Supporting Information

Palladium- and Copper-Catalyzed 1,4-Additions of Organozinc Compounds to Conjugated Aldehydes

James A. Marshall, Martin Herold, Hilary S. Eidam, and Patrick Eidam

Department of Chemistry, University of Virginia
PO Box 400319, Charlottesville VA 22904
jam5x@virginia.edu

Table of Contents

Experimentals	S2-S16
Proton and Carbon NMR Spectra	S17-S68

Experimental Section

General Procedure for Conjugate Addition to (*E*)-2-Nonenal.

3-Ethylnonanal (2): A flame-dried 50 mL round bottom flask containing a magnetic stir bar, 15 mL of THF and 16.8 mg (0.075 mmol) of $\text{Pd}(\text{OAc})_2$ was cooled to -78°C . Then, 19.7 mg (0.075 mmol) of PPh_3 were added and, after 5 min, 210.4 mg (1.5 mmol) of freshly distilled (*E*)-2-nonenal **1** were added followed by dropwise addition of 3 mL (1 M in hexanes, 3 mmol) of Et_2Zn . The reaction mixture was warmed to -20°C and after stirring overnight, it was poured into a stirring solution of sat. NH_4Cl (aq.). The mixture was extracted with Et_2O and the combined organic extracts were dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexanes-5% Et_2O -hexanes) to afford aldehyde **2** as a slightly yellowish oil (213 mg, 83%). R_f (20% Et_2O -hexanes) = 0.63 ; IR (film): 2959, 2926, 2857, 2711, 1727; ^1H -NMR (CDCl_3): δ (ppm) = 9.75 (t, J = 2.4 Hz, 1H), 2.33 (d, J = 2.4 Hz, 1H), 2.30 (d, J = 2.4 Hz, 1H), 1.88 (m, 1H), 1.22-1.44 (m, 12H), 0.86 (t, J = 7.3 Hz, 6H), ^{13}C -NMR (CDCl_3): δ (ppm) = 203.7, 48.4, 34.6, 33.9, 32.0, 29.7, 26.9, 26.8, 22.8, 14.3, 11.1.

3-Methylnonanal (3): The general procedure was followed with 12.0 mg (0.054 mmol) of $\text{Pd}(\text{OAc})_2$ in 10 mL of THF, 14.0 mg (0.054 mmol) of PPh_3 , 150 mg (1.07 mmol) of (*E*)-2-nonenal **1** and 5 mL (~ 0.79 M in hexanes, 4 mmol) of Me_2Zn . Aldehyde **3** was obtained as a slightly yellowish oil (130 mg, 78%). R_f (20% Et_2O -hexanes) = 0.68 ; IR (film): 2957, 2926, 2856, 2712, 1727; ^1H -NMR (CDCl_3): δ (ppm) = 9.73 (t, J = 2.4 Hz, 1H), 2.37 (ddd, J = 15.9 Hz, J = 5.7 Hz, J = 2.1 Hz, 1H), 2.20 (ddd, J = 15.9 Hz, J = 7.8 Hz, J = 2.6 Hz, 1H), 2.03 (m, 1H), 1.24 (m, 10H), 0.93 (d, J = 2.4 Hz, 3H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C -NMR (CDCl_3): δ (ppm) = 203.4, 51.3, 37.1, 32.0, 29.6, 28.4, 27.1, 22.9, 20.2, 14.3.

3-Butylnonanal (4): The general procedure was followed with 11.2 mg (0.05 mmol) of $\text{Pd}(\text{OAc})_2$ in 10 mL of THF, 13.1 mg (0.05 mmol) of PPh_3 , 140 mg (1 mmol) of (*E*)-2-nonenal and 2.5 mL (1 M in toluene, 2.5 mmol) of Bu_2Zn . After column chromatography (hexanes-5% Et_2O -hexanes), aldehyde **4** was obtained as a clear liquid (190 mg, 96%). R_f (20% Et_2O -hexanes) = 0.70 ; IR (film) : 2956, 2926, 2857, 2710, 1727; ^1H -NMR (CDCl_3): δ (ppm) = 9.75 (t, J = 2.4 Hz, 1H), 2.33 (d, J = 2.4 Hz, 1H), 2.31 (d, J = 2.4 Hz, 1H), 1.95 (m, 1H), 1.23-1.35 (m, 16H), 0.89 (m, 6H); ^{13}C -NMR (CDCl_3): δ (ppm) = 203.5, 48.6, 34.2, 33.8,

32.9, 31.8, 29.5, 28.8, 26.6, 22.9, 22.6, 14.1, 14.0; Anal. Calcd. for $C_{13}H_{26}O$: C 78.72, H 13.21; found: C 78.94, H 13.41.

3-Phenylnonananal (5): The general procedure was followed with 12.0 mg (0.054 mmol) of $Pd(OAc)_2$ in 10 mL of THF, 14.0 mg (0.054 mmol) of PPh_3 , 150 mg (1.07 mmol) of (*E*)-2-nonenal and 704.5 mg (3.2 mmol) of Ph_2Zn which was dissolved in 4 mL of toluene. The phenyl-substituted aldehyde **5** was obtained as a clear oil (131 mg, 56%); R_f = 0.58 (20% Et_2O -hexanes); IR (film): 3028, 2953, 2926, 2855, 2718, 1725, 1602; 1H -NMR ($CDCl_3$): δ (ppm) = 9.66 (t, J = 2.1 Hz, 1H), 7.25 (m, 5H), 3.16 (m, 1H), 2.72 (d, J = 2.1 Hz, 1H), 2.70 (d, J = 2.1 Hz, 1H), 1.64 (m, 2H), 1.2 (m, 8H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C -NMR ($CDCl_3$): δ (ppm) = 202.4, 128.8, 127.7, 126.8, 50.9, 40.3, 36.9, 31.9, 29.4, 27.5, 22.8, 14.3; Anal. Calcd. for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.43, H 10.25.

6-(*tert*-Butyldiphenylsilyloxy)-2-hexenal (6): To a stirring solution of 1.0 g (2.82 mmol) of 6-(*tert*-Butyldiphenylsilyloxy)-2-hexenol¹ in 28 mL of CH_2Cl_2 was added 2.37 g (28.2 mmol) of $NaHCO_3$ and 1.79 g (4.23 mmol) of Dess-Martin periodinane. After one hour, TLC analysis indicated completion of the reaction and sat. $NaHCO_3$ (aq.) and sat. $Na_2S_2O_3$ (aq.) were added. The organic phase was diluted with Et_2O and the aqueous phase was further extracted with Et_2O . The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. After flash chromatography (10%-20% Et_2O -hexanes) the enal **6** was isolated as clear liquid (872 mg, 88%). R_f = 0.47 (20% Et_2O -hexanes); 1H -NMR ($CDCl_3$): δ (ppm) = 9.49 (d, J = 7.9 Hz, 1H), 7.67 (m, 4H), 7.43 (m, 6H), 6.85 (td, J = 15.6 Hz, J = 6.8 Hz, 1H), 6.13 (tdd, J = 15.6 Hz, J = 7.9 Hz, J = 1.5 Hz, 1H), 3.7 (t, J = 6 Hz, 2H), 2.48 (m, 2H), 1.77 (ddd, J = 13.4 Hz, J = 7.2 Hz, J = 6.1 Hz, 2H), 1.07 (s, 9H); ^{13}C -NMR ($CDCl_3$): δ (ppm) = 194.1, 158.6, 135.5, 133.6, 133.1, 129.7, 127.7, 62.8, 30.7, 29.3, 26.9, 19.2.

6-(*tert*-Butyldiphenylsilyloxy)-3-ethylhexanal (11): The general procedure was followed with 9.6 mg (0.042 mmol) of $Pd(OAc)_2$, 8.5 mL of THF, 11.2 mg (0.042 mmol) of PPh_3 , 300 mg (0.85 mmol) of enal **6** and 1.7 mL (1.7 mmol, 1 M in hexanes) of Et_2Zn . After column chromatography (hexanes-5% Et_2O -hexanes) aldehyde **11** was obtained as a yellowish liquid (239 mg, 73%). R_f = 0.68 (20% Et_2O -hexanes); IR (film): 2931, 2857, 2712; 1724; 1H -NMR ($CDCl_3$): δ (ppm) = 9.76, (t, J = 2.4 Hz, 1H), 7.68 (m, 4H), 7.43 (m, 6H), 3.67 (t, J = 6.4 Hz, 2H), 2.35 (ddd, J = 6.8 Hz, J = 5.5 Hz, J = 2.1 Hz, 1H), 2.31 (ddd,

[1] Carter, R. G.; Weldon, D. J.; *Org Lett*, **2000**, 2, 3913

$J = 8.8$ Hz, $J = 5.3$ Hz, $J = 2.0$ Hz, 1H), 1.92 (m, 1H), 1.55 (m, 2H), 1.29-1.49 (m, 4H), 1.07 (s, 9H), 0.89 (t, $J = 7.4$ Hz, 3H); ^{13}C -NMR (CDCl_3): δ (ppm) = 203.3, 135.6, 133.9, 129.6, 127.6, 63.9, 48.1, 34.1, 29.7, 29.6, 26.9, 26.5, 19.2, 10.9; Anal. Calcd. for $\text{C}_{24}\text{H}_{34}\text{O}_2\text{Si}$: C 75.34, H 8.96; found: C 75.59, H 8.96.

3-Cyclohexylpentanal (12) : The general procedure was followed with 12 mg (0.054 mmol) of $\text{Pd}(\text{OAc})_2$ in 10 mL of THF, 14 mg (0.054 mmol) of PPh_3 , 150 mg (1.08 mmol) of 2-(*E*)-3-cyclohexyl-2-propenal² **7** and 2.2 mL (2.2 mmol, 1 M in hexanes) of Et_2Zn . After column chromatography (hexanes-5% Et_2O -hexanes), aldehyde **12**³ was obtained as a yellowish liquid (162 mg, 89%). R_f (20% Et_2O -hexanes) = 0.65; IR (film): 2924, 2852, 1717; ^1H -NMR (CDCl_3): δ (ppm) = 9.74 (t, $J = 2.4$ Hz, 1H), 2.39 (ddd, $J = 16.3$ Hz, $J = 5.9$ Hz, $J = 2.2$ Hz, 1H), 2.23 (ddd, $J = 16.3$ Hz, $J = 7.1$ Hz, $J = 2.6$ Hz, 1H), 1.55-1.8 (m, 6H), 0.9-1.5 (m, 8H), 0.86 (t, $J = 7.4$ Hz, 3H); ^{13}C -NMR (CDCl_3): δ (ppm) = 204.0, 45.9, 40.5, 40.1, 30.6, 29.4, 26.9, 26.8, 24.4, 12.0.

3-Phenylpentanal (13): The general procedure was followed with 12.7 mg (0.057 mmol) of $\text{Pd}(\text{OAc})_2$ in 11 mL of THF, 14.9 mg (0.057 mmol) of PPh_3 , 150 mg (1.14 mmol) of (*E*)-cinnamaldehyde **8** and 2.27 mL (2.27 mmol, 1 M in hexanes) of Et_2Zn . Aldehyde **13**³ was isolated as an oil (95 mg, 52%). R_f (50% Et_2O -hexanes) = 0.71; IR (film): 3061, 3028, 2963, 2929, 2875, 2822, 2722, 1725, 1602; ^1H -NMR (CDCl_3): δ (ppm) = 9.67 (t, $J = 2.0$ Hz, 1H), 7.17-7.35 (m, 5H), 3.09 (m, 1H), 2.74 (d, $J = 2.1$ Hz, 1H), 2.72 (d, $J = 2.1$ Hz, 1H), 1.68 (m, 2H), 0.82 (t, $J = 7.36$ Hz, 3H); ^{13}C -NMR (CDCl_3): δ (ppm) = 202.4, 143.9, 128.8, 127.8, 126.8, 50.4, 41.9, 29.7, 12.1.

3-Ethyl-3,7-dimethyl-6-octenal (14) : The general procedure was followed with 11.0 mg (0.049 mmol) of $\text{Pd}(\text{OAc})_2$ in 10 mL of THF, 12.9 mg (0.049 mmol) of PPh_3 , 150 mg (0.98 mmol) of geranial **9** and 1.97 mL (1.97 mmol, 1 M in hexanes) of Et_2Zn . Aldehyde **14** was obtained as a yellowish liquid (143 mg, 80%). R_f = 0.78 (20% Et_2O -hexanes); IR (film): 2965, 2916, 2880, 2957, 2729, 1720, 1461, 1379; ^1H -NMR (CDCl_3): δ (ppm) = 9.84 (t, $J = 3.2$ Hz, 1H), 5.07 (m, 1H), 2.26 (d, $J = 3.2$ Hz, 2H), 1.92 (dd, $J = 16.59$ Hz, $J = 7.3$ Hz, 2H), 1.67 (s, 3H), 1.59 (2, 3H), 1.40 (q, $J = 7.4$ Hz, 2H), 1.34 (m, 2H), 1.02 (s,

[2] Gung, B. W.; Karipides, A.; Wolf, M. A.; *Tetrahedron Lett.* **1992**, 33, 713.

[3] Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, 127, 32.

3H), 0.85 (t, $J = 7.5$ Hz, 3H); ^{13}C -NMR (CDCl_3): δ (ppm) = 204.1, 131.8, 124.5, 52.6, 39.8, 36.4, 32.4, 25.9, 25.0, 22.4, 17.8, 8.2; Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{O}$: C 79.06, H 12.16; found: C 78.95, H 12.22.

4-Cyclohexyl-3-hexanone (15): The general procedure was followed with 18.4 mg (0.08 mmol) of $\text{Pd}(\text{OAc})_2$ in 16.5 mL of THF, 21.5 mg (0.08 mmol) of PPh_3 , 250 mg (1.64 mmol) of enone **10**⁴ and 3.28 mL (3.28 mmol, 1 M in hexanes) of Et_2Zn . After column chromatography, ketone **15** was obtained as a yellow oil (237 mg, 79%). R_f (20% Et_2O -hexanes) = 0.61; IR (film): 2925, 2852, 1716; ^1H -NMR (CDCl_3): δ (ppm) = 2.32 (ddd, $J = 23.6$ Hz, $J = 16.2$ Hz, $J = 6.5$ Hz, 2H), 2.12 (s, 3H), 1.50-1.77 (m, 6H), 0.89-1.41 (m, 8H), 0.83 (t, $J = 7.4$ Hz, 3H); ^{13}C -NMR (CDCl_3): δ (ppm) = 210.0, 45.9, 40.9, 40.3, 30.5, 30.4, 29.4, 26.9, 24.2, 12.0; Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{O}$: C 79.06, H 12.16; found: C 79.30, H 12.25.

General Procedure for Conjugate Addition to (*E*)-2-Nonenal Without Triphenylphosphine.

3-Ethylnonanal (2): A flame-dried 50 mL flask containing 11.2 mg (0.05 mmol) of $\text{Pd}(\text{OAc})_2$ in 10 mL of THF was cooled to -78 °C and 140.2 mg (1 mmol) of (*E*)-2-nonenal **1** was added. After 5 min, 2 mL (2 mmol, 1 M in hexanes) of Et_2Zn was added dropwise and the reaction mixture was warmed to -20 °C. After 16 h, the reaction mixture was quenched by pouring it into a rapidly stirring solution of sat. NH_4Cl (aq.). The aqueous phase was extracted with Et_2O and the combined organic extracts were dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The crude product was subjected to flash chromatography to yield aldehyde **2** (156 mg, 92%). All spectral data were identical to the results with triphenylphosphine.

6-(*tert*-Butyldiphenylsilyloxy)-3-ethylhexanal (11): The general procedure was followed with 5.6 mg (0.025 mmol) of $\text{Pd}(\text{OAc})_2$ in 5 mL of THF, 176.3 mg (0.5 mmol) of enal **6** and 1.5 mL (1.5 mmol, 1 M in hexanes) of Et_2Zn . The product **11** was isolated in 76% yield (146 mg).

[4] Fraser, P. K.; Woodward, S.; *Chem. Eur. J.* **2003**, 9, 776.

3-Cyclohexylpentanal (12) : The general procedure was followed with 8.1 mg (0.36 mmol) of Pd(OAc)₂ in 7 mL of THF, 100 mg (0.72 mmol) of enal **7** and 1.45 mL (1.45 mmol, 1 M in hexanes) of Et₂Zn. The product **12** was obtained in 90% yield (110 mg).

3-Phenylpentanal (13): The general procedure was followed with 16.8 mg (0.075 mmol) of Pd(OAc)₂ in 15 mL of THF, 198.2 mg (1.5 mmol) of cinnamaldehyde **8** and 3 mL (3 mmol, 1 M in hexanes) of Et₂Zn. The conjugate addition product **13** was obtained in 51% yield (125 mg).

General Procedure for Palladium-Catalyzed Conjugate Addition and Subsequent Trapping with TBSOTf.

(E)-1-(tert-Butyldimethylsilyloxy)-3-ethyl-1-nonene (16): A flame-dried 50 mL round bottom flask containing a magnetic stir bar, 15 mL of THF and 16.84 mg (0.075 mmol) of Pd(OAc)₂ was cooled to -78 °C. Then, 19.67 mg (0.075 mmol) of PPh₃ was added and, after 5 min, freshly distilled 210.3 mg (1.5 mmol) of (*E*)-2-nonenal **1** was added followed by dropwise addition of 3 mL (3 mmol, 1 M in hexanes) of Et₂Zn. The reaction mixture was warmed to -20 °C and after stirring overnight, 0.41 mL (1.8 mmol) of TBSOTf was added at once and the reaction mixture was further stirred at -20 °C until completion, as judged by TLC analysis on deactivated silica gel. The reaction was subsequently quenched by addition of 0.5 mL of NEt₃ and pouring the reaction mixture into vigorously stirring NaHCO₃ (sat.). The mixture was extracted with Et₂O and the combined extracts were dried over MgSO₄, filtered and, after rotary evaporation of the solvent, the crude product was purified by flash chromatography on deactivated silica gel (100% hexanes) to yield the silyl enol ether **16** as a >20:1 mixture of diastereomers as judged by ¹H-NMR analysis (357 mg, 84%), R_f (20% Et₂O-hexanes) = 0.98; IR (film): 2957, 2927, 2857, 1661; ¹H-NMR (CDCl₃): δ (ppm) = 6.15 (d, *J* = 11.9 Hz, 1H), 4.69 (dd, *J* = 11.9 Hz, 9.8 Hz, 1H), 1.68 (m, 1H), 1.25 (m, 12H), 0.92 (s, 9H), 0.84 (m, 6H), 0.13 (s, 6H); ¹³C-NMR (CDCl₃): δ (ppm) = 140.1, 116.6, 40.1, 36.0, 32.2, 29.3, 29.1, 27.6, 26.0, 22.9, 18.7, 14.3, 12.1, -4.9; Anal. Calcd. for C₁₇H₃₆OSi: C 71.76, H 12.75; found C 72.05, H 12.94.

(E)-1-(tert-Butyldimethylsilyloxy)-3-butyl-1-nonene (17): The general procedure was followed with 11.2 mg (0.05 mmol) of Pd(OAc)₂ in 10 mL of THF, 13.1 mg (0.05 mmol) of PPh₃, 140.2 mg (1 mmol) of (E)-2-nonenal, 2.5 mL (2.5 mmol, 1 M in toluene) of Bu₂Zn and 0.53 mL (2.3 mmol) of TBSOTf. After column chromatography on deactivated silica gel (100% hexanes), the product contained an impurity of TBS butanol that was removed under reduced pressure (along with some of the product) (HV, ~0.5 mm Hg) to afford silyl enol ether **17** (208 mg, 64%). R_f = 0.98 (20% Et₂O-hexanes); IR (film): 2956, 2927, 2857, 1660; ¹H-NMR (CDCl₃): δ (ppm) = [6.20 (d, *J* = 5.9 Hz, 1H) minor], 6.14 (d, *J* = 11.9 Hz, 1H), 4.69 (dd, *J* = 11.9 Hz, *J* = 9.8 Hz, 1H), [4.1 (dd, *J* = 9.7 Hz, *J* = 5.9 Hz, 1H)], 1.75 (m, 1H), 1.1-1.37 (m, 16H), 0.93 (s, 9H), [0.91 (s, 9H)], 0.87 (t, *J* = 6.3 Hz, 3H), 0.13 (s, 6H), [0.11 (s, 3H)], [0.10 (s, 3H)]; ¹³C-NMR (CDCl₃): δ (ppm) = 139.9, 116.9, 38.3, 36.4, 36.1, 32.2, 29.8, 29.6, 27.5, 26.0, 25.9, 22.9, 22.8, 18.7, 14.4, -4.9.

(E)-1-(tert-Butyldimethylsilyloxy)-6-(tert-butyldiphenylsilyloxy)-3-ethyl-1-hexene (18): The general procedure was followed with 9.55 mg (0.42 mmol) of Pd(OAc)₂ in 8.5 mL of THF, 11.1 mg (0.042 mmol) of PPh₃, 300 mg (0.85 mmol) of enal **6**, 1.7 mL (1.7 mmol, 1 M in hexanes) of Et₂Zn and 0.25 mL (1.1 mmol) of TBSOTf. Silyl enol ether **18** was obtained as a clear oil (400 mg, 95%). R_f (20% Et₂O-hexanes) = 0.97; IR (film): 3071, 3049, 2929, 2856, 1660, 1589; ¹H-NMR (CDCl₃): δ (ppm) = 7.68 (m, 4H), 7.41 (m, 6H), 6.15 (d, *J* = 11.92 Hz, 1H), 4.70 (dd, *J* = 13.1 Hz, *J* = 8.58 Hz, 1H), 3.64 (m, 2H), 1.6-1.73 (m, 2H), 1.34-1.54 (m, 3H), 1.14-1.28 (m, 2H), 1.06 (s, 9H), .94 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.15 (s, 6H); ¹³C-NMR (CDCl₃): δ (ppm) = 140.1, 135.6, 134.2, 129.5, 127.6, 116.1, 64.0, 39.6, 31.8, 30.4, 28.8, 26.9, 25.8, 19.2, 11.8, -5.2; Anal. Calcd. for C₃₀H₄₈O₂Si₂: C 72.52, H 9.74; found: C 72.80, H 9.72.

(E)-1-(tert-Butyldimethylsilyloxy)-3-cyclohexyl-1-pentene (19): The general procedure was followed with 8.1 mg (0.036 mmol) of Pd(OAc)₂ in 7.2 mL of THF, 9.5 mg (0.036 mmol) of PPh₃, 100 mg (0.72 mmol) of enal **7**, 1.3 mL (1.3 mmol, 1 M in hexanes) of Et₂Zn and 0.19 mL (0.87 mmol) of TBSOTf. The silyl enol ether **19** was isolated as a >20:1 mixture of diastereomers (143 mg, 70%). R_f = 0.98 (20% Et₂O-hexanes); IR (film): 2925, 2853, 1658; ¹H-NMR (CDCl₃): δ (ppm) = 6.10 (d, *J* = 11.9 Hz, 1H), 4.73 (dd, *J* = 11.8 Hz, *J* = 10.1 Hz, 1H), 1.37-1.76 (m, 8H), 0.96-1.28 (m, 6H), 0.93 (s, 9H), 0.82 (t, *J* = 7.3 Hz, 3H), 0.13 (s, 6H); ¹³C-NMR (CDCl₃): δ (ppm) = 140.4, 114.3, 46.0, 42.4, 29.6, 27.0, 26.9, 26.0, 25.7, 18.6, 12.5, -4.8, -4.9.

(E)-1-(tert-Butyldimethylsilyloxy)-3-phenyl-1-pentene (20): The general procedure was followed with 12.7 mg (0.057 mmol) of $\text{Pd}(\text{OAc})_2$ in 11 mL of THF, 14.9 mg (0.057 mmol) of PPh_3 , 150 mg (1.14 mmol) of cinnamaldehyde and 2.27 mL (2.27 mmol, 1 M in hexanes) of Et_2Zn . After column chromatography on deactivated silica, silyl enol ether **20** was obtained as a clear oil (198 mg, 63%). R_f (20% Et_2O -hexanes) = 0.95; IR (film) : 3027, 2957, 2929, 2858, 1659; ^1H -NMR (CDCl_3): δ (ppm) = 7.12-7.31 (m, 5H), 6.28 (dd, $J = 11.9$ Hz, $J = 0.8$ Hz, 1H), 5.2 (dd, $J = 11.9$ Hz, $J = 9.02$ Hz, 1H), [4.38 (dd, $J = 5.0$ Hz, $J = 1.7$ Hz, 1H), minor], 3.03 (dd, $J = 15.6$ Hz, $J = 8.0$ Hz, 1H), 1.69 (m, 2H), 0.92 (s, 9H), 0.88 (t, $J = 7.3$ Hz, 3H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C -NMR (CDCl_3): δ (ppm) = 146.1, 140.6, 128.5, 127.6, 126.0, 115.0, 46.3, 29.8, 25.9, 18.6, 12.5, -4.9; Anal. Calcd. for $\text{C}_{17}\text{H}_{28}\text{OSi}$: C 73.85, H 10.21; found: C 74.08, H 10.29.

(4R)-5-(tert-Butyldiphenylsilyloxy)-4-methyl-2-pentenal (21): To a stirring solution of 1.50 g (4.58 mmol) of (2R)-3-(tert-butyldiphenylsilyloxy)-2-methylpropanal⁵ in 46 mL of THF was added 2.40 g (6.89 mmol) of carbethoxymethylenetriphenylphosphorane and the reaction mixture was subsequently heated at reflux overnight. The reaction mixture was cooled to room temperature and quenched with NH_4Cl (aq.). The layers were separated and the aqueous phase was extracted with Et_2O . The combined organic extracts were dried over MgSO_4 , filtered and the solvent was removed by rotary evaporation under reduced pressure. The crude product was purified by flash chromatography to afford the conjugate ester as a single isomer by ^1H -NMR analysis (1.70 g, 93%). R_f = 0.71 (20% Et_2O -hexanes), $[\alpha]_D^{20} = +7.7$ ($c = 1.51$, CHCl_3); IR (film): 3071, 3049, 2960, 2858, 1721, 1651, 1651, 1589; ^1H -NMR (CDCl_3): δ (ppm) = 7.71 (m, 4H), 7.44 (m, 6H), 7.03 (dd, $J = 18.8$ Hz, $J = 7.2$ Hz, 1H), 5.90 (dd, $J = 15.8$ Hz, $J = 1.29$ Hz, 1H), 4.25 (q, $J = 7.1$ Hz, 2H), 3.64 (m, 2H), 2.61 (m, 1H), 1.33 (t, $J = 7.1$ Hz, 3H), 1.12 (m, 12H); ^{13}C -NMR (CDCl_3): δ (ppm) = 166.7, 151.3, 165.6, 133.6, 133.5, 129.7, 127.7, 121.1, 67.6, 60.2, 39.1, 26.9, 19.3, 15.6, 14.3.

The ester (3.74 g, 9.43 mmol) was dissolved in 95 mL of CH_2Cl_2 , cooled to -78°C and 37.72 mL (37.72 mmol, 1 M in hexanes) of Dibal-H was added dropwise. Upon completion of the reaction, as judged by TLC analysis, the reaction was quenched by pouring the mixture into a vigorously stirring solution of Rochelle's salt and diluted with Et_2O . The phases were separated and the aqueous phase was further extracted with Et_2O . The combined organic phases were dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (30%

[5] Johns, B. A.; Grant, C. M.; Marshall, J. A.; *Org. Synth.* **2004**, *Coll. Vol. 10*, 170.

Et₂O-hexanes) to afford the allylic alcohol (3.3 g, 99%). R_f = 0.41 (50% Et₂O-hexanes); $[\alpha]_D^{20}$ = +3.3 (c = 1.0, CHCl₃); IR (film): 3334 (br), 3070, 3048, 2958, 2930, 2857, 1589; ¹H-NMR (CDCl₃): δ (ppm) = 7.65 (m, 4H), 7.40 (m, 6H), 5.63 (m, 2H), 4.07 (m, 2H), 3.53 (dq, J = 9.8 Hz, J = 6.5 Hz, 2H), 2.41 (m, 1H), 1.05 (s, 9H), 1.03 (d, J = 6.8 Hz, 3H); ¹³C-NMR (CDCl₃): δ (ppm) = 135.6, 135.5, 133.9, 129.6, 128.7, 127.6, 68.5, 63.9, 38.9, 26.9, 19.3, 16.4.

To a stirring solution of 1.5 g (4.23 mmol) of the allylic alcohol in 42 mL of CH₂Cl₂ was added 7.36 g (84.61 mmol) of activated MnO₂. The reaction mixture was stirred for 1 h and then filtered through a short plug of Celite. After removal of the solvent under reduced pressure, enal **21** was obtained as a yellowish liquid (1.28 g, 86%). The enal was subjected to the conjugate addition protocol without further purification. R_f = 0.53 (20% Et₂O-hexanes); $[\alpha]_D^{20}$ = +15.4 (c = 1.0, CHCl₃); IR (film): 3070, 3049, 2930, 2857, 2811, 2737, 1693, 1637; ¹H-NMR (CDCl₃): δ (ppm) = 9.48 (d, J = 7.9 Hz, 1H), 7.64 (m, 4H), 7.42 (m, 6H), 6.82 (dd, J = 15.8 Hz, J = 6.9 Hz, 1H), 6.13 (ddd, J = 15.8 Hz, J = 7.9 Hz, J = 1.3 Hz, 1H), 3.65 (dq, J = 9.9 Hz, J = 6.2 Hz, 2H), 2.68 (m, 1H), 1.10 (d, J = 6.8 Hz, 3H), 1.05 (s, 9H); ¹³C-NMR (CDCl₃): δ (ppm) = 194.5, 161.3, 135.9, 135.8, 133.6, 132.6, 130.0, 127.9, 67.6, 39.8, 27.1, 15.6.

(3*S*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3-butyl-4-methylpentanal (24): The general procedure was followed with 3.2 mg (0.014 mmol) of Pd(OAc)₂ in 3 mL of THF, 3.7 mg (0.014 mmol) of PPh₃, 100 mg (0.28 mmol) of enal **21** and 0.71 mL (0.71 mmol, 1 M in toluene) of Bu₂Zn. The conjugate addition product was obtained as a mixture of diastereomers (72 mg, 62%). R_f = 0.51 (20% Et₂O-hexanes); IR (film): 3070, 3049, 2957, 2930, 2858, 2711, 1726; ¹H-NMR (CDCl₃): δ (ppm) = [9.71 (t, J = 2.5 Hz, 1H), minor], 9.69 (m, 1H), 7.66 (m, 4H), 7.41 (m, 6H), 3.51 (m, 2H), 2.30 (m, 2H), 2.12 (m, 1H), 1.90 (m, 1H), [1.77 (m, 1H)], 1.29 (m, 6H), 1.06 (s, 9H), 0.89 (m, 3H), [0.83 (d, J = 6.9 Hz, 3H)], 0.77 (d, J = 6.9 Hz, 3H); ¹³C-NMR (CDCl₃): δ (ppm) = 203.8, 135.8, 133.9, 129.9, 127.9, 66.9, 45.1, 37.2, 33.3, 32.2, 29.7, 27.1, 23.0, 19.5, 14.3, 12.1.

Proof of Stereochemistry for 1,4-Adducts **22-24**:

(3R,4R)-3,4-Dimethyl-5-pentanolide (i): Aldehyde **22** (500 mg, 1.35 mmol) was dissolved in 13 mL of THF and 1.5 mL (2.03 mmol, 1 M in THF) of TBAF was added at room temperature. Upon complete cleavage of the silyl group, as judged by TLC analysis, the reaction was quenched with NH_4Cl (aq.). The aqueous phase was extracted with Et_2O and the combined organic extracts were dried over MgSO_4 , filtered and the solvent was removed by rotary evaporation under reduced pressure. The crude product was purified by column chromatography (20% Et_2O) to yield the lactol as a mixture of diastereomers (181 mg, 100%).

Oxidation was achieved according to literature⁶: In a flame-dried 50 mL flask, 50 mg (0.38 mmol) of the lactol were dissolved in 4 mL of CH_2Cl_2 and cooled to 0 °C. Then, 10 mg of 4 Å molecular sieves, 67.5 mg (0.58 mmol) of NMO and 6.8 mg (0.02 mmol) of TPAP were added. After one hour, the solvent was removed under reduced pressure and the crude product was directly subjected to column chromatography (20-40% Et_2O -hexanes) to afford the lactone **i** as a 20:1 mixture of diastereomers (46 mg, 93%). R_f = 0.26 (50% Et_2O -hexanes) ; $[\alpha]_D^{20}$ = +51.7 (c = 1.1, MeOH) {ref⁷ $[\alpha]_D^{20}$ = +42.6 (c = 1.85, MeOH)}; IR (film): 2964, 1731; $^1\text{H-NMR}$ (CDCl_3): δ (ppm) = 4.26 (dd, J = 11.2 Hz, J = 4.3 Hz, 1H), 4.09 (dd, J = 11.2 Hz, J = 6.8 Hz, 1H), 3.83 (t, J = 10.6 Hz, 1H, minor), 2.58 (dd, J = 17.9 Hz, J = 6.1 Hz, 1H), 2.27 (dd, J = 17.9 Hz, J = 7.5 Hz, 1H), 2.7 (m, 2H), 0.95 (t, J = 7.0 Hz, 6H); $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) = 171.1, 73.6, 36.6, 31.4, 30.1, 16.1, 11.7.

(3R,4R)-3-Ethyl-4-methyl-5-pentanolide (ii): The procedure for preparation of lactone **25** was followed with 80 mg (0.21 mmol) of aldehyde **23** in 2 mL of THF, 0.4 mL (0.4 mmol, 1 M in THF) of TBAF. The oxidation was carried out in 3 mL of CH_2Cl_2 and with 29.2 mg (0.25 mmol) of NMO, 10 mg of 4 Å molecular sieves and 2.9 mg (0.01 mmol) of TPAP. The lactone **ii** was obtained as a 3:1 mixture of diastereomers. R_f = 0.27 (50% Et_2O -hexanes); IR (film): 2963, 2878, 1731; $^1\text{H-NMR}$ (CDCl_3): δ (ppm) = 4.31 (dd, J = 11.1 Hz, J = 3.6 Hz, 1H), [4.24 (dd, J = 11.3 Hz, J = 4.6 Hz, 1H), minor], 4.17 (dd, J = 11.1 Hz, J = 4.0 Hz, 1H), [3.87 (dd, J = 11.2 Hz, J = 9.4 Hz, 1H)], [2.66 (dd, J = 18.4 Hz, J = 6.3 Hz, 1H)], 2.60 (dd, J = 18.4 Hz, J = 6.3 Hz, 1H), 2.26 (dd, J = 18.4 Hz, J = 10.3 Hz, 1H), [2.18 (dd, J = 16.9 Hz, J = 8.8 Hz, 1H)], 2.06 (m, 1H), 1.88 (m, 1H), [1.45-1.65 (m, 2H)], 1.16-1.46 (m, 2H), [0.98 (d, J = 6.7 Hz, 3 H)], 0.97 (d, J = 7.1 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H); $^{13}\text{C-NMR}$ (CDCl_3): δ (ppm) = 171.2, 75.3, 37.3, 33.6, 29.9, 24.8, 11.5, 10.6.

[6] Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, 127, 5322.

[7] Ozegowski, R.; Kunath, A.; Schick, H.; *Liebigs Ann. Org. Bioorg. Chem.* **1996**, 1443.

(3R,4R)-3-Butyl-4-methyl-5-pentanolide (iii): The procedure described above was carried out with 90 mg (0.22 mmol) of aldehyde **24** in 2 mL of THF and 0.6 mL (0.6 mmol, 1 M in THF) of TBAF. The oxidation was achieved with 39 mg (0.22 mmol) of the corresponding lactol in 3 mL of CH₂Cl₂, 8 mg of 4 Å molecular sieves, 39.8 mg (0.34 mmol) of NMO and 4 mg (0.01 mmol) of TPAP. The lactone **iii** was obtained as a 6.5:1 mixture of diastereomers by ¹H-NMR analysis. *R_f* = 0.29 (50% Et₂O-hexanes); IR (film): 2958, 2927, 2859, 1737; ¹H-NMR (CDCl₃): δ (ppm) = 4.31 (dd, *J* = 11.1 Hz, *J* = 3.5 Hz, 1H), [4.24 (dd, *J* = 11.3 Hz, *J* = 4.6 Hz, 1H), minor], 4.16 (dd, *J* = 11.1 Hz, *J* = 4.1 Hz, 1H), [3.87 (dd, *J* = 11.2 Hz, *J* = 9.3 Hz, 1H)], [2.66 (dd, *J* = 16.9 Hz, *J* = 6.2 Hz, 1H)], 2.58 (dd, *J* = 18.4 Hz, *J* = 10.0 Hz, 1H), [2.17 (dd, *J* = 17.3 Hz, *J* = 9.1 Hz, 1H)], 1.91-2.1 (m, 2H), 1.16-1.39 (m, 6H), [0.98 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 6.7 Hz, 3H)]; ¹³C-NMR (CDCl₃): δ (ppm) = 171.1, 75.2, 35.5, 33.9, 31.5, 30.2, 29.1, 22.9, 14.9, 10.7.

(3R,4S)-4-Benzyloxy-3-methylpentanal (26): The general procedure was followed with 5.9 mg (0.026 mmol) of Pd(OAc)₂ in 5 mL of THF, 6.89 mg (0.026 mmol) of PPh₃, 100 mg (0.53 mmol) of enal **25**⁸ and 1.5 mL (1.05 mmol, 0.7 M in hexanes). After column chromatography the conjugate addition product **26** was obtained as a 4:1 mixture of diastereomers by ¹H-NMR analysis. *R_f* = 0.54 (20% Et₂O-hexanes); IR (film): 3030, 2971, 2877, 2721, 1723, 1453; ¹H-NMR (CDCl₃): δ (ppm) = [9.75 (t, *J* = 2.1 Hz, 1H), minor], 9.72 (m, 1H), 7.31 (m, 5H), [4.57 (d, *J* = 11.9 Hz, 1H)], 4.56 (d, *J* = 11.5 Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), [3.5 (dq, *J* = 6.3 Hz, *J* = 3.8 Hz, 1H)], 3.28 (p, *J* = 6.22 Hz, 1H), [2.62 (ddd, *J* = 18.3 Hz, *J* = 6.4 Hz, *J* = 2.8 Hz, 1H)], 2.54 (ddd, *J* = 18.4 Hz, *J* = 8.3 Hz, *J* = 2.5 Hz, 1H), 2.25 (m, 2H), 1.20 (d, *J* = 6.1 Hz, 3H), [1.14 (d, *J* = 6.3 Hz, 3H)], 0.98 (d, *J* = 6.5 Hz, 3H), [0.97 (d, *J* = 6.9 Hz, 3H)]; ¹³C-NMR (CDCl₃): δ (ppm) = 202.7, 138.7, 128.6, 128.1, 127.8, 78.9, 70.9, 48.4, [46.7], 34.9, [32.9], 16.9, 15.8, [15.5]; Anal. Calcd. for C₁₃H₁₈O₂: C 75.69, H 8.80; found: 75.42, H 8.81.

(3R,4S)-4-Benzyloxy-3-ethylpentanal (27): The general procedure was followed with 5.9 mg (0.026 mmol) of Pd(OAc)₂ in 5 mL of THF, 6.89 mg (0.026 mmol) of PPh₃, 100 mg (0.53 mmol) of enal **25** and 1.05 mL (1.05 mmol, 1 M in hexanes) of Et₂Zn. The aldehyde **27** was obtained as a 2:1 mixture of diastereomers (90 mg, 78%). *R_f* = 0.56 (20% Et₂O-hexanes); IR (film): 3030, 2965, 2934, 2875, 2721, 1723, 1454; ¹H-NMR (CDCl₃): δ (ppm) = [9.75 (t, *J* = 2.2 Hz, 1H) minor], 9.72 (m, 1H), 7.30 (m, 5H),

4.55 (d, $J = 11.6$ Hz, 1H), [4.54 (d, $J = 11.9$ Hz, 1H)], [4.44 (d, $J = 11.9$ Hz, 1H)], 4.37 (d, $J = 11.5$ Hz, 1H), [3.62 (dq, $J = 6.3$ Hz, $J = 3.9$ Hz, 1H)], 3.41 (p, $J = 6.2$ Hz, 1H), [2.59 (m, 1H)], 2.42 (m, 2H), [2.25 (m, 2H)], 2.03 (m, 1H), [1.57 (m, 2H)], 1.33 (m, 2H), 1.20 (d, $J = 6.2$ Hz, 3H), [1.12 (d, $J = 6.4$ Hz, 3H)], [0.91 (m, 3H)], 0.89 (t, $J = 7.5$ Hz, 3H); ^{13}C -NMR (CDCl_3): δ (ppm) = [203.2, minor], 203.0, [138.9], 138.7, 128.5, 128.0, 127.75, [127.70], 77.0, [76.2], 70.9, [70.6], 45.2, [44.1], 41.7, [39.7], [24.1], 23.9, 17.3, [14.9], [12.3], 11.5; Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_2$: C 76.33, H 9.15; found: C 76.13, H 9.27.

(3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-methylpentanal (29): The general procedure was followed with 10.5 mg (0.046 mmol) of $\text{Pd}(\text{OAc})_2$ in 9 mL of THF, 12.2 mg (0.046 mmol) of PPh_3 , 200 mg (0.93 mmol) of enal **28**⁹ and 1.87 mL (3.73 mmol, 2 M in toluene) of Me_2Zn . The conjugate addition product was obtained as a 4:1 mixture of diastereomers (107 mg, 50%). $R_f = 0.67$ (20% Et_2O -hexanes); IR (film): 2957, 2857, 2711, 1727; ^1H -NMR (CDCl_3): δ (ppm) = 9.75 (m, 1H), [3.78 (dq, $J = 6.3$ Hz, $J = 3.4$ Hz, 1H) minor], 3.62 (p, $J = 6.0$ Hz, 1H), 2.54 (ddd, $J = 16.2$ Hz, $J = 4.7$ Hz, $J = 1.6$ Hz, 1H), 2.19 (ddd, $J = 16.2$ Hz, $J = 8.1$ Hz, $J = 2.7$ Hz, 1H), 2.03 (m, 1H), 1.11 (d, $J = 6.2$ Hz, 3H), [1.04 (d, $J = 6.3$ Hz, 3H)], 0.94 (d, $J = 6.8$ Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C -NMR (CDCl_3): δ (ppm) = 203.4 [203.2, minor], 72.2, [71.2], 46.9, [46.8], 36.3, [35.6], 26.1, [21.5], [19.4], 18.3, 17.2, [15.6], -4.0, [-4.2], -4.6, [-4.7].

(3S,4R)-4-(tert-Butyldimethylsilyloxy)-3-ethylpentanal (30): The general procedure was followed with 5.2 mg (0.023 mmol) of $\text{Pd}(\text{OAc})_2$ in 5 mL of THF, 5.8 mg (0.023 mmol) of PPh_3 , 100 mg (0.47 mmol) of enal **28** and 0.93 mL (0.9 mmol, 1 M in hexanes) of Et_2Zn . Aldehyde **30** was obtained after column chromatography (hexanes-5% Et_2O -hexanes) as a 2:1 mixture of diastereomers (81 mg, 71%). $R_f = 0.73$ (20% Et_2O -hexanes); IR (film): 2958, 2930, 2883, 2857, 2710, 1727; ^1H -NMR (CDCl_3): δ (ppm) = 9.78 (m, 1H), [9.73 (dd, $J = 2.8$ Hz, $J = 2.1$ Hz, 1H), minor], [3.91 (dq, $J = 6.3$ Hz, $J = 4.0$ Hz, 1H)], 3.82 (dq, $J = 6.2$ Hz, $J = 4.2$ Hz, 1H), [2.53 (m, 1H)], 2.47 (ddd, $J = 16.8$ Hz, $J = 5.7$ Hz, $J = 2.1$ Hz, 1H), 2.31 (ddd, $J = 16.8$ Hz, $J = 6.2$ Hz, $J = 2.6$ Hz, 1H), [2.18 (ddd, $J = 16.0$ Hz, $J = 6.1$ Hz, $J = 2.1$ Hz, 1H)], [2.06 (m, 1H)], 1.82 (m, 1H), 1.50 (m, 1H), 1.32 (m, 2H), [1.23 (m, 2H)], 1.11 (d, $J = 6.2$ Hz, 3H), [1.02 (d, $J = 6.3$ Hz, 3H)], [0.91 (t, $J = 7.4$ Hz, 3H)], 0.90 (t, $J = 7.5$ Hz, 3H), 0.861 (s, 9H), [0.859 (s, 9H)], 0.04 (s, 3H), [0.03 (s, 3H)], 0.02 (s, 3H); ^{13}C -NMR (CDCl_3): δ (ppm) = 203.3 [203.1, minor], [69.6], 69.5, 43.9, [43.8], 42.9, [42.7], 25.8, 24.3, [24.0], [21.8], 18.1, [18.0], 17.9, [12.1], 11.7, -4.2, [-4.5], -4.9; Anal. Calcd. for $\text{C}_{13}\text{H}_{28}\text{O}_2\text{Si}$: C 63.87, H 11.55; found: C 63.84, H 11.65.

General Procedure for Copper-Catalyzed Conjugate Addition to Enals.

3-Ethylnonanal (2): A flame-dried 25 mL round bottom flask containing a magnetic stir bar, 1 mL of THF and 25.44 mg (0.28 mmol) of CuCN was cooled to -78°C . Then, 0.35 mL (0.57 mmol, 1.6 M in Et_2O) of MeLi was added dropwise. The mixture was allowed to warm to ambient temperature and once the mixture became homogeneous cooled back to -78°C . To a separate flame-dried 50 mL flask, containing 10 mL of THF, 2 mL (2 mmol, 1 M in hexanes) of Et_2Zn were added at -78°C . Then, 0.4 mL (0.11 mmol, 0.28 M in THF) of the preformed catalyst solution¹⁰ was added dropwise to the Et_2Zn solution by syringe, followed by 0.38 mL (3 mmol) of TMSCl and 140 mg (1 mmol) of (*E*)-2-nonenal. The mixture was stirred at -78°C for 4 h and completion of the addition. The reaction was quenched by pouring it into a rapidly stirring NH_4Cl (aq.) and the phases were separated. The organic phase was treated with TBAF, and extracted with NH_4Cl . The organic phase was dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexanes-5% Et_2O -hexanes) to afford 3-ethylnonanal **2** (140 mg, 82%). The spectra matched those of the palladium-catalyzed reaction.

3-Phenylpentanal (13): The general procedure was followed with 132.2 mg (1 mmol) of cinnamaldehyde. The product was obtained as an oil (129 mg, 88%). The spectral data were identical to those obtained in the palladium-catalyzed reaction.

3-Ethyl-3,7-dimethyl-6-octenal (14): The general procedure for the copper-catalyzed reaction was followed with 2 mL (2 mmol, 1 M in hexanes) of Et_2Zn in 10 mL of THF, 0.4 mL (0.11 mmol, 0.284 M in THF) of $\text{Me}_2\text{CuCNLi}_2$, 0.38 mL (3 mmol) of TMSCl and 152.2 mg (1 mmol) of geranial. After column chromatography the 1,4-adduct was afforded as a yellowish liquid (177 mg, 97%). The spectral data were identical to those obtained in the palladium-catalyzed reaction.

[10] The reaction was also carried out with 5 mol% of the catalyst on a 3.5 mmol scale in 87% yield.

(3*S*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3,4-dimethylpentanal (22): The general procedure was followed with 0.2 mL (0.056 mmol, 0.28 M in THF) of $\text{Me}_2\text{CuCNLi}_2$, 0.28 mL (0.568 mmol, 2 M in toluene) of Me_2Zn in 2 mL of THF, 0.11 mL (0.85 mmol) of TMSCl and 105 mg (0.29 mmol) of enal **21**. Aldehyde **22** was obtained as a single diastereomer by $^1\text{H-NMR}$ (110 mg, 100%). $[\alpha]_{\text{D}}^{20} = -12.2$ ($c = 1.05$, CHCl_3).

(3*S*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3-ethyl-4-methylpentanal (23): The general procedure was followed with 0.1 mL (0.028 mmol, 0.28 M in THF) of $\text{Me}_2\text{CuCNLi}_2$, 0.6 mL (0.6 mmol, 1 M in hexanes) of Et_2Zn in 3 mL of THF, 0.11 mL (0.85 mmol) of TMSCl and 100 mg (0.27 mmol) of enal **21**. Aldehyde **23** was isolated as a 4.5:1 mixture of diastereomers (85 mg, 81%).

(3*R*,4*S*)-4-Benzyloxy-3-methylpentanal (26): The general procedure was followed with 190.24 mg (1 mmol) of enal **25**. The conjugate addition product was obtained as a 4.5:1 mixture of diastereomers (190 mg, 92%) with matching spectra to those of the palladium-catalyzed reaction.

Unambiguous Stereoselective Synthesis of the 1,4-Adduct **26**.

Anti-4-Benzyloxy-3-methylpentanal (26): To a flame-dried flask containing a magnetic stir bar and 15.4 mg (0.07 mmol) of $\text{Pd}(\text{OAc})_2$ in 14 mL of THF was cooled to $-78\text{ }^\circ\text{C}$ and 17.9 mg (0.07 mmol) of PPh_3 were added. Then, 500 mg (1.64 mmol) of racemic 4-triisopropylsilyl-3-butyn-2-yl mesylate¹¹, 0.07 mL (1.37 mmol) of acetaldehyde and 4.1 mL (4.1 mmol, 1 M in hexanes) of Et_2Zn were added sequentially. The reaction was warmed to $-20\text{ }^\circ\text{C}$ and stirred overnight. The reaction was quenched by pouring it into a rapidly stirring solution of sat. NH_4Cl (aq.). The aqueous phase was extracted with Et_2O and the combined organic extracts were dried over MgSO_4 , filtered and the solvent was removed under

[11] Marshall, J. A.; Eidam, P.; Eidam, H. S.; *J. Org. Chem.* **2006**, *71*, 4840.

reduced pressure. The crude material was subjected to column chromatography (20% Et₂O-hexanes) to yield the homopropargylic alcohol together with unreacted mesylate.

The alcohol was dissolved in 6.5 mL of dioxane, then, 9.84 mg (3.9 mmol) of *O*-benzyl-2,2,2-trichloroacetimidate¹² and 39 mg (0.26 mmol) of TfOH were added at room temperature. Upon completion of the reaction, as judged by TLC analysis, the reaction was quenched with sat. NH₄Cl (aq.). The aqueous phase was extracted with Et₂O and the combined organic extracts were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (100% hexanes) to yield 298 mg (67%) of alkyne as a 11:1 mixture of diastereomers. *R*_f = 0.84 (20% Et₂O); ¹H-NMR (CDCl₃): δ (ppm) = 7.25-7.45 (m, 5H), 4.56 (s, 2H), 3.67 (m, 1H), [3.44 (p, *J* = 6.2 Hz, 1H), minor], 2.85 (dq, *J* = 7.0 Hz, *J* = 4.7 Hz, 1H), [2.67 (m, 1H)], 1.27 (d, *J* = 6.3 Hz, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.07 (m, 21H).

The alkyne was dissolved in 5 mL of THF and treated with 2.72 mL (2.72 mmol, 1 M in THF) of TBAF. Upon completion of the reaction, as judged by TLC analysis, the reaction was quenched with sat. NH₄Cl (aq.) and the aqueous layer was extracted with Et₂O. The combined organic extracts were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The terminal alkyne was isolated after column chromatography (100% hexanes-5% Et₂O-hexanes) as a clear oil (107 mg, 42%). *R*_f = 0.71 (20% Et₂O-hexanes); ¹H-NMR (CDCl₃): δ (ppm) = 7.28-7.44 (m, 5H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 3.62 (dq, *J* = 6.2 Hz, *J* = 4.9 Hz, 1H), 2.76 (ddq, *J* = 7.0 Hz, *J* = 4.5 Hz, *J* = 2.5 Hz, 1H), 2.12 (d, *J* = 2.5 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 7.1 Hz, 3H).

To a 50 mL flame-dried flask containing 0.08 mL (0.85 mmol) of BH₃·SMe₂ in 3 mL of DME at 0 °C was added 0.18 mL (1.76 mmol) of freshly distilled cyclohexene dropwise¹³. After 15 min, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was cooled back to 0 °C and 107 mg (0.57 mmol) of the terminal alkyne in 3 mL of DME was added. The reaction mixture was stirred for 6.5 h at room temperature, cooled to 0 °C and 3 mL of 10% NaOH along with 2 mL of 30% H₂O₂ was added dropwise. After 1 h, unreacted H₂O₂ was decomposed by addition of sat. Na₂S₂O₃ (aq.) (Caution: the reaction is very exothermic and vigorous bubbling may result after 5 min!). The aqueous phase was extracted with Et₂O, the combined organic extracts were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to yield aldehyde **26** (26 mg, 22%) with matching spectral data to the compound previously prepared.

[12] Enders, D.; von Berg, S.; Jandeleit, B.; *Org. Synth.* **2004**, *Coll. Vol. 10*, 66.

[13] Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **2000**, *65*, 1501.

Unambiguous Stereoselective Synthesis of the 1,4-Adduct **29**.

(3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-methylpentanal (29): To a flame-dried flask containing a magnetic stir bar and 33.9 mg (0.15 mmol) of Pd(OAc)₂ in 30 mL of THF was cooled to -78 °C and 39.7 mg (0.15 mmol) of PPh₃ was added. Then, 800 mg (3.63 mmol) of (*R*)-4-TMS-3-butyn-2-yl mesylate¹⁴, 0.2 mL (3.63 mmol) of acetaldehyde and 9.1 mL (9.1 mmol, 1 M in hexanes) of Et₂Zn were added sequentially. The reaction was warmed to -20 °C and stirred overnight. The reaction was quenched by pouring it into a rapidly stirring solution of sat. NH₄Cl (aq.). The aqueous phase was extracted with Et₂O and the combined organic extracts were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude material was subjected to column chromatography (20% Et₂O-hexanes) to yield the homopropargylic alcohol together with unreacted mesylate.

The alcohol was dissolved in 20 mL of CH₂Cl₂ at 0 °C together with 1.4 mL (12 mmol) of 2,6-lutidine and

2.1 mL (9 mmol) of TBSOTf was added dropwise. The reaction mixture was allowed to slowly warm to room temperature. After 3 h, the reaction was quenched with sat. NH₄Cl (aq.), the aqueous phase was extracted with Et₂O and the combined organic extracts were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The silyl ether was obtained after column chromatography (100% hexanes) as a clear liquid (221 mg, 21% over two steps). R_f = 0.91; ¹H-NMR (CDCl₃): δ (ppm) = 3.84 (m, 1H), [3.67 (m, 1H), minor], 2.50 (dq, *J* = 7.0 Hz, *J* = 4.8 Hz, 1H), [2.38 (p, *J* = 6.9 Hz, 1H)], [1.23 (d, *J* = 6.1 Hz, 3H)], 1.15 (d, *J* = 6.2 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.14 (s, 6H).

The TBS ether (221 mg, 0.77 mmol) was dissolved in 1.5 mL of MeOH with 322.1 mg (2.33 mmol) of K₂CO₃. After 1 h, the reaction mixture was directly subjected to column chromatography (100% hexanes) to yield 118 mg (72%) of the terminal alkyne. R_f = 0.86.

In a flame-dried flask, 0.08 mL (0.83 mmol) of BH₃·SMe₂ was dissolved in 2 mL of DME and 0.17 mL (1.72 mmol) of cyclohexene was added. Then, 118 mg (0.55 mmol) of the terminal alkyne in 3 mL of DME was added upon complete formation of the borane. After column chromatography the aldehyde was obtained as a 4:1 mixture of diastereomers (33 mg, 26%) with matching spectral data to the previously prepared compound.

[14] Marshall, J. A.; Yanik, M. M.; Adams, N. D.; Ellis, K. C.; Chobanian, H. R.; *Org. Synth.* **2004**, *81*, 157.

S18

48,431
34,604
33,887
32,031
29,735
26,852
26,807
22,859
14,306
11,115

203,713

S19

S20

14,299
20,193
22,855
27,112
28,366
29,591
32,039
37,127
51,310

S24

50,860
40,331
36,856
31,908
29,401
27,495
22,828
14,299

128,833
127,682
126,762

202,383

250
ppm (t1)

200

150

100

50

0

S25

S27

S29

S34

S35

S38

40,143
36,014
32,167
29,627
29,057
27,563
26,001
22,919
18,661
14,352
12,075
-4,981

116,595
140,092

0

50

100

150

ppm²⁰⁰
(t1)

S40

5.0

ppm (t_1)

S54

12,126
14,285
19,479
23,006
27,107
29,720
32,235
33,322
37,257
45,116
66,947

127,895
129,875
133,938
135,834

203,869

S55

S58

37,307
33,598
29,935
24,813
11,560
10,627

75,276

171,179

ppm (t1)

-50

0

50

100

150

200

ppm (t1)

10,738
14,214
22,901
29,135
30,209
31,525
33,930
35,464

75,180

171,155

S63

S64

11,540
12,281
14,964
17,297
23,995
24,095
39,684
41,718
44,132
45,260
70,607
70,911
76,179
77,052

127,701
127,754
128,040
128,558
138,713
138,967

203,274
203,005

0

50

100

150

ppm (t1) 200