmol) and sodium cyanide (58.8 mg, 1.20 mmol). After the reaction apparatus was flushed with molecular oxygen (1 atm), methanol (1.2 mL) and acetic acid (0.4 mL) were added. After the flask was immersed in an oil bath at 60 ˚C for 1 h to stabilize, *N*,*N*-dimethylaniline (121 mg, 1.00 mmol) was added to start the reaction. The absorption of O_2 was monitored in every 10 min. The absorption of O_2 was stopped, after 0.5 mmol of O_2 was consumed (ca. 2 h).

References

1 Mitchell, R. W.; Spencer, A.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1973**, 846-854.
2 Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673-1674.
3 Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1996**, *52*, 8545-8564.