Alkene-Directed, Nickel-Catalyzed Alkyne Coupling Reactions

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Experimental Section

General Methods. All reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Bis(cyclooctadienyl)nickel(0) (Ni(cod)_2), tricyclopentylphosphine, (S)-(+)-neomenthyl-diphenylphosphine (NMDPP), $\text{RhCl(PPh}_3)_3$ (Wilkinson's catalyst), and tetrakis(triphenylphosphine) palladium(0) were purchased from Strem Chemicals, Inc. and used without further purification. Triethylborane (98%), tributylphosphine, 1,2-epoxyoctane, vinyl bromide, 1-octyne, phenylacetylene, cyclohexanecarboxaldehyde, and 4-(dimethylamino)-pyridine (DMAP) were purchased from Aldrich Chemical Co. and used as received. Imidazole, *tert*-butyldimethylsilyl chloride (TBSCl), and carbon tetrabromide were purchased from Alfa Aesar and used as received. 3-Methyl-1-butyne and 3,3-dimethyl-1-butyne were purchased from GFS Chemicals and used without further purification. Isobutyraldehyde was purchased from Alfa Aesar and distilled over magnesium sulfate prior to use. Zinc chloride (ZnCl_2) was purchased from Alfa Aesar and dried in vacuo at 150 °C for 16 h prior to use. 2-Methyl-1-hexen-3-yne was purchased from Aldrich Chemical Co. and distilled prior to use. 2-Methyl-3-hexyne was prepared by $\text{LiNH}_2/\text{NH}_3$ deprotonation of 3-methyl-1-butyne followed by addition of ethyl bromide.¹ Tetrahydrofuran, diethyl ether and toluene were freshly distilled over blue solutions of sodium/benzophenone ketyl. Methylene chloride and pyrrolidine were distilled over calcium hydride; ethyl acetate was distilled over magnesium sulfate under argon atmosphere. Dimethylformamide, 99.9+%, was purchased from Aldrich Chemical Co. and dried over activated molecular sieves (3 Å) prior to use.

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ aluminum plates precoated with a fluorescent indicator or EM reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was accomplished with UV light and ethanolic phosphomolybdic acid (PMA) or aqueous potassium permanganate. Liquid chromatography was performed using a forced flow (flash chromatography)² of the indicated solvent system on Silicycle silica gel 60 (230 – 400 mesh). ¹H and ¹³C NMR spectra were recorded on Varian Inova 300 and 500MHz and Bruker Advance 400MHz instruments. Infrared (IR) spectra were recorded as a thin film between NaCl plates on a Perkin-Elmer Model 2000 FT-IR System transform spectrometer. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with ChiralDEX B-PH, B-DA, and G-TA capillary columns. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter at 589 nm.

Enyne Synthesis. General procedure for the synthesis of 1-buten-3-ynes:³ In an oven-dried, 100 mL round-bottom flask, a terminal alkyne (15 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. Then *n*-BuLi (15 mmol, 6 mL of 2.5 M solution in hexanes) was added dropwise, and the mixture was stirred at 0 °C for 30 min. A solution of dry ZnCl_2 (2.04 g, 15 mmol) in THF (10 mL) was added via cannula and the mixture was allowed to warm to room temperature. In a 250 mL round bottom flask, vinyl bromide (25 mmol, 25 mL of a 1 M solution in THF) and $\text{Pd(PPh}_3)_4$ (0.69g, 0.6 mmol)

were combined. The alkynyl zinc solution was transferred to the palladium solution via cannula. The bright yellow solution was stirred for 2 h, and then quenched with 1 M HCl (75 mL). The organics were extracted with pentanes (2 x 75 mL), washed with saturated NaCl, dried over MgSO₄, and filtered. Pentanes were removed via distillation, and the residue was then distilled under reduced pressure to provide the desired 1-buten-3-yne.

3-buten-1-ynyl-benzene⁴ (1a): The general procedure was followed except that the scale was doubled. Thus, phenylacetylene (3.3 mL, 30 mmol) provided after reaction and purification the title compound (2.24 g, 17 mmol, 58% yield) as a clear liquid. ¹H NMR (300 MHz, CDCl₃) δ 7.42 – 7.46 (m, 2H); 7.29 – 7.34 (m, 3H); 6.02 (dd, *J* = 17.4, 11.1 Hz, 1H); 5.73 (ddd, *J* = 17.4, 2.1, 0.5 Hz, 1H); 5.54 (ddd, *J* = 11.1, 2.1, 0.5 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 131.77, 128.52, 128.50, 127.14, 123.31, 117.38, 90.16, 88.28.

5,5-dimethyl-1-hexen-3-yne⁵ (1b): The general procedure was followed except that the reaction was performed on 50 mmol scale. Thus, 3,3-dimethylbutyne (6.1 mL, 50 mmol) provided after reaction and purification the title compound (2.14 g, 20 mmol, 40% yield) as a clear liquid. ¹H NMR (300 MHz, CDCl₃) δ 5.78 (dd, *J* = 17.4, 10.8 Hz, 1H); 5.52 (*J* = 17.4, 2.4 Hz, 1H); 5.35 (dd, *J* = 10.8, 2.4 Hz, 1H); 1.24 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 125.48, 117.84, 99.44, 77.94, 31.81, 31.12.

3-buten-1-ynyl-cyclohexane (1c): Cyclohexanecarboxaldehyde (2.28g, 20 mmol, 2.44 mL) and triphenylphosphine (17.28g, 66 mmol) were dissolved in CH₂Cl₂ (80 mL) and cooled to 0 °C. A solution of carbon tetrabromide (14.68g, 44 mmol) in CH₂Cl₂ was added over 10 min, and the reaction was stirred at 0 °C for 1.5 h. Hexanes (600 mL) was added, and the precipitated triphenylphosphine oxide was removed by filtration through a pad of silica gel. Removal of solvent in vacuo provided 1,1-dibromo-2-cyclohexylethene as a clear oil (5.43 g, 20 mmol, 100% yield). The 1,1-dibromo-2-cyclohexylethene was dissolved in THF (40 mL) and cooled to –78 °C. Then *n*-BuLi (55 mmol, 22 mL of a 2.5 M solution in hexanes) was added dropwise, and the solution was stirred for 1 h at –78 °C, then warmed to 0 °C and stirred for an additional 45 min. Dried ZnCl₂ (3.4 g, 25 mmol) in THF (12 mL) was then added via cannula and the solution was allowed to warm to room temperature. The alkynyl zinc was then transferred via cannula into a solution of vinyl bromide (40 mmol, 40 mL of a 1M solution in THF) and palladium tetrakis (0.93 g, 0.80 mmol). The bright yellow solution was stirred overnight at room temperature. The reaction was quenched with 1M HCl (100 mL), and the organics were extracted with pentane (2x 100 mL), washed with saturated NaCl, dried over MgSO₄, and filtered. Pentanes were removed via distillation, and the residue was distilled under reduced pressure to provide the title compound (0.61 g, 5.42 mmol, 47% yield) as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ 5.81 (ddd, *J* = 29, 18, 1 Hz, 1H); 5.57 (ddd, *J* = 29, 5, 1 Hz, 1H); 5.38 (dd, *J* = 18, 4 Hz, 1H); 2.42 – 2.53 (m, 1H); 1.65 – 1.88 (m, 4H); 1.22 – 1.58 (m, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 125.55, 117.89, 95.46, 79.35, 32.84, 29.85, 26.07, 25.15. IR (thin film NaCl): 3099, 3009, 2932, 2855, 2663, 2224, 1829, 1608, 1449, 1362, 1349, 1298, 1234, 1168, 973, 914.

5-methyl-1-hexen-3-yne (1d): The general procedure was followed except that the reaction was performed on 50 mmol scale. Thus, 3-methyl-1-butyne (5.13 mL, 50 mmol)

provided after reaction and purification the title compound (1.30 g, 23 mmol, 46% yield) as a clear liquid. ^1H NMR (300 MHz, CDCl_3) δ 5.79 (ddd, $J = 17.5, 13, 2$ Hz, 1H); 5.55 (dd, $J = 17.5, 2.5$ Hz, 1H); 5.38 (dd, $J = 11, 2$ Hz, 1H); 2.68 (doublet of septets, $J = 7, 2$ Hz, 1H); 1.20 (d, $J = 7$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 125.63, 117.80, 96.73, 78.65, 23.11, 21.25. IR (thin film NaCl): 3101, 3011, 2971, 2933, 2874, 2228, 1832, 1609, 1466, 1411, 1383, 1364, 1319, 1292, 1190, 1135, 1105, 1071, 974, 916.

1-Decen-3-yne³ (1e): The standard procedure was followed. Thus, 1-octyne (2.21 mL, 15 mmol) provided after reaction and purification the title compound (0.95 g, 7.0 mmol, 47% yield) as a clear liquid. ^1H NMR (300 MHz, CDCl_3) δ 5.78 (ddt, $J = 17.4, 10.8, 2.1$ Hz, 1H); 5.54 (dd, $J = 17.4, 2.3$ Hz, 1H); 5.37 (dd, $J = 10.8, 2.3$ Hz, 1H); 2.29 (dt, $J = 10.2, 2.1$ Hz, 2H); 1.48 – 1.57 (m, 2H); 1.25 – 1.44 (m, 6H); 0.89 (t, $J = 7$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 125.65, 117.86, 91.49, 76.48, 31.57, 28.86, 28.80, 22.77, 19.55, 14.28.

(Z)-Pent-1-en-3-ynyl-cyclohexane (1g): $\text{Pd}(\text{PPh}_3)_4$ (277 mg, 0.24 mmol) and copper iodide (23 mg, 0.12 mmol) were added to a 250 mL, three-necked round-bottom flask under inert atmosphere. Pyrrolidine (16 mL) was added, followed by (Z)-(2-iodoethenyl)cyclohexane⁶ (1.9 g, 8 mmol). The mixture was cooled to -78°C and the flask was then evacuated. The vacuum outlet was closed, and with the flask still evacuated, propyne was bubbled in slowly. The flask was removed from the cold bath and allowed to warm gradually to room temperature. Propyne was bubbled in until atmospheric pressure was reached, at which point the reaction was placed under argon and stirred for 15 h. The reaction was then diluted with Et_2O (75 mL) and saturated aqueous NH_4Cl (75 mL). The organics were extracted with Et_2O (2 x 75 mL), dried over MgSO_4 , filtered, and concentrated in vacuo to give a crude oil. Purification via flash chromatography on silica gel (100% hexanes) provided the title compound as a clear liquid (0.86 g, 73% yield). $R_f = 0.50$ (hexanes). ^1H NMR (500 MHz, CDCl_3) δ 5.64 (t, $J = 10$ Hz, 1H); 5.32 (dd, $J = 11, 2$ Hz, 1H); 2.56 (m, 1H); 1.99 (d, $J = 1.5$ Hz, 3H); 1.73 – 1.65 (m, 5H); 1.38 – 1.29 (m, 2H); 1.22 – 1.16 (m, 1H); 1.14 – 1.04 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.44, 107.32, 89.46, 76.74, 39.22, 32.61, 26.21, 25.92, 4.70. IR (thin film NaCl): 3015, 2925, 2852, 2213, 1710, 1681, 1620, 1449, 1401.

1-prop-1-ynyl-cyclohexene⁷ (1h): ^1H NMR (300 MHz, CDCl_3) δ 5.98 (s, 1H); 2.10 – 2.00 (m, 4H); 1.94 (s, 3H); 1.62 – 1.50 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3) δ 133.1, 121.1, 82.7, 81.6, 29.6, 25.6, 22.5, 21.7, 4.11.

(E)-2,3-dimethyl-non-2-en-4-yne (1i): $\text{Pd}(\text{PPh}_3)_4$ (277 mg, 0.24 mmol) and copper iodide (23 mg, 0.12 mmol) were added to a 100 mL, oven-dried round-bottom flask under inert atmosphere. Pyrrolidine (24 mL) was added, followed by 1-hexyne (1.38 mL, 12 mmol) and 2-iodo-3-methyl-2-butene⁸ (2.52 g, 12 mmol). The mixture was heated to 50°C and stirred for 15 h. The reaction was then cooled and diluted with Et_2O (100 mL) and saturated aqueous NH_4Cl (100 mL). The organics were extracted with Et_2O (2 x 75 mL), dried over MgSO_4 , filtered, and concentrated in vacuo to give a crude oil. Purification via flash chromatography on silica gel (100% hexanes) provided the title compound as a clear liquid (1.52 g, 84% yield). $R_f = 0.44$ (hexanes). ^1H NMR (500

MHz, CDCl₃) δ 2.35 (t, J = 7 Hz, 2H); 1.92 (s, 3H); 1.78 (s, 3H); 1.72 (s, 3H); 1.56 – 1.49 (m, 2H); 1.48 – 1.41 (m, 2H); 0.93 (t, J = 7 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 138.20, 112.13, 91.45, 82.47, 31.46, 23.61, 22.20, 19.94, 19.39, 19.14, 13.87. IR (thin film NaCl): 2959, 2931, 2873, 2862, 1682, 1466, 1458, 1445, 1372, 1329.

Standard Experimental Procedure for the Catalytic Reductive Coupling of Enynes and Aldehydes.

In a glovebox, Ni(cod)₂ (14 mg, 0.5 mmol), and tricyclopentylphosphine (28 μ L, 0.1 mmol) were placed into a 25 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et₃B (0.15 mL, 1.0 mmol). The resulting solution was stirred at ambient temperature for 5 minutes and then cooled to 0 °C. Once the solution had cooled, isobutyraldehyde (90 μ L, 1.0 mmol) was added dropwise via microsyringe. After stirring for 5 min, the enyne (0.5 mmol) was added. The reaction was allowed to gradually warm to room temperature over 4 h, and the reaction continued to stir until complete by TLC (6 – 15 h). The septa was then removed and the reaction opened to air for 30 min to promote quenching of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 50:1 to 10:1). Note: Compounds formed are prone to rapid (over 2-3 days) decomposition, and so should either be used immediately or stored as solutions in benzene at –20 °C.

(4E)-4-Phenyl-2-methyl-hepta-4,6-dien-3-ol (2a): In the reductive coupling of **1a** (64 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (72 mg, 71% yield, 95:5 regioselectivity, >95:5 *E/Z*). R_f = 0.27 (10:1 hexanes: ethyl acetate). The structure of the title compound was confirmed by ozonolysis, which provided α -hydroxyisovalerophenone⁹ as the major product. ¹H NMR (500 MHz, CDCl₃) δ 7.35 – 7.40 (m, 2H); 7.29 – 7.33 (m, 1H); 7.22 – 7.24 (m, 2H); 6.25 – 6.37 (m, 2H); 5.31 (dd, J = 15.5, 2 Hz, 1H); 5.06 (dd, J = 10, 2 Hz, 1H); 4.18 (dd, J = 5, 5 Hz, 1H); 1.65 (d, J = 5 Hz, 1H); 1.63 (oct., J = 6.5 Hz, 1H); 0.92 (d, J = 6.5 Hz, 3H); 0.90 (d, J = 6.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 145.22, 138.44, 134.04, 129.44, 128.37, 128.29, 127.50, 118.31, 81.46, 31.54, 20.04, 16.72. IR (thin film NaCl): 3427, 3082, 3057, 3036, 2961, 2930, 2871, 1951, 1814, 1637, 1602, 1494, 1467, 1442, 1419, 1385, 1366, 1293, 1137, 1074, 998. HRMS (EI) m/z 202.134 [M^+ ; calcd for C₁₄H₁₈O: 202.135].

(4E)-4-tert-Butyl-2-methyl-hepta-4,6-dien-3-ol (2b): In the reductive coupling of **1b** (54 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used except that (+)-NMDPP (32 mg, 0.1 mmol) was employed as the phosphine ligand. Silica gel chromatography afforded the title compound as a clear oil (63 mg, 69% yield, >95:5 regioselectivity, >95:5 *E/Z*). $R_f = 0.33$ (10:1 hexanes: ethyl acetate). ^1H NMR (500 MHz, CDCl_3) δ 7.00 – 6.92 (m, 1H); 6.11 (d, $J = 11.5$ Hz, 1H); 5.13 (dt, $J = 16.5$, 1 Hz, 1H); 5.10 (dd, $J = 10$, 2 Hz, 1H); 4.02 (t, $J = 5$ Hz, 1H); 1.81 (oct., $J = 6.5$ Hz, 1H); 1.21 (s, 9H); 0.95 (d, $J = 6$ Hz, 3H); 0.94 (d, $J = 7$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.91, 134.39, 126.12, 118.03, 76.98, 35.96, 33.46, 31.34, 20.55, 16.79. IR (thin film NaCl): 3432, 3086, 2958, 2872, 1813, 1630, 1584, 1470, 1366, 1230, 1206, 1133. HRMS (EI) m/z 182.167 [M^+ ; calcd for $\text{C}_{12}\text{H}_{22}\text{O}$: 182.167].

(4E)-4-Cyclohexyl-2-methyl-hepta-4,6-dien-3-ol (2c): In the reductive coupling of **1c** (136 mg, 1.0 mmol) and isobutyraldehyde (180 μL , 2.0 mmol), the standard procedure was used except that the scale was doubled and (+)-NMDPP (64 mg, 0.2 mmol) was employed as the phosphine ligand. Silica gel chromatography afforded the title compound as a clear oil (131 mg, 63% yield, >95:5 regioselectivity, >95:5 *E/Z*). $R_f = 0.36$ (10:1 hexanes: ethyl acetate). ^1H NMR (500 MHz, CDCl_3) δ 6.83 – 6.75 (m, 1H); 6.04 (d, $J = 11.5$ Hz, 1H); 5.20 (dd, $J = 16.5$, 2 Hz, 1H); 5.11 (dd, $J = 10$, 2 Hz, 1H); 3.78 (dd, $J = 7$, 3.5 Hz, 1H); 2.42 (tt, $J = 12$, 3.5 Hz, 1H); 1.85 (oct., $J = 7$ Hz, 1H); 1.82 – 1.59 (m, 4H); 1.54 (dq, $J = 12.5$, 3.5 Hz, 1H); 1.44 (dq, $J = 12.5$, 3.5 Hz, 1H); 1.35 – 1.25 (m, 3H); 1.21 (tt, $J = 13$, 3.5 Hz, 1H); 0.98 (d, $J = 6.5$ Hz, 3H); 0.89 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 149.10, 133.06, 126.11, 117.36, 79.72, 40.02, 32.21, 32.18, 32.08, 27.16, 27.13, 26.33, 20.51, 17.79. IR (thin film NaCl): 3420, 3084, 2928, 2853, 2668, 1809, 1729, 1636, 1593, 1449, 1420, 1384, 1365, 1260, 1140. HRMS (EI) m/z 208.183 [M^+ ; calcd for $\text{C}_{14}\text{H}_{24}\text{O}$: 208.182].

(4E)-4-Isopropyl-2-methyl-hepta-4,6-dien-3-ol (2d): In the reductive coupling of **1d** (47 mg, 0.5 mmol) and isobutyraldehyde the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (54 mg, 64% yield, >95:5 regioselectivity, >95:5 *E/Z*). $R_f = 0.30$ (10:1 hexanes: ethyl acetate). ^1H NMR (500 MHz, CDCl_3) δ 6.80 – 6.72 (m, 1H); 6.03 (dd, $J = 11$, 0.5 Hz, 1H); 5.20 (ddd, $J = 17$, 2, 0.5 Hz, 1H); 5.12 (ddd, $J = 10$, 2, 0.5 Hz, 1H); 3.78 (dd, $J = 7$, 1.5 Hz, 1H); 2.82 (sept., J

= 7 Hz, 1H); 1.86 (oct., J = 7 Hz, 1H); 1.18 (d, J = 7.5 Hz, 3H); 1.12 (d, J = 7.5 Hz, 3H); 0.99 (d, J = 7 Hz, 3H); 0.90 (d, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 149.73, 132.87, 125.84, 117.46, 79.17, 32.26, 28.83, 22.25, 22.08, 20.42, 17.84. IR (thin film NaCl): 3456, 3086, 2962, 2933, 2874, 1743, 1729, 1640, 1595, 1466, 1418, 1374, 1244, 1170, 1130, 1105, 1047, 993. HRMS (EI) m/z 168.151 [M^+ ; calcd for $\text{C}_{11}\text{H}_{20}\text{O}$: 168.151].

(4E)-4-Hexyl-2-methyl-hepta-4,6-dien-3-ol (2e): In the reductive coupling of **1e** (68 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (67 mg, 64% yield, >95:5 regioselectivity, >95:5 E/Z). R_f = 0.53 (10:1 hexanes: ethyl acetate). ^1H NMR (500 MHz, CDCl_3) δ 6.60 (m, 1H); 6.04 (d, J = 11 Hz, 1H); 5.21 (dd, J = 17, 2 Hz, 1H); 5.11 (dd, J = 10, 2 Hz, 1H); 3.76 (d, J = 6.5 Hz, 1H); 2.22 – 2.16 (m, 1H); 2.11 – 2.05 (m, 1H); 1.83 (oct., J = 7 Hz, 1H); 1.46 – 1.41 (m, 2H); 1.36 – 1.25 (m, 4H); 0.95 (d, J = 6.5 Hz, 3H); 0.90 – 0.88 (m, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 145.21, 132.88, 126.70, 117.12, 82.04, 32.04, 31.88, 30.63, 30.10, 28.71, 22.88, 20.08, 17.88, 14.32. IR (thin film NaCl): 3428, 2958, 2930, 2872, 2860, 1717, 1700, 1669, 1467, 1380, 1366, 1265, 1174, 1015. HRMS (EI) m/z 210.198 [M^+ ; calcd for $\text{C}_{14}\text{H}_{26}\text{O}$: 210.198].

Irradiation of the carbinol methine proton resulted in a 12% nOe of the closest vinyl proton, consistent with an E olefin geometry in the observed allylic alcohol regioisomer.

(4E)-4-Ethyl-2,6-dimethyl-hepta-4,6-dien-3-ol (2f): In the reductive coupling of **1f** (47 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (60 mg, 71% yield, 95:5 regioselectivity, 95:5 E/Z). R_f = 0.40 (10:1 hexanes: ethyl acetate). ^1H NMR (500 MHz, CDCl_3) δ 5.88 (s, 1H); 4.96 (sext., J = 1 Hz, 1H); 4.87 (t, J = 1 Hz, 1H); 3.77 (dd, J = 7, 3 Hz, 1H); 2.33 (dq, J = 13.5, 7.5 Hz, 1H); 2.14 (dq, J = 14, 7.5 Hz, 1H); 1.88 (s, 3H); 1.86 (oct., J = 7 Hz, 1H); 1.41 (d, J = 3.5 Hz, 1H); 1.09 (t, J = 7 Hz, 3H); 0.96 (d, J = 6.5 Hz, 3H); 0.90 (d, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 144.74, 141.91, 128.18,

114.52, 82.18, 31.94, 23.76, 21.73, 20.11, 17.87, 15.04. IR (thin film NaCl): 3407, 3081, 2966, 2935, 2873, 1633, 1599, 1464, 1373, 1292, 1246, 1172, 1127, 1071, 1011. HRMS (ESI) m/z 267.113 $[(M + Na)^+]$; calcd for $C_{13}H_{21}ClO_2$: 267.112] (HRMS was determined for the corresponding chloroacetate derivative).

(Z),(E)-7-cyclohexyl-2,4-dimethyl-hepta-4,6-dien-3-ol (2g): In the reductive coupling of **1g** (74 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (99 mg, 89% yield, 95:5 regioselectivity, >95:5 *E/Z*). R_f = 0.32 (10:1 hexanes: ethyl acetate). 1H NMR (500 MHz, $CDCl_3$) δ 6.26 (d, J = 12 Hz, 1H); 6.10 (t, J = 13 Hz, 1H); 5.32 (t, J = 10 Hz, 1H); 3.70 (d, J = 8 Hz, 1H); 2.45 (m, 1H); 1.82 (sept., J = 7 Hz, 1H); 1.73 (s, 3H); 1.70 – 1.60 (m, 4H); 1.35 – 1.25 (m, 3H); 1.22 – 1.16 (m, 1H); 1.13 – 1.04 (m, 2H); 1.00 (d, J = 7 Hz, 3H); 0.82 (d, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.92, 138.63, 122.14, 122.09, 84.18, 36.78, 33.45, 33.40, 31.52, 26.21, 26.07 (two isochronous signals), 19.67, 18.69, 12.05. IR (thin film NaCl): 3372, 3016, 2924, 2851, 1717, 1605, 1448, 1381, 1317, 1297, 1258, 1101, 1010. HRMS (EI) m/z 222.197 $[M^+]$; calcd for $C_{15}H_{26}O$: 222.198].

(E)-1-cyclohex-1-enyl-2,4-dimethyl-pent-1-en-3-ol (2h): In the reductive coupling of **1h** (60 mg, 0.5 mmol) and isobutyraldehyde, the standard procedure was used. Silica gel chromatography afforded the title compound as a clear oil (77 mg, 79% yield, 90:10 regioselectivity). R_f = 0.42 (10:1 hexanes: ethyl acetate). 1H NMR (500 MHz, $CDCl_3$) δ 5.75 (s, 1H); 5.63 (s, 1H); 3.61 (dd, J = 14, 5 Hz, 1H); 2.13 (m, 4H); 1.88 – 1.78 (m, 1H); 1.78 (s, 3H); 1.67 – 1.56 (m, 4H); 1.46 (d, J = 5 Hz, 1H); 1.02 (d, J = 11 Hz, 3H); 0.83 (d, J = 11 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.26, 135.06, 130.19, 127.36, 84.94, 31.47, 29.47, 25.80, 23.14, 22.37, 19.72, 18.85, 13.36. IR (thin film NaCl): 3379, 3026, 2927, 2870, 2834, 1648, 1459, 1448, 1437, 1380, 1366, 1296, 1243, 1170, 1133, 1113, 1077, 1010. HRMS (EI) m/z 194.167 $[M^+]$; calcd for $C_{13}H_{22}O$: 194.167].

(*E*)-(*E*)-4-butyl-2,6,7-trimethyl-octa-4,6-dien-3-ol (2i): In the reductive coupling of **1i** (75 mg, 0.5 mmol) with isobutyraldehyde, the standard procedure was used except that (+)-NMDPP (64 mg, 0.2 mmol) was employed as the phosphine ligand. After 6 h, standard work-up followed by silica gel chromatography afforded the title compound as a clear oil (99 mg, 88% yield, 95:5 regioselectivity, >95:5 *E/Z*). R_f = 0.36 (10:1 hexanes: ethyl acetate). ^1H NMR (500 MHz, CDCl_3) δ 5.92 (s, 1H); 3.75 (ddd, J = 7, 4, 1 Hz, 1H); 1.99 – 2.05 (m, 1H); 1.90 – 1.82 (m, 2H); 1.70 (bs, 6H); 1.62 (bs, 3H); 1.24 – 1.40 (m, 5H); 0.96 (d, J = 7 Hz, 3H); 0.91 (d, J = 7 Hz, 3H); 0.88 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 141.69, 129.16, 126.97, 125.80, 81.53, 31.89, 31.27, 28.97, 23.45, 22.12, 20.14, 19.08, 17.88, 14.12. IR (thin film NaCl): 3432, 2959, 2872, 2723, 1629, 1467, 1379, 1290, 1247, 1168, 1128, 1010. HRMS (ESI) m/z 247.204 [(M + Na) $^+$; calcd for $\text{C}_{15}\text{H}_{28}\text{O}$: 247.203].

(3*E*)-*tert*-Butyl-(3-ethyl-1-hexyl-5-methyl-hexa-3,5-dienyloxy)-dimethyl-silane (2j): To $\text{Ni}(\text{cod})_2$ (22 mg, 0.08 mmol) at 23 °C were added PBU_3 (40 μL , 0.16 mmol), Et_3B (240 μL , 1.66 mmol), (*S*)-1,2-epoxyoctane¹⁰ (180 μL , 1.00 mmol), and **1f** (100 μL , 0.80 mmol). The brownish solution was stirred at room temperature for 24 h. Et_2O (2 mL) was added, and the resulting solution was quenched with 2M aqueous NaOH (2 mL) and 30% aqueous H_2O_2 (drops). The resulting biphasic solution was vigorously stirred for 5 min. The layers were separated and the organic phase was dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (0-5% $\text{Et}_2\text{O}/\text{Hex}$) and protected as the TBS ether (TBSCl (225 mg, 1.50 mmol), imidazole (103 mg, 1.50 mmol), DMAP (183 mg, 1.50 mmol), and DMF (0.75 mL)) to afford the title compound as a clear liquid (135 mg, 50% yield, >95:5 regioselectivity, >99% ee). R_f = 0.13 (hexanes). ^1H NMR (500 MHz, CDCl_3) δ 5.64 (s, 1H); 4.90 (m, 1H); 4.76 (s, 1H); 3.77 (quin., J = 6 Hz, 1H); 2.12 – 2.25 (m, 4H); 1.84 (s, 3H); 1.25 – 1.50 (m, 10H); 1.02 (t, J = 7.5 Hz, 3H); 0.89 (t, J = 7.5 Hz, 3H); 0.89 (s, 9H); 0.05 (s, 3H); 0.03 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 142.32, 140.96, 129.97, 113.53, 71.54, 44.98, 37.45, 32.11, 29.71, 26.14, 25.45, 24.41, 23.94, 22.86, 18.35, 14.34, 13.88, -4.20, -4.29. IR (thin film NaCl): 3.082, 2959, 2930, 2858, 1634, 1463, 1406, 1374, 1361, 1254, 1187, 1094, 1005. HRMS (ESI) m/z 361.2891 [(M + Na) $^+$; calcd for $\text{C}_{21}\text{H}_{42}\text{OSi}$: 361.2891]. $[\alpha]_D$ = -0.5 (c 1.0, CHCl_3). Chiral HPLC analysis was performed on the corresponding alcohol.

(3E)-tert-Butyl-(1-hexyl-3-isopropyl-hexa-3,5-dienyloxy)-dimethyl-silane (2k): To $\text{Ni}(\text{cod})_2$ (27 mg, 0.098 mmol) at 23 °C were added PBU_3 (40 μL , 0.16 mmol), Et_3B (200 μL , 2.11 mmol), (*S*)-1,2-epoxyoctane¹⁰ (100 μL , 0.65 mmol), and **1d** (162 mg, 1.72 mmol). The brownish solution was stirred at 23 °C for 42 h. Et_2O (2 mL) was added, and the resulting solution was quenched with 2M aqueous NaOH (2 mL) and 30% aqueous H_2O_2 (drops). The resulting biphasic solution was vigorously stirred for 5 min. The layers were separated and the organic phase was dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (0-5% $\text{Et}_2\text{O}/\text{Hex}$) and protected as the TBS ether (TBSCl (140 mg, 1.42 mmol), imidazole (130 mg, 1.91 mmol), DMAP (130 mg, 1.06 mmol), THF (0.75 mL), DMF (0.25 mL)) to afford the title compound as a yellow liquid (112 mg, 51%, >95:5 regioselectivity, >99% ee). ^1H NMR (500 MHz, CDCl_3) δ 6.64 – 6.72 (m, 1H); 5.81 (d, J = 11.5 Hz, 1H); 5.10 (dd, J = 16.5, 1.5 Hz, 1H); 5.00 (dd, J = 10, 1.5 Hz, 1H); 3.82 (quin., J = 6 Hz, 1H); 3.01 (sept., J = 7 Hz, 1H); 2.18 (dd, J = 14.5, 6.5 Hz, 1H); 2.11 (dd, J = 15, 6.5 Hz, 1H); 1.24 – 1.55 (m, 10 H); 1.03 (d, J = 6.5 Hz, 3H); 1.01 (d, J = 6.5 Hz, 3H); 0.87 – 0.92 (m, 12H); 0.05 (s, 3H); 0.04 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 145.24, 132.80, 127.23, 115.34, 72.00, 40.36, 37.40, 32.13, 29.74, 29.70, 26.16, 25.50, 22.86, 21.82, 21.23, 18.33, 14.34, -3.97, -4.19. IR (thin film NaCl): 3085, 2958, 2929, 2857, 1800, 1638, 1592, 1463, 1378, 1361, 1254, 1092. HRMS (ESI) m/z 361.289 [$\text{M} + \text{Na}$]⁺; calcd for $\text{C}_{21}\text{H}_{42}\text{OSi}$: 361.290]. $[\alpha]_{\text{D}} = -1.0$ (c 1.0, CHCl_3).

Standard Experimental Procedure for the Selective Hydrogenation of Dienes **2a** –

2k: In a glovebox, RhCl(PPh₃)₃ (11 mg, 0.012 mmol) was added to a 10 mL, oven-dried round-bottom flask. The flask was then removed from the glovebox and a solution of dienol (0.12 mmol) in toluene (1 mL) was added. H₂ was bubbled through the solution for 2-3 min, and it was then stirred under a balloon of H₂ until the reaction was complete by TLC analysis (2-3 h). The solution was then passed through a plug of Celite (EtOAc eluant), concentrated under reduced pressure, and purified by flash chromatography on silica gel using a solvent gradient (50:1 to 10:1 hexanes: EtOAc). Note: Certain dienes required higher pressures of H₂ to effect reduction; in these cases, a Lab-Crest® Pressure Reaction Vessel was employed.

(*E*)-4-Phenyl-2-methyl-hept-4-en-3-ol (3a): RhCl(PPh₃)₃ (14 mg, 0.015 mmol) and a solution of **2a** (30 mg, 0.15 mmol) in toluene (1 mL) was placed in a reaction vessel and the vessel was charged with H₂ (3 atm). After 15 h, silica gel chromatography provided the title compound as a clear oil (24 mg, 80% yield). *R_f* = 0.32 (10:1 hexanes: ethyl acetate). ¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.37 (m, 2H); 7.26 – 7.31 (m, 1H); 7.17 – 7.20 (m, 2H); 5.68 (dt, *J* = 7.5 Hz, 1H); 4.00 (dd, *J* = 6, 6 Hz, 1H); 1.90 – 1.98 (m, 2H); 1.56 (sept., *J* = 6.5 Hz, 1H); 1.55 (d, *J* = 5 Hz, 1H); 0.95 (t, *J* = 7.5 Hz, 3H); 0.91 (d, *J* = 7 Hz, 3H); 0.90 (d, *J* = 7 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 142.16, 138.98, 131.30, 129.41, 128.26, 127.03, 82.37, 31.88, 22.13, 20.07, 17.24, 14.64. IR (thin film NaCl): 3418, 3080, 3056, 3022, 2961, 2871, 1947, 1809, 1600, 1574, 1494, 1461, 1442, 1385, 1366, 1292, 1259, 1174, 1142, 1123, 1082, 1012. HRMS (ESI) *m/z* 227.140 [(M + Na)⁺; calcd for C₁₄H₂₀O: 227.141].

(E)-4-tert-Butyl-2-methyl-hept-4-en-3-ol (3b): Using the standard procedure, $\text{RhCl}(\text{PPh}_3)_3$ (11 mg, 0.012 mmol) and **2b** (23 mg, 0.124 mmol) after 1.5 h provided the title compound as a clear oil (19 mg, 83% yield). $R_f = 0.30$ (10:1 hexanes: ethyl acetate). ^1H NMR (500 MHz, CDCl_3) δ 5.40 (t, $J = 7.5$ Hz, 1H); 3.92 (t, $J = 6$ Hz, 1H); 2.40 – 2.23 (m, 2H); 1.80 (oct., $J = 6.5$ Hz, 1H); 1.18 (s, 9H); 1.00 (t, $J = 7$ Hz, 3H); 0.95 (d, $J = 7$ Hz, 3H); 0.90 (d, $J = 7$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 147.40, 128.98, 77.32, 35.48, 33.38, 30.91, 22.98, 20.58, 17.13, 15.09. IR (thin film NaCl): 3612, 3424, 2959, 2872, 1727, 1641, 1469, 1397, 1383, 1364, 1305, 1260, 1228, 1198, 1173, 1122, 1099, 1015, 993. HRMS (EI) m/z 184.182 [M^+ ; calcd for $\text{C}_{12}\text{H}_{24}\text{O}$: 184.182].

(E)-4-Cyclohexyl-2-methyl-hept-4-en-3-ol (3c): Using the standard procedure, $\text{RhCl}(\text{PPh}_3)_3$ (17 mg, 0.018 mmol) and **2c** (38 mg, 0.18 mmol) after 2.5 h provided **3c** as a clear oil (33 mg, 87% yield). $R_f = 0.34$ (10:1 hexanes: ethyl acetate). ^1H NMR (500 MHz, CDCl_3) δ 5.35 (t, $J = 7.5$ Hz, 1H); 3.65 (d, $J = 8$ Hz, 1H); 2.28 (tt, $J = 12.5$, 4 Hz, 1H); 2.15 (dq, $J = 7.5$, 7.5 Hz, 1H); 2.14 (dq, $J = 7.5$, 7.5 Hz, 1H); 1.81 (oct., $J = 6.5$ Hz, 1H); 1.79 – 1.52 (m, 4H); 1.50 (dq, $J = 12.5$, 4 Hz, 1H); 1.39 (dq, $J = 12.5$, 3.5 Hz, 1H); 1.34 – 1.12 (m, 4H); 0.99 (t, $J = 7.5$ Hz, 3H); 0.98 (d, $J = 6.5$ Hz, 3H); 0.85 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 145.32, 128.74, 80.13, 39.41, 32.17, 32.09, 31.80, 27.73, 27.22, 26.41, 21.37, 20.54, 18.27, 14.90. IR (thin film NaCl): 3615, 3428, 2958, 2928, 2870, 2853, 1448, 1382, 1365, 1292, 1260, 1170, 1010. HRMS (EI) m/z 210.197 [M^+ ; calcd for $\text{C}_{16}\text{H}_{26}\text{O}$: 210.198].

(E)-4-Isopropyl-2-methyl-hept-4-en-3-ol (3d): Using the standard procedure, $\text{RhCl}(\text{PPh}_3)_3$ (12 mg, 0.013 mmol), **2d** (43 mg, 0.25 mmol), and toluene (1.5 mL) after 2 h provided the title compound as a clear oil (33 mg, 76% yield). $R_f = 0.38$ (10:1 hexanes: ethyl acetate). ^1H NMR (500 MHz, CDCl_3) δ 5.35 (t, $J = 7$ Hz, 1H); 3.64 (d, $J = 8$ Hz, 1H); 2.68 (sept., $J = 7$ Hz, 1H); 2.14 (dq, $J = 7.5$, 7.5 Hz, 1H); 2.13 (dq, $J = 7.5$, 7.5 Hz, 1H); 1.81 (oct., $J = 7$ Hz, 1H); 1.12 (d, $J = 7.5$ Hz, 3H); 1.05 (d, $J = 7$ Hz, 3H); 0.99 (d, $J = 6.5$ Hz, 3H); 0.99 (t, $J = 7.5$ Hz, 3H); 0.85 (d, $J = 7$ Hz, 3H). ^{13}C NMR (125 MHz,

CDCl₃) δ 145.99, 128.37, 79.46, 32.25, 28.19, 22.15, 21.80, 21.17, 20.47, 18.31, 14.76. IR (thin film NaCl): 3616, 3406, 2961, 2933, 2873, 1730, 1661, 1465, 1382, 1365, 1291, 1252, 1169, 1109, 1067, 1013. HRMS (EI) m/z 170.165[M⁺; calcd for C₁₁H₂₂O: 170.167].

(E)-4-Hexyl-2-methyl-hept-4-en-3-ol (3e): Using the standard procedure, RhCl(PPh₃)₃ (11 mg, 0.012 mmol) and **2e** (25 mg, 0.12 mmol) after 3 h provided the title compound as a clear oil (23 mg, 92% yield). R_f = 0.41 (10:1 hexanes: ethyl acetate). ¹H NMR (500 MHz, CDCl₃) δ 5.34 (t, J = 7 Hz, 1H); 3.64 (d, J = 8 Hz, 1H); 2.09 – 1.92 (m, 4H); 1.78 (oct., J = 7 Hz, 1H); 1.42 – 1.24 (m, 8H); 0.98 (t, J = 8 Hz, 3H); 0.96 (d, J = 7 Hz, 3H); 0.89 (t, J = 7 Hz, 3H); 0.84 (d, J = 7 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 140.83, 129.53, 82.93, 31.94, 31.79, 30.36, 30.20, 28.06, 22.91, 21.07, 20.09, 18.29, 14.65, 14.33. IR (thin film NaCl): 3624, 3417, 2959, 2930, 2872, 1728, 1660, 1467, 1379, 1366, 1295, 1260, 1170, 1100, 1068, 1012. HRMS (ESI) m/z 235.203 [(M + Na)⁺; calcd for C₁₄H₂₈O: 235.203].

(E)-4-Ethyl-2,6-dimethyl-hept-4-en-3-ol (3f): RhCl(PPh₃)₃ (17 mg, 0.018 mmol) and a solution of **2f** (31 mg, 0.19 mmol) in toluene (1 mL) were placed in a reaction vessel and the vessel was charged with H₂ (3 atm). After 2 h, silica gel chromatography provided the title compound as a clear oil (30 mg, 96% yield). R_f = 0.31 (10:1 hexanes: ethyl acetate). ¹H NMR (500 MHz, CDCl₃) δ 5.14 (d, J = 10 Hz, 1H); 3.63 (d, J = 7 Hz, 1H); 2.62 – 2.54 (m, 1H); 2.10 – 1.99 (m, 2H); 1.78 (oct., J = 7 Hz, 1H); 1.73 (d, J = 2.5 Hz, 1H); 1.04 (t, J = 8 Hz, 3H); 0.98 (d, J = 7 Hz, 3H); 0.96 (d, J = 1.5 Hz, 3H); 0.95 (d, J = 1 Hz, 3H); 0.84 (d, J = 6.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 140.07, 135.18, 82.90, 31.78, 26.95, 23.53, 23.46, 20.79, 20.09, 18.30, 15.43.

IR (thin film NaCl): 3395, 2960, 2871, 1467, 1378, 1363, 1293, 1248, 1169, 1131, 1102, 1070, 1018. HRMS (ESI) m/z 170.166 [(M + Na)⁺; calcd for C₁₁H₂₂O: 170.167].

(*E*)-tert-Butyl-(3-ethyl-1-hexyl-5-methyl-hex-3-enyloxy)-dimethyl-silane (3g): RhCl(PPh₃)₃ (14 mg, 0.015 mmol) and a solution of **2j** (50 mg, 0.15 mmol) in toluene (1 mL) were added to a reaction vessel and the vessel was charged with H₂ (3 atm). After 16 h, the solution was condensed and then purified via flash chromatography on silica gel (hexanes) to provide the title compound as a clear oil (47 mg, 94% yield). *R*_f = 0.17 (hexanes). ¹H NMR (500 MHz, CDCl₃) δ 4.93 (d, *J* = 9 Hz, 1H); 3.72 (quin., *J* = 6 Hz, 1H); 2.48 – 2.55 (m, 1H); 2.15 (ddd, *J* = 14, 6.5, 1 Hz, 1H); 1.95 – 2.10 (m, 3H); 1.24 – 1.45 (m, 10 H); 0.97 (t, *J* = 8 Hz, 3H); 0.94 (d, *J* = 6.5 Hz, 3H); 0.93 (d, *J* = 6.5 Hz, 3H); 0.89 (t, *J* = 7 Hz, 3H); 0.89 (s, 9H); 0.04 (s, 3H); 0.04 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 136.03, 135.19, 71.61, 44.66, 36.98, 32.10, 29.94, 29.69, 27.07, 26.16, 25.41, 23.76, 23.68, 23.65, 22.86, 18.37, 14.34, 13.90, -4.15, -4.29. IR (thin film NaCl): 2958, 2858, 2709, 1740, 1662, 1465, 1406, 1376, 1361, 1255, 1190, 1093, 1005. HRMS (ESI) *m/z* 363.3051 [(M + Na)⁺; calcd for C₂₁H₄₄OSi: 363.3054]. [α]_D = -0.4 (*c* 1.0, CHCl₃).

(*E*)-tert-Butyl-(1-hexyl-3-isopropyl-hex-3-enyloxy)-dimethyl-silane (3h): Using the standard procedure, RhCl(PPh₃)₃ (6 mg, 6.5 μmol) and **2k** (46 mg, 0.14 mmol) after 2.5 h provided the title compound as a clear oil (39 mg, 85% yield). *R*_f = 0.18 (hexanes). ¹H NMR (500 MHz, CDCl₃) δ 5.07 (t, *J* = 7 Hz, 1H); 3.76 – 3.81 (m, 1H); 2.78 (sept., *J* = 7 Hz, 1H); 2.14 (dd, *J* = 14, 5 Hz, 1H); 1.95 – 2.08 (m, 3H); 1.24 – 1.56 (m, 10 H); 0.94 – 0.99 (m, 9H); 0.87 – 0.92 (m, 12H); 0.06 (s, 3H); 0.05 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 140.54, 128.42, 72.09, 40.62, 36.89, 32.13, 29.69, 29.15, 26.19, 25.51, 22.88, 21.85, 21.34, 20.88, 18.37, 14.92, 14.35, -3.92, -4.17. IR (thin film NaCl): 2960, 2858, 1653, 1463, 1406, 1378, 1361, 1306, 1254, 1092, 1065, 1005. HRMS (ESI) *m/z* 363.305 [(M + Na)⁺; calcd for C₂₁H₄₄OSi: 363.305]. [α]_D = -1.3 (*c* 1.0, CHCl₃).

Reductive coupling of 2-methyl-3-hexyne with isobutyraldehyde (3f + 3d): In a glovebox, Ni(cod)₂ (14 mg, 0.5 mmol), and tricyclopentylphosphine (28 μL, 0.1 mmol) were placed into a 25 mL oven-dried, single-necked round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox and placed under argon, and ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et₃B (0.15 mL, 1 mmol). The resulting solution was stirred at ambient temperature for 5 minutes and then cooled to 0 °C. Once the solution had cooled, isobutyraldehyde (90 μL, 1.0 mmol) was added dropwise via microsyringe. After stirring for 5 min, 2-methyl-3-hexyne (48 mg, 0.5 mmol) was added. The reaction was allowed to gradually warm to 23 °C over 6 h. The septa was then removed, and the reaction was opened to air for 30 min to promote quenching of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (hexanes: ethyl acetate; 50:1 to

10:1) to afford a clear oil (64 mg, 75% yield) that was a 1.7:1 mixture of regioisomers **3f** and **3d**, respectively,

Reductive coupling of 2-methyl-3-hexyne with 1,2-epoxyoctane (3g** + **3h**):** To Ni(cod)₂ (55.8 mg, 0.20 mmol) at 23 °C were added PBu₃ (100 μL, 0.40 mmol), Et₃B (610 μL, 4.21 mmol), 1,2-epoxyoctane (380 μL, 2.49 mmol), and 2-methyl-3-hexyne (200 mg, 2.08 mmol). The brownish solution was stirred at 23 °C for 16 h. Et₂O (4 mL) was added, and the resulting solution was quenched with 2M aqueous NaOH (4 mL) and 30% aqueous H₂O₂ (drops). The resulting biphasic solution was vigorously stirred for 5 min. The layers were separated and the organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (0-10% EtOAc/Hex) and protected as the TBS ether [TBSCl (395 mg, 2.62 mmol), imidazole (304 mg, 4.46 mmol), THF (10 mL), DMF (5 mL)] to afford a colorless liquid (344 mg, 49%) that was a 2:1 mixture of regioisomers **3g** and **3h**, respectively.

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2f

2i

2k

2k