Development, Scope, and Mechanism of the Palladium-Catalyzed Intramolecular Hydroalkylation of 3-Butenyl β -Diketones

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Supporting Information

Experimental procedures, analytical and spectroscopic data for new compounds and cyclohexanones (22 pages).

Experimental

General Methods. All catalytic reactions were performed under an atmosphere of dry nitrogen at room temperature. NMR spectra were obtained on a Varian spectrometer operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR in CDCl_3 unless otherwise noted. Alkenyl β -diketones exist in solution as mixtures of enol and keto tautomers; only resonances corresponding to the predominant enol tautomer are given unless specified otherwise. For deuterated isotopomers, only resonances that differ from the corresponding unlabeled isotopomer are reported; isotopic shifts (IS) are reported relative to the appropriate resonance in the corresponding unlabeled isotopomer. IR spectra were obtained on a Bomen MB-100 FT IR spectrometer. Gas chromatography was performed on a HP 5890 gas chromatography equipped with a 25 m polydimethylsiloxane capillary column. Flash column chromatography was performed employing 200-400 mesh silica gel (EM). Thin layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ eluting with a 5:1 mixture of hexanes and ethyl acetate unless noted otherwise. Elemental analyses were performed by Complete Analysis Laboratories (Parsippany, NJ). 1,4-Dioxane, acetonitrile, and DMSO (Aldrich, anhydrous) were used as received, THF and ether were distilled from sodium benzophenone ketyl under nitrogen, methylene chloride was distilled from CaH_2 under nitrogen.

$\text{PdCl}_2(\text{MeCN})_2$ (**4**) was purchased from Strem and used as received or was prepared from PdCl_2 (Strem) employing a literature procedure.^[1] Authentic samples of **5** (Aldrich), **13** (Lancaster), and **15** (Aldrich) were obtained from commercial suppliers. An authentic sample of **14** was synthesized employing the procedure of Reich.^[2] Substrates **3**,^[3] 8-methyl-7-nonene-2,4-dione (Table 2, entry 11),^[4] ethyl 3-oxo-6-heptenoate (Table 2, entry 12),^[5] methyl 3-oxo-6-heptenoate (Table 2, entry 13)^[6] and all new substrates were prepared from the appropriate 1,3-diketone or β -keto ester and allylic halide or tosylate employing a modified published procedure unless otherwise noted.^[7] 3-Methyl-7-octene-2,4-dione (Table 2, entry 5)^[8] and (*E*)-2,3-dibromo-1-phenylsulfonylpropene^[9] were prepared according to the published procedures. 3,3-Dideuterioallyl methanesulfonate (**S1**) was prepared from 3,3-dideuterio-2-propene-1-ol^[10] employing a procedure analogous to that used to synthesize unlabeled allyl methanesulfonate.^[11] (*Z*)-3-Bromo-1,2-dideuteriopropene (**S2**) and 3-bromo-3,3-dideuterio-1-propene (**S3**) were synthesized from reaction of (*Z*)-2,3-dideuterio-2-propene-1-ol^[12] and 1,1-dideuterio-2-propene-1-ol,^[13] respectively, with

dibromotriphenylphosphorane. 1-Deuterio-2-propene-1-ol was synthesized according to a literature procedure.^[14]

Synthesis of Alkenyl β -Diketones

8-Nonene-3,5-dione (Table 2, entry 3). 8-Nonene-3,5-dione was synthesized from 5-hexen-2-one and methyl propionate in 12% yield employing a modified literature procedure.^[15] Enol:dione = 4:1. TLC: R_f = 0.53. ^1H NMR: δ 5.96-5.85 (m, 1 H), 5.59 (s, 1 H), 5.18-5.07 (m, 2 H), 2.47 (m, 4 H), 2.41 (q, J = 7.6 Hz, 2 H), 1.23 (t, J = 7.6 Hz, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 195.6, 193.6, 137.2, 115.8, 98.8, 37.9, 31.8, 29.8, 10.0. IR (neat, cm^{-1}): 3078, 2977, 2938, 2918, 1726, 1613, 1444, 1416, 1377, 1352, 1323, 1202, 1142, 1064, 994, 914. Anal. calcd (found) for $\text{C}_9\text{H}_{14}\text{O}_2$: C, 70.10 (70.21); H, 9.15 (9.25).

2,2-Dimethyl-8-nonene-3,5-dione (Table 2, entry 4). Enol:dione = 13:1. TLC: R_f = 0.71. ^1H NMR: δ 5.87-5.77 (m, 1 H), 5.60 (s, 1 H), 5.08-4.97 (m, 2 H), 2.43-2.35 (m, 4 H), 1.16 (s, 9 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 200.4, 195.1, 137.3, 115.7, 95.5, 51.8, 38.4, 29.9, 27.6. IR (neat, cm^{-1}): 3079, 2968, 2927, 2874, 1697, 1620, 1455, 1362, 1275, 1221, 1133, 1087. Anal. calcd (found) for $\text{C}_{11}\text{H}_{18}\text{O}_2$: C, 72.49 (72.35); H, 9.95 (9.91).

3-Benzyl-7-octene-2,4-dione (Table 2, entry 6). 3-Benzyl-7-octene-2,4-dione was synthesized from 7-octene-2,4-dione (**3**) and benzyl bromide in 35% yield employing a modified literature procedure.^[16] Enol:dione = 1:1.3. TLC: R_f = 0.43. ^1H NMR: δ 7.30-7.14 (m, 5 H), 5.69 (tdd, J = 6.4, 10.4, 17.2 Hz, 1 H), 4.96-4.92 (m, 2 H), 4.00 (t, J = 7.6 Hz, 1 H), 3.15 (dd, J = 4.0, 7.6 Hz, 2 H), 2.46-2.36 (m, 2 H), 2.27-2.22 (m, 2 H), 2.12 (s, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 205.2, 203.8, 136.8, 129.1, 129.0, 127.8, 127.1, 115.9, 69.8, 42.4, 34.7, 32.7, 27.5. IR (neat, cm^{-1}): 3083, 3072, 3028, 2933, 1728, 1697, 1643, 1603, 1495, 1454, 1358, 1259, 1183, 1162, 1092, 995, 915. Anal. calcd (found) for $\text{C}_{15}\text{H}_{18}\text{O}_2$: C, 78.23 (78.07); H, 7.88 (8.02).

cis-7-Nonene-2,4-dione (Table 2, entry 7). A suspension of Lindlar's catalyst (115 mg, 5 mol %) and 7-nonyne-2,4-dione (780 mg, 5.13 mmol) in acetone (20 mL) was stirred under hydrogen (1 atm) overnight at room temperature, concentrated, and chromatographed (hexanes–EtOAc = 125:1) to give *cis*-7-nonene-2,4-dione (540 mg, 69%) as a pale yellow oil.

For 7-nonyne-2,4-dione: Enol:dione = 5:1. TLC: R_f = 0.35. ^1H NMR : δ 5.52 (s, 1 H), 2.48-2.42 (m, 4 H), 2.05 (s, 3 H), 1.76-1.73 (m, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 193.1, 190.8, 100.2, 77.7, 76.8, 38.1, 25.0, 15.2, 3.8. IR (neat, cm^{-1}): 2969, 2919, 1857, 2357, 1729, 1713, 1620, 1417, 1360, 1236, 1132, 1005. Anal. calcd (found) for $\text{C}_9\text{H}_{12}\text{O}_2$: C, 71.03 (71.04); H, 7.95 (7.90).

For cis-7-nonene-2,4-dione. Enol:dione = 5:1. TLC: R_f = 0.46. ^1H NMR: δ 5.53-5.46 (m, 1 H), 5.50 (s, 1 H), 5.38-5.32 (m, 1 H), 2.38-2.30 (m, 4 H), 2.05 (s, 3 H), 1.63-1.60 (m, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 193.9, 191.7, 128.8, 125.7, 100.2, 38.3, 25.3, 23.3, 13.1. IR (neat, cm^{-1}): 3015, 2958, 2920, 2860, 1709, 1613, 1443, 1359, 1234, 1138, 1096, 1030, 998, 963, 929. Anal. calcd (found) for $\text{C}_9\text{H}_{14}\text{O}_2$: C, 70.10 (70.12); H, 9.15 (9.14).

trans-7-Nonene-2,4-dione (Table 2, entry 8). Enol:dione = 6:1. TLC: R_f = 0.44. ^1H NMR: δ 5.48 (s, 1 H), 5.47-5.36 (m, 2 H), 2.34-2.22 (m, 4 H), 2.04 (s, 3 H), 1.64-1.62 (m, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 194.0, 191.5, 129.6, 126.4, 100.2, 38.6, 28.8, 25.2, 18.2. IR (neat, cm^{-1}): 3013, 2965, 2919, 2863, 1713, 1620, 1454, 1360, 1236, 1142, 967. HRMS (EI) calcd (found) for $\text{C}_9\text{H}_{14}\text{O}_2$ (M^+): 154.0994 (154.0995).

7-Dodecene-2,4-dione (Table 2, entry 9). Enol:dione = 5:1. ^1H NMR (300 MHz): δ 5.47 (s, 1 H), 5.45-5.35 (m, 2 H), 2.34-2.21 (m, 4 H), 2.03 (s, 3 H), 1.98-1.92 (m, 2 H), 1.31-1.24 (m, 4 H), 0.86 (t, J = 7.4 Hz, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 193.8, 191.5, 132.0, 128.2, 100.1, 38.4, 32.3, 31.8, 28.7, 25.1, 22.3, 14.1. IR (neat, cm^{-1}): 3056, 2956, 2925, 2855, 1706, 1616, 1436, 1361, 1236, 1148, 967. HRMS (EI) calcd (found) for $\text{C}_{12}\text{H}_{20}\text{O}_2$ (M^+): 196.1463 (196.1460).

8-Phenyl-7-octene-2,4-dione (Table 2, entry 10). Enol:dione = 5:1. TLC: R_f = 0.38. ^1H NMR: δ 7.31-7.23 (m, 4 H), 7.19-7.16 (m, 1 H), 6.39 (d, J = 16.0 Hz, 1 H), 6.17 (td, J = 6.8, 16.0 Hz, 1 H), 5.49 (s, 1 H), 2.52-2.47 (m, 2 H), 2.46-2.40 (m, 2 H), 2.03 (s, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 193.7, 191.4, 137.7, 131.2, 128.9, 128.8, 127.5, 126.4, 100.3, 38.3, 29.1, 25.2. IR (neat, cm^{-1}): 3080, 3057, 3024, 2919, 2849, 1948, 1881, 1806, 1725, 1705, 1620, 1494, 1445, 1416, 1359, 1304, 1254, 1234, 1136, 1077, 965, 784, 744, 693. Anal. calcd (found) for $\text{C}_{14}\text{H}_{16}\text{O}_2$: C, 77.75 (77.81); H, 7.46 (7.42).

Benzyl 3-oxo-6-heptenoate (Table 2, entry 14). Enol:dione = 1:13. TLC: R_f = 0.39. ^1H NMR : δ 7.37-7.35 (m, 5 H), 5.77 (tdd, J = 6.6, 10.2, 17.0 Hz, 1 H), 5.18 (s, 2 H), 5.05-4.96 (m, 2 H), 3.49 (s, 2 H), 2.62 (t, J = 7.2 Hz, 2 H), 2.36-2.30 (m, 2 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 201.9, 167.2, 136.7, 135.5,

128.8, 128.7, 128.6, 115.8, 67.3, 49.5, 42.3, 27.6. IR (neat, cm^{-1}): 3067, 3032, 2976, 2930, 1742, 1716, 1641, 1497, 1454, 1409, 1374, 1313, 1268, 1223, 1152, 1081, 997, 915. Anal. calcd (found) for $\text{C}_{14}\text{H}_{16}\text{O}_3$: C, 72.39 (72.16); H, 6.94 (6.78).

Synthesis of (*E*)-6-octene-2,4-dione [(*E*)-17]. (*E*)-17 was synthesized in 19% overall yield from condensation of (*E*)-3-pentenal with acetone followed by Swern oxidation following a literature procedure (Scheme S1).^[17]

Scheme S1

(*E*)-3-Pentenal.^[18] DIBAL (10.8 mL, 60 mmol) was added dropwise to a solution of methyl (*E*)-3-pentenoate (3.68 mL, 30 mmol) in CH_2Cl_2 (120 mL) at $-78\text{ }^\circ\text{C}$ and stirred for 2 h. The resulting mixture was treated sequentially with methanol (10 mL) and water (20 mL) and the resulting mixture was warmed to room temperature and poured into 1 N aqueous HCl (150 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic extracts were dried (MgSO_4), filtered through a pad of silica gel, and concentrated to give a pale yellow oil (1.70 g, 67 %). ^1H NMR: δ 9.60 (t, $J = 2.0$ Hz, 1 H), 5.63-5.53 (m, 1 H), 5.51-5.43 (m, 1 H), 3.07-3.04 (m, 2H), 1.69-1.66 (qd, $J = 1.2, 6.4$ Hz, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 200.6, 131.5, 120.6, 47.5, 18.3.

For (*E*)-4-hydroxy-6-octene-2-one: 28%. TLC: $R_f = 0.12$. ^1H NMR: δ 5.58-5.49 (tqd, $J = 1.2, 6.2, 15.2$ Hz, 1 H), 5.45-5.37 (qtd, $J = 3.2, 7.0, 15.2$ Hz, 1 H), 4.08-4.01 (m, 1 H), 2.89 (d, $J = 3.2$ Hz, 1 H), 2.64-2.49 (m, 2 H), 2.22-2.10 (m, 2 H), 2.17 (s, 3 H), 1.68-1.66 (tdd, $J = 1.0, 2.4, 6.4$ Hz, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 210.0, 129.2, 126.8, 67.6, 49.6, 40.0, 31.1, 18.4. IR (neat, cm^{-1}): 3426, 1711, 1681. HRMS (EI): Calcd (found) for $\text{C}_8\text{H}_{12}\text{O}$ ($\text{M}^+ - \text{H}_2\text{O}$): 124.0888 (124.0884).

For (*E*)-17: 44%. Enol: ketone = 6:1. TLC: R_f = 0.32. ^1H NMR: δ 15.4 (br s, 1 H), 5.62-5.44 (m, 2 H), 5.48 (s, 1 H), 2.96 (d, J = 6.8 Hz, 2 H), 2.03 (s, 3 H), 1.69 (dd, J = 1.4, 6.2 Hz, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 193.6, 191.1, 130.1, 123.9, 99.7, 42.3, 25.0, 18.3. IR (neat, cm^{-1}): 3405, 3028, 1726, 1710, 1613. Anal. Calcd (found) for $\text{C}_8\text{H}_{12}\text{O}_2$: C, 68.54 (68.35); H, 8.63 (8.41).

Synthesis of (*E*)-5-octene-2,4-dione [(*E*)-18]. (*E*)-18 was synthesized starting from (*E*)-2-pentenal employing a two-step procedure similar to that used to synthesize (*E*)-17.

(*E*)-4-Hydroxy-5-octene-2-one. 76%. TLC (hexanes–ether = 1:1): R_f = 0.62. ^1H NMR: δ 5.69 (dtd, J = 1.2, 6.4, 15.2 Hz, 1 H), 5.41 (tdd, J = 1.6, 6.6, 15.4 Hz, 1 H), 4.50-4.44 (m, 1 H), 3.04-3.01 (m, 1 H), 2.61 (d, J = 6.4 Hz, 1 H), 2.60 (s, 1 H), 2.14 (s, 3 H), 2.03-1.96 (m, 2 H), 0.94 (t, J = 7.4 Hz, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 209.4, 134.1, 130.0, 68.8, 50.4, 31.1, 25.4, 13.5. IR (neat, cm^{-1}): 3426, 3029, 1711. Anal. Calcd (found) for $\text{C}_8\text{H}_{14}\text{O}_2$: C, 67.57 (67.24); H, 9.92 (10.07).

For (*E*)-18:^[19] 43%. Enol:ketone = 13:1. TLC: R_f = 0.38. ^1H NMR: δ 15.4 (br s, 1 H), 6.89 (td, J = 6.6, 15.6 Hz, 1 H), 5.82 (td, J = 1.8, 15.6 Hz, 1 H), 5.49 (s, 1 H), 2.29-2.20 (m, 2 H), 2.11 (s, 3 H), 1.07 (t, J = 7.4 Hz, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 197.2, 178.7, 146.4, 125.1, 100.0, 27.0, 26.1, 12.8. IR (neat, cm^{-1}): 1722, 1651, 1589. Anal. Calcd. (found) for $\text{C}_8\text{H}_{12}\text{O}_2$: C, 68.54 (68.36); H, 8.63 (8.53).

3-Butenyl β -Diketone Isotopomers

6-Deuterio-7-octene-2,4-dione (3-6- d_1). Isotopomer 3-6- d_1 was synthesized from 2,4-pentanedione and 1-deuterio-2-propene-1-ol methanesulfonate employing a procedure analogous to that used to synthesize 8-nonene-2,4-dione^[7] in 28% yield. ^1H NMR: δ 5.79 (ddd, J = 5.2, 10.2, 17.0 Hz, 1 H), 2.36-2.26 (m, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 137.1 (s, IS = 68 ppb), 37.7 (s, IS = 72 ppb), 29.4 (t, J_{CD} = 19.6 Hz, IS = 333 ppb).

(*E*)-7,8-dideuterio-7-octene-2,4-dione [(*E*)-3-7,8- d_2]. 7-Octyne-2,4-dione (**S4**) was prepared employing a procedure similar to that used to synthesize methyl 3-oxo-6-heptynoate.^[20] 2,4-Pentanedione (3.1 mL, 30 mmol) was added dropwise to a suspension of NaH (0.77 g, 32 mmol) in THF (120 mL) at 0 °C and stirred for 10 min. *n*-BuLi (2.5 M in hexanes, 8.0 mL, 20 mmol) was added slowly to the resulting solution at –30 °C and stirred for 15 min. Propargyl bromide (80% solution in toluene, 3.4 mL, 32 mmol)

was added rapidly to the resulting pale yellow solution and stirred for 1 h at $-20\text{ }^{\circ}\text{C}$. Following addition of saturated aqueous NH_4Cl , the reaction mixture was extracted with ether ($2 \times 50\text{ mL}$). The combined ether extracts were washed with brine, dried (MgSO_4), concentrated, and chromatographed (hexanes–ether = 50:1 $\rightarrow$ 10:1) to give **S4** as a colorless oil (2.20 g, 53%).

A suspension of Lindlar's catalyst (40 mg), quinoline (16 mg), and **S4** (400 mg, 2.90 mmol) in acetone (5 mL) under D_2 (1 atm) was stirred vigorously for 1 h, filtered through Celite, concentrated, and chromatographed (hexanes–ether = 100:1) to give (*E*)-**3-7,8- d_2** (280 mg, 68%) as a colorless oil. ^1H NMR and MS analysis revealed formation of a $\sim 5:1$ mixture of (*E*)-**3-7,8- d_2** and **3-7,8,8- d_3** ; the presence of the d_3 isotopomer did not complicate stereochemical analysis of the products generated from (*E*)-**3-7,8- d_2** (see below).

For S4: TLC: $R_f = 0.26$. ^1H NMR (enol: ketone = $\sim 3:1$): δ 15.3 (br s, 1 H), 5.51 (s, 1 H), 2.53–2.42 (m, 4 H), 2.04 (s, 3 H), 1.96 (t, $J = 2.6\text{ Hz}$, 1 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 192.7, 190.5, 100.2, 83.0, 69.4, 37.5, 24.9, 14.7. IR (neat, cm^{-1}): 3293, 2119, 1730, 1706, 1615. Anal. calcd (found) for $\text{C}_8\text{H}_{10}\text{O}_2$: C, 69.54 (69.68); H, 7.30 (7.24).

For (*E*)-3-7,8- d_2 : This sample consisted of a $\sim 5:1$ mixture of (*E*)-**3-7,8- d_2** and **3-7,8,8- d_3** . ^1H NMR: δ 5.04 (br s, 1 H, $-\text{CH}_2\text{CD}=\text{CHD}$). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 136.7 (t, $J_{\text{CD}} = 23\text{ Hz}$, IS = 447 ppb, $-\text{CH}_2\text{CD}=\text{CHD}$), 136.6 (t, $J_{\text{CD}} = 23\text{ Hz}$, IS = 526 ppb, $-\text{CH}_2\text{CD}=\text{CD}_2$), 115.4 (t, $J_{\text{CD}} = 24\text{ Hz}$, IS = 413 ppb, $-\text{CH}_2\text{CD}=\text{CHD}$), 29.5 (s, IS = 159 ppb, $-\text{CH}_2\text{CD}=\text{CHD}$). The quintet corresponding to $-\text{CH}_2\text{CD}=\text{CD}_2$ was not resolved from the triplet at δ 115.4.

(*Z*)-7,8-dideuterio-7-octene-2,4-dione [(*Z*)-3-7,8- d_2]. Reaction of 2,4-pentanedione and **S2** that contained $\sim 25\%$ 3-bromo-1,1,2-trideuteriopropene employing a procedure analogous to that used to synthesize 8-nonene-2,4-dione,^[7] gave (*Z*)-**3-7,8- d_2** that contained $\sim 25\%$ **3-7,8,8- d_3** by ^1H NMR and MS analysis in 56% yield; the presence of the d_3 isotopomer did not complicate stereochemical analysis of the products generated from (*Z*)-**3-7,8- d_2** (see below). ^1H NMR: δ 4.98 (br s, 1 H, $-\text{CH}_2\text{CD}=\text{CHD}$). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 136.7 (t, $J_{\text{CD}} = 23\text{ Hz}$, IS = 451 ppb, $-\text{CH}_2\text{CD}=\text{CHD}$), 136.6 (t, $J_{\text{CD}} = 23\text{ Hz}$, IS = 564 ppb, $-\text{CH}_2\text{CD}=\text{CD}_2$), 115.3 (t, $J_{\text{CD}} = 24\text{ Hz}$, IS = 463 ppb, $-\text{CH}_2\text{CD}=\text{CHD}$), 29.5 (s, IS = 167 ppb,

–CH₂CD=CHD). The quintet corresponding to –CH₂CD=CD₂ was not resolved from the triplet at δ 115.3.

3,3-Dideuterio-7-octene-2,4-dione (3-3,3-*d*₂). Alkenyl dione **3-3,3-*d*₂** was prepared from **3** and D₂O in 87% yield employing a procedure analogous to that used to synthesize 3,3-dideuterio-2,4-pentanedione.^[21] ¹H NMR analysis of **3-3,3-*d*₂** revealed ~75% deuteration of the C(3) position with no detectable ($\leq 5\%$) accumulation of deuterium at the C(1) and C(5) positions. The presence of **3** did not complicate analysis of the cyclization of **3-3,3-*d*₂**. ¹³C{¹H} NMR: δ 99.8 (t, J_{CD} = 25.2 Hz, IS = 375 ppb, –COCD₂CO–).

8,8-Dideuterio-7-octene-2,4-dione (3-8,8-*d*₂). Alkenyl dione **1-8,8-*d*₂** was synthesized from 2,4-pentanedione and **S1** in 32% yield employing a procedure analogous to that used to synthesize 8-nonene-2,4-dione.^[7] ¹H NMR analysis revealed complete ($\geq 95\%$) deuteration of the C(8) position. ¹H NMR: δ 5.79 (br s, 1 H, –CH₂CH=CD₂). ¹³C{¹H} NMR: δ 136.9 (s, IS = 212 ppb, –CH₂CH=CD₂), 115.3 (quintet, J_{CD} = 24 Hz, IS = 645 ppb, –CH₂CH=CD₂).

1,1,1,5,5-Pentadeuterio-7-octene-2,4-dione (3-1,1,1,5,5-*d*₅). Alkenyl dione **3** was converted to 1,1,1,3,3,5,5-heptadeuterio-7-octene-2,4-dione (**3-1,1,1,3,3,5,5-*d*₇**) employing a procedure analogous to that used to synthesize 1,1,1,3,3,5,5-octadeuterio-2,4-pentanedione.^[21] Compound **3-1,1,1,3,3,5,5-*d*₇** was then flushed through a short column of silica gel to give **3-1,1,1,5,5-*d*₅** in 10% yield from **3**. ¹H and ¹³C NMR analysis of **1-1,1,1,5,5-*d*₅** revealed complete ($\geq 95\%$) deuteration of the acyl methyl group and C(5) methylene group with no detectable deuteration ($\leq 5\%$) of the C(3) methylene group. ¹H NMR: δ 2.34 (d, J = 6.8 Hz, 2 H, –CD₂CH₂CH=CH₂). ¹³C{¹H} NMR: δ 37.2 (quintet, J_{CD} = 20 Hz, IS = 645 ppb, –CD₂CH₂CH=CH₂), 29.6 (s, IS = 100 ppb, –CD₂CH₂CH=CH₂), 24.4 (m, –COCD₃).

6,6-Dideuterio-7-octene-2,4-dione (3-6,6-*d*₂). Alkenyl diketone **3-6,6-*d*₂** was synthesized from 2,4-pentanedione and **S3** in 28% yield employing a procedure analogous to that used to synthesize 8-nonene-2,4-dione.^[7] ¹H and ¹³C NMR analysis of **3-6,6-*d*₂** revealed complete ($\geq 95\%$) deuteration of the C(6) position. ¹H NMR: δ 5.80 (dd, J = 10.0, 17.2 Hz, 1 H, –CH₂CD₂CH=CH₂), 2.35 (br s, 2 H, –CH₂CD₂CH=CH₂). ¹³C{¹H} NMR: δ 137.1 (s, IS = 129 ppb, –CH₂CD₂CH=CH₂), 37.7 (s, IS = 144 ppb, –CH₂CD₂CH=CH₂), 29.1 (quintet, J = 20 Hz, IS = 661 ppb, –CH₂CD₂CH=CH₂).

Syntheses of Palladium(II) Catalysts

PdCl₂(NCCH₂CH₃)₂. A suspension of PdCl₂ (500 mg, 2.82 mmol) in propionitrile (10 mL) was stirred at room temperature for 2 days, poured into hexanes (100 mL), filtered, washed with hexanes, and dried under vacuum. A pale yellow solid was obtained (760 mg, 94%). ¹H NMR: δ 2.66 (q, *J* = 7.6 Hz, 4 H), 1.33 (t, *J* = 7.6 Hz, 6 H). Anal. calcd (found) for C₆H₁₀Cl₂N₂Pd: C, 25.07 (24.79); H, 3.51 (3.23); N, 9.74 (9.39).

PdCl₂(NCCH₂CH₂CH₃)₂. Bis(butyronitrile)palladium dichloride was isolated as a yellow solid (850 mg, 97%) from the reaction of PdCl₂ (500 mg, 2.82 mmol) in butyronitrile (10 mL) at room temperature for 2 days, employing a procedure similar to that used to synthesize PdCl₂(EtCN)₂. ¹H NMR: δ 2.62 (t, *J* = 6.8 Hz, 4 H), 1.78-1.69 (m, 4 H), 1.06 (t, *J* = 7.4 Hz, 6 H). Anal. calcd (found) for C₈H₁₄Cl₂N₂Pd: C, 30.45 (30.10); H, 4.47 (4.28); N, 8.88 (8.81).

PdCl₂[NCCH(CH₃)₂]₂. Bis(isobutyronitrile)palladium dichloride was isolated as a reddish orange solid (800 mg, 92%) from the reaction of PdCl₂ (500 mg, 2.82 mmol) in isobutyronitrile (10 mL) at room temperature for 2 days, employing a procedure similar to that used to synthesize PdCl₂(EtCN)₂. ¹H NMR: δ 2.97 (septet, *J* = 6.8 Hz, 2 H), 1.35 (d, *J* = 6.8 Hz, 12 H). Anal. calcd (found) for C₈H₁₄Cl₂N₂Pd: C, 30.45 (30.43); H, 4.47 (4.22); N, 8.88 (8.49).

PdCl₂[NC-3,5-C₆H₃(CF₃)₂]₂. Bis(3,5-bis(trifluoromethyl)benzonitrile) palladium dichloride was isolated as a yellow solid (560 mg, 100%) from the reaction of PdCl₂ (150 mg, 0.85 mmol) 3,5-bis(trifluoromethyl)benzonitrile (5.0 g, 21 mmol) at room temperature for 32 h, employing a procedure similar to that used to synthesize PdCl₂(EtCN)₂. ¹H NMR: δ 8.11 (broad singlet, 6 H). Anal. calcd (found) for C₁₈H₆N₂Cl₂F₁₂Pd: C, 32.98 (32.70); H, 0.92 (0.88); N, 4.27 (4.43).

Cyclohexanones

2-Propionylcyclohexanone (Table 2, entry 3).^[22] Enol:dione ≥15:1. TLC: *R_f* = 0.59. ¹H NMR: δ 2.43 (q, *J* = 7.2 Hz, 2 H), 2.33-2.29 (m, 4 H), 1.69-1.66 (m, 4 H), 1.10 (t, *J* = 7.2 Hz, 3 H). ¹³C{¹H} NMR: δ 203.2, 180.6, 106.9, 31.1, 30.7, 24.0, 23.1, 22.0, 8.5.

2-(2',2'-Dimethylpropionyl)cyclohexanone (Table 2, entry 4).^[23] Enol:dione $\geq 15:1$. TLC: $R_f = 0.41$. ^1H NMR: δ 3.95-3.92 (m, 1 H), 2.55-2.48 (m, 1 H), 2.39-2.31 (m, 1 H), 2.12-2.03 (m, 1 H), 2.00-1.90 (m, 3 H), 1.87-1.81 (m, 1 H), 1.70-1.62 (m, 1 H), 1.11 (s, 9 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 212.7, 208.5, 57.8, 45.4, 42.2, 31.3, 27.4, 26.0, 23.6.

2-Acetyl-2-methylcyclohexanone (Table 2, entry 5).^[24] TLC: $R_f = 0.45$. ^1H NMR: δ 2.49-2.46 (m, 1 H), 2.45-2.43 (m, 1 H), 2.34-2.26 (m, 1 H), 2.10 (s, 3 H), 2.01-1.94 (m, 1 H), 1.75-1.62 (m, 3 H), 1.49-1.46 (m, 1 H), 1.24 (s, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 210.9, 207.9, 64.2, 41.6, 37.1, 27.6, 26.0, 22.6, 21.1.

2-Acetyl-2-benzylcyclohexanone (Table 2, entry 6). TLC: $R_f = 0.42$. ^1H NMR: δ 7.24-7.20 (m, 3 H), 7.08-7.05 (m, 2 H), 3.16, 3.08 (ABq, $J = 6.0$ Hz, 2 H), 2.54-2.48 (m, 1 H), 2.39-2.33 (m, 1 H), 2.28-2.20 (m, 1 H), 2.09 (s, 3 H), 1.99-1.95 (m, 1 H), 1.73-1.70 (m, 1 H), 1.64-1.58 (m, 2 H), 1.46-1.39 (m, 1 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 209.8, 206.1, 136.5, 130.6, 128.5, 127.1, 69.0, 42.4, 40.3, 34.3, 27.3, 27.2, 22.5. IR (neat, cm^{-1}): 3085, 3061, 3028, 2941, 2866, 1956, 1881, 1811, 1713, 1693, 1603, 1495, 1453, 1434, 1358, 1311. Anal. calcd (found) for $\text{C}_{15}\text{H}_{18}\text{O}_2$: C, 78.23 (78.13); H, 7.88 (7.80).

2-Acetyl-3-methylcyclohexanone (Table 2, entry 7 and 8).^[25] Enol:dione $\geq 15:1$. TLC: $R_f = 0.49$. ^1H NMR: δ 2.77-2.73 (m, 1 H), 2.35-2.31 (m, 2 H), 2.18 (s, 3 H), 1.84-1.75 (m, 1 H), 1.72-1.60 (m, 3 H), 1.10 (d, $J = 6.8$ Hz, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 198.3, 184.4, 113.2, 31.7, 30.3, 28.2, 24.2, 22.0, 17.0.

2-Acetyl-3-butylcyclohexanone (Table 2, entry 9).^[26] Enol:dione $\geq 15:1$. TLC: $R_f = 0.44$. ^1H NMR: δ 2.50-2.46 (m, 1 H), 2.34-2.31 (m, 2 H), 2.15 (s, 3 H), 1.83-1.62 (m, 3 H), 1.55-1.50 (m, 1 H), 1.42-1.20 (m, 6 H), 0.90 (t, $J = 7.0$ Hz, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 198.0, 184.4, 113.3, 35.1, 33.5, 31.5, 30.4, 25.6, 24.2, 23.1, 16.9, 14.4.

2-Acetyl-3-phenylcyclohexanone (Table 2, entry 10).^[27] Enol:dione $\geq 15:1$. TLC: $R_f = 0.12$. ^1H NMR: δ 7.33-7.29 (m, 2 H), 7.23-7.16 (m, 3 H), 3.93 (dd, $J = 3.2, 5.6$ Hz, 1 H), 2.45-2.42 (m, 2 H), 2.07-1.94 (m, 1 H), 1.85 (s, 3 H), 1.84-1.80 (m, 1 H), 1.60-1.53 (m, 2 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 201.4, 183.1, 145.7, 128.8, 128.2, 126.6, 109.9, 40.5, 32.4, 31.2, 25.7, 16.9.

2-Acetyl-3,3-dimethylcyclohexanone (Table 2, entry 11).^[28] Enol:dione $\leq$ 1:15. TLC: R_f = 0.34. ^1H NMR: δ 3.44 (s, 1 H), 2.57 (ddd, J = 6.4, 10.0, 16.4 Hz, 1 H), 2.31-2.25 (m, 1 H), 2.17 (s, 3 H), 2.04 (ddd, J = 4.4, 10.4, 14.8 Hz, 1 H), 1.95-1.89 (m, 1 H), 1.85-1.77 (m, 1 H), 1.41-1.35 (m, 1 H), 1.04 (s, 3 H), 0.95 (s, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 208.1, 205.3, 75.1, 39.6, 39.5, 35.3, 33.9, 28.3, 26.4, 22.2.

2-Ethoxycarbonylcyclohexanone (Table 2, entry 12).^[29] Enol:dione = 3:1. TLC: R_f = 0.59. ^1H NMR: δ 12.24 (s, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 2.27-2.20 (m, 4 H), 1.70-1.64 (m, 2 H), 1.62-1.58 (m, 2 H), 1.29 (t, J = 7.2 Hz, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 173.1, 172.3, 98.1, 60.5, 29.4, 22.8, 22.7, 22.3, 14.6.

Cyclization of Methyl 3-Oxo-6-heptenoate (Table 2, entry 13). A solution of **4** (17 mg, 0.06 mmol) and methyl 3-oxo-6-heptenoate (100 mg, 0.64 mmol) in dioxane (25 mL) was stirred at room temperature for 24 h, concentrated, and chromatographed (hexanes–EtOAc = 125:1) to give two fractions. The first eluting fraction consisted of pure 2-methoxycarbonylcyclohexanone (21 mg, 21%) as a pale yellow oil. The second fraction consisted of a ~1:1:3 mixture of methyl 3-oxo-6-heptenoate, (*Z*)-methyl 3-oxo-5-heptenoate, and (*E*)-methyl 3-oxo-5-heptenoate (51 mg, 55 %) as a colorless oil. The methyl 3-oxo-5-heptenoate isomers were characterized via ^1H and ^{13}C NMR analysis of the mixture and by comparison to the NMR spectra of pure methyl 3-oxo-6-heptenoate.

For 2-methoxycarbonylcyclohexanone. TLC: R_f = 0.67. ^1H NMR (enol tautomer): δ 12.19 (s, 1 H), 3.75 (s, 3 H), 2.27 (t, J = 6.4 Hz, 2 H), 2.21 (t, J = 6.0 Hz, 2 H), 1.69-1.66 (m, 2 H), 1.62-1.58 (m, 2 H). $^{13}\text{C}\{^1\text{H}\}$ NMR (enol tautomer): δ 173.4, 172.5, 98.0, 51.7, 29.4, 22.8, 22.7, 22.2.

For (*E*)-methyl 3-oxo-5-heptenoate: ^1H NMR (partial): δ 3.72 (s, 3 H), 3.46 (s, 2 H), 3.20 (br d, J = 6.8 Hz, 2 H), 1.69 (br d, J = 5.6 Hz, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 201.6, 167.9, 131.2, 122.3, 52.6, 48.5, 47.1, 18.3.

For (*Z*)-methyl 3-oxo-5-heptenoate: ^1H NMR (partial): δ 3.72 (s, 3 H), 3.47 (s, 2 H), 3.29 (br d, J = 7.2 Hz, 2 H), 1.63 (br d, J = 6.8 Hz, 3 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 201.0, 167.9, 129.1, 121.1, 52.6, 49.4, 48.7, 13.4.

2-Benzoxycarbonylcyclohexanone (Table 2, entry 14).^[30] Enol:dione = 4:1. TLC: R_f = 0.66. ^1H NMR: δ 12.16 (s, 1 H), 7.38-7.31 (m, 5 H), 5.21 (s, 2 H), 2.30-2.27 (m, 4 H), 1.70-1.66 (m, 2 H),

1.64-1.58 (m, 2 H). $^{13}\text{C}\{^1\text{H}\}$ NMR: δ 172.9, 172.8, 136.5, 128.9, 128.4, 128.2, 98.0, 66.0, 29.5, 22.7, 22.6, 22.2.

Figure S1. Concentration versus time plot for the reaction of **3** ($[\mathbf{3}]_0 = 250$ mM) with **4** ($[\mathbf{4}]_0 = 25$ mM) in dioxane at room temperature.

Figure S2. Aliphatic region of the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 2-acetylcyclohexanone (**5**).

Figure S3. Aliphatic region of the ^1H - ^{13}C COSY NMR spectrum of **5**.

Figure S4. Aliphatic region of the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of an ~5:1 mixture of *cis*-5-3,4- d_2 and 5-3,3,4- d_3 .

Figure S5. Aliphatic region of the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of a ~3:1 mixture of *trans*-5-3,4- d_2 and 5-3,3,4- d_3 .

Figure S6. Aliphatic region of the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of a ~3:1 mixture of **5-6- d_1** and **5**.

Figure S7. Aliphatic region of the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **5-2,3- d_2 -6-COCD₃**.

Figure S8. Aliphatic region of the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of a 1:1 mixture of **5-5- d_1** and **5-4- d_1** .

Figure S9. Aliphatic region of the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of *trans*-**5-4,5- d_2** .

Figure S10. Aliphatic region of the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **5-3,3- d_2** .

Figure S11. Aliphatic region of the ^1H - ^1H COSY NMR spectrum of **6**.

Figure S12. Aliphatic region of the ^1H NMR spectrum of a ~5:1 mixture of *anti*-6-4,5- d_2 and 6-4,5,5- d_3 .

Figure S13. Aliphatic region of the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of a ~5:1 mixture of *anti*-6-4,5- d_2 and 6-4,5,5- d_3 .

Figure S14. Aliphatic region of the ^1H NMR spectrum of a ~3:1 mixture of *syn*-**6**-4,5- d_2 and **6**-4,5,5- d_3 .

Figure S15. Aliphatic region of the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of a ~3:1 mixture of *syn*-**6**-4,5- d_2 and **6**-4,5,5- d_3 .

Figure S16. Aliphatic region of the ^1H NMR spectrum of *syn*-6-3,4- d_2 with selective decoupling of the C(5) methylene group at δ 1.8.

Figure S17. Aliphatic region of the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of *syn*-6-3,4- d_2 .

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