Electronic Supplementary Material (ESI) for ChemComm.

Supplementary Information:

Cu-catalyzed asymmetric allylic alkenylation using alkenylzirconium nucleophiles

Mireia Sidera and Stephen P. Fletcher

Department of Chemistry, Chemistry Research Laboratory, University of Oxford
stephen.fletcher@chem.ox.ac.uk

Contents:

General Information

Procedures using oxygen- and/or moisture-sensitive materials were performed with anhydrous solvents (vide infra) under an atmosphere of anhydrous argon in flame-dried flasks, using standard Schlenk techniques. Analytical thin-layer chromatography was performed on precoated glass-backed plates (Silica Gel 60 F254; Merck), and visualised using a combination of UV light (254 nm) and aqueous ceric ammonium molybdate (CAM), aqueous basic potassium permanganate stains or vanillin solution. Flash column chromatography was carried out using Apollo Scientific silica gel 60 (0.040 – 0.063 nm), Merck 60 Å silica gel, VWR (40-63 µm) silica gel and Sigma Aldrich silica gel. Pressure was applied at the column head via hand bellows or a flow of nitrogen with the solvent system used in parentheses.

Reactions at 0 °C were performed using an ice-water bath, covered with cotton and foil if overnight stirring is needed. Other temperatures were obtained using a Julabo FT902 immersion cooler or the heating plate of the stirrer.

Unless stated otherwise, solution NMR spectra were recorded at room temperature; ^{1}H and ^{13}C NMR experiments were carried out using Bruker AVN-400 (400/100 MHz), DQX-400 (400/100 MHz) or AVC-500 (500/125 MHz) spectrometers. Chemical shifts are reported in ppm from the residual solvent peak. Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Labels H and H' refer to diastereotopic protons attached to the same carbon and impart no stereochemical information. Assignments were made with the assistance of gCOSY, gHSQC and gHMBC or gHMQC NMR spectra.

Chiral HPLC separations were achieved using an Agilent 1230 Infinity series normal phase HPLC unit and HP Chemstation software. Chiralpak® columns (250 × 4.6 mm), fitted with matching Chiralpak® Guard Cartridges (10 × 4 mm), were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Alrich or Rathburn); all eluent systems were isocratic.

The absolute stereochemistry of the products is tentatively assigned by optical rotation and correlation to related products obtained in our previous work.[1]

Chemicals

Dry CH_2Cl_2, THF, Et_2O and toluene were collected fresh from an mBraun SPS-800 solvent purification system having been passed through anhydrous alumina columns. Dry 2-Me-THF was purchased from Acros with an AcroSeal® All other dry solvents used were dried over 3 Å molecular sieves and stored under argon. All other solvents were used as purchased from Sigma Aldrich, Rathburn or Fisher Scientific.
Unless stated otherwise, commercially available reagents were purchased from Sigma-Aldrich, Fisher Scientific, Apollo Scientific, Acros Organics, Strem Chemicals, Alfa Aesar, AK Scientific or TCI UK and were used without purification. Petroleum ether refers to light

petroleum boiling in the range 40–60 °C. Deuterated solvents were purchased from Sigma-Aldrich ($CDCl_3$). Schwartz reagent was prepared according to the literature procedure from Cp_2ZrCl_2 provided by Alfa Aesar or Strem Chemicals.[2] Ligand **L3** was prepared according to a know procedure.[3] (*S*)-4-((dimethyl-*tert*-butyl)silyl)oxy-1-pentyne, (*S*)-**7** was prepared according to the literature.[4] (*R*)-4-((dimethyl-*tert*-butyl)silyl)oxy-1-pentyne, (*R*)-**7** was prepared in an analogous way using (*R*)-propylene oxide in the first step. The enantiomeric purity of both alkynes was determined by derivatising the unprotected alcohol in a benzoate derivative: to a stirred solution of the unprotected alkyne (0.19 mmol) in CH_2Cl_2 (2.0 mL), Et_3N (48µL, 0.27 mmol, 1.40 eq), DMAP (11.6 mg, 0.10, 0.50 eq) and benzoyl chloride (31 µL, 0.27 mmol, 1.40 eq) were added. The resulting mixture was stirred for 6 h at room temperature before adding H_2O (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3x1 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The ee of the crude product was determined by HPLC using a chiral column CHIRALPAK® IC eluting with hexane:iPA (99.4:0.6) at 0.6 mL/min: t_R (major enantiomer) = 12.5 min, no minor enantiomer observed. 3-bromocyclohept-1-ene was prepared according to the literature.[5]

General Methods

Synthesis of racemic products

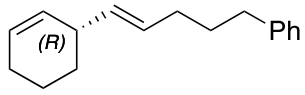
Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkyne (1.0 mmol, 2.5 eq) in CH_2Cl_2 (2.0 mL) under an argon atmosphere. After stirring for 20 to 40 min, CuBr·Me_2S (82 mg, 0.40 mmol 1.0 eq), was added to the resulting clear yellow solution and the resulting black mixture was allowed to stir for an additional 10 min before a cyclic allylbromide (0.40 mmol, 1.0 eq) was added via microsyringe over about 1 min. Stirring at room temperature was continued arbitrarily overnight before the reaction was diluted and quenched by addition of petrol (ca 3 mL) and then NH_4Cl (1M aq., ca 1.5 mL). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Flash column chromatography of the residue (pentane; SiO_2) gave the desired cyclic allylic product. In most cases, Kugelrohr distillation was used to remove excess starting alkene.

General procedure for asymmetric allylic alkenylation

CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand **L3** (22.0 mg, 0.040 mmol, 0.10 eq) were dissolved in the reaction solvent (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. Then the silver salt (0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 minutes. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkyne (1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the hydrozirconation solution. The resulting black mixture was cooled to –40

°C and allowed to stir for an additional 20 minutes before the allyl bromide (0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h at –40 °C before the reaction was quenched by the addition of CH_2Cl_2 (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography (pentane; SiO_2) of the residue afforded the desired product.

***(R,E)*-3-(5-phenylpent-1-en-1-yl)cyclohex-2-ene (*R*)-1**



CuCl (4.0 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*R*,*R*,*R*)-**L3** (22.0 mg, 0.040 mmol, 0.10 eq) were dissolved in CH_2Cl_2 (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. Then AgOTs (12.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 minutes. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 5-phenylpent-1-yne (0.15 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the hydrozirconation solution. The resulting black mixture was cooled to –40 °C and allowed to stir for an additional 20 minutes before the 2-cyclohexenyl bromide (46 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h at –40 °C before the reaction was quenched by the addition of CH_2Cl_2 (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography (hexane; SiO_2) of the residue afforded the desired product (*R,E*)-3-(5-phenylpent-1-en-1-yl)cyclohex-2-ene in 94% yield (85.0 mg, 0.37 mmol).

Enantiomeric ratio of 81:19 was determined by HPLC using a chiral column CHIRALPAK® IA eluting with hexane at 0.2 mL/min: t_R (major enantiomer) = 22.6 min, t_R (minor enantiomer) = 23.8 min.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 5.75 - 5.68 (m, 1 H), 5.57 (d, *J* = 2.5 Hz, 1 H), 5.43 - 5.39 (m, 2 H), 3.80 (m, 1 H), 2.22 - 2.13 (m, 2 H), 2.09 (m, 1 H), 2.02 - 1.94 (m, 2 H), 1.82 - 1.75 (m, 1 H), 1.70 (m, 1 H), 1.59 - 1.49 (m, 1 H), 1.43 - 1.34 (m, 1 H), 1.12 (d, *J* = 6.1 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

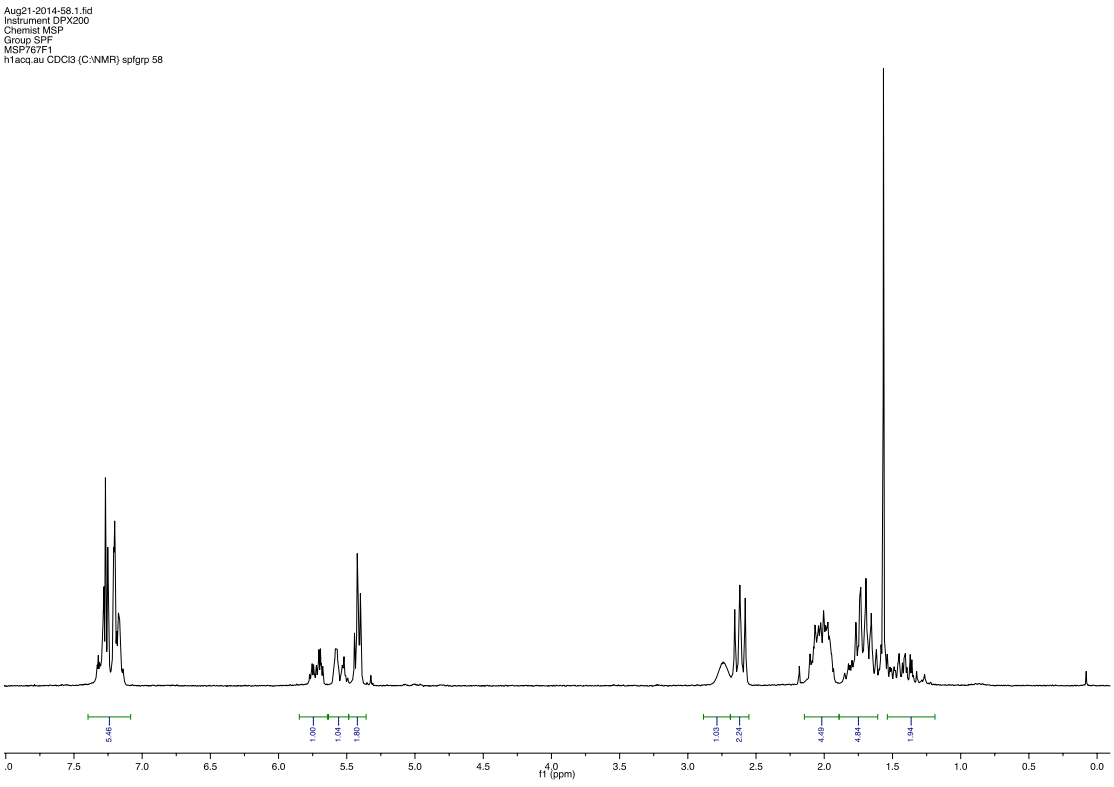
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 142.7, 134.8, 130.4, 129.2, 128.5 (2C), 128.3 (2C), 127.4, 125.6, 38.4, 35.4, 32.1, 31.3, 29.5, 25.1, 20.6.

HRMS (EI) *m/z* calcd for $C_{17}H_{22}Na$ $[M+Na]^+$: 249.1619, found: 249.1621.

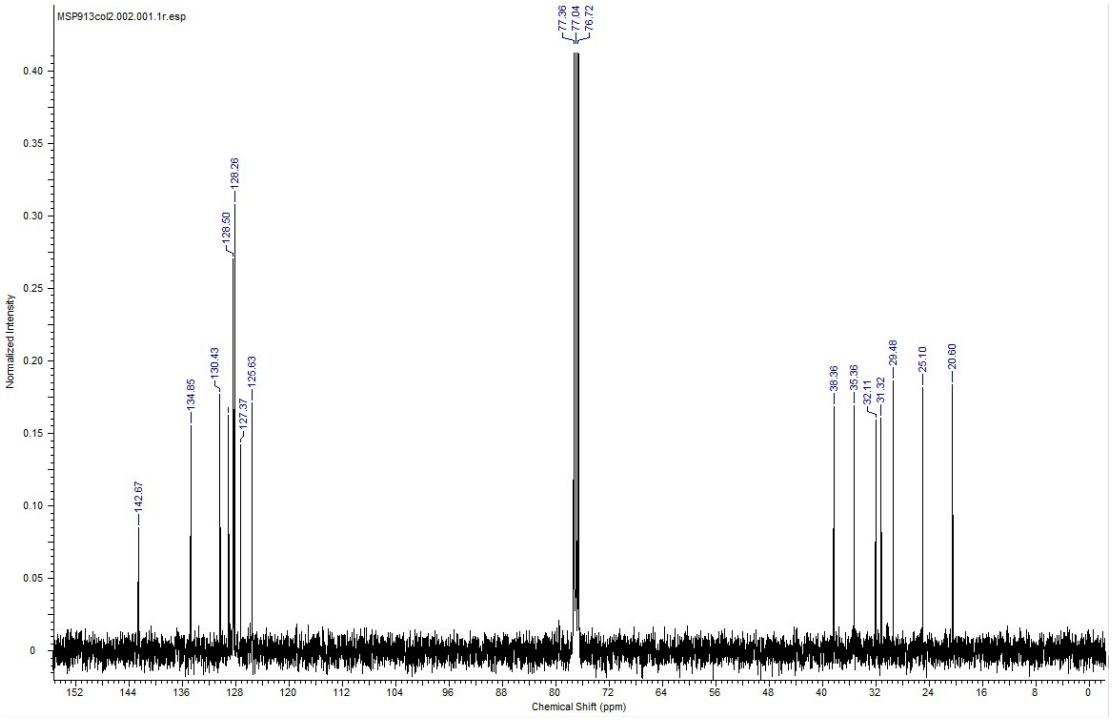
$[\alpha]^{20}_{589}$ = +45.0 (*c* 1.40, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 1472.3, 2854.8, 2929.2.

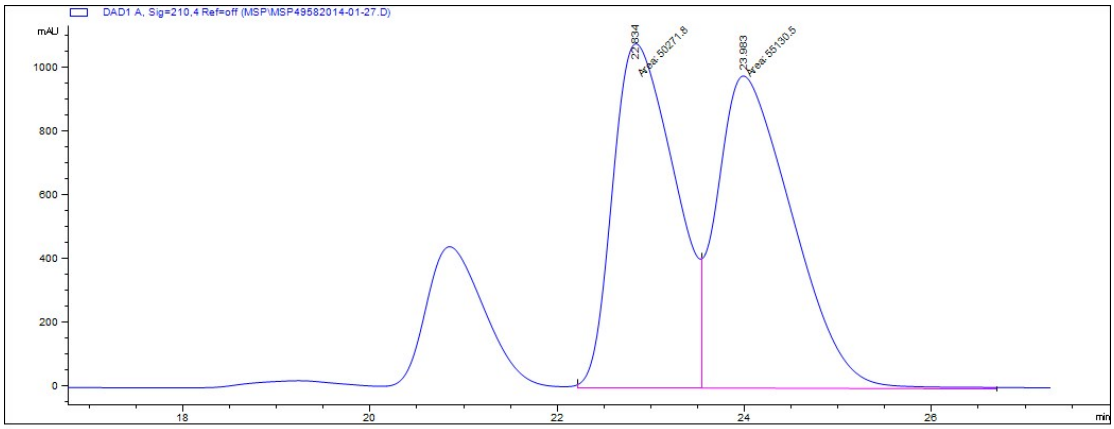
^{1}H NMR:

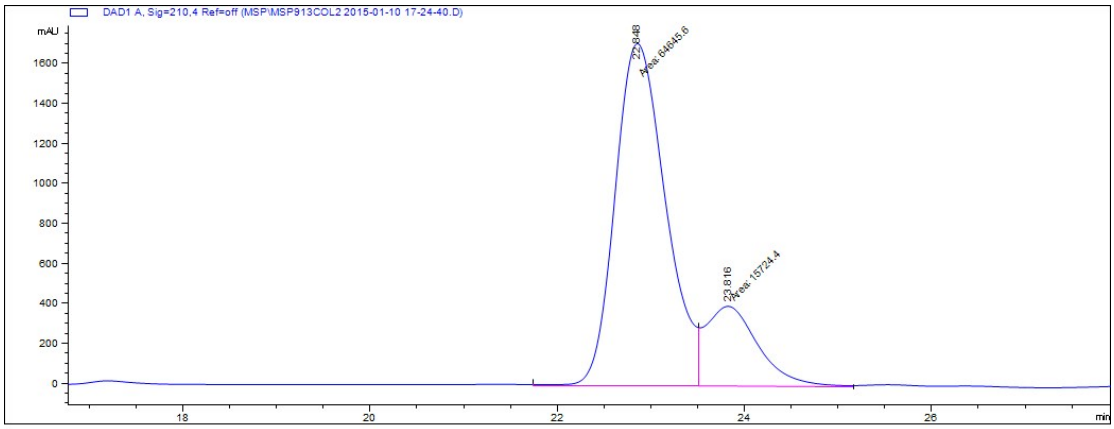


^{13}C NMR:

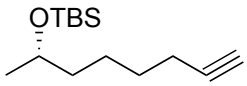

MSP913col2.002.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
142.67
134.85
130.43
128.50
128.26
127.37
125.63
77.36
77.04
76.72
38.36
35.36
32.11
31.32
29.48
25.10
20.60

HPLC traces:





(*S*)-7-((dimethyl-*tert*-butyl)silyl)oxy-1-octyne (*S*)-5



Imidazole (0.98 g, 14.4 mmol, 1.40 eq) and TBSCl (1.86 g, 12.4 mmol, 1.20 eq) was added to a solution of (*S*)-oct-7-yn-2-ol[6] (1.30 g, 10.3 mmol, 1.00 eq) in CH_2Cl_2 (52 mL). The solution was stirred at 30 °C for 18 h. The reaction was quenched with water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3x5 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated. The crude was purified by flash column chromatography eluting with hexane:EtOAc (9:1) to afford (*S*)-**5** in 76% yield (1.87 g, 7.80 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 3.83 – 3.74 (m, 1H), 2.22 – 2.14 (m, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.60 – 1.32 (m, 5H), 1.12 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.91 (s, 6H).

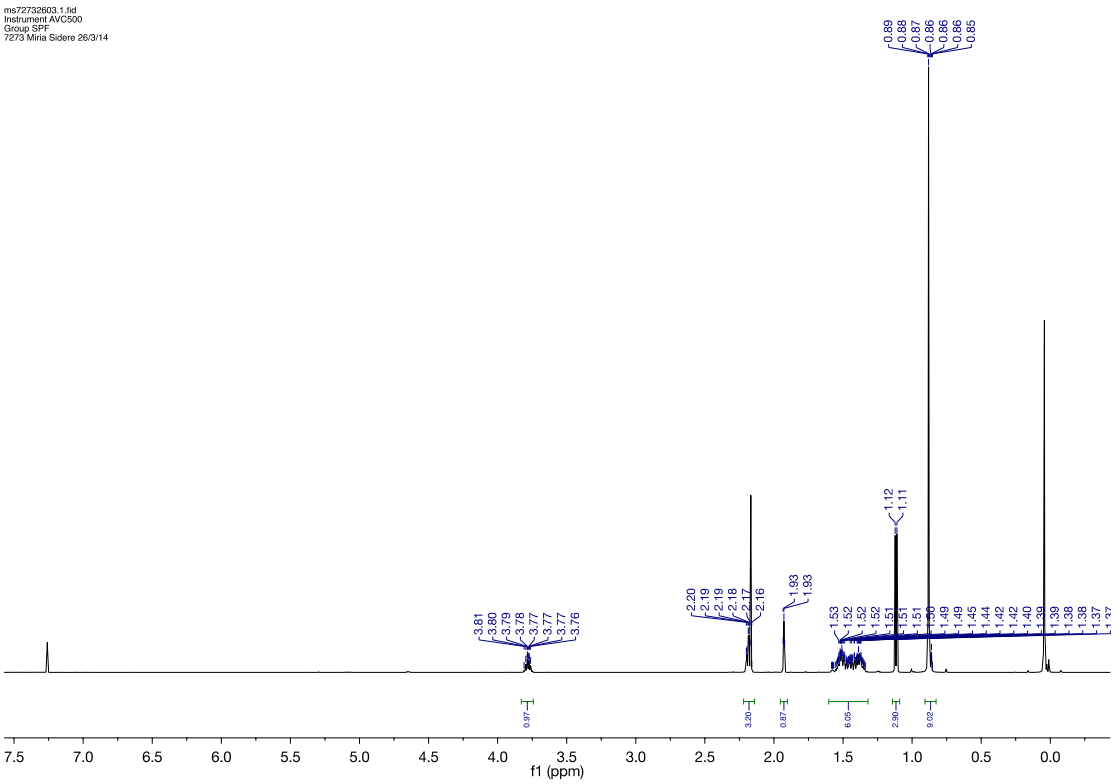
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 84.7, 68.6, 68.3, 39.3, 31.1, 28.7, 26.1 (2C), 25.1, 24.0, 18.6, 18.3, -4.2, -4.6.

HRMS (EI) *m*/*z* calcd for $C_{14}H_{28}OSi$ $[M]^+$: 240.1909, found: 240.1911.

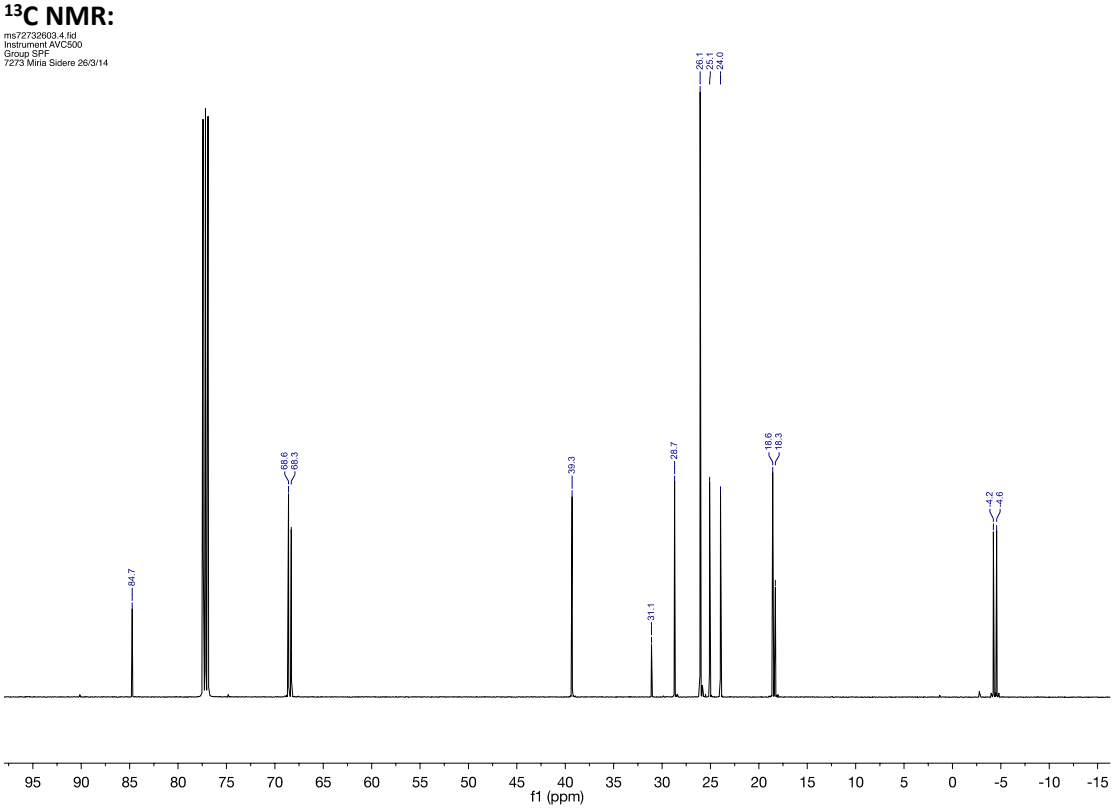
$[\alpha]^{20}_{589}$ = +13.4 (c 1.94 $CHCl_3$)

IR (ν_{max} /cm^{-1}): 1254.6, 1463.1, 2858.5, 2930.3, 3314.9.

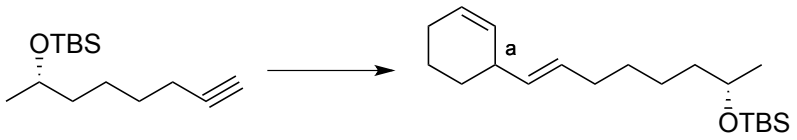
^{1}H NMR:



^{13}C NMR:



(±)-3-((*S*,E)-7-(*tert*-Butyldimtheylsilyloxy)oct-1-en-1-yl)cyclohex-1-ene (±,*S*)-6



Cp_2ZrHCl (103.1 mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkyne (*S*)-**5** (0.12 mL, 0.50 mmol, 2.5 eq) in CH_2Cl_2 (1.0 mL) under an argon atmosphere. After stirring for 20 min, CuBr.Me_2S (41.1 mg, 0.20 mmol 1.0 eq), was added to the resulting clear yellow solution and the resulting black mixture was allowed to stir for an additional 10 min before a 3-bromocyclohex-1-ene (23 µL, 0.20, 1.0 eq) was added via microsyringe over about 1 min. Stirring at room temperature was continued arbitrarily overnight before the reaction was diluted and quenched by addition of petrol (ca 2 mL) and then NH_4Cl (1M aq., ca 1.5 mL). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Flash column chromatography of the residue eluting with pentane (100% to 1% Et_2O) gave (±,*S*)-**6** in 56% yield (11.7 mg, 0.36 mmol).

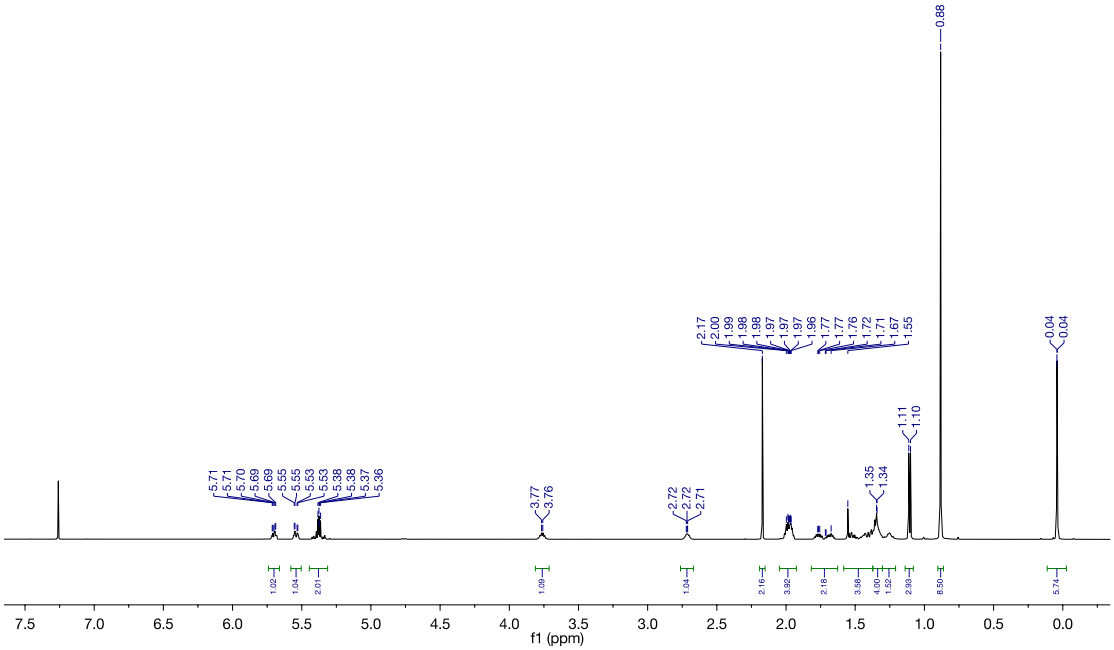
^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 5.70 (m, 1H), 5.54 (dq, *J* = 10.0, 2.3 Hz, 1H), 5.45 – 5.31 (m, 2H), 3.81 – 3.71 (m, 1H), 2.72 (m, 1H), 2.05 – 1.92 (m, 4H), 1.73 (m, 2H), 1.58 – 1.37 (m, 4H), 1.37 – 1.30 (m, 4H), 1.25 (m, 2H), 1.11 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 134.5, 130.7, 129.7, 127.4, 68.8, 39.8, 38.5, 38.5, 32.7, 32.7, 31.1, 29.8, 29.6, 26.1, 25.5, 25.5, 25.2, 24.0, 20.8, 20.8, 18.3, -4.3, -4.5.

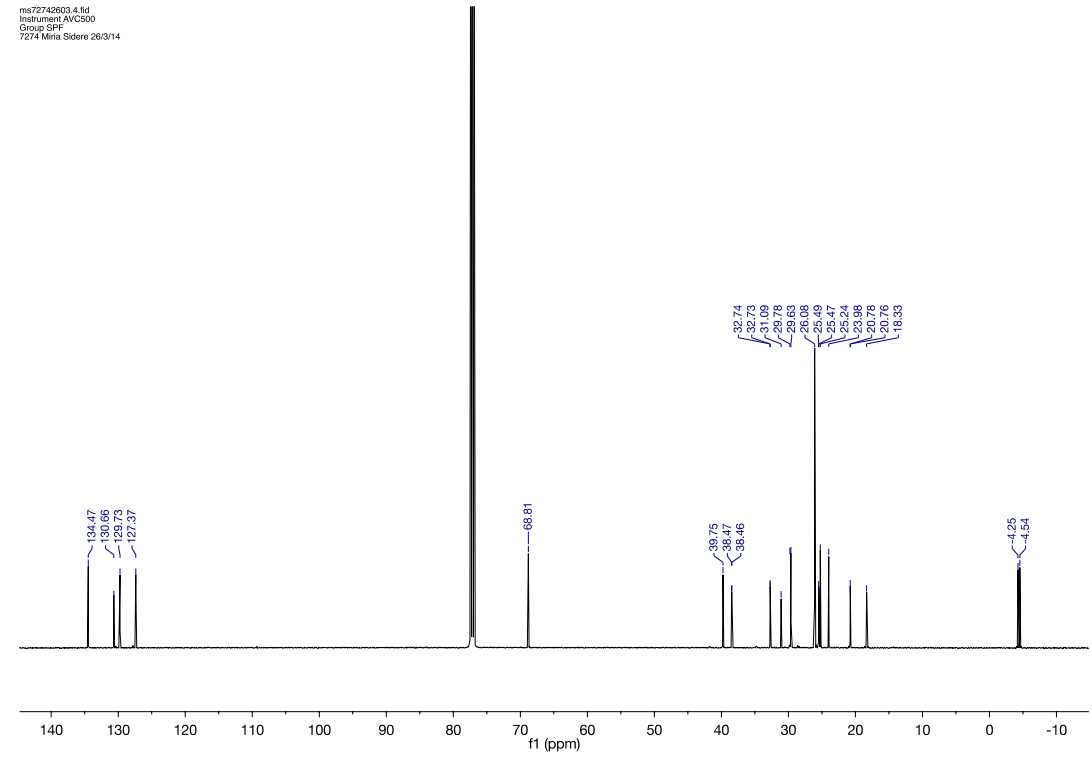
HRMS (EI) *m*/*z* calcd for $C_{20}H_{38}OSi$ $[M]^+$: 322.2692, found: 322.2698.

^{1}H NMR:

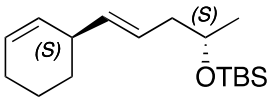
ms72742603.1.fid
Instrument AVC500
Group SPF
7274 Miria Sidere 26/3/14



^{13}C NMR:



(*S*)-3-((*S*,E)-4-(*tert*-Butyldimtheylsilyloxy)pent-1-en-1-yl)cyclohex-1-ene (*S*,*S*)-8



CuCl (4.0 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*S*,*S*,*S*)-**L3** (22.0 mg, 0.040 mmol, 0.10 eq) were dissolved in CH_2Cl_2 (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. Then AgOTs (12.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 minutes. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkyne (*S*)-**7** (0.24 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the hydrozirconation solution. The resulting black mixture was cooled to –40 °C and allowed to stir for an additional 20 minutes before the 2-cyclohexenyl bromide (46 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h at –40 °C before the reaction was quenched by the addition of CH_2Cl_2 (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography (hexane; SiO_2) of the residue afforded the desired product *tert*-butyl(((*S*,*E*)-5-((*S*)-cyclohex-2-en-1-yl)pent-4-en-2-yl)oxy)dimethylsilane in 81% yield (90.9 mg, 0.32 mmol).

Diastereomeric ratio of 89:11 was determined by ^{13}C NMR integration.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 5.75 - 5.68 (m, 1 H), 5.57 (d, *J* = 2.5 Hz, 1 H), 5.43 - 5.39 (m, 2 H), 3.80 (m, 1 H), 2.22 - 2.13 (m, 2 H), 2.09 (m, 1 H), 2.02 - 1.94 (m, 2 H), 1.82 - 1.75 (m, 1 H), 1.70 (m, 1 H), 1.59 - 1.49 (m, 1 H), 1.43 - 1.34 (m, 1 H), 1.12 (d, *J* = 6.1 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

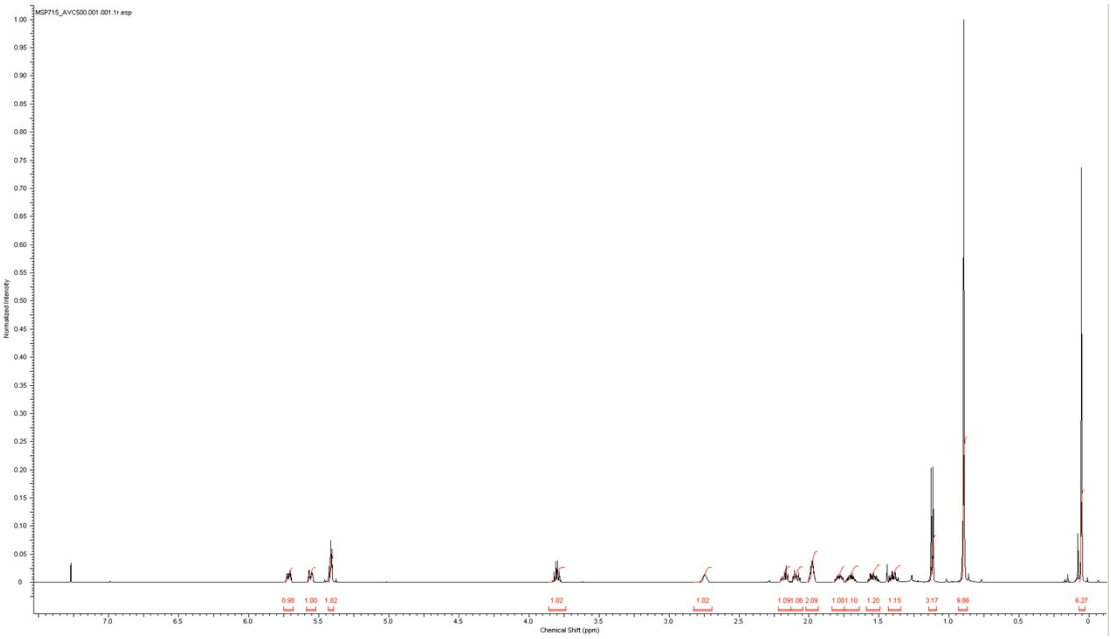
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 136.4, 130.3 (D), 130.2 (d), 127.4 (d), 127.3 (D), 126.4 (d), 126.3 (D), 43.1 (d), 43.0 (D), 38.5 (D), 38.4 (d), 29.4 (D), 29.3 (d), 25.9, 25.1, 23.5 (d), 23.4 (D), 20.7 (D), 20.6 (d), 18.2, -4.5, -4.7.

HRMS (EI) *m*/*z* calcd for $C_{17}H_{32}NaOSi$ $[M+Na]^+$: 303.2120, found: 302.2125.

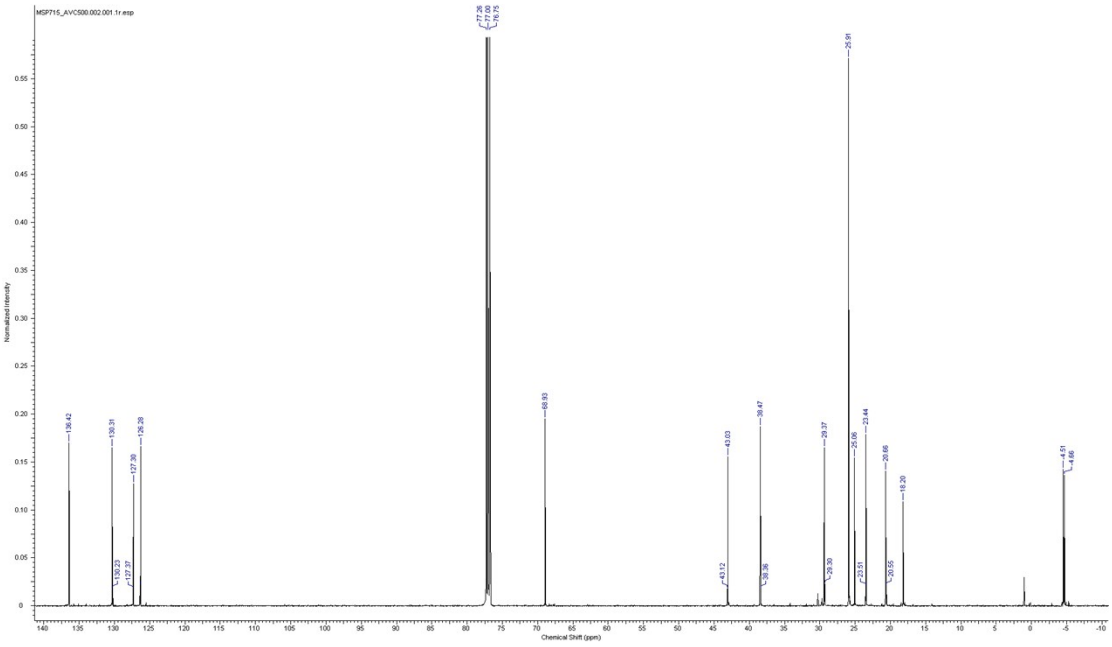
$[\alpha]^{20}_{589}$ = –58.7 (*c* 1.26, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 1254.7, 1375.5, 1472.0, 2857.0, 2928.6.

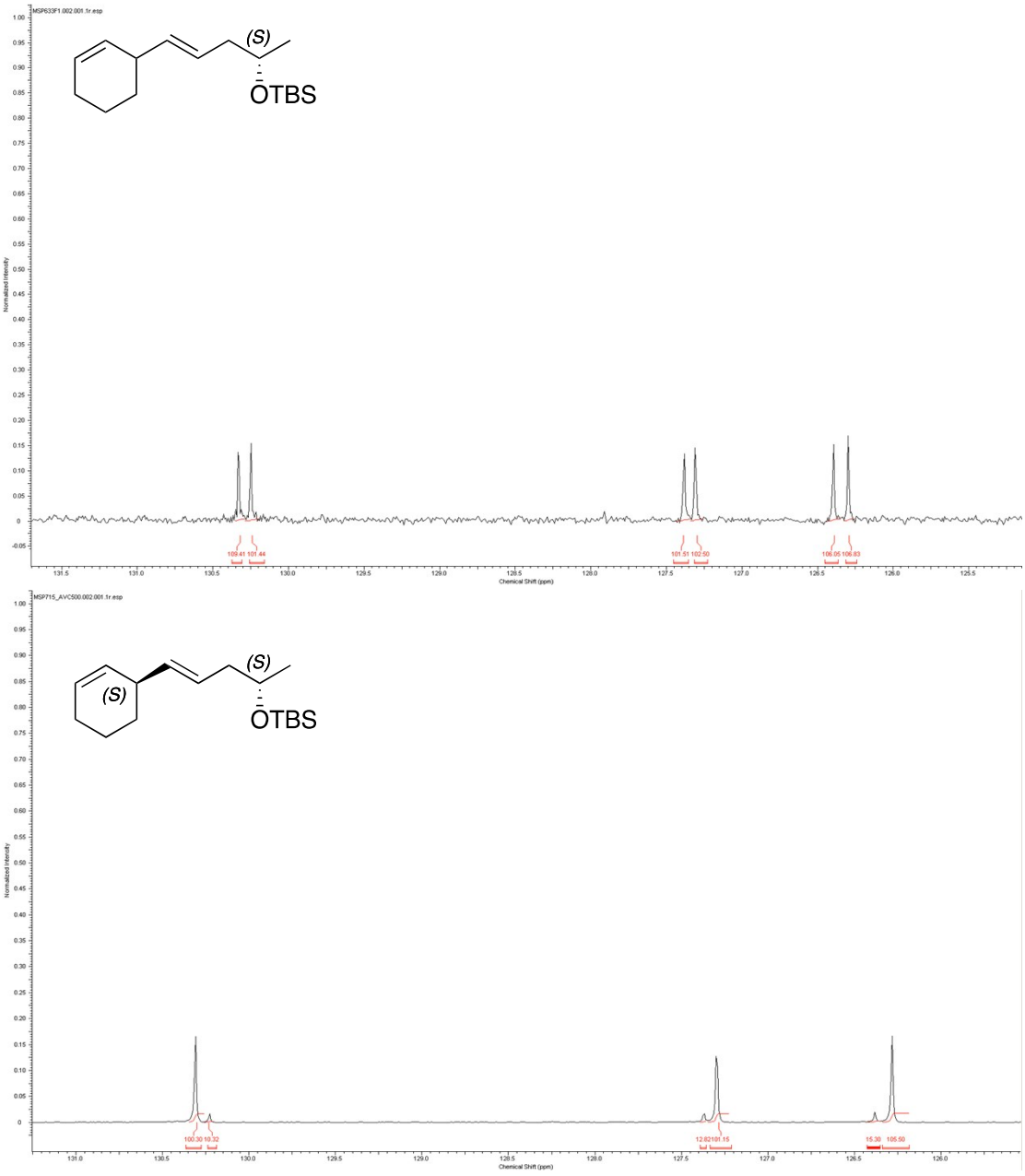
^{1}H NMR:



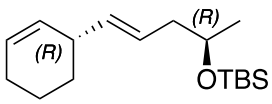
^{13}C NMR:



d.r. determination:



(*R*)-3-((*R*,E)-4-(*tert*-Butyldimtheylsilyloxy)pent-1-en-1-yl)cyclohex-1-ene (*R*,*R*)-8



CuCl (4.0 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*R*,*R*,*R*)-**L3** (22.0 mg, 0.040 mmol, 0.10 eq) were dissolved in CH_2Cl_2 (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. Then AgOTs (12.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 minutes. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkyne (*R*)-**7** (0.24 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After

stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the hydrozirconation solution. The resulting black mixture was cooled to –40 °C and allowed to stir for an additional 20 minutes before the 2-cyclohexenyl bromide (46 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h at –40 °C before the reaction was quenched by the addition of CH_2Cl_2 (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography (hexane; SiO_2) of the residue afforded the desired product *tert*-butyl(((*R*,*E*)-5-((*R*)-cyclohex-2-en-1-yl)pent-4-en-2-yl)oxy)dimethylsilane in 76% yield (85.1 mg, 0.30 mmol).

Diastereomeric ratio of 89:11 was determined by ^{13}C NMR integration.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 5.75 - 5.68 (m, 1 H), 5.57 (d, *J* = 2.5 Hz, 1 H), 5.43 - 5.39 (m, 2 H), 3.80 (m, 1 H), 2.22 - 2.13 (m, 2 H), 2.09 (m, 1 H), 2.02 - 1.94 (m, 2 H), 1.82 - 1.75 (m, 1 H), 1.70 (m, 1 H), 1.59 - 1.49 (m, 1 H), 1.43 - 1.34 (m, 1 H), 1.12 (d, *J* = 6.1 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

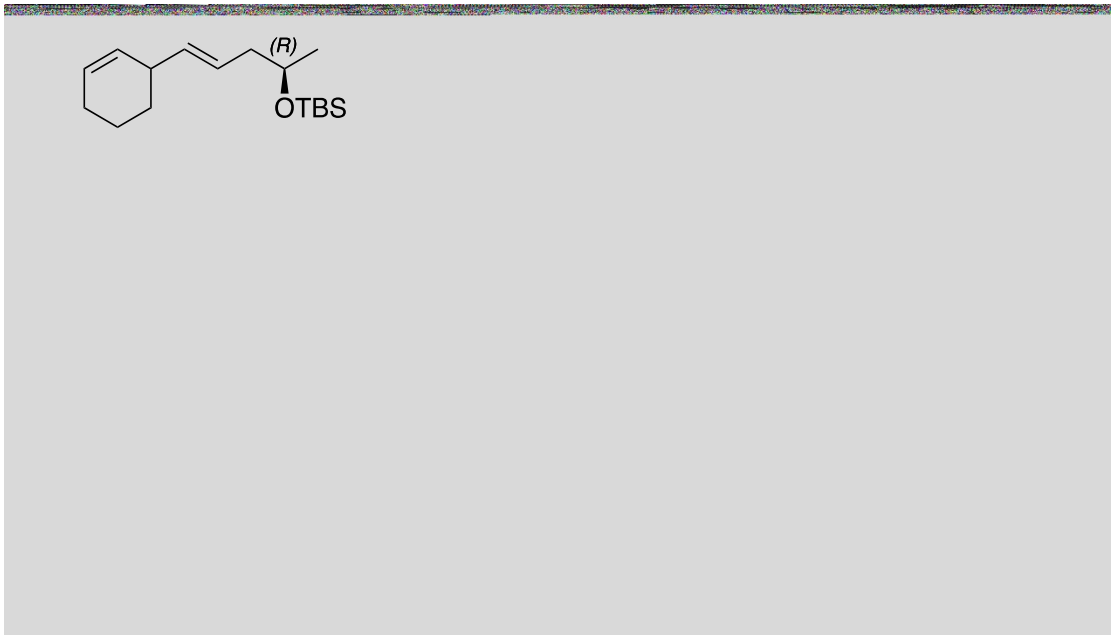
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 136.4, 130.3 (D), 130.2 (d), 127.4 (d), 127.3 (D), 126.4 (d), 126.3 (D), 43.1 (d), 43.0 (D), 38.5 (D), 38.4 (d), 29.4 (D), 29.3 (d), 25.9, 25.1, 23.5 (d), 23.4 (D), 20.7 (D), 20.6 (d), 18.2, -4.5, -4.7.

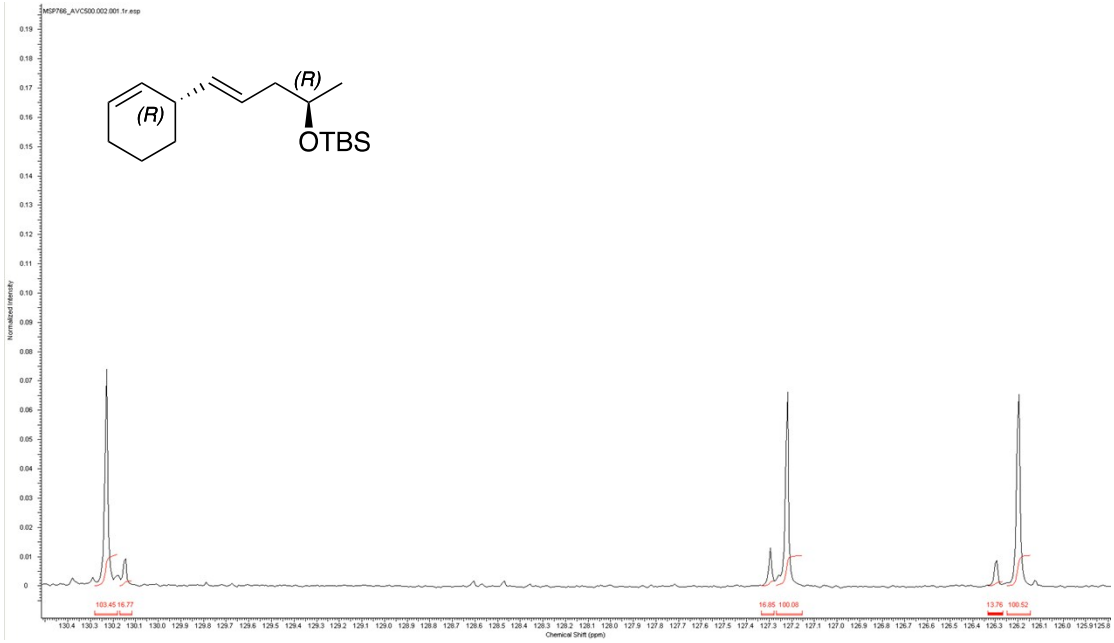
HRMS (EI) *m*/*z* calcd for $C_{17}H_{32}NaOSi$ $[M+Na]^+$: 303.2120, found: 302.2124.

$[\alpha]^{20}_{589}$ = +50.3 (*c* 1.10, $CHCl_3$).

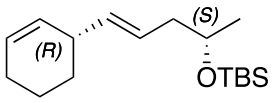
IR (ν_{max} /cm^{-1}): 1376.5, 1473.1, 2857.6, 2929.0.

d.r. determination:





(*R*)-3-((*S*,E)-4-(*tert*-Butyldimtheylsilyloxy)pent-1-en-1-yl)cyclohex-1-ene (*S*,*R*)-8



CuCl (4.0 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*R*,*R*,*R*)-**L3** (22.0 mg, 0.040 mmol, 0.10 eq) were dissolved in CH_2Cl_2 (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. Then AgOTs (12.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 minutes. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkyne (*S*)-**7** (0.24 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the hydrozirconation

solution. The resulting black mixture was cooled to –40 °C and allowed to stir for an additional 20 minutes before the 2-cyclohexenyl bromide (46 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h at –40 °C before the reaction was quenched by the addition of CH_2Cl_2 (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography (hexane; SiO_2) of the residue afforded the desired product *tert*-butyl(((*S*,*E*)-5-((*R*)-cyclohex-2-en-1-yl)pent-4-en-2-yl)oxy)dimethylsilane in 76% yield (88.5 mg, 0.32 mmol).

Diastereomeric ratio of 88:12 was determined by ^{13}C NMR integration.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 5.75 - 5.68 (m, 1 H), 5.57 (d, *J* = 2.5 Hz, 1 H), 5.43 - 5.39 (m, 2 H), 3.80 (m, 1 H), 2.22 - 2.13 (m, 2 H), 2.09 (m, 1 H), 2.02 - 1.94 (m, 2 H), 1.82 - 1.75 (m, 1 H), 1.70 (m, 1 H), 1.59 - 1.49 (m, 1 H), 1.43 - 1.34 (m, 1 H), 1.12 (d, *J* = 6.1 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

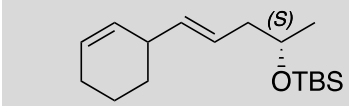
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 136.4, 130.3 (d), 130.2 (D), 127.4 (D), 127.3 (d), 126.4 (D), 126.3 (d), 43.1 (D), 43.0 (d), 38.5 (d), 38.4 (D), 29.4 (d), 29.3 (D), 25.9, 25.1, 23.5 (D), 23.4 (d), 20.7 (d), 20.6 (D), 18.2, -4.5, -4.7.

HRMS (EI) *m*/*z* calcd for $C_{17}H_{32}NaOSi$ $[M+Na]^+$: 303.2120, found: 302.2127.

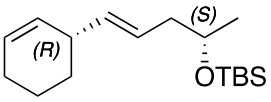
$[\alpha]^{20}_{589}$ = +54.3 (*c* 1.10, $CHCl_3$).

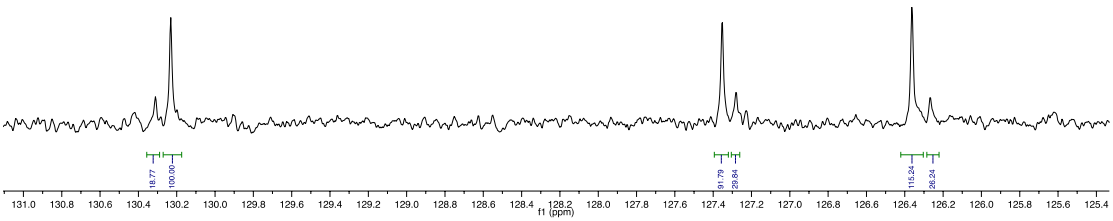
IR (ν_{max}/cm^{-1}): 1254.8, 1377.2, 1471.8, 2858.1, 2928.7.

d.r. determination:

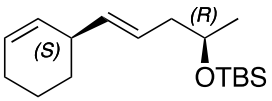


1882.42.2.fid
Instrument AVB400





(*S*)-3-((*R*,E)-4-(*tert*-Butyldimtheylsilyloxy)pent-1-en-1-yl)cyclohex-1-ene (*S*,*R*)-8



CuCl (4.0 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*R*,*R*,*R*)-**L3** (22.0 mg, 0.040 mmol, 0.10 eq) were dissolved in CH_2Cl_2 (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. Then AgOTs (12.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 minutes. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkyne (*S*)-**7** (0.24 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the hydrozirconation solution. The resulting black mixture was cooled to –40 °C and allowed to stir for an additional 20 minutes before the 2-cyclohexenyl bromide (46 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h at –40 °C before the reaction was quenched by the addition of CH_2Cl_2 (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography (hexane; SiO_2) of the residue afforded the desired product *tert*-butyl(((*R*,*E*)-5-((*S*)-cyclohex-2-en-1-yl)pent-4-en-2-yl)oxy)dimethylsilane in 81% yield (90.8 mg, 0.32 mmol).

Diastereomeric ratio of 88:12 was determined by ^{13}C NMR integration.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm 5.75 - 5.68 (m, 1 H), 5.57 (d, *J* = 2.5 Hz, 1 H), 5.43 - 5.39 (m, 2 H), 3.80 (m, 1 H), 2.22 - 2.13 (m, 2 H), 2.09 (m, 1 H), 2.02 - 1.94 (m, 2 H), 1.82 - 1.75 (m, 1 H), 1.70 (m, 1 H), 1.59 - 1.49 (m, 1 H), 1.43 - 1.34 (m, 1 H), 1.12 (d, *J* = 6.1 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

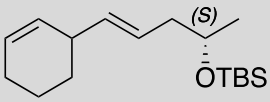
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 136.4, 130.3 (d), 130.2 (D), 127.4 (D), 127.3 (d), 126.4 (D), 126.3 (d), 43.1 (D), 43.0 (d), 38.5 (d), 38.4 (D), 29.4 (d), 29.3 (D), 25.9, 25.1, 23.5 (D), 23.4 (d), 20.7 (d), 20.6 (D), 18.2, -4.5, -4.7.

HRMS (EI) *m*/*z* calcd for $C_{17}H_{32}NaOSi$ $[M+Na]^+$: 303.2120, found: 302.2122.

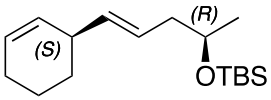
$[\alpha]^{20}_{589}$ = –54.4 (*c* 0.62, $CHCl_3$).

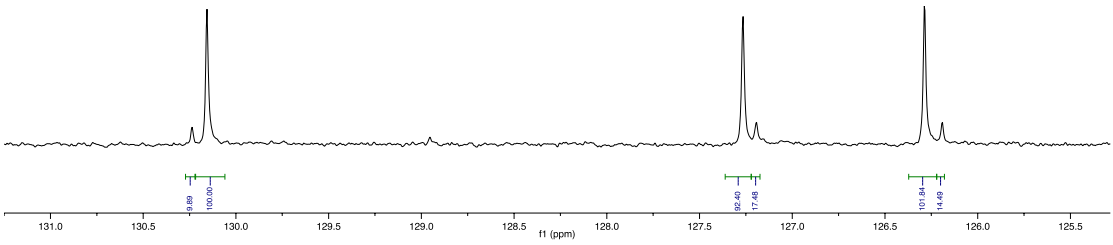
IR (ν_{max} /cm^{-1}): 1472.1, 2856.5, 2929.1.

d.r. determination:

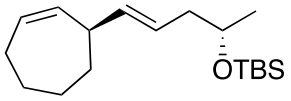


MSP764B.1.fid
Instrument AVB400





(*R*)-3-((*R*,E)-4-(*tert*-Butyldimtheylsilyloxy)pent-1-en-1-yl)cyclohept-1-ene (*R*,*R*)-9



CuCl (4.0 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*R*,*R*,*R*)-**L3** (22.0 mg, 0.040 mmol, 0.10 eq) were dissolved in CH_2Cl_2 (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. Then AgOTs (12.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 minutes. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkyne (*R*)-**5** (0.24 mL, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the hydrozirconation solution. The resulting black mixture was cooled to –40 °C and allowed to stir for an additional 20 minutes before the 2-cyclohexenyl bromide (46 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h at –40 °C before the reaction was quenched by the addition of CH_2Cl_2 (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and CH_2Cl_2 layers and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., *ca* 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil. Flash column chromatography (hexane; SiO_2) of the residue afforded the desired product (*R*)-3-((*R*,E)-4-(*tert*-Butyldimtheylsilyloxy)pent-1-en-1-yl)cyclohept-1-ene in 56% yield (63.0 mg, 0.21 mmol).

Diastereomeric ratio of 83:17 was determined by ^{13}C NMR integration.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppm ^{1}H NMR (500 MHz, Chloroform-*d*) 5.76 (m, 1H), 5.60 (m, 1H), 5.54 – 5.46 (m, 1H), 5.47 – 5.38 (m, 1H), 3.79 (m, 1H), 2.97 – 2.84 (m, 1H), 2.24 – 1.99 (m, 4H), 1.89 (m, 1H), 1.72 – 1.57 (m, 3H), 1.50 – 1.33 (m, 2H), 1.33 – 1.19 (m, 9H), 1.11 (d, *J* = 6.1 Hz, 3H), 0.92 – 0.85 (m, 6H).

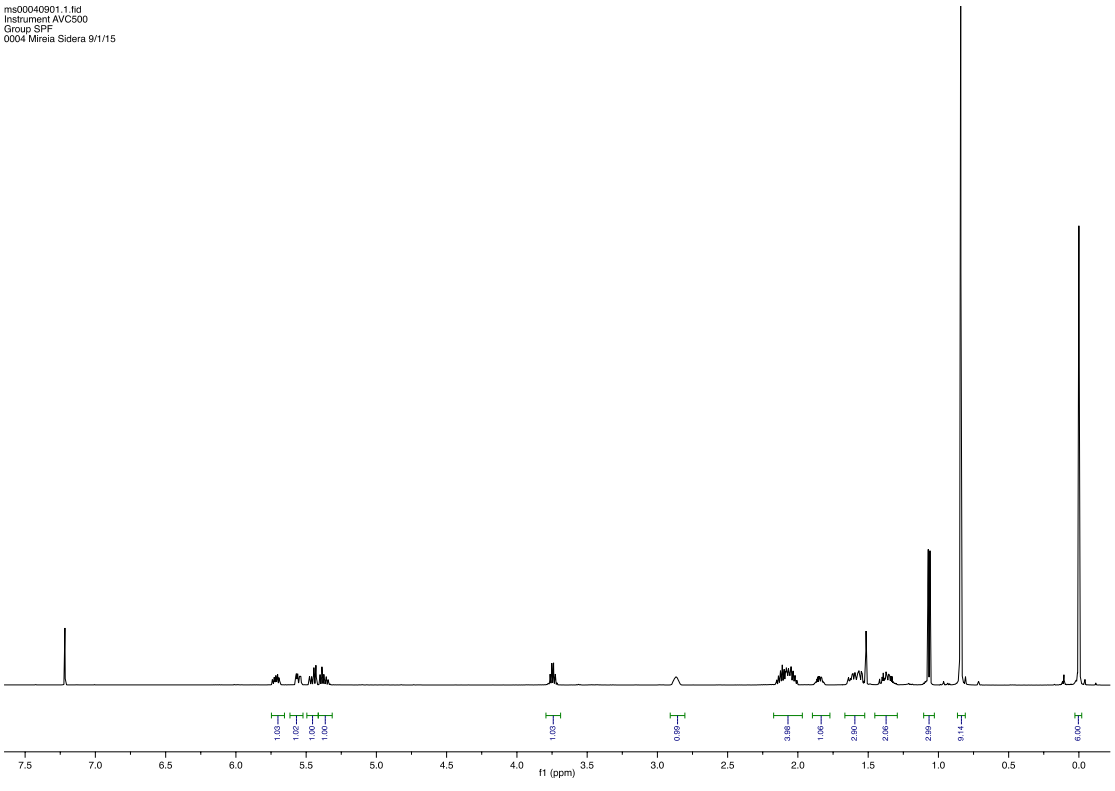
^{13}C NMR (126 MHz, $CDCl_3$) δ_C /ppm 137.0 (D), 136.9(d), 136.1 (D), 136.0 (d), 131.3, 125.6, 69.1 (D), 69.0 (d), 43.5(D), 43.4 (d), 43.2 (d), 43.2(D), 34.2 (D), 34.1 (d), 31.8, 29.8 (D), 29.6 (d), 28.9, 27.3, 27.2, 26.1, 26.0, 23.6, 22.8, 18.4, 14.3, -4.4, -4.5.

HRMS (EI) *m*/*z* calcd for $C_{18}H_{34}Na$ $[M+Na]^+$: 317.2277, found: 317.2280.

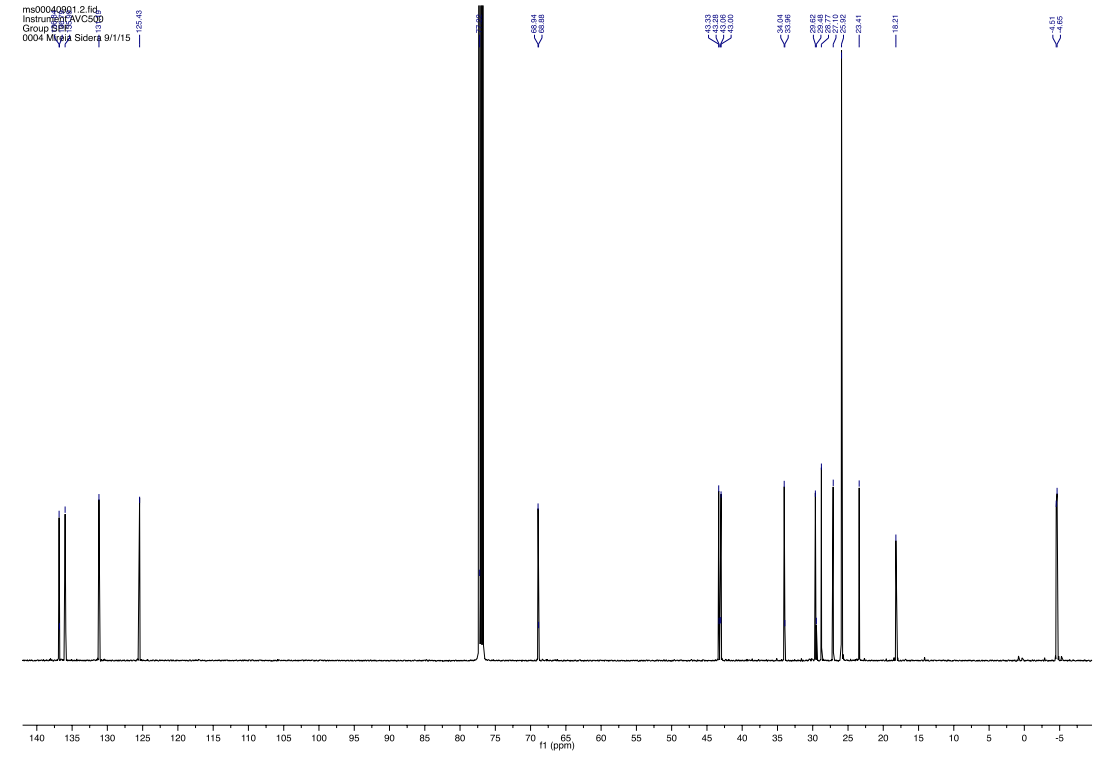
$[\alpha]^{20}_{589}$ = +34.3 (*c* 0.75, $CHCl_3$).

IR (ν_{max} /cm^{-1}): 1472.0, 2855.0, 2929.0.

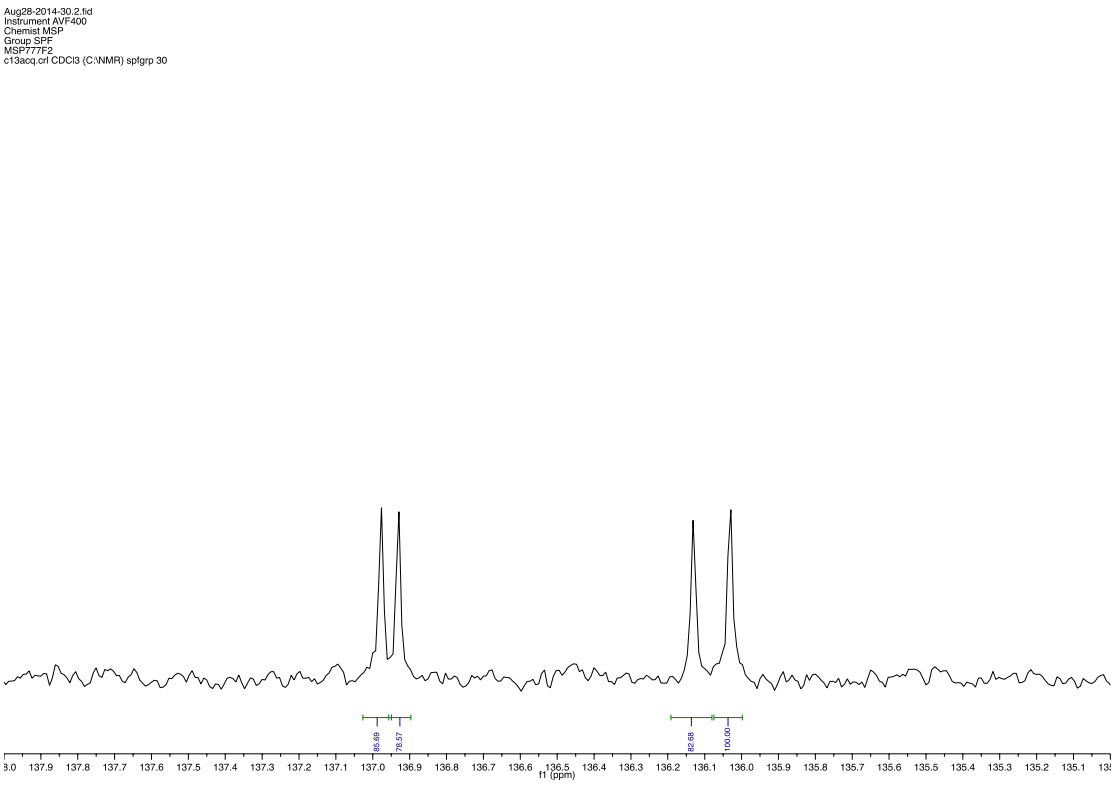
^{1}H NMR:

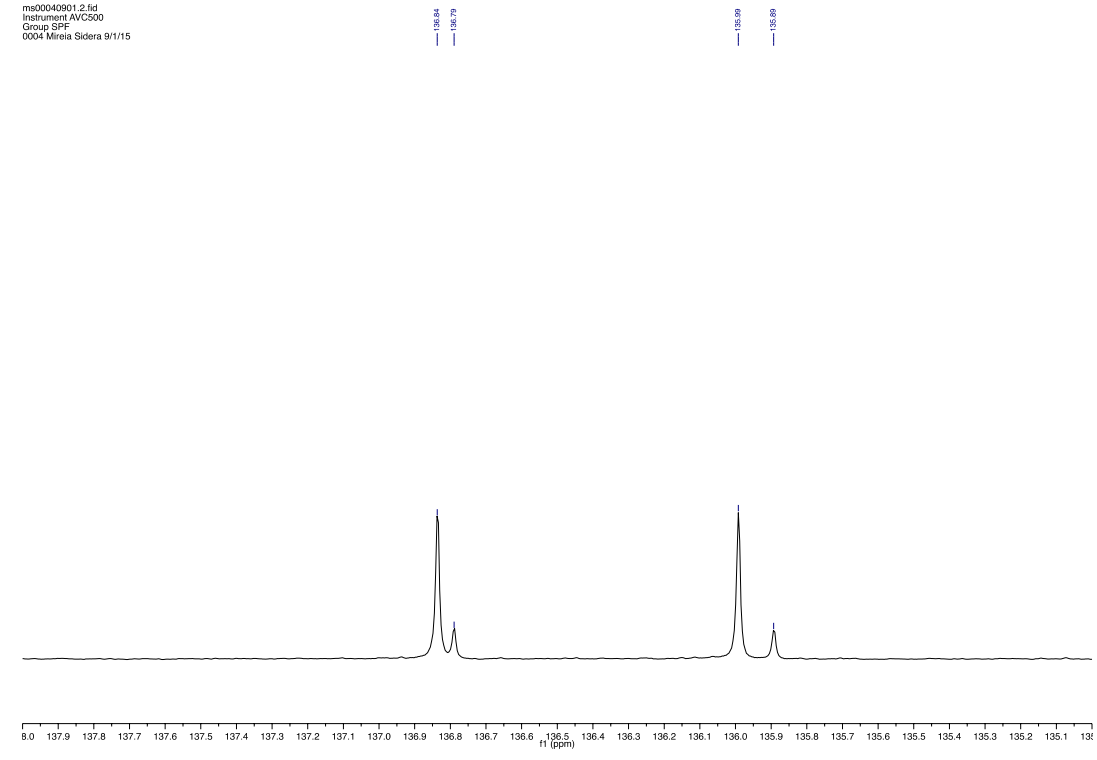


^{13}C NMR:



d.r. determination:





[1] H. You, E. Rideau, M. Sidera and S. P. Fletcher, *Nature*, 2015, **517**, 351.

[2] Stephen L. Buchwald1, Susan J. LaMaire, Ralph B. Nielsen, Brett T. Watson, and S. M. K. Schwartz's reagent. *Org. Synth.*, **71**, 77–82 (1993).

[3] Z. Yang and J. Zhou, *J. Am. Chem. Soc.*, 2012, **134**, 11833–5.

[4] Rink, Christian; Sasse, Florenz; Zubrienae -, Asta; Matulis, Daumantas; Maier, Martin E. *Chemistry - A European Journal*, **2010**, *16*, 14469 – 14478.

[5] Langlois, Jean-Baptiste; Alexakis, Alexandre *Adv. Synt. Cat.*, **2010**, *352*, 447 – 457.
[6] Shin, J.; Hong, S.-C.; Shin, S.; Cho, Cheon-Gyu *Org. Lett.*, **2006** , *8*, 3339 – 3341.