Nickel-Catalyzed Reductive Coupling of Alkynes and Epoxides

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Supporting Information

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran and ether were distilled from a blue solution of sodium benzophenone ketyl. Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was accomplished with UV light and aqueous cerium molybdate, ethanolic phosphomolybdic acid, or aqueous potassium permanganate. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh).¹ ¹H and ¹³C NMR spectra were recorded in deuteriochloroform (CDCl₃), unless otherwise noted, on a Varian Unity 300, Varian Mercury 300, Bruker Avance 400 or Varian Inova 500 MHz. Chemical shifts of ¹H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ¹³C NMR spectra are reported in ppm from the central peak of CDCl₃ (77.0 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR System transform spectrometer. High Resolution mass spectra (HMRS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by the Massachusetts Institute of Technology Mass Spectrometry Laboratory. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm. Data are reported as follows : $[\alpha]_{\lambda}^{\text{temp}}$, concentration (c g/100 mL), and solvent. R.t.= ambient temperature.

¹ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

Standard Procedure :

(+) (4E)-4-Methyl-5-phenylpent-4-en-2-ol (1a) : To Ni(cod)₂ (137 mg, 0.50 mmol) at r.t. were added PBu₃ (250 μ L, 1.00 mmol), Et₃B (300 μ L, 2.07 mmol), (*R*)-propylene oxide (700 μ L, 9.99 mmol), 3-phenyl-1-propyne (630 μ L, 5.02 mmol) and additional Et₃B (1.20 mL, 8.28 mmol) *via* syringe pump over 4 hours. The brownish solution was stirred at r.t. for 24 hours. EtOAc (2.5 mL) was added and the resulting solution was quenched with 2M aqueous NaOH (2.5 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 washed with saturated aqueous NaHCO₃, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (0-20% EtOAc/Hex) to afford the title compound (0.63 g, 71%) as a white solid: *R*_f 0.24 (20% EtOAc/Hex); [α]_D = + 1.9 (*c* 1.9, EtOH) [lit.²: [α]_D = + 3 (*c* 1, EtOH)]; ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.21 (m, 5H), 6.39 (s, 1H), 4.09-4.01 (m, 1H), 2.36-2.34 (m, 2H), 2.20 (s, 1H), 1.95 (s, 3H), 1.31 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 137.7, 135.5, 128.7, 127.94, 127.91, 126.1, 65.3, 50.6, 22.8, 17.8; IR (film) 3374, 3081, 3056, 3023, 2966, 2926, 1946, 1884, 1806, 1721, 1650, 1599, 1490, 1445, 1374, 1314, 1269, 1118, 1073, 1022, 940, 918, 815, 744, 699 cm⁻¹; HRMS EI (*m/z*): [*M*]⁺ calcd for C₁₂H₁₆O, 176.1196; found 176.1202. The enantiomeric ratio was determined by HPLC (chiralcel-OD : 0.5% *i*PrOH/hexanes) *t*_R (minor) 39.7 min, *t*_R (major) 42.4 min.

² Fuganti, C.; Grasselli, P.; Spreafico, F.; Zirotti, C.; Casati, P. *J. Org. Chem.* **1984**, *49*, 543-546.

(1E)-2-Methyl-1-phenyldec-1-en-4-ol (1b) : The reductive coupling was performed according to the previously described procedure using Ni(cod)₂ (134 mg, 0.50 mmol), PBu₃ (250 μL, 1.00 mmol), Et₃B (1.44 mL, 10.01 mmol), 1,2-epoxyoctane (1.50 mL, 9.81 mmol), and 3-phenyl-1-propyne (630 μL, 5.02 mmol). The residue was purified by flash chromatography on silica gel (0-5% EtOAc/Hex) to afford the title compound (0.83 g, 68%) as a colorless liquid: R_f 0.48 (20% EtOAc/Hex); ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.22 (m, 5H), 6.40 (s, 1H), 3.87-3.81 (m, 1H), 2.40 (dd, *J* = 13.3, 3.5 Hz, 1H), 2.25 (dd, *J* = 13.5, 9.2 Hz, 1H), 1.94 (s, 3H), 1.81 (s, 1H), 1.58-1.26 (m, 10H), 0.94-0.89 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 137.6, 135.6, 128.7, 128.07, 128.02, 127.9, 126.1, 69.0, 49.1, 37.2, 31.9, 29.5, 25.8, 22.7, 18.1, 14.2; IR (film) 3387, 3081, 3056, 3024, 1710, 1651, 1599, 1491, 1443, 1379, 1125, 1074, 1055, 1028, 916, 829, 744, 699 cm⁻¹; HRMS ESI (*m/z*): [M+Na]⁺ calcd for C₁₇H₂₆ONa, 269.1876; found 269.1883.

(1E)-4-tert-Butyldiphenylsilyloxy-2-phenylpent-1-enylbenzene and (1E)-4-tert-Butyldiphenylsilyloxy-2-phenyl-3-methylbut-1-enylbenzene (1c) : The reductive coupling was performed according to the previously described procedure using Ni(cod)₂ (142 mg, 0.51 mmol), PBu₃ (250 μL, 1.00 mmol), Et₃B (1.50 mL, 10.36 mmol), styrene oxide (1.20 mL, 10.52 mmol), and 3-phenyl-1-propyne (630 μL, 5.02 mmol). The residue was purified by flash chromatography on neutral alumina (50% Et₂O/Hex) and protected as the TBDPS ether to afford the title compound (1.19 g, 50%) as a yellow viscous oil: R_f 0.54 (10% EtOAc/Hex); ¹H NMR (400 MHz, CDCl₃) δ 7.89-7.07 (m, 52H), 5.87 (s, 1H), 5.68 (d, *J* = 2.8 Hz, 0.3 H), 5.37 (q, *J* = 6.7 Hz, 0.2H), 5.01-4.93 (m, 1.3H), 4.67 (dd, *J* = 8.0, 5.6 Hz, 0.1H), 4.57-4.51 (m, 0.3H), 4.41 (dd, *J* = 9.8, 8.6 Hz, 0.2H), 4.05-3.97 (m, 0.6H), 3.72-3.59 (m, 0.7H), 3.16-3.10 (m, 0.1H), 3.00 (dd, *J* = 13.0, 6.5 Hz, 0.4H), 2.85 (d, *J* = 6.6Hz, 0.2H), 2.77 (dd, *J* = 12.4, 6.0 Hz, 1H), 5.53 (dd, *J* = 12.6, 6.8 Hz, 1H), 2.32 (s, 0.4H), 1.60 (s, 3H), 1.25 -0.99 (m, 28H); ¹³C NMR (100 MHz, CDCl₃) δ 144.5, 138.3, 135.9, 135.8, 135.5, 134.7, 129.6, 129.5, 129.4, 128.6, 127.8, 127.7, 127.58, 127.54,

127.50, 127.3, 106.0, 75.0, 74.2, 71.8, 65.1, 53.5, 54.3, 51.9, 27.1, 27.0, 26.9, 26.8, 26.5, 19.3, 19.2, 19.0, 18.2, 9.0; IR (film) 3070, 3050, 3028, 2998, 2958, 2931, 2892, 2857, 1959, 1890, 1823, 1600, 1589, 1492, 1472, 1462, 1453, 1428, 1390, 1361, 1111, 1067, 1028, 938, 822, 740, 700, 613, 504 cm^{-1} ; HRMS ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{33}\text{H}_{36}\text{OSiNa}$, 499.2428; found 499.2422.

(4E)-7-tert-Butyldiphenylsilyloxy-5-propyloct-4-ene (1d) :

The reductive coupling was performed according to the previously described procedure using $\text{Ni}(\text{cod})_2$ (149 mg, 0.54 mmol), PBU_3 (250 μL , 1.00 mmol), Et_3B (1.50 mL, 10.36 mmol), 1,2-epoxybutane (860 μL , 9.98 mmol), and 4-octyne (730 μL , 4.97 mmol). The residue was purified by flash chromatography on silica gel (10% EtOAc/Hex) and protected as the TBDPS ether to afford the title compound (0.73 g, 35%) as a yellow liquid : R_f 0.90 (10% EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 7.76-7.73 (m, 4H), 7.48-7.39 (m, 6H), 5.11 (t, $J = 7.1$ Hz, 1H); 3.85-3.79 (m, 1H), 2.19-2.10 (m, 2H), 1.93 (q, $J = 7.3$ Hz, 2H), 1.85-1.78 (m, 1H), 1.65-1.49 (m, 2H), 1.46-1.37 (m, 2H), 1.34 (q, $J = 7.4$ Hz, 2H), 1.10 (s, 9H), 0.91 (q, $J = 7.3$ Hz, 6H), 0.76 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.3, 135.97, 135.94, 134.6, 129.40, 129.34, 127.86, 127.41, 127.35, 72.8, 43.9, 31.9, 29.8, 28.2, 27.0, 23.0, 21.4, 19.4, 14.1, 13.9, 8.9; IR (film) 3071, 3050, 2959, 2931, 2859, 1957, 1888, 1823, 1590, 1472, 1463, 1427, 1389, 1378, 1361, 1111, 1037, 1006, 821, 738, 702, 612 cm^{-1} ; HRMS ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{28}\text{H}_{42}\text{OSiNa}$, 445.2897; found 445.2907.

(3E)-3-Benzylidenecyclohexanol (3a) :

To $\text{Ni}(\text{cod})_2$ (5 mg, 0.18 mmol) at r.t. were added PBU_3 (1 M in toluene, 20 μL , 0.19 mmol), Et_3B (2 M in toluene, 110 μL , 0.22 mmol), and 2-(5-phenylpent-4-ynyl)oxirane (20 mg, 0.10 mmol). The brownish solution was stirred at r.t. for 3 hours. Et_2O (1 mL) was added and the resulting solution was quenched with 2M aqueous NaOH (0.5 mL) and 30% aqueous H_2O_2 (drop). The resulting biphasic solution was vigorously stirred for 5 min. The layers were separated and the organic phase was washed with saturated aqueous NaHCO_3 , dried over NaSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography

on silica gel (10% EtOAc/Hex) to afford the title compound (9 mg, 45%) as a white solid: R_f 0.25 (15% EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.32 (m, 2H), 7.24-7.21 (m, 3H), 6.34 (s, 1H), 3.87 (sept, $J = 4.1$ Hz, 1H), 2.64 (dd, $J = 12.8, 4.0$ Hz, 1H), 2.55 (dt, $J = 13.5, 5.2$ Hz, 1H), 2.27 (dd, $J = 12.7, 8.4$ Hz, 1H), 2.20-2.13 (m, 1H), 1.99-1.94 (m, 1H), 1.83-1.76 (m, 1H), 1.67 (s, 1H), 1.63-1.53 (m, 2H), 1.47-1.37 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.2, 137.8, 128.9, 128.1, 126.1, 125.0, 70.4, 46.0, 34.7, 28.3, 23.5; IR (film) 3350, 3081, 3056, 3023, 2927, 2857, 1947, 1883, 1808, 1651, 1598, 1491, 1447, 1353, 1051, 959, 742, 698 cm^{-1} ; HRMS EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{13}\text{H}_{16}\text{O}$, 188.1196; found 188.1192.

(5Z)-5-Benzylidenetetrahydro-2H-pyran-3-ol (3b) : The reductive coupling was performed according to the previously described procedure using $\text{Ni}(\text{cod})_2$ (12 mg, 0.04 mmol), PBU_3 (1 M in ether, 90 μL , 0.09 mmol), Et_3B (130 μL , 0.90 mmol), 2-[(3-phenylprop-2-ynyl)oxy]methyl}oxirane (83 mg, 0.44 mmol) in ether (900 μL). The residue was purified by flash chromatography on silica gel (2% EtOAc/ 2% Et_3N /96% Hex) to afford the title compound (42 mg, 50%) as a yellow liquid : R_f 0.29 (20% EtOAc/Hex). The product was characterized as its TBDPS protected ether.

(5Z)-3-tert-Butyldiphenylsilyloxy-5-benzylidenetetrahydro-2H-pyran : R_f 0.44 (15% EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 7.75-7.69 (m, 5H), 7.51-7.39 (m, 6H), 7.35-7.21 (m, 4H), 7.10 (d, $J = 7.3$ Hz, 2H), 6.28 (s, 1H), 4.49 (d, $J = 12.6$ Hz, 1H), 4.01 (d, $J = 12.9$ Hz, 1H), 3.91 (sept, $J = 4.3$ Hz, 1H), 3.81 (ddd, $J = 10.8, 4.3, 1.5$ Hz, 1H), 3.41 (dd, $J = 10.9, 8.4$ Hz, 1H), 2.62 (dd, $J = 13.2, 4.3$ Hz, 1H), 2.44 (ddd, $J = 13.1, 9.1, 1.8$ Hz, 1H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.6, 135.7, 135.6, 134.8, 134.0, 133.8, 129.7, 128.8, 127.7, 127.6, 126.6, 126.5, 72.6, 68.7, 66.6, 42.8, 26.9, 19.2; IR (film) 3071, 3052, 3025, 2960, 2932, 2894, 2858, 2247, 1960, 1891, 1824, 1724, 1660, 1599, 1589, 1489, 1472, 1462, 1446, 1428, 1380, 1362, 1248, 1110, 1081, 909, 822, 736, 700 cm^{-1} ; HRMS ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{28}\text{H}_{32}\text{O}_2\text{SiNa}$, 451.2064; found 451.2047.

(5Z)-1-Benzyl-5-benzylidenepiperidin-3-ol (3c) : The reductive coupling was performed according to the previously described procedure using $\text{Ni}(\text{cod})_2$ (26 mg, 0.09 mmol), PBU_3 (40 μL , 0.16 mmol), Et_3B (230 μL , 1.59 mmol), *N*-benzyl-*N*-(oxiran-2-ylmethyl)-*N*-(3-phenylprop-2-ynyl)amine (176 mg, 0.64 mmol) in ether (2.5 mL). The residue was purified by flash chromatography on silica gel (4% Et_3N / 45% Hex/ 51% EtOAc) to afford the title compound (115 mg, 65%) as a yellow liquid : R_f 0.36 (50% EtOAc/Hex); ^1H NMR (400 MHz, C_6D_6) δ 7.27-7.09 (m, 10H), 6.45 (s, 1H), 3.89 (s(br), 1H), 3.46 (d, J = 12.1 Hz, 1H), 3.31 (q, J = 13.0 Hz, 2H), 2.85 (d, J = 12.1 Hz, 1H), 2.63 (dd, J = 11.1, 5.3 Hz, 1H), 2.54 (s(br), 1H), 2.45-2.35 (m, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.7, 137.9, 135.6, 129.8, 129.6, 128.8, 128.7, 127.7, 127.5, 127.0, 67.2, 63.0, 60.9, 54.6, 44.0, 24.6, 19.5, 14.1; IR (film) 3383, 3082, 3060, 3026, 2940, 2796, 2751, 2279, 2268, 1950, 1886, 1811, 1763, 1722, 1661, 1599, 1575, 1494, 1453, 1393, 1330, 1300, 1275, 1118, 1061, 1048, 1029, 995, 970, 919, 899, 882, 848, 813, 745, 698, 618 cm^{-1} ; HRMS ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{21}\text{NO}$, 280.1701; found 280.1705.

Dimethyl (3E)-3-benzylidene-5-hydroxycyclohexane-1,1-dicarboxylate and Methyl (3Z)-3-benzylidene-7-oxo-6-oxabicyclo[3.2.1]octane-1-carboxylate (3d) :

The reductive coupling was performed according to the previously described procedure using $\text{Ni}(\text{cod})_2$ (5 mg, 0.02 mmol), PBU_3 (1 M in ether, 30 μL , 0.03 mmol), Et_3B (50 μL , 0.34 mmol), dimethyl (oxiran-2-ylmethyl)(3-phenylprop-2-ynyl)malonate (46 mg, 0.15 mmol) in ether (600 μL). The residue was purified by flash chromatography on silica gel (20% EtOAc/Hex) to afford the title compounds in an inseparable mixture of the alcohol and the lactone (3 : 1 ratio) (40 mg, 88%) as a yellow liquid : R_f 0.13 (30% EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.07 (m, 20H), 6.46 (s, 3H), 6.38 (s, 1H), 4.18-4.07 (m, 4H), 3.77 (d, J = 14.4 Hz, 1H), 3.49 (d, J = 13.9 Hz, 3H), 3.35 (s, 3H), 3.28 (s, 9H), 3.23 (s, 9H), 2.81 (dd, J = 13.8, 1.4 Hz, 3H), 2.73 (dd, J = 13.1, 4.3 Hz, 3H), 2.68-2.62 (m, 1H), 2.48 (dd, J = 12.9, 4.3 Hz, 3H), 2.39-2.32 (m, 1H), 2.20 (ddd, J = 12.9, 9.3, 1.5 Hz, 3H), 2.02 (dd, J = 13.1, 9.1 Hz,

3H), 1.85 (d, $J = 15.4$ Hz, 1H), 1.79 (s(br), 3H), 1.39 (d, $J = 11.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.5, 171.3, 137.6, 133.6, 132.9, 129.8, 129.3, 129.0, 128.8, 128.5, 127.5, 126.9, 75.9, 69.6, 55.9, 53.4, 53.3, 52.9, 45.1, 41.0, 39.3, 34.8, 33.5; IR (film) 3469, 3023, 2955, 2847, 1786, 1732, 1493, 1436, 1310, 1254, 1217, 1165, 1096, 1066, 1029, 755, 700, 668 cm^{-1} ; HRMS ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{20}\text{O}_5\text{Na}$ (alcohol), 327.1203; found 327.1205; HRMS ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{16}\text{O}_4\text{Na}$ (lactone), 295.0941; found 295.0946.

(3E)-3-Benzylidenecyclopentanol (3e) : The reductive coupling was performed according to the previously described procedure using $\text{Ni}(\text{cod})_2$ (7 mg, 0.02 mmol), PBU_3 (1 M in ether, 40 μL , 0.04 mmol), Et_3B (60 μL , 0.41 mmol), 2-(4-phenylbut-3-ynyl)oxirane (34 mg, 0.20 mmol) in ether (250 μL). The residue was purified by flash chromatography on silica gel (20% EtOAc/Hex) to afford the title compound (18 mg, 54%) as a white solid: R_f 0.54 (10% EtOAc/Hex); R_f 0.20 (20% EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.30 (m, 3H), 7.24-7.16 (m, 2H), 6.43-6.41 (m, 1H), 4.45-4.40 (m, 1H), 2.85-2.80 (m, 1H), 2.79-2.76 (m, 1H), 2.69-2.60 (m, 1H), 2.54 (two m, 1H), 2.05-1.87 (m, 2H), 1.48 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.3, 138.3, 128.2, 128.0, 125.9, 122.8, 71.9, 45.0, 35.6, 28.2; IR (film) 3295, 3091, 3022, 2941, 1705, 1654, 1595, 1572, 1490, 1445, 1417, 1338, 1298, 1239, 1075, 1041, 1018, 959, 791, 753, 693 cm^{-1} ; HRMS EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{O}$, 174.1039; found 174.1039.

[(1E, 4R)-4-(tert-Butyldiphenylsilyloxy)-2-methylpent-1-enyl]benzene :

To a stirred solution of (4E)-4-methyl-5-phenylpent-4-en-2-ol (0.20 g, 1.13 mmol) in anh. DMF (1 mL) and THF (4 mL) at r.t., is added imidazole (0.23 g, 3.38 mmol) and TBDPSCl (0.35 mL, 1.34 mmol). The reaction mixture is stirred for 16 h. The resulting solution is diluted with ether and aqueous NH_4Cl and extracted. The organic layer is washed with saturated aqueous NaHCO_3 , dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (100% Hex) to afford the title compound (455 mg, 97%) as a colorless liquid: R_f 0.75 (20% EtOAc/Hex); $[\alpha]_D = +36.9$ (c 2.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.74-7.70 (m, 4H), 7.46-7.28 (m, 11H), 7.21-7.17 (m, 3H), 6.25 (s, 1H), 4.13-4.01 (m, 1H), 2.40 (dd, $J = 13.8, 5.8$ Hz, 1H), 2.24 (dd, $J = 13.0, 6.8$ Hz, 1H), 1.64 (d, $J = 1.2$ Hz, 3H), 1.13 (d, $J = 6.1$ Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.3, 136.0, 135.9, 134.6, 134.3, 129.49, 129.45, 128.7, 127.9, 127.48, 127.43, 125.8, 68.2, 51.1, 27.0, 23.2, 19.2, 18.0; IR (film) 3071, 3024, 2964, 2931, 2894, 2857, 1959, 1889, 1824, 1651, 1599, 1589, 1488, 1472, 1462, 1446, 1427, 1390, 1376, 1361, 1111, 1084, 1027, 997, 910, 822, 739, 700, 613 cm^{-1} ; HRMS ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{28}\text{H}_{34}\text{OSiNa}$, 437.2271; found 437.2269.

(4R)-4-(tert-Butyldiphenylsilyloxy)pentan-2-one (4) :

Ozone is bubbled for 5 min. into a stirred solution of [(1E, 4R)-4-(tert-butyldiphenylsilyloxy)-2-methylpent-1-enyl]benzene (86 mg, 0.21 mmol) in anh. CH_2Cl_2 (4 mL) at -78°C . DMS (0.7 mL) is then added and allowed to warm to r.t. The resulting solution is concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (0-5% Et_2O /Hex) to afford the title compound (53 mg, 78%) as a colorless liquid:³ R_f 0.50 (20% EtOAc/Hex); $[\alpha]_D = -5.0$ (c 0.40, CHCl_3) [lit.³ $>97\%$ ee : $[\alpha]_D = -3.2$ (c 0.53, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.73-7.68 (m, 5H), 7.47-7.38 (m, 8H), 4.37-4.28 (m, 1H), 2.66 (dd, $J = 15.2, 5.9$ Hz, 1H), 2.24 (dd, $J = 15.2, 6.3$ Hz, 1H), 2.08 (s, 3H), 1.11 (d, $J = 6.1$ Hz, 3H), 1.05 (s, 9H).

³ Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1997**, 62, 2678-2679.

Preparation of Starting Materials

6-Phenylhex-5-yn-1-ol : To a stirred solution of CuI (63 mg, 0.33 mmol), Pd(PPh₃)₄ (213 mg, 0.18 mmol) in Et₃N (40 mL) at r.t., is added iodobenzene (1.85 mL, 16.5 mmol). The reaction mixture is stirred at r.t. for 30 min. Hex-5-yn-1-ol (2.0 mL, 18.1 mmol) is then added and the mixture is stirred for an additional 18 h at 60 °C. The resulting solution is diluted with ether, filtered over celite and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (5-10% EtOAc/Hex) to afford the title compound (1.92 g, 67%) as a light yellow liquid: *R_f* 0.18 (20% EtOAc/Hex); ¹H NMR (400 MHz, CDCl₃) δ 7.44-7.42 (m, 2H), 7.33-7.26 (m, 3H), 3.68 (t, *J* = 6.2 Hz, 2H), 2.89 (s(br), 1H), 2.45 (t, *J* = 6.7 Hz, 2H), 1.78-1.64 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 131.3, 128.0, 127.4, 123.7, 89.8, 80.7, 61.9, 31.6, 24.8, 19.0; IR (film) 3335, 2940, 2865, 1598, 1490, 1441, 1068, 756, 692 cm⁻¹; HRMS ESI (*m* / *z*): [M+Na]⁺ calcd for C₁₂H₁₄ONa, 197.0937; found 197.0943.

2-[(3-Phenylprop-2-ynyl)oxy]methyl}oxirane (2b): To a vigorously stirred solution of 50% w/w aqueous sodium hydroxide (3 mL), epichlorohydrin (1.50 mL, 19.2 mmol) and tetrabutylammonium hydrogen sulfate (133 mg, 0.4 mmol) at 0 °C, was slowly added propargyl alcohol (0.529 g, 4.0 mmol). The aqueous phase is extracted with ether and the organic phase is washed with brine to neutrality, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is ozonolyzed and purified by flash chromatography on silica gel (0-10% EtOAc/Hex) to afford the title compound (0.54 g, 71%) as a colorless liquid: *R_f* 0.26 (20% EtOAc/Hex); ¹H NMR (400 MHz, CDCl₃) δ 7.47-7.45 (m, 2H), 7.33-7.31 (m, 3H), 4.48 (d, *J* = 15.0 Hz, 1H), 4.43 (d, *J* = 15.0 Hz, 1H), 3.90 (dd, *J* = 11.1, 3.0 Hz, 1H), 3.56 (dd, *J* = 11.2, 5.9 Hz, 1H), 3.24-3.20 (m, 1H), 2.83 (t, *J* = 4.5 Hz, 1H), 2.67 (dd, *J* = 4.9, 2.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 131.6, 128.4, 128.2, 122.3, 86.5, 84.5, 70.3, 59.1, 50.5, 44.2; IR (film) 3056, 2999, 2919, 2901, 2852, 2238, 1598, 1571, 1490, 1442, 1381, 1360, 1257, 1160, 1095, 964, 897, 857, 758, 693 cm⁻¹; HRMS ESI (*m* / *z*): [M+Na]⁺ calcd for C₁₂H₁₂O₂Na, 211.0730; found 211.0735.

***N*-Benzyl-*N*-prop-2-ynylamine** : To benzylamine (15.0 mL, 201.3 mmol) at r.t. is added dropwise over a period of 30 min propargyl bromide (3.0 mL, 33.6 mmol). The resulting solution is stirred for an additional 18 h and diluted with ether and water. The solution is extracted, washed with saturated aqueous NaHCO₃, dried over K₂CO₃, filtered and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (0-10% EtOAc/Hex) to afford the title compound (3.08 g, 63%) as a colorless liquid: *R*_f 0.51 (50% EtOAc/Hex); ¹H NMR (400 MHz, CDCl₃) δ 7.39-7.27 (m, 5H), 3.91 (s, 2H), 3.46 (d, *J* = 2.3 Hz, 2H), 2.28 (t, *J* = 2.5 Hz, 1H), 1.55 (s(br), 1H); ¹³C NMR (100 MHz, CDCl₃) δ 139.1, 128.1, 126.8, 81.9, 71.4, 51.9, 36.9; IR (film) 3292, 3086, 3063, 3028, 2915, 2840, 1640, 1495, 1454, 1361, 1330, 1106, 1028, 907, 738, 699, 645 cm⁻¹; HRMS ESI (*m/z*): [M+H]⁺ calcd for C₁₀H₁₂N, 146.0964; found 146.0960.

***N*-Benzyl-*N*-(3-phenylprop-2-ynyl)amine** : To a stirred solution of CuI (120 mg, 0.63 mmol), Pd(PPh₃)₄ (105 mg, 0.09 mmol) in Et₃N (15 mL) at r.t., is added iodobenzene (0.79 mL, 7.0 mmol). The reaction mixture is stirred at r.t. for 30 min. *N*-Benzyl-*N*-prop-2-ynylamine (1.026 g, 7.1 mmol) is then added and the mixture is stirred for an additional 18 h at 65 °C. The resulting solution is diluted with ether, filtered over celite and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (5-10% EtOAc/Hex) to afford the title compound (0.74 g, 47%) as a light yellow liquid: *R*_f 0.47 (50% EtOAc/Hex); ¹H NMR (400 MHz, CDCl₃) δ 7.48-7.28 (m, 10H), 3.98 (s, 2H), 3.68 (s, 2H), 1.62 (s(br), 1H); ¹³C NMR (100 MHz, CDCl₃) δ 139.4, 131.5, 128.3, 128.1, 127.9, 127.0, 123.0, 87.4, 83.5, 52.3, 38.0; IR (film) 3321, 3061, 3028, 2912, 2836, 1951, 1881, 1787, 1673, 1598, 1489, 1453, 1359, 1328, 1253, 1103, 1071, 1028, 913, 756, 739, 692 cm⁻¹; HRMS ESI (*m/z*): [M+H]⁺ calcd for C₆H₁₆N, 222.1277; found 222.1277.

***N*-Benzyl-*N*-(oxiran-2-ylmethyl)-*N*-(3-phenylprop-2-ynyl)amine (2c)** : A stirred solution *N*-benzyl-*N*-(3-phenylprop-2-ynyl)amine (0.381 g, 1.72 mmol), epichlorohydrin (0.40 mL, 5.11 mmol) and K₂CO₃ (1.01 g, 7.31 mmol) is stirred at r.t. for 18 h. The reaction mixture is diluted with ether, filtered over celite and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (5-10% EtOAc/Hex) to afford the title compound (0.15 g, 39%) as a colorless liquid: *R*_f 0.47 (50% EtOAc/Hex); ¹H NMR (400 MHz, CDCl₃) δ 7.48-7.28 (m, 10H), 3.98 (s, 2H), 3.68 (s, 2H), 1.62 (s(br), 1H); ¹³C NMR (100 MHz, CDCl₃) δ 139.4, 131.5, 128.3, 128.1, 127.9, 127.0, 123.0, 87.4, 83.5, 52.3, 38.0; IR (film) 3321, 3061, 3028, 2912, 2836, 1951, 1881, 1787, 1673, 1598, 1489, 1453, 1359, 1328, 1253, 1103, 1071, 1028, 913, 756, 739, 692 cm⁻¹; HRMS ESI (*m/z*): [M+H]⁺ calcd for C₁₈H₂₀N, 260.1507; found 260.1507.

mmol) in anh. acetonitrile were heated at 75 °C for 18 hours. The solution was cooled to r.t., filtered over celite, rinsed with ether and concentrated under reduced pressure. The residue purified by flash chromatography on silica gel (0-5% EtOAc/Hex) to afford the title compound (181 mg, 46%) as a yellow liquid: R_f 0.66 (50% EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 7.49-7.29 (m, 10H), 3.89 (d, J = 13.1 Hz, 1H), 3.76 (d, J = 13.1 Hz, 1H), 3.67 (d, J = 17.3 Hz, 1H), 3.63 (d, J = 17.3 Hz, 1H), 3.20-3.14 (m, 1H), 2.92 (dd, J = 13.6, 4.0 Hz, 1H), 2.81 (dd, J = 4.1, 4.0 Hz, 1H), 2.71 (dd, J = 13.6, 6.2 Hz, 1H), 2.60 (dd, J = 5.0, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.2, 131.5, 129.0, 128.2, 128.1, 127.9, 127.1, 123.0, 85.7, 84.0, 58.1, 55.8, 50.8, 45.0, 43.1; IR (film) 3060, 3030, 2993, 2922, 2836, 2806, 1953, 1881, 1811, 1720, 1704, 1678, 1599, 1490, 1453, 1442, 1371, 1327, 1254, 1121, 1070, 1020, 971, 948, 921, 857, 837, 757, 741, 692 cm^{-1} ; HRMS ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{NONa}$, 300.1359; found 300.1366.

Dimethyl (oxiran-2-ylmethyl)(3-phenylprop-2-ynyl)malonate

(2d) : Was prepared according to literature procedure from dimethyl (oxiran-2-ylmethyl)malonate and (3-bromoprop-1-ynyl)benzene⁴ : R_f 0.22 (20% EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.35

(m, 2H), 7.33-7.27 (m, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.19 (s, 2H), 3.09-3.04 (m, 1H), 2.79 (dd, J = 4.9, 3.9 Hz, 1H), 2.53 (dd, J = 4.9, 3.9 Hz, 1H), 2.51 (dd, J = 14.8, 4.7 Hz, 1H), 2.20 (dd, J = 14.6, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.2, 170.1, 131.5, 131.4, 128.1, 128.0, 122.8, 83.8, 83.7, 55.9, 52.9, 52.8, 48.2, 46.6, 36.1, 24.6; IR (film) 3054, 2999, 2954, 2254, 1733, 1598, 1572, 1491, 1437, 1325, 1294, 1221, 1156, 1117, 1086, 1049, 1028, 915, 853, 759, 733, 693 cm^{-1} ; HRMS ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{19}\text{O}_5$, 303.1227; found 303.1230.

5-Phenylpent-4-yn-1-ol : To a stirred solution of CuI (107 mg, 0.563 mmol), $\text{Pd}(\text{PPh}_3)_4$ (226 mg, 0.19 mmol) in Et_3N (40 mL) at

r.t., is added iodobenzene (2.20 mL, 19.6 mmol). The reaction mixture is stirred at r.t. for 30 min. Pent-4-yn-1-ol (2.0 mL, 21.5 mmol) is then added and the mixture is stirred for an additional 18 h at 60 °C. The resulting solution is diluted with ether, filtered over

celite and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (0-10% EtOAc/Hex) to afford the title compound (3.02 g, 96%) as a yellow liquid: R_f 0.20 (20% EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 7.44-7.40 (m, 2H), 7.31-7.28 (m, 2H), 3.81 (t, J = 6.2 Hz, 2H), 2.71 (s, 1H), 2.54 (t, J = 6.9 Hz, 2H), 1.87 (qn, J = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 131.9, 128.7, 128.1, 124.1, 89.9, 81.5, 61.9, 31.8, 16.4; IR (film) 3335, 2948, 2879, 1598, 1490, 1442, 1061, 915, 756, 692 cm^{-1} ; HRMS ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{11}\text{H}_{12}\text{ONa}$, 183.0780; found 183.0785.

4-Phenylbut-3-yn-1-ol: To a stirred solution of CuI (210 mg, 1.10 mmol), $\text{Pd}(\text{PPh}_3)_4$ (284 mg, 0.24 mmol) in Et_3N (40 mL) at r.t., is added iodobenzene (2.70 mL, 24.1 mmol). The reaction mixture is stirred at r.t. for 30 min. But-3-yn-1-ol (2.0 mL, 26.4 mmol) is then added and the mixture is stirred for an additional 18 h at 60 °C. The resulting solution is diluted with ether, filtered over celite and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (5% EtOAc/Hex) to afford the title compound (3.15 g, 90%) as a light yellow liquid: R_f 0.24 (20% EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 7.49-7.46 (m, 2H), 7.31-7.29 (m, 3H), 3.82 (q, J = 6.3 Hz, 2H), 3.67 (s, 1H), 2.69 (t, J = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 131.3, 127.9, 127.5, 123.1, 86.5, 81.8, 60.7, 23.3; IR (film) 3347, 3079, 3056, 2942, 2886, 1953, 1883, 1807, 1598, 1490, 1442, 1420, 1046, 756, 692 cm^{-1} ; HRMS ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_{10}\text{ONa}$, 169.0624; found 169.0630.

⁴ Gansauer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849-12859.

-S24-

-S31-