Supporting Information

for

"Diverse Cyclization Catalyzed by $In(OTf)_3$ for the Convergent Assembly of Substituted Tetrahydrofurans and Tetrahydropyrans"

by Teck-Peng Loh, Qi-Ying Hu, Kui-Thong Tan and Hin-Soon Cheng

(10 pages)

5-Cyclohexyl-2,2-dimethyl-3-(3-phenyl-propylidene)-tetrahydrofuran (3a)

A suspension of $In(OTf)_3$ (15 mg, 0.027 mmol) in CH_2Cl_2 (1 mL) was refluxed for 5 minutes and followed by slowly addition of α-adduct of homoallylic alcohol **1** (50 mg, 0.27 mmol) and 3-phenyl-propionaldehyde (40 mg, 0.3 mmol) in CH_2Cl_2 (2 mL). The reaction mixtures were stirred for 12 hours at 40 °C. 1M HCl (10 mL) was added and the reaction mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and rotary evaporated. The crude product was purified by column chromatography to afford homoallylic alcohol **3a** as a colorless oil (52 mg, 65%). R_f 0.69 (4:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.15 (m, 5H), 5.12 (ddt, *J* = 7.2, 2.8, 2.4 Hz, 1H), 3.55 (dt, *J* = 8.8, 6.6 Hz, 1H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.28 (dt, *J* = 7.7, 7.2 Hz, 2H), 2.06–1.85 (m, 2H), 1.26 (s, 3H), 1.19 (s, 3H), 1.79–0.85 (m, 11H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 148.3, 141.9, 128.6, 128.2, 125.8, 117.4, 81.1, 80.0, 42.8, 35.8, 32.9, 31.7, 29.9, 29.0, 28.5, 27.7, 26.6, 26.1, 26.0; IR (film) 3086, 3063, 3028, 2970, 2926, 2854, 2361, 1359, 1452, 1046, 909, 734, 699 cm^{-1}; HRMS Calcd for $C_{19}H_{26}O$ [M^+]: 298.2297. Found 298.2288.

Analogous procedures were employed for the preparation of the following tetrahydrofurans **3**.

5-Cyclohexyl-3-isopropenyl-2-phenethyltetrahydrofuran (4a)

A suspension of $In(OTf)_3$ (15 mg, 0.027 mmol) in CH_2Cl_2 (1 mL) at 0°C was treated with α-adduct of homoallylic alcohol **1** (50 mg, 0.27 mmol) and 3-phenyl-propionaldehyde (40mg, 0.3 mmol) in CH_2Cl_2 (2 mL). The reaction mixtures were slowly warmed to room temperature and stirred for 12 hours. 1M HCl (10 mL) was

added and the reaction mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and rotary evaporated. The crude product was purified by column chromatography to afford homoallylic alcohol **4a** as a colorless oil (76 mg, 95%). R_f 0.64 (4:1 hexane/ethyl acetate); major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.13 (m, 5H), 4.81 (s, 1H), 4.73 (s, 1H), 3.98 (dt, *J* = 8.3, 7.6, 1H), 3.64 (ddd, *J* = 9.7, 7.6, 4.2, 1H); 2.93–2.79 (m, 2H), 2.64–2.54 (m, 1H), 2.05 (brd, *J* = 11.2 Hz, 1H), 1.91 (dt, *J* = 12.5, 6.3 Hz, 1H), 1.70 (s, 3H), 1.77–0.83 (m, 11H); minor isomer: δ 7.29–7.13 (m, 5H), 4.74 (s, 2H), 3.72–3.50 (m, 2H), 2.87–2.77 (m, 1H), 2.71–2.61 (m, 1H), 2.53–2.36 (m, 1H), 1.70 (s, 3H), 2.04–0.83 (m, 13H); major isomer: ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 143.6, 142.7, 128.5, 128.2, 125.6, 111.4, 83.6, 79.0, 49.4, 44.2, 33.8, 32.6, 32.5, 30.3, 29.0, 26.6, 26.1, 26.0, 22.9; minor isomer: 145.3, 142.5, 128.4, 128.2, 125.6, 111.4, 82.9, 81.1, 51.9, 43.4, 36.7, 34.8, 32.6, 29.7, 29.0, 26.7, 26.1, 26.0, 20.2; IR (film) 3084, 3062, 3026, 2924, 2852, 1649, 1450, 1377, 1059, 889, 699 cm^{-1}; HRMS Calcd for $C_{19}H_{26}O$ [M$^+$]: 298.2297. Found 298.2311.

Analogous procedures were employed for the preparation of the following tetrahydrofurans **4**.

5-Cyclohexyl-2,2-dimethyl-3-nonylidenetetrahydrofuran (3b)

R_f 0.79 (4:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08 (tt, broad, *J* = 6.97, 2.79 Hz, 1H), 3.70–3.58 (m, 1H), 2.52 (dd, broad, *J* = 15.33, 6.27 Hz, 1H), 2.18 (dd, broad, *J* = 16.03, 9.75 Hz, 1H), 2.02–0.81 (m, 34H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 147.15, 118.79, 81.18, 80.15, 42.96, 34.71, 33.05, 31.96, 31.65, 29.98, 29.80, 29.56, 29.38, 28.64, 27.73, 26.97, 26.70, 26.15, 25.32, 22.71, 14.11; FTIR

(film) 2925, 2854, 1450, 1376, 1358, 1161, 1084, 1038, 891 cm^{-1}; HRMS Calcd for $C_{11}H_{20}O$ [M^+]: 306.2923. Found: 306.2930.

5-Cyclohexyl-3-isopropenyl-2-octyltetrahydrofuran (4b)

R_f 0.80 (4:1 hexane/ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) : δ 4.74 (s, 2H), 3.54–3.70 (m, 2H), 2.34 (dd, *J* = 9.1, 7.7 Hz, 1H), 1.98–1.12 (m, 30H),1.02–0.82 (m, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 145.67, 111.16, 82.79, 81.92, 51.90, 43.40, 34.95, 34.88, 31.91, 29.87, 29.77, 29.56, 29.31, 28.94, 26.66, 26.30, 26.13, 26.04, 22.69, 20.25, 14.11; FTIR (film) 2925, 2854, 1451, 1377, 1261, 1064, 890, 803 cm^{-1}; HRMS Calcd for $C_{11}H_{20}O$ [M^+]: 306.2923. Found: 306.2913.

3-Benzylidene-5-cyclohexyl-2,2-dimethyltetrahydrofuran (3c)

R_f0.78 (4:1 hexane/ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.19 (m, 4H), 7.06–7.08 (m, 1H), 6.09 (t, broad, *J* = 2.09 Hz, 1H), 3.63 (dt, *J* = 9.06, 6.27 Hz, 2H), 2.78 (ddd, *J* = 16.0, 6.27, 1.39 Hz, 1H), 2.49 (ddd, *J* = 16.0, 9.06, 2.79 Hz, 1H), 1.88 (d, broad, *J* = 13.2 Hz, 1H), 1.72–1.52 (m, 4H), 1.48–1.36 (m, 1H), 1.34 (s, 3H), 1.27 (s, 3H), 1.23–0.85 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 149.99, 138.04, 128.32, 128.12, 126.33, 119.09, 82.66, 80.60, 42.83, 35.19, 29.88, 29.15, 28.64, 27.44, 26.60, 26.06, 25.94; FTIR (film) 3056, 3024, 2970, 2924, 2852, 1598, 1448, 1377, 1359, 1261, 1190, 1160, 1097, 1039, 1012, 943, 913, 866, 742, 694 cm^{-1}; HRMS Calcd for $C_{11}H_{20}O$ [M^+]: 270.1984. Found: 270.1983.

5-Cyclohexyl-3-cyclohexylmethylene-2,2-dimethyltetrahydrofuran (3d)

R_f 0.78 (4:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.92 (dt, *J* = 9.06, 2.79 Hz, 1H), 2.67–2.58 (m, 1H), 2.52 (ddd, *J* = 15.3, 6.27, 2.09, 1H), 2.19 (ddd, *J* = 16.0, 9.75, 2.79 Hz, 1H), 2.02–1.86 (m, 2H), 1.84–1.52 (m, 10H), 1.49–0.80 (m, 16H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 145.38, 124.63, 81.04, 80.14, 42.92, 38.97, 33.12, 32.93, 32.81, 29.97, 29.14, 29.07, 28.60, 27.79, 26.67, 26.51, 26.12, 26.04, 26.01; FTIR (film) 2969, 2924, 2852, 1449, 1376, 1161, 1037, 969, 893 cm^{-1}; HRMS Calcd for $C_{11}H_{20}O$ [M^+]: 276.2453. Found: 276.2443.

5-Cyclohexyl-3-isopropenyl-2-phenyltetrahydrofuran (4c)

R_f 0.64 (4:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.21 (m, 5H), 4.76 (dd, *J* = 1.6, 1.6 Hz, 1H), 4.69 (dd, *J* = 1.6, 0.8 Hz, 1H), 4.64 (d, *J* = 8.4 Hz, 1H), 3.83 (dt, *J* = 7.0, 7.0 Hz,1H), 2.63 (dt, *J* = 17.0, 8.4 Hz, 1H), 2.06–1.93 (m, 2H), 1.73 (s, 3H), 1.82–0.98 (m, 11H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.2, 142.0, 128.1, 127.3, 126.2, 112.0, 84.0, 83.1, 54.8, 43.2, 34.9, 29.5, 29.0, 26.6, 26.1, 26.0, 20.5; IR (film) 3068, 3030, 2922, 2851, 1645, 1450, 1060, 890, 750, 698 cm^{-1}; HRMS Calcd for $C_{19}H_{26}O$ [M^+]: 270.1984. Found 270.1988.

2,5-Dicyclohexyl-3-isopropenyltetrahydrofuran (4d)

R_f 0.78 (4:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (dt, *J* = 11.8, 1.4 Hz, 2H), 3.58 (dd, *J* = 14.6, 7.5 Hz, 1H), 3.53–3.49 (m, 1H), 2.55 (dt, *J* = 7.5, 6.3 Hz, 1H), 1.99–1.84 (m, 2H), 1.73 (s, 3H), 1.85-0.87 (m, 22H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 146.9, 110.8, 85.9, 82.6, 48.7, 43.4, 42.7, 35.6, 29.9, 29.7, 28.9, 28.7. 26.7, 26.4, 26.3, 26.1, 26.1, 20.5; IR (film) 3074, 2724, 2851, 1644, 1450, 1262, 1114,

1085, 1064, 1018, 888 cm^{-1}; HRMS Calcd for $C_{19}H_{32}O$ [M^+]: 276.2453. Found 276.2452.

3-Isopropenyl-6-methyl-2-phenethyltetrahydropyran (6a). A solution of 6-Methyl-hept-5-en-2-ol (1.2 mmol, 154 mg) and 3-Phenyl-propionaldehyde (1.0 mmol, 134 mg) in 3 mL CH_2Cl_2 was added dropwise to a stirred suspension of $In(OTf)_3$ (0.1 mmol, 56.2 mg) in 2 mL CH_2Cl_2 at 0 °C. The reaction mixture was allowed to stir at room temperature for 14 hours. At the end of which, 5 mL H_2O was added and the mixture was extracted with ether (3 × 20 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated *via vacuo*. The residual oil was purified *via* column chromatography (100:1 hexane/ether), yielding **6a** (215 mg, 88% yield) as a colorless oil. R_f 0.41 (30:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.13 (m, 5H), 4.70–4.68 (m, 2H), 3.41 (ddq, *J* = 12.6, 6.27, 2.09 Hz, 1H), 3.19 (dt, *J* = 9.75, 2.44 Hz, 1H), 2.85 (ddd, *J* = 13.6, 9.75, 4.88 Hz, 1H), 2.63 (ddd, *J* = 13.6, 9.06, 7.66 Hz, 1H), 1.95 (dt, *J* = 9.75, 3.48 Hz, 1H), 1.85–1.49 (m, 5H), 1.32 (dt, *J* = 12.19, 3.83 Hz, 1H), 1.23 (d, *J* = 6.27, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 147.1, 142.8, 128.6, 128.2, 125.5, 111.8, 78.7, 73.7, 49.6, 35.2, 33.6, 31.7, 30.2, 22.1, 19.9; IR (film) 3072, 3027, 2970, 2930, 2859, 2846, 11087, 1074, 891, 699 cm^{-1}; HRMS Calcd for $C_{17}H_{24}O$ [M^+]: 244.1827. Found: 244.1821.

Analogous procedures were employed for the preparation of the following tetrahydropyrans.

3-Isopropenyl-6-methyl-2-octyltetrahydropyran (6b). R_f 0.31 (30:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72–4.71 (m, 2H), 3.40 (ddq, *J*

= 12.5, 6.27, 2.09 Hz, 1H), 3.24 (t, *J* = 8.01 Hz, 1H), 1.90 (dt, *J* = 9.76, 3.83 Hz, 1H), 1.65 (s, 3H), 1.77–1.47 (m, 3H), 1.25 (brs, 15H), 1.17 (d, *J* = 6.27 Hz, 3H), 0.87 (t, *J* = 6.97 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 147.4, 111.6, 79.9, 73.7, 49.6, 33.6, 31.9, 30.3, 29.73, 29.68, 29.3, 25.7, 22.7, 22.0, 20.1, 14.1; IR (film) 3074, 2955, 2928, 2855, 1644, 1457, 1380, 1116, 1076, 890 cm^{-1}; HRMS Calcd for $C_{17}H_{32}O$ [M^+]: 252.2453. Found: 252.2453.

3-Isopropenyl-6-methyl-2-phenyltetrahydropyran (6c). R_f 0.30 (30:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.21 (m, 5H), 4.63–4.61 (m, 1H), 4.59 (s, 1H), 4.23 (d, *J* = 10.1 Hz, 1H), 3.40 (ddq, *J* = 12.2, 6.27, 2.09 Hz, 1H), 2.26 (ddd, *J* = 11.8, 10.1, 3.83 Hz, 1H), 1.95–1.86 (m, 1H), 1.82–1.68 (m, 2H), 1.60–1.40 (m, 1H), 1.43 (s, 3H), 1.25 (d, *J* = 6.27, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 146.4, 141.4, 128.0, 127.53, 127.46, 112.0, 84.3, 74.3, 50.3, 33.7, 30.5, 22.2, 21.5; IR (film) 3071, 3032, 2970, 2931, 2849, 1644, 1452, 1367, 1149, 1123, 1102, 1069, 1051, 889, 757, 698 cm^{-1}; HRMS Calcd for $C_{15}H_{20}O$ [M^+]: 216.1514. Found: 216.1509.

3-Isopropenyl-6-methyl-2-styryltetrahydropyran (6e). R_f 0.25 (30:1 hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.17 (m, 5H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.18 (dd, *J* = 16.0, 6.97 Hz, 1H), 4.77 (brs, 2H), 3.92 (ddd, *J* = 10.1, 6.97, 1.05 Hz, 1H), 3.40 (ddq, *J* = 12.5, 6.27, 2.09 Hz, 1H), 2.08 (ddd, *J* = 11.8, 10.1, 3.83 Hz, 1H), 1.85–1.78 (m, 1H), 1.74–1.57 (m, 2H), 1.66 (s, 3H), 1.44–1.32 (m, 1H), 1.26 (d, J = 6.27 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 146.3, 137.2, 131.3, 129.1, 128.4, 127.4, 126.6, 112.1, 81.0, 73.7, 49.7, 33.4, 30.0, 22.1, 20.9; IR (film) 3077,

3028, 2970, 2933, 2845, 1644, 1601, 1497, 1449, 1378, 1368, 1317, 1154, 1122, 1070, 967, 891, 746, 694 cm^{-1}; HRMS Calcd for $C_{17}H_{22}O$ [M^+]: 242.1671. Found: 242.1674.

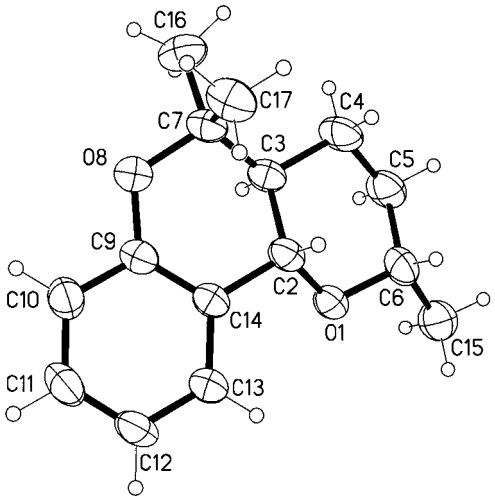
4-(3-Isopropenyl-6-methyltetrahydropyran-2-yl)-benzonitrile (6f). R_f 0.45 (10:1 hexane/ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.36 Hz, 2H), 7.41 (d, *J* = 8.36 Hz, 2H), 4.64 (s, 1H), 4.55 (s, 1H), 4.28 (d, *J* = 10.1 Hz, 1H), 3.64 (ddq, *J* = 11.1, 6.27, 2.09 Hz, 1H), 2.13 (ddd, *J* = 13.6, 10.5, 3.49 Hz, 1H), 1.93–1.86 (m, 1H), 1.81–1.67 (m, 2H), 1.51–1.38 (m, 1H), 1.42 (s, 3H), 1.24 (d, *J* = 6.27 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 146.8, 145.3, 131.9, 128.1, 119.0, 112.8, 111.2, 83.3, 74.4, 50.8, 33.4, 30.2, 22.0, 21.5; IR (film) 3076, 2971, 2933, 2859, 2228, 1645, 1611, 1506, 1445, 1385, 1369, 1148, 1102, 1070, 926, 915, 894, 824 cm^{-1}; HRMS Calcd for $C_{16}H_{19}NO$ [M^+]: 241.1467. Found: 241.1468.

2-Furan-2-yl-3-isopropenyl-6-methyltetrahydropyran (6g). R_f 0.44 (10:1 hexane/ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 1H), 6.28 (dd, *J* = 3.13, 2.09 Hz, 1H), 6.24 (d, *J* = 3.13 Hz, 1H), 4.66 (brs, 2H), 4.36 (d, *J* = 10.5 Hz, 1H), 3.61 (ddq, *J* = 12.5, 6.27, 2.09 Hz, 1H), 2.58–2.50 (m, 1H), 1.93–1.86 (m, 1H), 1.76–1.66 (m, 2H), 1.54 (s, 3H), 1.50–1.28 (m, 1H), 1.24 (d, *J* = 6.27 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 153.7, 146.2, 141.9, 111.8, 109.9, 107.8, 76.5, 74.5, 47.2, 33.2, 30.3, 22.0, 20.5; IR (film) 3116, 3076, 2971, 2933, 2859, 1644, 1504, 1452, 1444, 1380, 1367, 1313, 1243, 1233, 1154, 1121, 1100, 1076, 1049, 1012, 901, 805, 735, 599 cm^{-1}; HRMS Calcd for $C_{13}H_{18}O_2$ [M^+]: 206.1307. Found: 206.1304.

2,5,5-Trimethyl-3,4,4a,10b-tetrahydro-2*H*,5*H*-pyrano[3,2-*c*]chromene (6h').

R_f 0.65 (4:1 hexane/ethyl acetate); mp: 81.8–82.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.67 Hz, 1H), 7.16 (dt, *J* = 8.36, 1.04 Hz, 1H), 6.92 (t, *J* = 7.67 Hz, 1H), 6.79 (d, *J* = 8.36 Hz, 1H), 4.27 (d, *J* = 10.8 Hz, 1H), 3.72 (ddq, *J* = 12.5, 6.27, 2.44 Hz, 1H), 1.98–1.63 (m, 4H), 1.52–1.39 (m, 1H), 1.42 (s, 3H), 1.33 (d, *J* = 6.27 Hz, 1H), 1.21 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 152.7, 128.6, 126.0, 122.6, 119.8, 116.6, 78.3, 73.8, 73.1, 44.6, 33.4, 27.7, 25.2, 21.8, 20.4; IR (film) 3040, 2972, 2938, 2926, 2857, 1609, 1584, 1485, 1457, 1386, 1372, 1321, 1308, 1267, 1142, 1100, 1084, 949, 937, 3116, 3076, 2971, 2933, 2859, 1644, 1504, 1452, 1444, 1380, 1367, 1313, 1243, 1233, 1154, 1121, 1100, 1084, 1076, 1049, 1012, 949, 937, 910, 752 cm^{-1}; HRMS Calcd for $C_{15}H_{20}O_2$ [M^+]: 232.1463. Found: 232.1462.

Single crystal X-ray diffraction analysis of 6h'.



Empirical formula	C15 H20 O2
Formula weight	232.31
Temperature	223(2) K
Wavelength	0.71073 Å

Crystal system	Triclinic	
Space group	P–1	
Unit cell dimensions	a = 8.9084(7) Å	α = 84.534(2)°
	b = 10.0653(8) Å	β = 84.355(2)°
	c = 14.7694(11) Å	γ = 78.480(2)°
Volume	1287.45(17) Å^3	
Z	4	
Density (calculated)	1.199 g/cm^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	504	
Crystal size	0.6 × 0.4 × 0.3 mm^3	
Theta range for data collection	1.39 to 30.05°.	
Index ranges	$-12 \le h \le 12$, $-14 \le k \le 14$, $-20 \le l \le 20$	
Reflections collected	15389	
Independent reflections	7428 [R(int) = 0.0406]	
Completeness to theta = 30.05°	98.4 %	
Absorption correction	Sadabs (Sheldrick, 1996)	
Max. and min. transmission	0.9748 and 0.2197	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7428 / 0 / 313	
Goodness-of-fit on F^2	1.005	
Final R indices [I>2sigma(I)]	R1 = 0.0566, wR2 = 0.1213	
R indices (all data)	R1 = 0.0865, wR2 = 0.1309	
Largest diff. peak and hole	0.196 and –0.276 e.Å^{-3}	