

SUPPORTING INFORMATION

Title: Highly Efficient CuBr-Catalyzed Cross-Dehydrogenative Coupling (CDC) between Tetrahydroisoquinolines and Activated Methylene Compounds

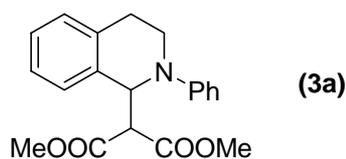
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Ref. No.: O200500226

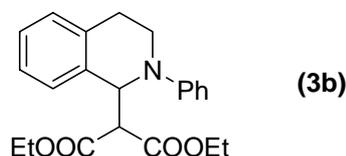
General information: ^1H NMR spectra were recorded on Varian 300 and 400 MHz spectrometer in CDCl_3 solution and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dt, doublet of triplet; dq, doublet of quartet; ddd, doublet of doublet of doublet; dddd, doublet of doublet of doublet of doublet; m, multiplet; q, quartet. The coupling constants, J , are reported in Hertz (Hz). ^{13}C NMR spectra were obtained at 75 and 100 MHz and referenced to the internal solvent signals (central peak is 77.00 ppm). MS data were obtained by Agilent 6890N Network GC System/Agilent 5973 Mass Selective Detector and KRATOS MS25RFA Mass Spectrometer. HRMS were obtained by Kratos MS25RFA Mass Spectrometer. IR spectra were recorded by an ABB Bomem MB100 instrument. Melting points were recorded by Melting Point Apparatus, Gallenkamp. Flash column chromatography was performed over SORBENT silica gel 30-60 μm . Thin layer chromatography was performed using Sorbent Silica Gel 60 F₂₅₄ TLC plates and visualized with ultraviolet light. All reagents were weighed and handled in air, and backfilled under an inert atmosphere of nitrogen at room temperature. All reagents were purchased from Aldrich and Acros and used without further purification. 2-Aryl-1,2,3,4-tetrahydroisoquinolines were prepared by the literature method^[1].

General procedure: To a mixture of CuBr (0.7 mg, 0.005 mmol) and 2-phenyl-1,2,3,4-tetrahydroisoquinoline (209 mg, 1.0 mmol), dimethyl molonate (116 μL , 1.0 mmol) were added. Then *tert*-butyl hydroperoxide (0.20 mL, 5-6M in decane) was dropped into the mixture under nitrogen at room temperature. The resulting mixture was stirred at the room temperature for a

certain time as mentioned in the tables. The resulting suspension was diluted with methylene chloride. The solvent was removed by rotary evaporation and purified by column chromatography on silica gel (eluting with hexane/ethyl acetate = 5:1), and the fraction with an $R_f = 0.5$ was collected and concentrated to give the desired product **3a**.

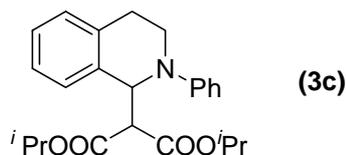


2-(2-Phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-malonic acid dimethyl ester (3a). Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, $R_f = 0.5$). IR (neat liquid): ν_{\max} 3065, 3022, 2959, 2911, 2843, 1765, 1754, 1740, 1596, 1577, 1504, 1476, 1450, 1436, 1386, 1344, 1307, 1273, 1232, 1199, 1162, 1136, 1111, 1019 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) $\delta = 7.21$ -7.15(m, 3H), 7.13-7.05(m, 3H), 6.96(d, $J = 8.1$ Hz, 2H), 6.73(dd, $J = 6.9, 6.9$ Hz, 1H), 5.69(d, $J = 9.3$ Hz, 1H), 3.94(d, $J = 9.3$ Hz, 1H), 3.72-3.56(m, 2H), 3.63(s, 3H), 3.52(s, 3H), 3.05(ddd, $J = 16.2, 8.7, 6.3$ Hz, 1H), 2.85(dt, $J = 16.2, 5.1$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3 , 25 $^\circ\text{C}$) $\delta = 168.00, 167.13, 148.55, 135.47, 134.58, 128.92, 128.79, 127.45, 126.86, 125.85, 118.45, 115.03, 59.05, 58.12, 52.48, 52.47, 42.15, 26.06$ ppm; MS (EI) m/z (%) 339, 209, 208(100), 193, 165, 128, 115, 104, 91, 77, 65, 51; HRMS calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_4$: 339.1471; found: 339.1475.

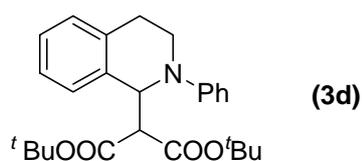


2-(2-Phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-malonic acid diethyl ester (3b). Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, $R_f = 0.5$). IR (neat liquid): ν_{\max} 3065, 3026, 2981, 2940, 2908, 2872, 1748, 1731, 1598, 1577, 1505, 1494, 1475, 1452, 1392, 1369, 1305, 1269, 1179, 1145, 1112, 1096, 1037, 933 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) $\delta = 7.24$ -7.05(m, 6H), 6.96(d, $J = 8.1$ Hz, 2H), 6.72(dd, $J = 7.2, 7.2$ Hz, 1H), 5.71(d, $J = 9.3$ Hz, 1H), 4.17-3.93(m,

4H), 3.88(d, $J = 9.0$ Hz, 1H), 3.74-3.58(m, 2H), 3.06(ddd, $J = 15.9, 8.7, 6.3$ Hz, 1H), 2.87(dt, $J = 16.5, 5.1$ Hz, 1H), 1.16(t, $J = 7.2$ Hz, 3H), 1.08(t, $J = 7.2$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3 , 25 °C) $\delta = 167.74, 166.90, 148.65, 135.78, 134.64, 128.90, 128.74, 127.36, 127.01, 125.85, 118.30, 114.93, 61.55, 59.51, 57.84, 42.26, 26.14, 14.00, 13.94$ ppm; MS (EI) m/z (%) 367, 209, 208(100), 193, 165, 128, 115, 104, 91, 77, 65, 51; HRMS calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_4$: 367.1784; found: 367.1789.

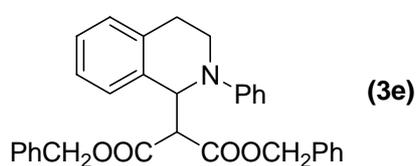


2-(2-Phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-malonic acid diisopropyl ester (3c). Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, $R_f = 0.7$). IR (neat liquid): ν_{max} 3062, 3029, 2981, 2934, 2879, 2836, 1726, 1599, 1577, 1505, 1495, 1466, 1453, 1429, 1387, 1374, 1270, 1180, 1146, 1102, 1033 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25 °C) $\delta = 7.28\text{-}7.05$ (m, 6H), 6.94(d, $J = 8.4$ Hz, 2H), 6.71(dd, $J = 7.2, 7.2$ Hz, 1H), 5.70(d, $J = 8.7$ Hz, 1H), 5.01(q, $J = 6.3$ Hz, 0.5H), 4.99(q, $J = 6.3$ Hz, 0.5H), 4.91(q, $J = 6.3$ Hz, 0.5H), 4.88(q, $J = 6.3$ Hz, 0.5H), 3.82(d, $J = 9.0$ Hz, 1H), 3.74-3.58(m, 2H), 3.04(ddd, $J = 15.9, 8.7, 6.0$ Hz, 1H), 2.85(dt, $J = 15.9, 5.1$ Hz, 1H), 1.19(d, $J = 6.6$ Hz, 3H), 1.11(d, $J = 6.6$ Hz, 3H), 1.10(d, $J = 6.6$ Hz, 3H), 1.01(d, $J = 6.6$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3 , 25 °C) $\delta = 167.38, 166.55, 148.78, 136.08, 134.68, 128.90, 128.71, 127.25, 127.13, 125.86, 118.20, 114.95, 69.16, 60.07, 57.49, 42.37, 26.16, 21.61, 21.58, 21.36$ ppm; MS (EI) m/z (%) 395, 209, 208(100), 193, 165, 115, 104, 91, 77; HRMS calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_4$: 395.2097; found: 395.2107.

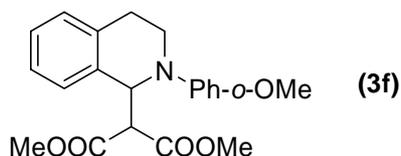


2-(2-Phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-malonic acid di-tert-butyl ester (3d). Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, $R_f = 0.8$). Melting point is 94.0-95.0

°C. IR (KBr): ν_{\max} 3009, 2976, 2932, 2860, 1745, 1717, 1598, 1508, 1473, 1392, 1369, 1327, 1294, 1246, 1179, 1151, 940, 847, 760, 749, 695, 505 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ = 7.30(d, J = 7.6 Hz, 1H), 7.22-7.07(m, 5H), 6.95(d, J = 9.2 Hz, 2H), 6.70(dd, J = 7.2, 7.2 Hz, 1H), 5.70(d, J = 8.4 Hz, 1H), 3.70-3.60(m, 2H), 3.65(d, J = 8.4 Hz, 1H), 3.05(ddd, J = 16.0, 8.4, 5.6 Hz, 1H), 2.89(dt, J = 16.4, 5.2 Hz, 1H), 1.40(s, 9H), 1.26(s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3 , 25 °C) δ = 167.21, 166.17, 148.65, 136.80, 134.66, 128.85, 128.48, 127.05, 126.98, 125.84, 117.64, 114.28, 81.73, 81.63, 61.99, 56.89, 42.34, 27.91, 27.64, 26.47 ppm; MS (EI) m/z (%) 423, 209, 208(100), 193, 165, 115, 104, 91, 77, 57; HRMS calcd for $\text{C}_{26}\text{H}_{33}\text{NO}_4$: 423.2410; found: 423.2414.



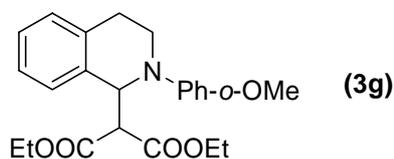
2-(2-Phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-malonic acid dibenzyl ester (3e). Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, R_f = 0.5). Melting point is 113.0-114.0 °C. IR (KBr): ν_{\max} 3065, 3033, 2980, 2956, 2932, 2892, 1753, 1732, 1596, 1499, 1387, 1294, 1233, 1174, 1146, 996, 948, 750, 703, 693, 590, 517, 473 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , 25 °C) δ = 7.31-7.06(m, 15H), 7.00(dd, J = 7.2, 7.2 Hz, 1H), 6.91(d, J = 8.0 Hz, 2H), 6.74(dd, J = 7.2, 7.2 Hz, 1H), 5.72(d, J = 9.2 Hz, 1H), 5.07(d, J = 12.0 Hz, 1H), 5.03(d, J = 12.0 Hz, 1H), 5.01(d, J = 12.0 Hz, 1H), 4.85(d, J = 12.0 Hz, 1H), 4.01(d, J = 9.2 Hz, 1H), 3.63-3.50(m, 2H), 3.00(ddd, J = 16.0, 8.8, 6.0 Hz, 1H), 2.78(dt, J = 16.4, 4.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3 , 25 °C) δ = 167.37, 166.60, 148.54, 135.41, 134.98, 134.81, 134.60, 128.95, 128.79, 128.35, 128.25, 128.22, 128.19, 128.03, 127.38, 126.96, 125.90, 118.51, 115.17, 67.37, 67.32, 59.40, 58.17, 42.28, 26.07 ppm; MS (EI) m/z (%) 491, 236, 209, 208, 207, 206(98), 193, 180, 178, 128, 107(100), 91, 79, 77, 65, 51; HRMS calcd for $\text{C}_{32}\text{H}_{29}\text{NO}_4$: 491.2096; found: 491.2085.



2-[2-(2-Methoxy-phenyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-malonic acid dimethyl ester (3f).

Isolated by flash column chromatography (hexane/ethyl acetate/triethylamine = 50:10:1, R_f = 0.4).

IR (neat liquid): ν_{\max} 3061, 3024, 3007, 2952, 2836, 1756, 1734, 1594, 1501, 1454, 1435, 1382, 1346, 1242, 1202, 1177, 1141, 1112, 1029 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ = 7.23-7.06(m, 4H), 6.97-6.91(m, 1H), 6.82-6.74(m, 3H), 5.39(d, J = 8.7 Hz, 1H), 3.98(d, J = 9.0 Hz, 1H), 3.80(s, 3H), 3.63-3.47(m, 2H), 3.56(s, 3H), 3.54(s, 3H), 2.86(ddd, J = 17.1, 11.4, 6.9 Hz, 1H), 2.66(ddd, J = 16.5, 4.2, 2.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ = 168.16, 167.44, 152.70, 139.32, 135.51, 134.94, 129.13, 127.07, 126.71, 125.65, 123.31, 121.90, 120.59, 111.51, 59.29, 58.86, 55.38, 52.29, 52.24, 42.97, 26.25 ppm; MS (EI) m/z (%) 369, 239, 238, 237, 236(100), 222, 220, 101, 86, 85, 84, 83, 74, 59, 47; HRMS calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_5$: 369.1576; found: 369.1584.

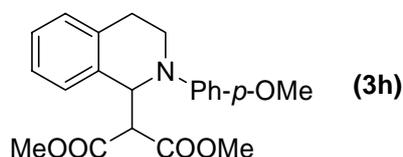


2-[2-(2-Methoxy-phenyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-malonic acid diethyl ester (3g).

Isolated by flash column chromatography (hexane/ethyl acetate/triethylamine = 50:10:1, R_f = 0.5).

IR (neat liquid): ν_{\max} 3062, 2981, 2942, 2907, 2835, 1753, 1733, 1594, 1501, 1464, 1454, 1369, 1339, 1300, 1243, 1178, 1140, 1112, 1031 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ = 7.25-7.05(m, 4H), 6.95-6.90(m, 1H), 6.80-6.74(m, 3H), 5.43(d, J = 8.4 Hz, 1H), 4.08-3.98(m, 4H), 3.92(d, J = 8.4 Hz, 1H), 3.79(s, 3H), 3.66-3.49(m, 2H), 2.87(ddd, J = 16.8, 11.1, 6.9 Hz, 1H), 2.66(ddd, J = 16.8, 4.2, 2.4 Hz, 1H), 1.11(t, J = 6.9 Hz, 3H), 1.07(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ = 167.91, 167.25, 152.55, 149.64, 139.28, 135.57, 134.92, 129.02, 126.96, 125.58, 123.15, 121.63, 120.54, 111.29, 61.31, 61.26, 59.02, 55.25, 42.81, 26.36, 13.91

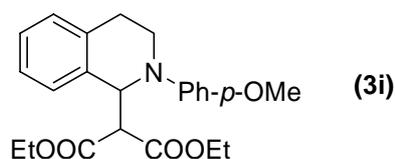
ppm; MS (EI) m/z (%) 397, 287, 238(100), 237, 236, 222, 220, 136, 133, 115, 88, 77, 43; HRMS calcd for $C_{23}H_{27}NO_5$: 397.1889; found: 397.1883.



2-[2-(4-Methoxy-phenyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-malonic acid dimethyl ester (3h).

Isolated by flash column chromatography (hexane/ethyl acetate/triethylamine = 50:10:1, R_f = 0.3).

IR (neat liquid): ν_{max} 2998, 2952, 2908, 2835, 1756, 1736, 1581, 1511, 1493, 1463, 1453, 1435, 1392, 1341, 1268, 1247, 1207, 1143, 1112, 1038, 998 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 7.19-7.14(m, 2H), 7.10-7.07(m, 2H), 6.98(d, J = 9.2 Hz, 2H), 6.75(d, J = 9.2 Hz, 2H), 5.47(d, J = 9.6 Hz, 1H), 3.95(t, J = 9.2 Hz, 1H), 3.71(s, 3H), 3.68-3.61(m, 1H), 3.62(s, 3H), 3.60(s, 3H), 3.54(ddd, J = 13.6, 5.6, 3.2 Hz, 1H), 3.00(ddd, J = 16.4, 10.0, 6.0 Hz, 1H), 2.74(dt, J = 16.8, 4.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ = 168.03, 167.23, 152.96, 143.18, 135.13, 134.57, 129.00, 127.30, 126.87, 125.77, 118.13, 114.22, 59.14, 55.54, 55.52, 52.57, 52.55, 52.53, 52.51, 42.99, 25.49 ppm; MS (EI) m/z (%) 369, 239, 238(100), 237, 236, 221, 193, 136, 115, 101, 77, 59; HRMS calcd for $C_{21}H_{23}NO_5$: 369.1576; found: 369.1583.

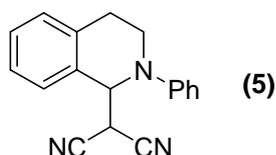


2-[2-(4-Methoxy-phenyl)-1,2,3,4-tetrahydro-isoquinolin-1-yl]-malonic acid diethyl ester (3i).

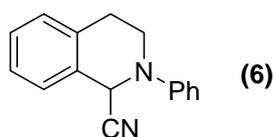
Isolated by flash column chromatography (hexane/ethyl acetate/triethylamine = 50:10:1, R_f = 0.4).

IR (neat liquid): ν_{max} 3065, 2981, 2936, 2905, 2834, 1752, 1731, 1609, 1581, 1512, 1493, 1464, 1444, 1391, 1369, 1335, 1300, 1266, 1249, 1181, 1145, 1039, 940 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$, 25 °C) δ = 7.24-7.21(m, 1H), 7.13(dd, J = 6.6, 1.5 Hz, 1H), 7.09-7.05(m, 2H), 6.89(d, J = 9.0 Hz, 2H), 6.75(d, J = 9.0 Hz, 2H), 5.50(d, J = 9.3 Hz, 1H), 4.13-3.97(m, 4H), 3.89(d, J = 9.0 Hz,

1H), 3.71(s, 3H), 3.69-3.62(m, 1H), 3.57-3.50(m, 1H), 2.99(ddd, $J = 16.5, 10.2, 6.3$ Hz, 1H), 2.75(dt, $J = 16.5, 4.5$ Hz, 1H), 1.14(t, $J = 7.2$ Hz, 3H), 1.12(t, $J = 7.5$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3 , 25 °C) $\delta = 167.78, 167.03, 152.94, 143.36, 135.49, 134.66, 128.92, 127.23, 127.11, 125.77, 117.95, 114.30, 61.47, 61.45, 59.53, 58.88, 55.57, 43.05, 25.65, 14.06, 13.98$ ppm; MS (EI) m/z (%) 397, 253, 239, 238, 237, 236(100), 221, 193, 173, 160, 133, 115, 88, 87, 69, 60, 59, 55, 43; HRMS calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_5$: 397.1889; found: 397.1884.



2-(2-Phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-malononitrile (5). Isolated by flash column chromatography (hexane/ethyl acetate/triethylamine = 50:10:1, $R_f = 0.4$). IR (neat liquid): ν_{max} 3063, 3033, 2906, 2854, 2252, 2229, 1599, 1580, 1504, 1496, 1476, 1454, 1429, 1394, 1367, 1319, 1296, 1265, 1231, 1157, 1115, 1033 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , 25 °C) $\delta = 7.45(\text{dd}, J = 7.2, 1.8$ Hz, 1H), 7.34-7.25(m, 5H), 6.98(d, $J = 8.7$ Hz, 3H), 5.34(d, $J = 4.2$ Hz, 1H), 4.18(d, $J = 4.8$ Hz, 1H), 3.80(ddd, $J = 12.0, 7.2, 4.8$ Hz, 1H), 3.50(ddd, $J = 12.0, 6.6, 5.4$ Hz, 1H), 3.16(ddd, $J = 16.2, 6.0, 6.0$ Hz, 1H), 3.03(ddd, $J = 17.1, 6.6, 6.6$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3 , 25 °C) $\delta = 147.53, 135.43, 130.47, 129.78, 129.16, 129.11, 127.26, 126.89, 121.05, 116.27, 61.55, 43.47, 29.58, 27.74$ ppm; MS (EI) m/z (%) 274, 273, 208(100), 207, 193, 170, 154, 144, 130, 115, 106, 104, 91, 77, 65, 51; HRMS calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_5$: 369.1576; found: 369.1583; HRMS calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3$: 273.1266; found: 273.1273.



2-Phenyl-1,2,3,4-tetrahydro-isoquinoline-1-carbonitrile (6). ^[2] Isolated by flash column chromatography (hexane/ethyl acetate/triethylamine = 50:10:1, $R_f = 0.6$). ^1H NMR (400 MHz,

CDCl₃, 25 °C) δ 7.37-7.21(m, 6H), 7.07(d, $J = 8.0$ Hz, 2H), 7.00(dd, $J = 7.2, 7.2$ Hz, 1H), 5.50(s, 1H), 3.77(dddd, $J = 12.4, 6.0, 2.8, 1.2$ Hz, 1H), 3.48(ddd, $J = 12.4, 11.2, 4.0$ Hz, 1H), 3.16(ddd, $J = 16.4, 10.8, 6.0$ Hz, 1H), 2.96(dt, $J = 16.4, 3.6$ Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, 25 °C) δ 148.18, 134.46, 129.43, 129.21, 128.62, 126.92, 126.71, 121.78, 117.62, 117.49, 53.28, 44.24, 28.64 ppm.

Reference:

[1] Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581-584.

[2] Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *115*, 15312.

