Heck-type Arylation of 2-Cycloalken-1-ones with Arylpalladium Intermediates formed by Decarboxylative Palladation and by Aryl Iodide Insertion

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Experimental Procedures and Spectral Data

Commercial materials ($\text{Pd}(\text{O}_2\text{CCF}_3)_2$, $\text{Pd}(\text{OAc})_2$, Ag_2CO_3) were purchased and used as received. $\text{Pd}(\text{O}_2\text{CCF}_3)_2$, $\text{Pd}(\text{OAc})_2$, and Ag_2CO_3 were purchased from Aldrich or Strem and were used as received. Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator. TLC plates were visualized by exposure to ultraviolet light, or by treatment with ethanolic ceric ammonium molybdate (CAM) or phosphomolybdic acid (PMA) solution, followed by heating on a hot plate. Organic solutions were concentrated by rotary evaporation at ~25 torr (house vacuum). Flash column chromatography was performed as described by Still et al.¹ HPLC analysis was performed on a Beckmann Ultrasphere ODS 4.6 $\times$ 25 mm reverse-phase column with an acetonitrile/methanol/trifluoroacetic acid/water eluent system. Peaks were detected by absorption intensities at 260 and 300 nm. 4-Methoxybiphenyl was employed as an internal standard.

Proton nuclear magnetic resonance spectra (^1H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were acquired on a Varian Mercury 400 (400 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million (δ) downfield from tetramethylsilane (TMS), referenced to residual protium in the NMR solvent. Chemical shifts for carbon are reported in parts per million (δ) downfield from TMS and are referenced to the carbon resonance of the solvent (δ CDCl_3 , 77.0). IR spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer. Melting points were obtained with a Thomas Hoover Uni-Melt Capillary Melting Point Apparatus and are uncorrected. Low- and high-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facilities.

Physical data for 3-(2,4-dimethoxyphenyl)-2-cyclohexen-1-one and 3-(2,4,6-trimethylphenyl)-2-cyclohexen-1-one have been previously reported.² 3-(4-Methylphenyl)-2-cyclohexen-1-one was identified by comparison to published NMR spectra (^1H and ^{13}C) and MS analysis.³ 4-Isopropyl-2-cyclohexen-1-one was prepared by a reported method.⁴

¹ Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

² Myers, A. G., Tanaka, D., Mannion, M. R., *J. Am. Chem. Soc.*, **2002**, *124*, 11250.

³ Cho, C. S., Motofusa, S., Ohe, K., Uemura, S., *J. Org. Chem.*, **1995**, *60*, 883.

⁴ Queiroga, C. L., Ferracini, V. L., Marsaioli, A. J., *Phytochemistry*, **1996**, *42*, 1097.

An Illustrative Procedure. A mixture of 2,4-dimethoxybenzoic acid (0.182 g, 1.00 mmol, 1.00 equiv), 4-isopropyl-2-cyclohexen-1-one (0.216 g, 1.56 mmol, 1.56 equiv), palladium (II) trifluoroacetate (0.067 g, 0.20 mmol, 0.20 equiv), and silver (I) carbonate (0.552 g, 2.00 mmol, 2.00 equiv) in 5% DMSO–DMF (4.2 mL) was heated at 80 °C under air. After 90 min, the reaction mixture was allowed to cool, and the cooled solution was diluted with ethyl acetate (30 mL). The resulting dark suspension was filtered through a Celite pad. The filtrate was washed sequentially with an aqueous solution of hydrochloric acid (1 M, 10 mL) and water (5 × 10 mL). The product solution was dried over MgSO₄, the dried solution was filtered, and the filtrate was concentrated. Purification of the residue by flash column chromatography (1:5 ethyl acetate in hexanes) afforded 4-isopropyl-3-(2,4-dimethoxyphenyl)-2-cyclohexen-1-one (0.235 g, 0.857 mmol, 86 %) as an oil.

All compounds were prepared analogously with the above procedure.

3-(2,6-Dimethoxyphenyl)-2-cyclohexen-1-one (Table 1, entry 2)

R_f 0.7 (hexanes:EtOAc = 1:1); mp = 91–92 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.23 (t, 1H, *J* = 8.4 Hz), 6.57 (d, 2H, *J* = 8.4 Hz), 5.97 (t, 1H, *J* = 1.6 Hz), 3.76 (s, 6H), 2.53 (dt, 2H, *J* = 1.5, 5.9 Hz), 2.48 (t, 2H, *J* = 6.8 Hz), 2.14–2.08 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 200.0, 158.1, 156.6, 130.1, 129.4, 118.6, 103.9, 55.8, 37.5, 30.2, 23.0; FTIR (CHCl₃) cm⁻¹ 3010, 1661, 1588, 1472, 1434, 1252, 1112; HRMS (EI) *m/z* calcd for C₁₄H₁₆O₃ 232.1100, found 232.1094.

3-(2,6-Difluorophenyl)-2-cyclohexen-1-one (Table 1, entry 4)

R_f 0.6 (hexanes:EtOAc = 2:1); ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.24 (m, 1H), 6.94–6.89 (m, 2H), 6.14 (s, 1H), 2.64 (t, 2H, *J* = 5.9 Hz), 2.50 (t, 2H, *J* = 6.6 Hz), 2.17–2.11 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 199.0, 159.3 (dd, *J* = 7.3, 250 Hz), 150.9, 131.5, 130.2 (t, *J* = 10.6 Hz), 111.8 (d, *J* = 13.2 Hz), 111.8 (d, *J* = 25.6 Hz), 37.3, 29.9 (t, *J* = 2.6 Hz), 22.9; FTIR (neat film) cm⁻¹ 2944, 1673, 1626, 1464, 1346, 1231, 1001, 786, 722; HRMS (EI) *m/z* calcd for C₁₂H₁₀F₂O 208.0700, found 208.0692.

3-(3-Bromo-2,6-dimethoxyphenyl)-2-cyclohexen-1-one (Table 1, entry 5)

R_f 0.5 (hexanes:EtOAc = 2:1); ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, 1H, *J* = 9.2 Hz), 6.59 (d, 1H, *J* = 8.8 Hz), 5.98 (t, 1H, *J* = 1.5 Hz), 3.74 (s, 3H), 3.71 (s, 3H), 2.55–2.52 (m, 2H), 2.48 (t, 2H, *J* = 6.8 Hz), 2.14–2.07 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 199.4, 157.0, 156.0, 153.9, 132.8, 130.1, 125.6, 108.3, 108.2, 61.6, 56.0, 37.4, 30.4, 23.1; FTIR (neat film) cm⁻¹ 2939, 1668, 1463, 1403, 1283, 1233, 1090, 800; HRMS (TOF) *m/z* calcd for C₁₄H₁₅BrO₃ 311.0283, found 311.0278.

3-(4,5-Dimethoxy-2-nitrophenyl)-2-cyclohexen-1-one (Table 1, entry 6)

R_f 0.2 (hexanes:EtOAc = 1:1); ¹H NMR (400 MHz, CDCl₃) δ 7.65 (s, 1H), 6.62 (s, 1H), 5.92 (s, 1H), 3.93 (s, 6H), 2.49–2.44 (m, 4H), 2.20–2.14 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 199.0, 161.9, 153.4, 148.7, 138.5, 131.2, 127.0, 110.9, 107.8, 56.5, 56.4, 37.2, 30.9, 23.2; FTIR (neat film) cm⁻¹ 2944, 1668, 1574, 1520, 1336, 1279, 1223, 1086,

1008, 797; HRMS (TOF) m/z calcd for $C_{14}H_{15}NO_5$ 278.1028, found 278.1024.

3-(2,4-Dimethoxypyridin-3-yl)-2-cyclohexen-1-one (Table 1, entry 7)

R_f 0.8 (hexanes:EtOAc = 2:1); mp = 78–79 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 1H, J = 8.1 Hz), 6.38 (s, 1H), 6.33 (d, 1H, J = 7.8 Hz), 3.96 (s, 3H), 3.93 (s, 3H), 2.71 (t, 2H, J = 6.0 Hz), 2.44 (t, 2H, J = 6.6 Hz), 2.11–2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 163.3, 159.9, 158.1, 140.0, 127.0, 113.8, 101.4, 53.7, 53.5, 37.3, 29.3, 23.1; FTIR ($CHCl_3$) cm^{-1} 3011, 2948, 1658, 1593, 1482, 1386, 1320, 1248, 1016; HRMS (TOF) m/z calcd for $C_{13}H_{15}NO_3$ 234.1130, found 234.1122.

3-(3-Methylbenzofuran-2-yl)-2-cyclohexen-1-one (Table 1, entry 8)

R_f 0.5 (hexanes:EtOAc = 2:1); mp = 136 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.53 (m, 1H), 7.44 (d, 1H, J = 8.1 Hz), 7.35 (ddd, 1H, 1.1, 7.3, 7.3 Hz), 7.26 (ddd, 1H, J = 1.1, 7.4, 7.4 Hz), 6.55 (s, 1H), 2.91–2.87 (m, 2H), 2.50 (t, 2H, J = 6.8 Hz), 2.46 (s, 3H), 2.19–2.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 154.1, 149.7, 148.7, 130.5, 126.3, 124.9, 122.8, 120.0, 118.4, 111.2, 37.4, 26.4, 22.5, 10.4; FTIR ($CHCl_3$) cm^{-1} 3011, 1654, 1594, 1256; HRMS (EI) m/z calcd for $C_{15}H_{14}O_2$ 226.0994, found 226.1004.

3-(2,4,5-Trimethoxyphenyl)-2-cyclopenten-1-one (Table 2, entry 1)

R_f 0.3 (hexanes:EtOAc = 1:1); mp = 126 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.83 (t, 1H, J = 1.6 Hz), 6.55 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.06–3.03 (m, 2H), 2.48–2.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 169.7, 154.7, 152.4, 142.8, 129.6, 114.8, 112.1, 96.7, 56.7, 56.0, 55.9, 34.1, 30.4; FTIR ($CHCl_3$) cm^{-1} 3011, 1671, 1563, 1511, 1466, 1262, 1216, 1031; HRMS (EI) m/z calcd for $C_{14}H_{16}O_4$ 248.1049, found 248.1053.

3-(3-Methylbenzofuran-2-yl)-2-cyclopenten-1-one (Table 2, entry 2)

R_f 0.5 (hexanes:EtOAc = 2:1); mp = 144 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, 1H, J = 0.7, 7.3 Hz), 7.45 (dd, 1H, J = 0.7, 8.1 Hz), 7.38 (ddd, 1H, J = 1.1, 7.7, 7.7 Hz), 7.27 (ddd, 1H, J = 1.1, 7.5, 7.5 Hz), 6.52 (d, 1H, J = 1.1 Hz), 3.13–3.10 (m, 2H), 2.54–2.51 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 162.9, 154.5, 147.0, 130.0, 127.4, 127.0, 122.9, 120.8, 120.2, 111.4, 34.3, 28.5, 9.7; FTIR ($CHCl_3$) cm^{-1} 3011, 1693, 1674, 1603, 1280, 1184; HRMS (TOF) m/z calcd for $C_{14}H_{12}O_2$ 213.0951, found 213.0925.

3-(2,4-Dimethoxyphenyl)-2-cyclohepten-1-one (Table 2, entry 3)

R_f 0.3 (hexanes:EtOAc = 4:1); 1H NMR (400 MHz, $CDCl_3$) δ 7.09–7.06 (m, 1H), 6.45–6.43 (m, 2H), 6.09 (s, 1H), 3.802 (s, 3H), 3.798 (s, 3H), 2.75–2.72 (m, 2H), 2.66–2.63 (m, 2H), 1.94–1.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 161.2, 159.0, 157.5, 131.5, 129.4, 125.7, 104.1, 98.8, 55.3, 55.3, 41.8, 32.5, 24.8, 20.8; FTIR (neat film) cm^{-1} 2941, 1652, 1606, 1504, 1463, 1456, 1300, 1261, 1209, 1160, 1031, 835; HRMS (EI) m/z calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1254.

(±)-3-(2,4-Dimethoxyphenyl)-4-isopropyl-2-cyclohexen-1-one (Table 2, entry 4)

R_f 0.6 (hexanes:EtOAc = 2:1); ^1H NMR (400 MHz, CDCl_3) δ 7.04 (d, 1H, J = 8.4 Hz), 6.46 (dd, 1H, J = 2.2, 8.4 Hz), 6.43 (d, 1H, J = 2.2 Hz), 6.02 (d, 1H, J = 1.8 Hz), 3.79 (s, 3H), 3.77 (s, 3H), 3.03–2.98 (m, 1H), 2.55–2.48 (m, 1H), 2.43–2.35 (m, 1H), 2.11–2.03 (m, 1H), 1.95–1.79 (m, 2H), 0.86 (d, 3H, J = 7.0 Hz), 0.66 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 200.1, 165.6, 161.2, 157.1, 129.7, 129.3, 122.3, 104.5, 98.5, 55.3, 55.2, 43.3, 35.9, 29.6, 22.2, 21.3, 17.7; FTIR (neat film) cm^{-1} 2958, 1668, 1607, 1504, 1304, 1250, 1209, 1160, 1031, 835; HRMS (TOF) m/z calcd for $\text{C}_{17}\text{H}_{22}\text{O}_3$ 275.1647, found 275.1652.

(±)-3-(3-Methylbenzofuran-2-yl)-4-isopropyl-2-cyclohexen-1-one (Table 2, entry 5)

R_f 0.6 (hexanes:EtOAc = 3:1); mp = 124 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.56 (dd, 1H, J = 0.7, 8.4 Hz), 7.46 (d, 1H, J = 8.4 Hz), 7.35 (ddd, 1H, J = 1.1, 7.1, 7.1 Hz), 7.27 (dd, 1H, J = 7.5, 7.5 Hz), 6.39 (s, 1H), 3.11–3.07 (m, 1H), 2.67–2.58 (m, 1H), 2.47–2.41 (m, 1H), 2.43 (s, 3H), 2.28–2.11 (m, 2H), 2.03–1.94 (m, 1H), 0.99 (d, 3H, J = 7.0 Hz), 0.87 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 199.5, 154.2, 153.9, 149.8, 130.4, 126.4, 125.9, 122.8, 120.0, 117.2, 111.2, 40.4, 33.9, 31.1, 23.8, 21.2, 20.6, 10.3; FTIR (neat film) cm^{-1} 2960, 1666, 1589, 1453, 1331, 1252, 1102, 879, 747; HRMS (TOF) m/z calcd for $\text{C}_{18}\text{H}_{20}\text{O}_2$ 269.1541, found 269.1539.

3-(2,4-Dimethoxyphenyl)-4,4-dimethyl-2-cyclohexen-1-one (Table 2, entry 6)

R_f 0.5 (hexanes:EtOAc = 2:1); ^1H NMR (400 MHz, CDCl_3) δ 6.85 (d, 1H, J = 7.7 Hz), 6.46–6.43 (m, 3H), 5.73 (s, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 2.55 (t, 2H, J = 6.8 Hz), 1.97 (t, 2H, J = 6.8 Hz), 1.10 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 199.6, 168.6, 160.5, 157.0, 129.3, 129.0, 121.3, 103.5, 98.5, 55.3, 55.2, 38.2, 36.4, 34.5, 26.7; FTIR (neat film) cm^{-1} 2963, 1673, 1614, 1579, 1505, 1463, 1304, 1264, 1209, 1159, 1131, 1032, 834; HRMS (TOF) m/z calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$ 261.1490, found 261.1487.

3-(2,4-Dimethoxyphenyl)-2-(2,4-dimethoxybenzyl)-2-cyclopenten-1-one (2)

R_f 0.5 (hexanes:EtOAc = 1:1); ^1H NMR (400 MHz, CDCl_3) δ 6.99 (d, 1H, J = 8.4 Hz), 6.88 (d, 1H, J = 8.8 Hz), 6.46 (d, 1H, J = 2.2 Hz), 6.43 (dd, 1H, J = 2.2, 8.4 Hz), 6.33–6.31 (m, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 3.69 (s, 3H), 3.62 (s, 3H), 3.43 (s, 2H), 2.95–2.92 (m, 2H), 2.53–2.51 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.6, 169.4, 161.3, 158.9, 157.8, 157.5, 139.8, 129.3, 129.1, 119.8, 118.8, 104.1, 103.4, 98.5, 97.9, 55.3, 55.2, 55.1, 54.9, 34.4, 30.7, 23.3; FTIR (neat film) cm^{-1} 2937, 1694, 1608, 1505, 1294, 1209, 1158, 1035, 829; HRMS (TOF) m/z calcd for $\text{C}_{22}\text{H}_{24}\text{O}_5$ 369.1702, found 369.1716.

(E)-3-(2,4-Dimethoxyphenyl)-2-(2,4-dimethoxybenzylidene)-cyclopentan-1-one (3)

R_f 0.6 (hexanes:EtOAc = 1:1); ^1H NMR (400 MHz, CDCl_3) δ 8.03 (s, 1H), 7.01 (d, 1H, J = 8.4 Hz), 6.82 (d, 1H, J = 8.1 Hz), 6.53 (d, 1H, J = 1.8), 6.38 (d, 1H, J = 2.2 Hz), 6.30 (dd, 1H, J = 2.2, 8.4 Hz), 6.25 (dd, 1H, J = 1.8, 8.8 Hz), 4.59 (d, 1H, J = 7.7 Hz), 3.90 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 2.42–2.18 (m, 3H), 2.05–1.97 (m,

¹H); ¹³C NMR (100 MHz, CDCl₃) δ 208.9, 162.2, 160.6, 159.6, 157.7, 135.8, 131.4, 128.3, 127.7, 124.0, 116.9, 104.7, 103.5, 99.1, 98.0, 55.5, 55.4, 55.3, 55.3, 40.0, 35.4, 29.0; FTIR (neat film) cm⁻¹ 2940, 1704, 1597, 1503, 1463, 1293, 1260, 1210, 1160, 1116, 1033, 833; HRMS (TOF) *m/z* calcd for C₂₂H₂₄O₅ 369.1702, found 369.1698.