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Supplementary Material:

Asymmetric remote C-H functionalization: Use of internal olefins in tandem hydrometallation – isomerization – asymmetric conjugate addition sequences

Laura Mola, Mireia Sidera and Stephen P. Fletcher*

[A]Department of Chemistry, Chemistry Research Laboratory, University of Oxford
*Corresponding author. Email: stephen.fletcher@chem.ox.ac.uk

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 F_{254}; 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, 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.

Unless stated otherwise, solution NMR spectra were recorded at room temperature; ^{1}H and ^{13}C nuclear magnetic resonance experiments were carried out using Bruker DPX-200 (200/50 MHz), AVF-400 (400/100 MHz), AVG-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). Assignments were made with the assistance of gCOSY, DEPT-135, gHSQC and gHMBC or gHMQC NMR spectra.

Numbering and names of structures accompanying reported data is non-IUPAC, and solely for reference.

Low-resolution mass spectra were recorded using a Walters LCT premier XE. High resolution mass spectra (EI and ESI) were recorded using a Bruker MicroTOF spectrometer by the internal service at the University of Oxford.

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.

Infrared measurements (neat, thin film) were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range 4000-600 cm^{-1}.

Optical rotations were recorded using a Perkin-Elmer 241 Polarimeter.

In those cases where silver salts were used the resulting solutions were filtered using syringe filters PTFE (0.2 µm, 13 mm diameter) from Camlab.

Chemicals

Dry THF, CH_2Cl_2, Et_2O, PhMe, hexane were collected fresh from an mBraun SPS-800 solvent purification system having been passed through anhydrous alumina columns. Dry *tert*-butyl methyl ether and 2-Me-THF were 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 Alrich, Rathburn or Fisher Scientific. 1,2-dichloroethane was distilled before use.

Unless stated otherwise, commercially available reagents were purchased from Sigma-Aldrich, Fisher Scientific, Apollo Scientific, Acros Organics, Strem Chemicals, Alfa Aesar or TCI UK and were used without purification. Petroleum ether refers to light petroleum boiling in the range 40–60 °C. TMSCl was distilled before use and stored in Schlenk flasks under an argon atmosphere. Deuterated solvents were purchased from Sigma-Aldrich (CD_2Cl_2, $CDCl_3$). Schwartz reagent was prepared according to the literature procedure[1] from Cp_2ZrCl_2 provided by Strem Chemicals. $(CuOTf)_2.C_6H_6$ was synthesised using a modified literature procedure[2] and carefully maintained under an inert atmosphere. $(CuOTf)_2.C_6H_6$ should be a white or off-white powder, not green or brown. Phosphoramidite ligand *O*,*O*'-(*S*)-(1,1'-dinaphthyl-2,2'-diyl)-*N*,*N*-di-(*RR*)-1-phenylethylphophoramidite was synthesised using the literature procedure.[3]

General Methods

Synthesis of racemic products

Using a modified procedure of Wipf *et al*.,[4] Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (2.0 mL) under an argon atmosphere.

After stirring for about 40 min, $CuBr.Me_2S$ (82 mg, 0.40 mmol 1.0 eq), was added to the reaction mixture and the resulting black mixture was allowed to stir for an additional 10 min before a cyclic enone (or lactone) (0.40 mmol, 1.0 eq) was added via syringe over about 1 min. Stirring at room temperature was continued arbitrarily for 15 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (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 of the residue (EtOAc/petrol; SiO_2) gave the desired cyclic ketone or lactone.

Catalytic asymmetric conjugate addition with copper-ligand complex formed *in situ*

Copper source (5.0 mg, 0.01 mmol, 0.05 eq) and the phosphoramidite ligand (10.7 mg, 0.02 mmol, 0.1 eq) were dissolved in the reaction solvent (1.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (103.0 mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (0.5 mmol, 2.5 eq) in THF (1 mL) under an argon atmosphere and heated at 60°C for 30 min until the hydrozirconation was complete (clear yellow solution). The THF was removed and the resulting oil was codistilled with CH_2Cl_2 before adding CH_2Cl_2 (0.4 mL). It was then transferred *via* syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before the enone (0.20 mmol, 1.0 eq) was added dropwise via syringe. The reaction was stirred overnight and was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase extracted with Et_2O (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 of the residue (EtOAc/petrol; SiO_2) gave the desired cyclic ketone.

Preparation of the complex *in situ*

CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (21.6 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 alkene (0.15 mL, 1.0 mmol, 2.5 eq) in THF (1 mL) under an argon atmosphere and heated at 60°C for 30 min until the hydrozirconation was complete (clear yellow solution). The THF was removed and the resulting oil was codistilled with CH_2Cl_2 before adding CH_2Cl_2 (0.4 mL). 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 allowed to stir for an additional 10 minutes before the lactone (45 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (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 (EtOAc/petrol; SiO_2) of the residue the desired lactone.

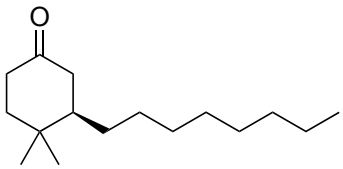
Derivatisation of cyclic ketones

Using the procedure from Alexakis and co-workers:[5] Crude material from the 1,4-addition was transferred to a vial with $CDCl_3$ and 3 Å molecular sieves. (+)-(*R*,*R*)-1,2-diphenylethylenediamine ((+)-(*R*,*R*)-DPEN *ca.* 2 eq.) was added and the vial was shaken and allowed to stand overnight before the mixture was filtered through a glass pipette containing a small cotton plug and transferred to a NMR tube. ^{13}C NMR spectroscopy (500 MHz, 1024 scans) and comparison with racemic material was used to determine the enantiomeric excess.

Derivatisation of cyclic lactones

Compounds lacking a suitable chromophore were derivatised via ring opening with benzylamine before HPLC analysis using the following procedure.
$AlMe_3$ (1.10 eq.) was added dropwise to a stirring solution of the desired substrate (1.0 eq.) and benzylamine (2.0 eq.) in CH_2Cl_2 (0.1 M) at 0˚C. The resulting solution was allowed to warm to RT overnight before quenching with HCl (1 M, aq.). The aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was dissolved in a minimum amount of EtOAc/CH_2Cl_2 and filtered through a pad of silica (eluent EtOAc:NEt_3, 99:1). The filtrate was concentrated in vacuo and used directly for HPLC analysis.

(–)-(*R*)-4,4-Dimethyl-3-octylcyclohexan-1-one (1)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*S*,*S*,*S*)-**L1** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in ^{t}BuOMe (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. AgOTf (11.3 mg, 0.044 mmol, 0.11 eq) was added and the suspension was stirred for another 5 min. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred solution of *trans*-4-Octene (0.16 mL, 1.0 mmol, 2.5 eq) in THF (1 mL) under an argon atmosphere and heated at 60°C for 30 min until the hydrozirconation was complete (clear yellow solution). The THF was removed and the resulting oil was codistilled with CH_2Cl_2 before adding CH_2Cl_2 (0.4 mL). The stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the solution. The resulting black mixture was allowed to stir for an additional 10 min before 4,4-dimethyl-2-cyclohexen-1-one (53 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 20.0 mmol, 5.0 eq) were added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (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. Flash column chromatography of the yellow residue (5:95 EtOAc/hexanes; SiO_2) gave (–)-(*R*)-4,4-Dimethyl-3-octylcyclohexan-1-one **1** (48 mg, 0.2 mmol, 50%) as yellow oil. Enantiomeric excess (90% ee) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 0.88 (t, *J*=6.9 Hz, 3 H), 0.96 - 1.06 (m, 7 H), 1.08 - 1.18 (m, 1 H), 1.19 - 1.41 (m, 11 H) 1.46 - 1.65 (m, 3 H), 1.73 (ddd, *J*=13.6, 6.2, 3.7 Hz, 1 H), 2.05 (ddd, *J*=14.9, 12.1, 0.9 Hz, 1 H), 2.22 – 2.31 (m, 1 H), 2.34 – 2.47 (m, 2 H).

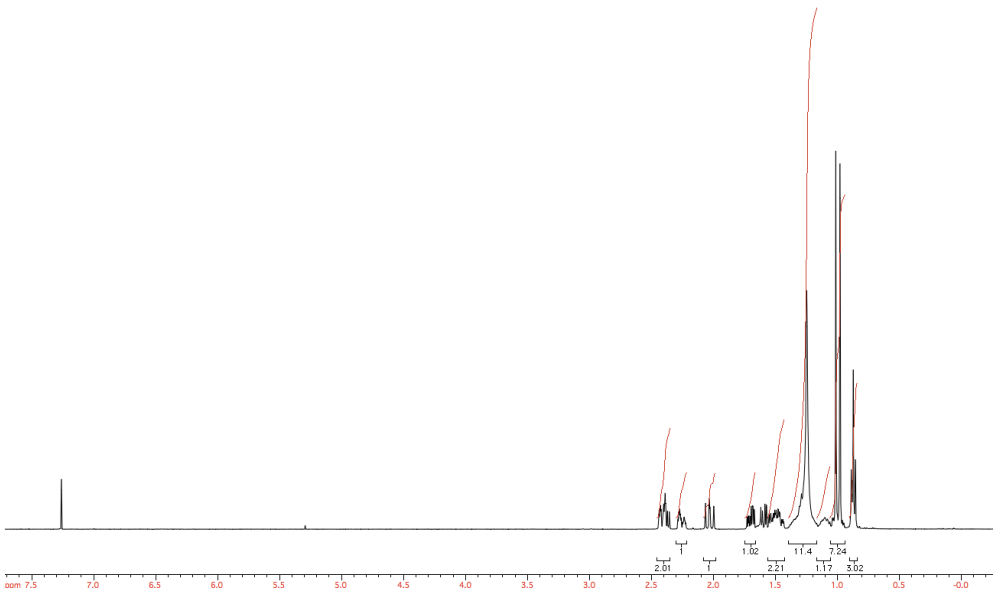
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 14.1, 19.5, 22.7, 27.5, 28.7, 29.3, 29.5, 29.7, 30.6, 31.9, 32.8, 38.3, 40.5, 42.9, 46.8, 212.4.

HRMS (ESI) *m/z* calcd for $C_{16}H_{31}O$ $[M+H]^+$: 239,2369, found 239.2366.

IR (ATR) ν (cm^{-1}): 2924, 2855, 1716, 1467, 1389, 1145.

$[\alpha]^{20}_{589}$ = – 16.7 (*c* 0.96, $CHCl_3$). [lit. $[\alpha]^{20}_{589}$ = – 17.1 (*c* 1.07, $CHCl_3$)][6].

^{1}H NMR:



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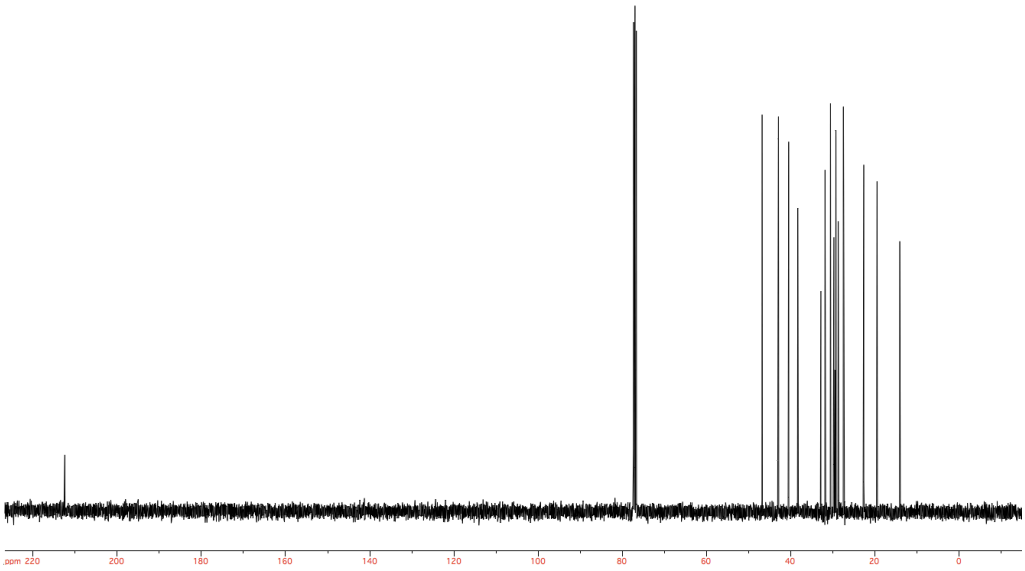

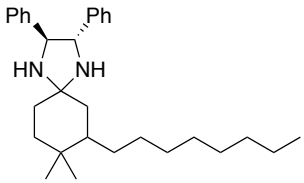
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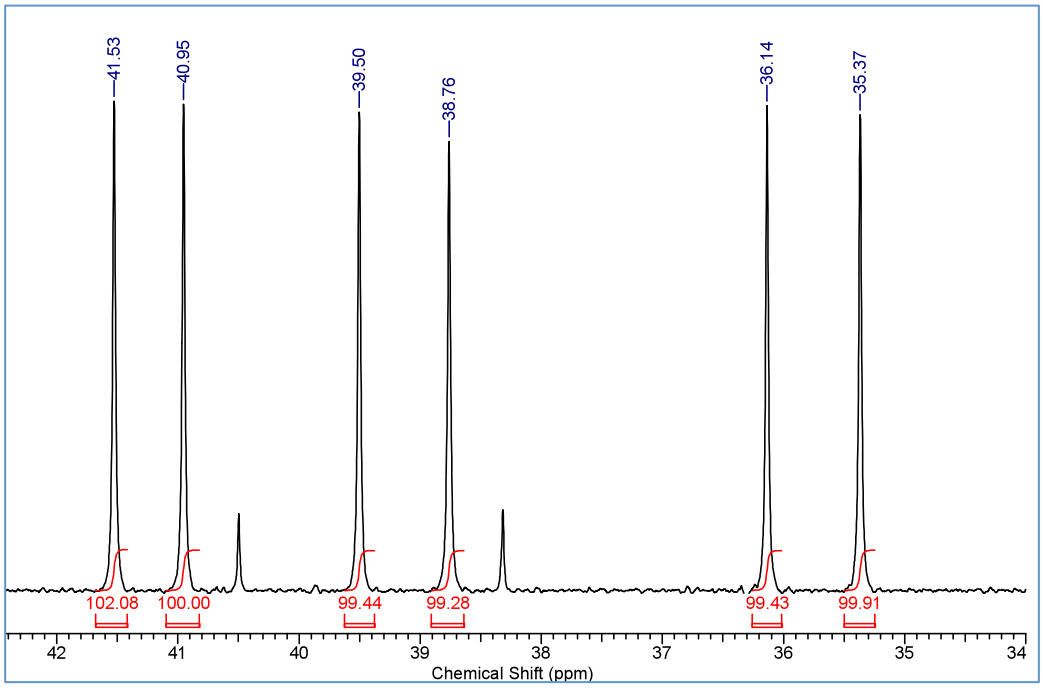
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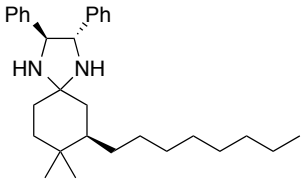
Chemical Shift (ppm)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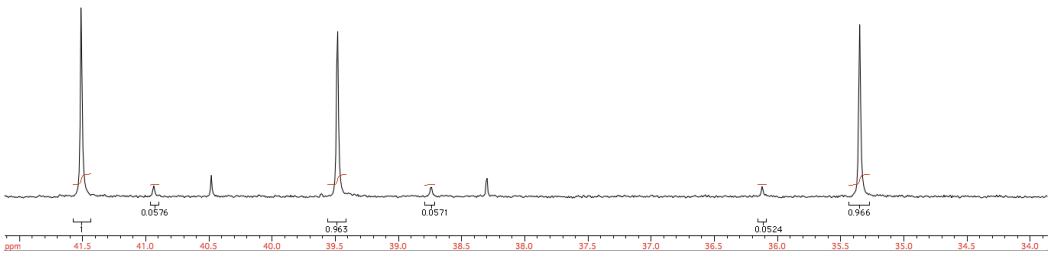
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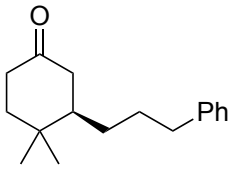
38.0
37.5
37.0
36.5
36.0
35.5
35.0
34.5
34.0

(–)-(*R*)-4,4-Dimethyl-3-(3-phenylpropyl)cyclohexan-1-one (2)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*S*,*S*,*S*)-**L1** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in ^{t}BuOMe (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. AgOTf (11.3 mg, 0.044 mmol, 0.11 eq) was added and the suspension was stirred for another 5 min. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred solution of *trans*-β-Methylstyrene (0.13 mL, 1.0 mmol, 2.5 eq) in THF (1 mL) under an argon atmosphere and heated at 60°C for 30 min until the hydrozirconation was complete (clear red solution). The THF was removed and the resulting oil was codistilled with CH_2Cl_2 before adding CH_2Cl_2 (0.4 mL). The stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the solution. The resulting black mixture was allowed to stir for an additional 10 min before 4,4-dimethyl-2-cyclohexen-1-one (53 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 20.0 mmol, 5.0 eq) were added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (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. Flash column chromatography of the yellow residue (1:9 EtOAc/hexanes; SiO_2) gave (–)-(*R*)-4,4-Dimethyl-3-(3-phenylpropyl)cyclohexan-1-one **2** (34 mg, 0.14 mmol, 35%) as yellow oil.

HPLC analysis indicated an enantiomeric excess of 84% [Chiralpak® IB; flow: 1 mL/min; hexane/^{i}PrOH: 99.5:0.5; λ = 210 nm; major enantiomer (–)-(*R*)-4,4-Dimethyl-3-(3-phenylpropyl)cyclohexan-1-one, t_R = 18.1 min; minor enantiomer (+)-(*S*)-4,4-Dimethyl-3-(3-phenylpropyl)cyclohexan-1-one, t_R = 19.5 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 0.98 (s, 3 H), 1.00 (s, 3 H), 1.42 - 1.66 (m, 5 H), 1.67 - 1.75 (m, 2 H), 2.05 (ddd, *J*=14.8, 12.0, 1.0 Hz, 1 H), 2.27 (m, 1 H), 2.36 - 2.46 (m, 2 H), 2.51 - 2.68 (m, 2 H), 7.13 - 7.20 (m, 3 H), 7.26 - 7.31 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 19.5, 28.7, 29.3, 30.2, 32.9, 35.9, 38.3, 40.4, 42.9, 46.7, 125.7, 128.3, 142.2, 212.2.

HRMS (EI) *m/z* calcd for $C_{17}H_{24}O$ $[M]^+$: 244.1827, found 244.1823.

IR (ATR) ν (cm^{-1}): 2930, 2861, 1713, 1495, 1453, 1389, 1151, 749, 700.

$[\alpha]^{20}_{589}$ = – 14.4 (*c* 1.09, $CHCl_3$)

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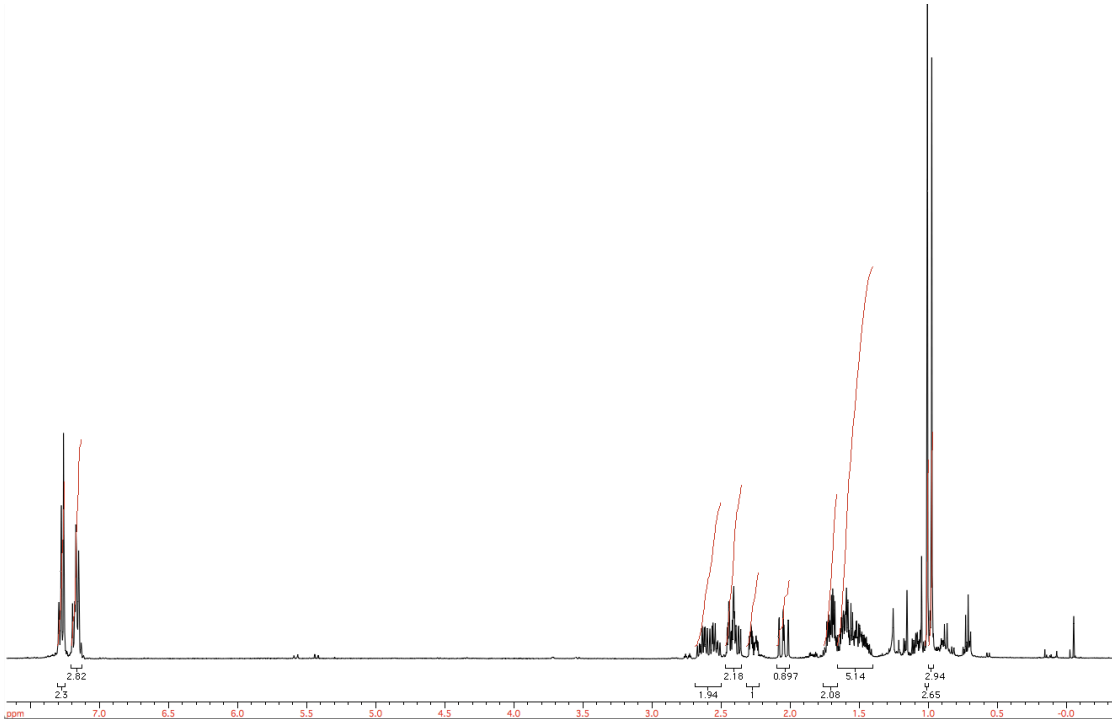
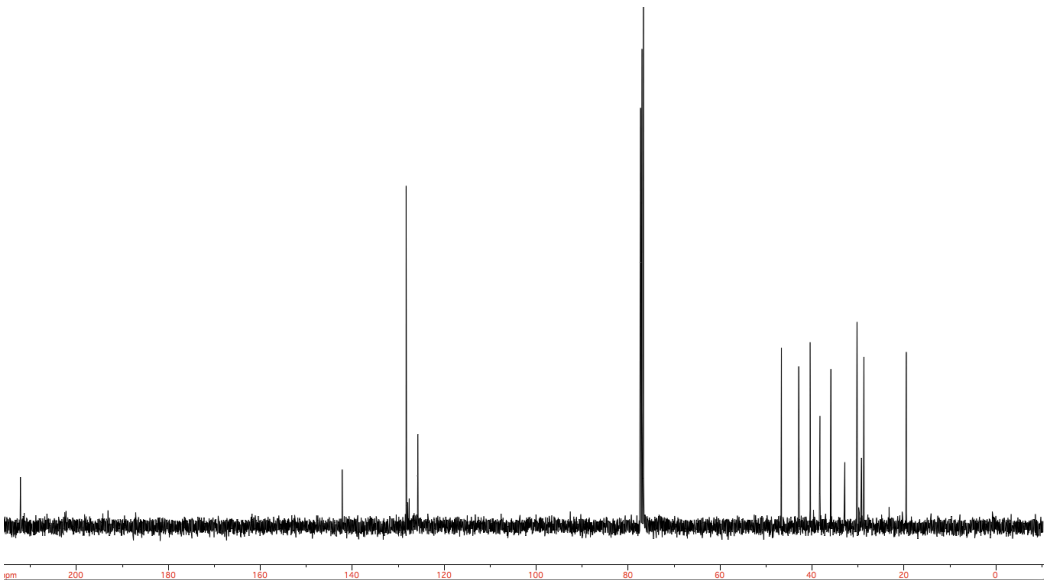
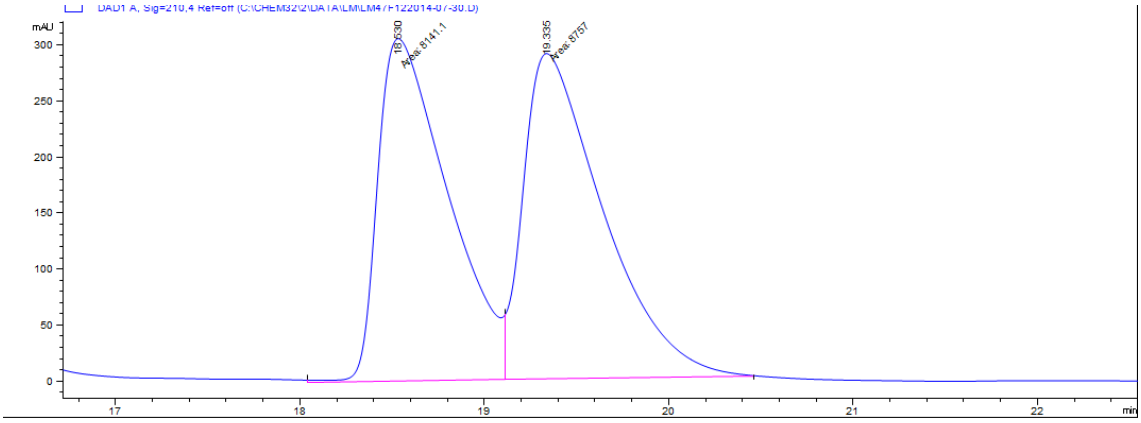
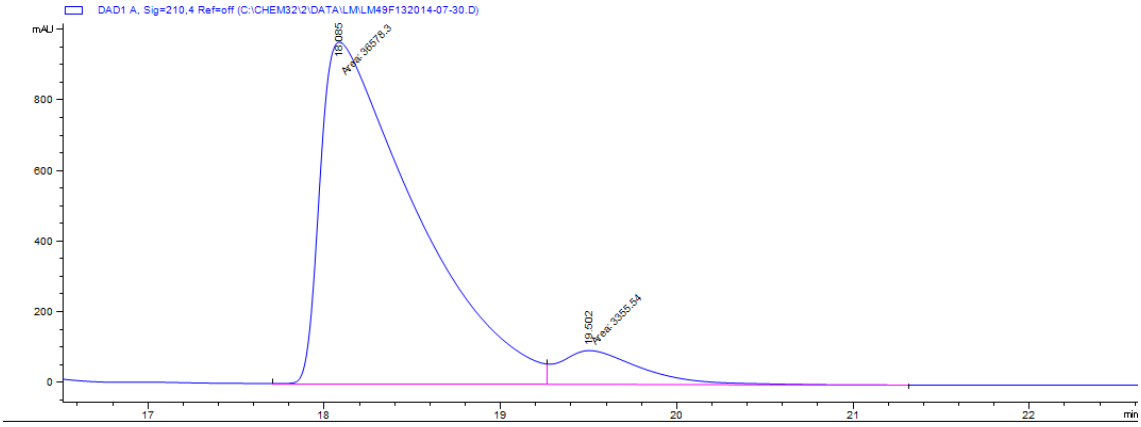


^{13}C NMR:

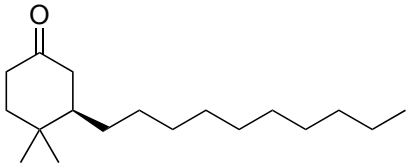


HPLC traces:





(–)-(*R*)-3-decyl-4,4-dimethylcyclohexan-1-one (3)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*S*,*S*,*S*)-**L1** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in ^{t}BuOMe (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. AgOTf (11.3 mg, 0.044 mmol, 0.11 eq) was added and the suspension was stirred for another 5 min. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred solution of *trans*-5-Decene 1(0.19 mL, 1.0 mmol, 2.5 eq) in THF (1 mL) under an argon atmosphere and heated at 60°C for 30 min until the hydrozirconation was complete (clear yellow solution). The THF was removed and the resulting oil was codistilled with CH_2Cl_2 before adding CH_2Cl_2 (0.4 mL). The stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the solution. The resulting black mixture was allowed to stir for an additional 10 min before 4,4-dimethyl-2-cyclohexen-1-one (53 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 20.0 mmol, 5.0 eq) were added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (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. Flash column chromatography of the yellow residue (1:9 EtOAc/hexanes; SiO_2) gave (–)-(R)-3-decyl-4,4-dimethylcyclohexan-1-one **3** (42 mg, 0.16 mmol, 39%) as a colorless oil. Enantiomeric excess (87% ee) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 0.88 (t, *J*=6.5 Hz, 3 H), 0.95 - 1.05 (m, 7H), 1.06 - 1.13 (m, 1 H), 1.17 - 1.38 (m, 16 H), 1.43 - 1.55 (m, 2 H), 1.60 (dd, *J*=13.1, 4.8 Hz, 1 H), 1.70 (ddd, *J*=13.6, 6.1, 3.75 Hz, 1 H), 2.22 - 2.29 (m, 1 H), 2.36 - 2.44 (m, 2 H).

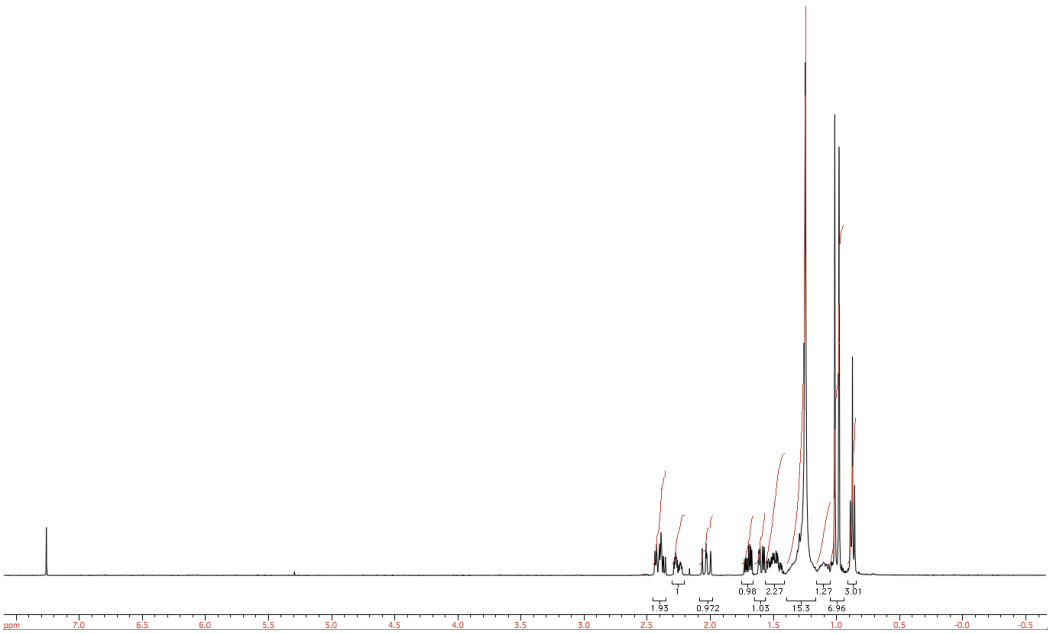
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 14.1, 19.5, 22.7, 27.5, 28.7, 29.3, 29.6 (2C), 29.7, 30.5, 31.9, 32.8, 38.3, 40.5, 42.9, 46.8, 212.4.

HRMS (EI) *m*/*z* calcd for $C_{16}H_{34}ONa$ $[M]^+$: 289.2502, found 289.2499.

IR (ATR) ν (cm^{-1}): 2923, 2854, 1715, 1466, 1366, 1145, 722.

$[\alpha]^{20}_{589}$ = – 13.8 (*c* 1.10, $CHCl_3$).

^{1}H NMR:



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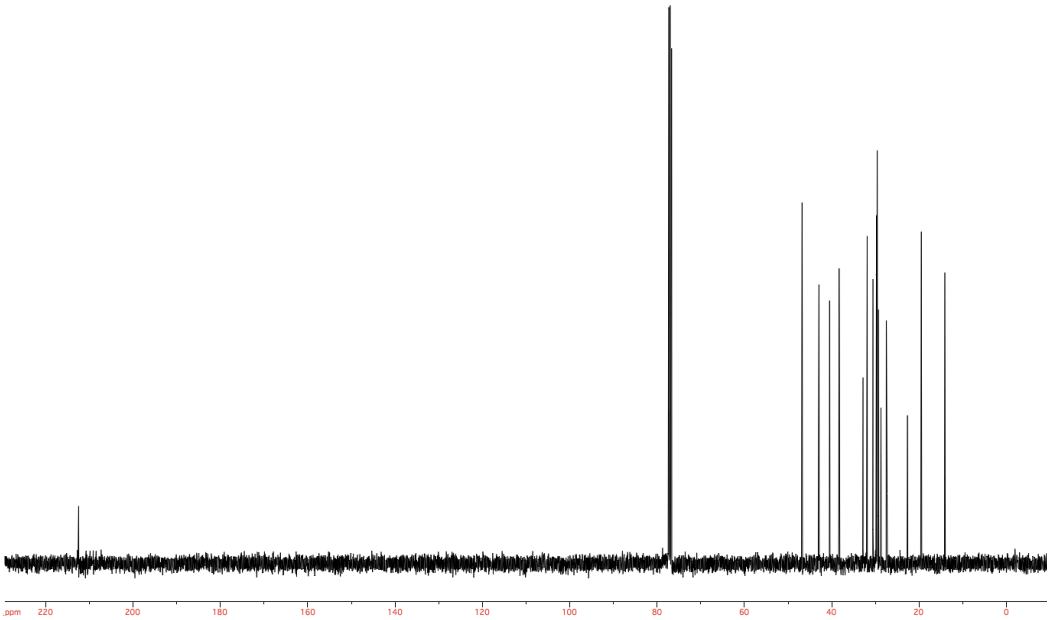
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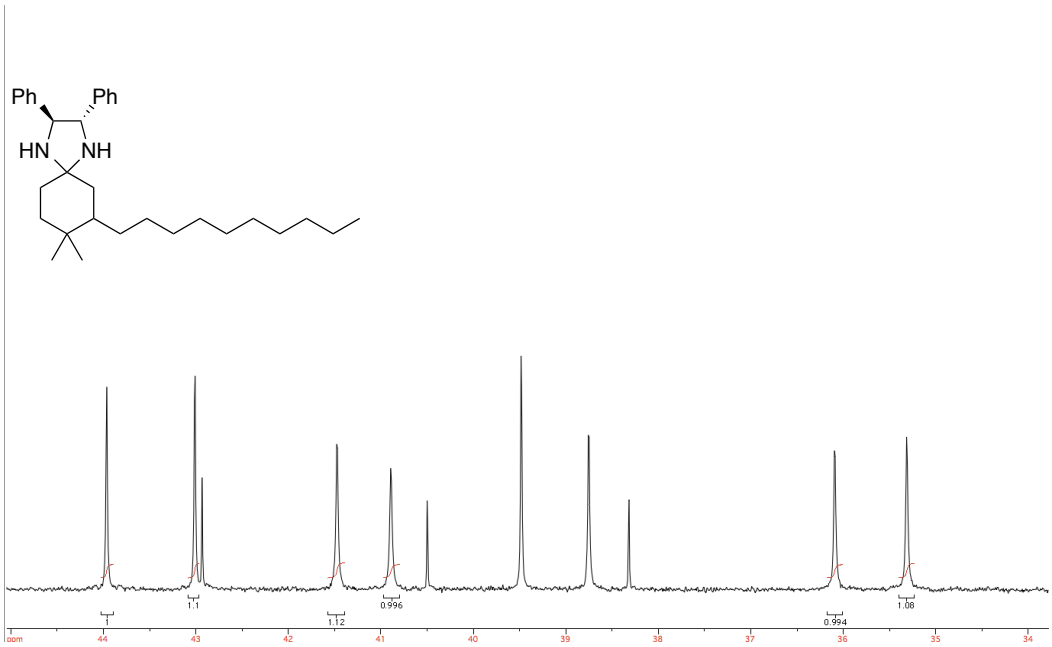
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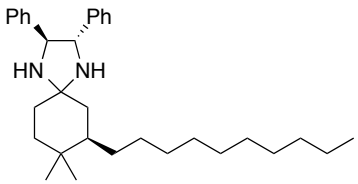
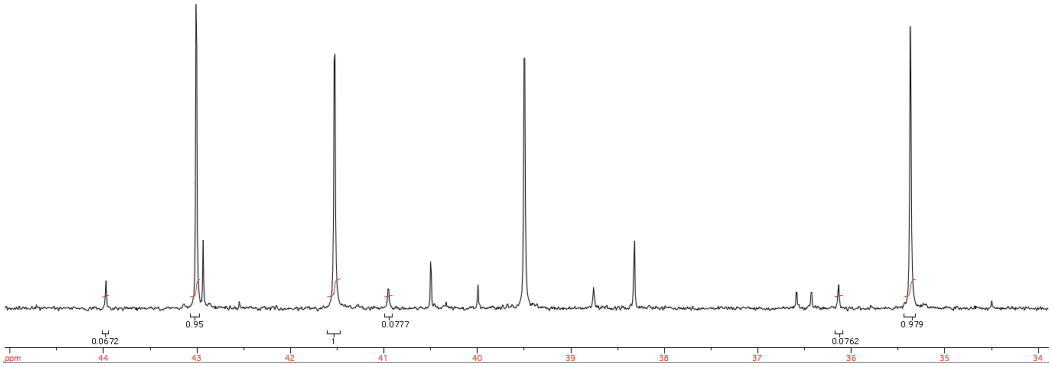
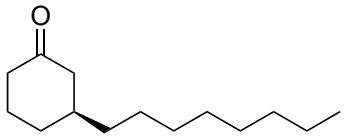
37
36
35
34





(–)-(*S*)-3-octylcyclohexan-1-one (4)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*S*,*S*,*S*)-**L1** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in ^{t}BuOMe (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. AgOTf (11.3 mg, 0.044 mmol, 0.11 eq) was added and the suspension was stirred for another 5 min. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred solution of *trans*-4-Octene (0.16 mL, 1.0 mmol, 2.5 eq) in THF (1 mL) under an argon atmosphere and heated at 60°C for 30 min until the hydrozirconation was complete (clear yellow solution). The THF was removed and the resulting oil was codistilled with CH_2Cl_2 before adding CH_2Cl_2 (0.4 mL). The stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the solution. The resulting black mixture was allowed to stir for an additional 10 min before 2-cyclohexen-1-one (39 µL, 0.40 mmol, 1.0 eq) and then TMSCl (0.25 mL, 20.0 mmol, 5.0 eq) were added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (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. Flash column chromatography of the yellow residue (1:9 EtOAc/hexanes; SiO_2) gave (-)-(*S*)-3-octylcyclohexan-1-one **4** (18 mg, 0.09 mmol, 22%) as a colorless oil. Enantiomeric excess (89% ee) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 0.89 (t, *J*=9.9 Hz, 3 H), 1.19 - 1.35 (m, 14 H), 1.59 - 1.71 (m, 1 H), 1.70 - 1.79 (m, 1 H), 1.86 - 1.92 (m, 1 H), 1.96 - 2.07 (m, 2 H), 2.21 - 2.29 (m, 1 H), 2.31 - 2.38 (m, 1 H), 2.41 (ddt, *J*=13.7, 4.1, 2.0 Hz, 1 H).

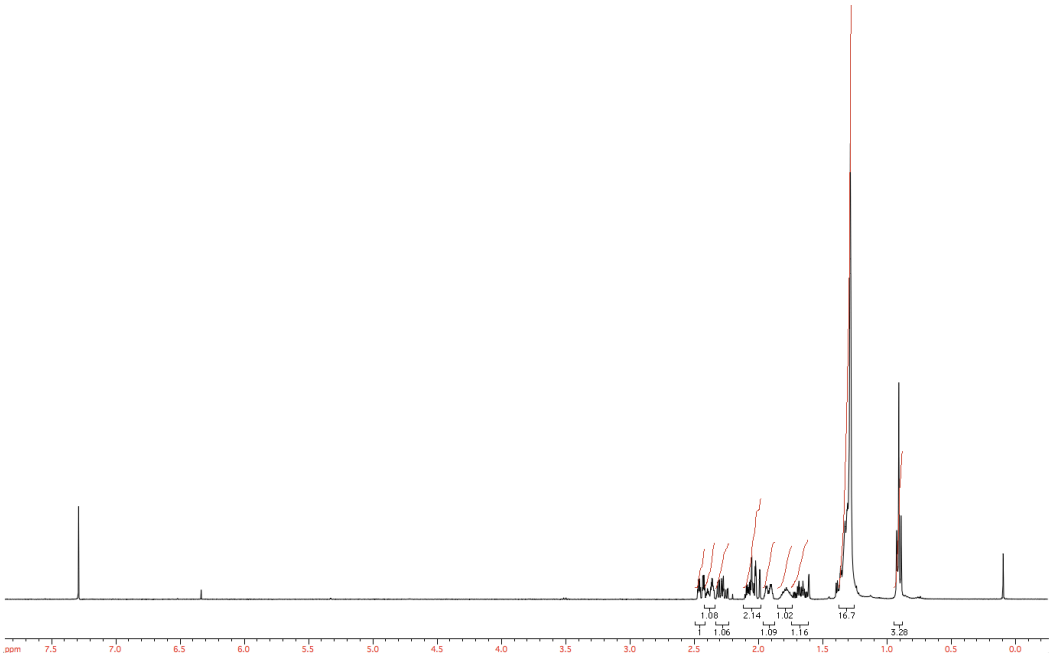
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 14.1, 22.7, 25.3, 26.6, 29.3, 29.5, 29.7, 31.3, 31.9, 36.6, 39.1, 41.5, 48.2, 212.1.

HRMS (ESI) *m/z* calcd for $C_{14}H_{27}O$ $[M+H]^+$ 211.2056, found 211.2054.

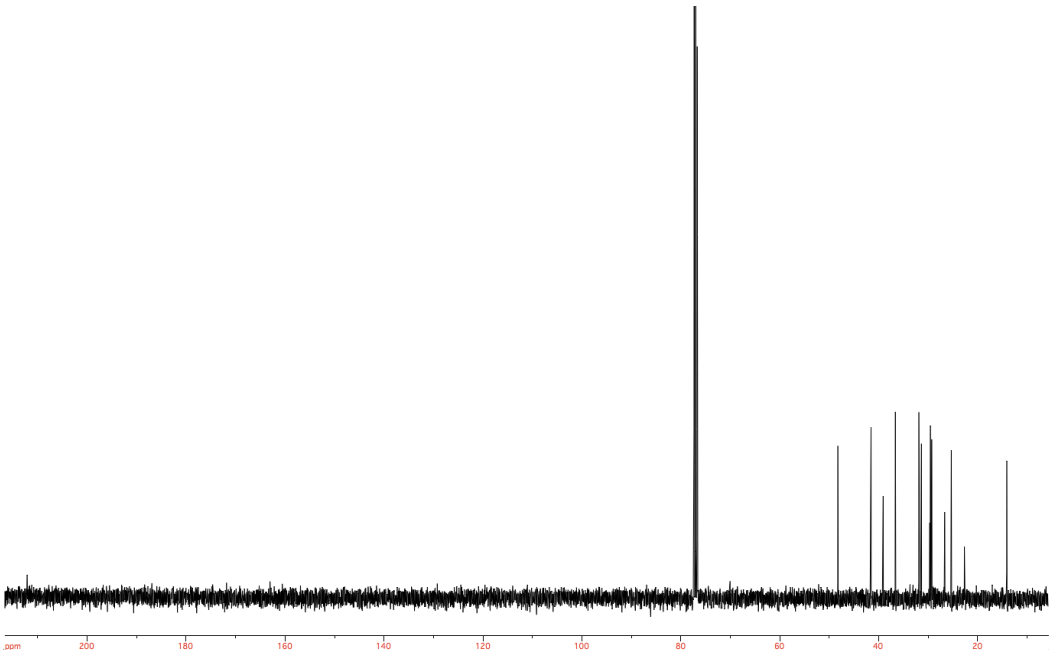
IR (ATR) ν (cm^{-1}): 2924, 2854, 1714, 1459, 1224.

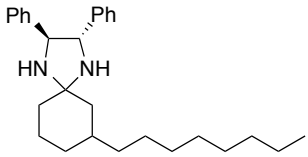
$[\alpha]^{20}_{589}$ = -9.6 (*c* 1.4, $CHCl_3$)

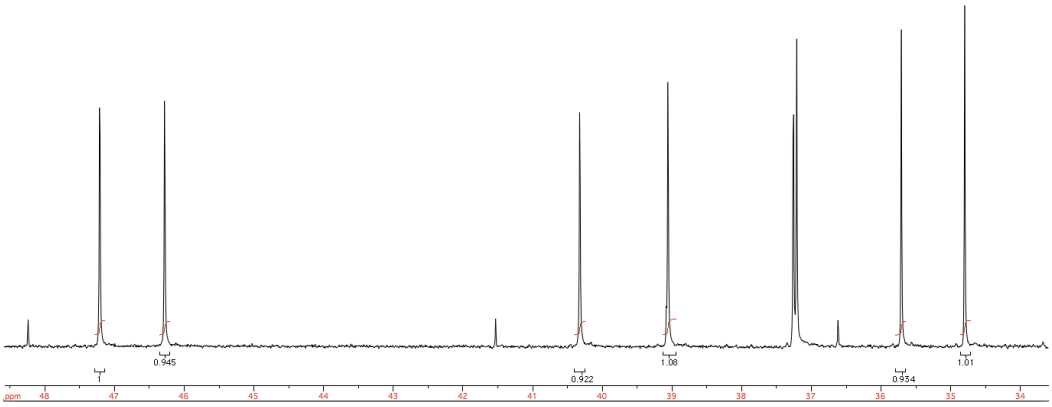
^{1}H NMR:

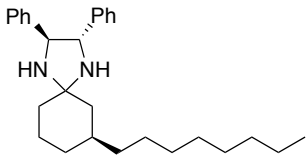


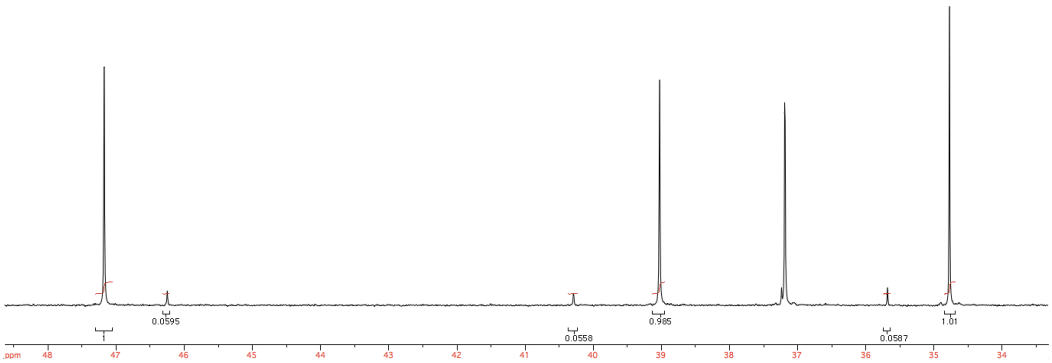
^{13}C NMR:



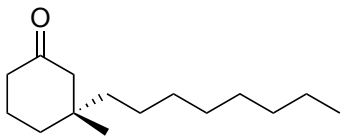








(+)-(*R*)-3-methyl-3-octylcyclohexan-1-one (5)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*R*)-**L2** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in ^{t}BuOMe (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. $AgNTf_2$ (17.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred solution of *trans*-4-Octene (0.16 mL, 1.0 mmol, 2.5 eq) in THF (1 mL) under an argon atmosphere and heated at

60°C for 30 min until the hydrozirconation was complete (clear yellow solution). The THF was removed and the resulting oil was codistilled with CH_2Cl_2 before adding CH_2Cl_2 (0.4 mL). The stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the solution. The resulting black mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone (45 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (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. Flash column chromatography of the yellow residue (1:9 EtOAc/hexanes; SiO_2) gave (+)-(*R*)-3-methyl-3-octylcyclohexan-1-one **5** (47 mg, 0.15 mmol, 37%) as a yellow oil. Enantiomeric excess (89% ee) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 0.87 (t, *J*=6.8 Hz, 3 H), 0.90 (s, 3H), 1.16 - 1.34 (m, 14 H), 1.48 - 1.55 (m, 1H), 1.59 - 1.65 (m, 1 H), 1.81 - 1.88 (m, 2H), 2.07 - 2.19 (m, 2 H), 2.60 (br t, *J*=6.8 Hz 2 H).

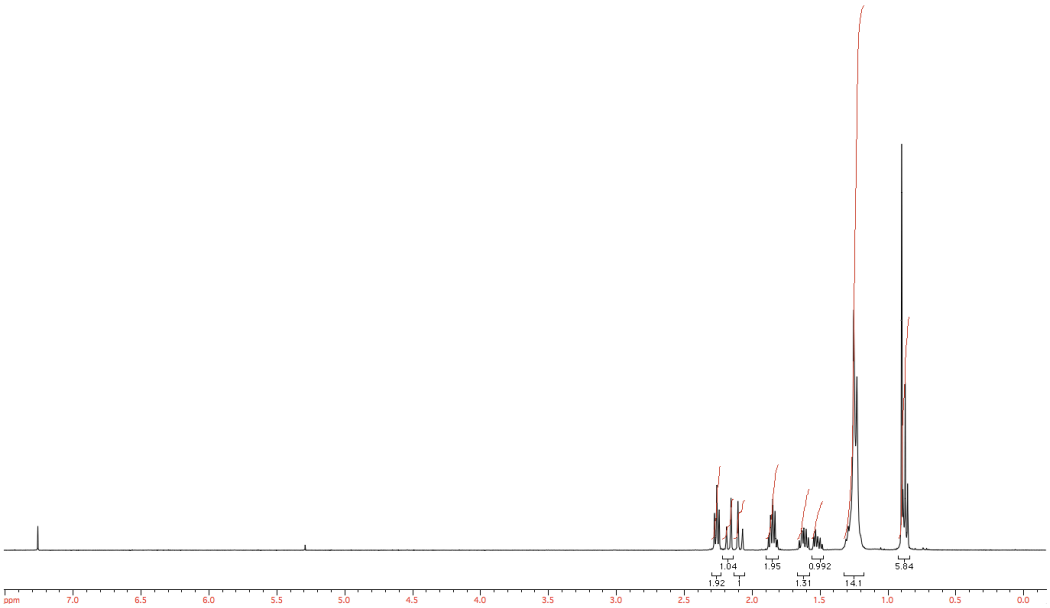
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 14.1, 22.1, 22.6, 23.3, 25.1, 29.3, 29.5, 30.3, 31.8, 35.6, 38.6, 41.0, 41.6, 53.8, 212.4.

HRMS (ESI) *m/z* calcd for $C_{15}H_{28}O$ $[M+H]^+$ 225.2213, found 225.2210.

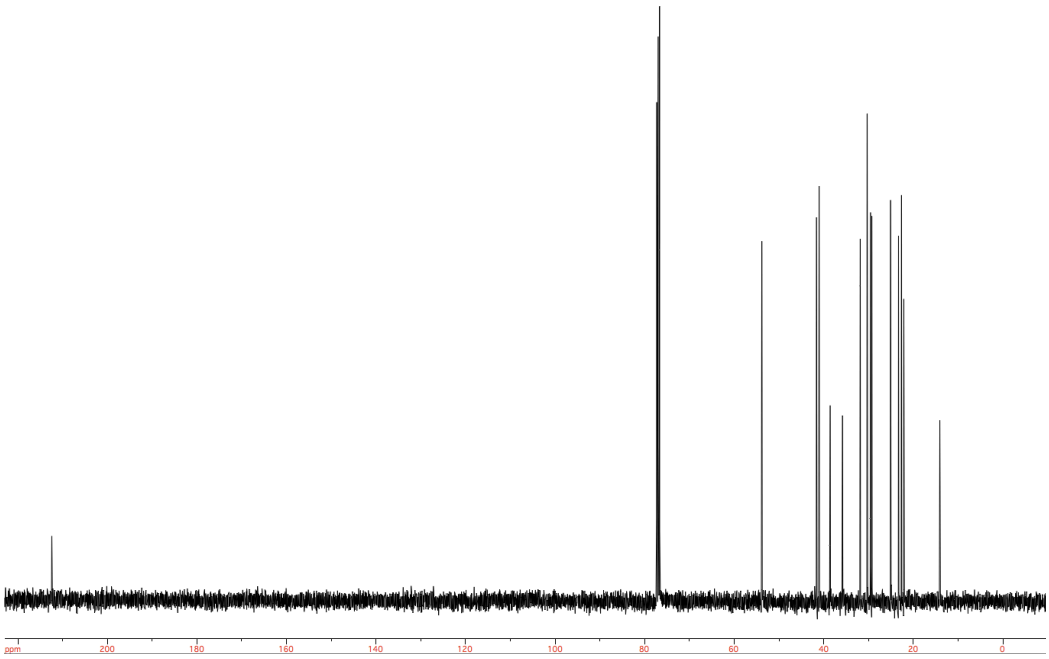
IR (ATR) ν (cm^{-1}): 2926, 2854, 1713, 1462, 1379, 1312, 723.

$[\alpha]^{20}_{589}$ = + 0.31 (*c* 1.14, $CHCl_3$).

^{1}H NMR:



^{13}C NMR: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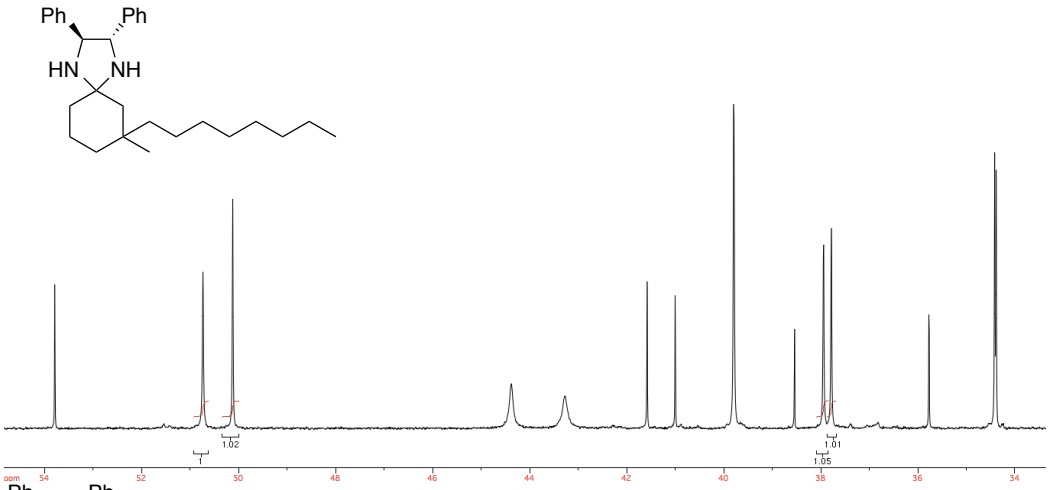
180
160
140
120
100
80
60
40
20
0


Ph
Ph
HN
NH
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1.01
1.05
ppm
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48
46
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42
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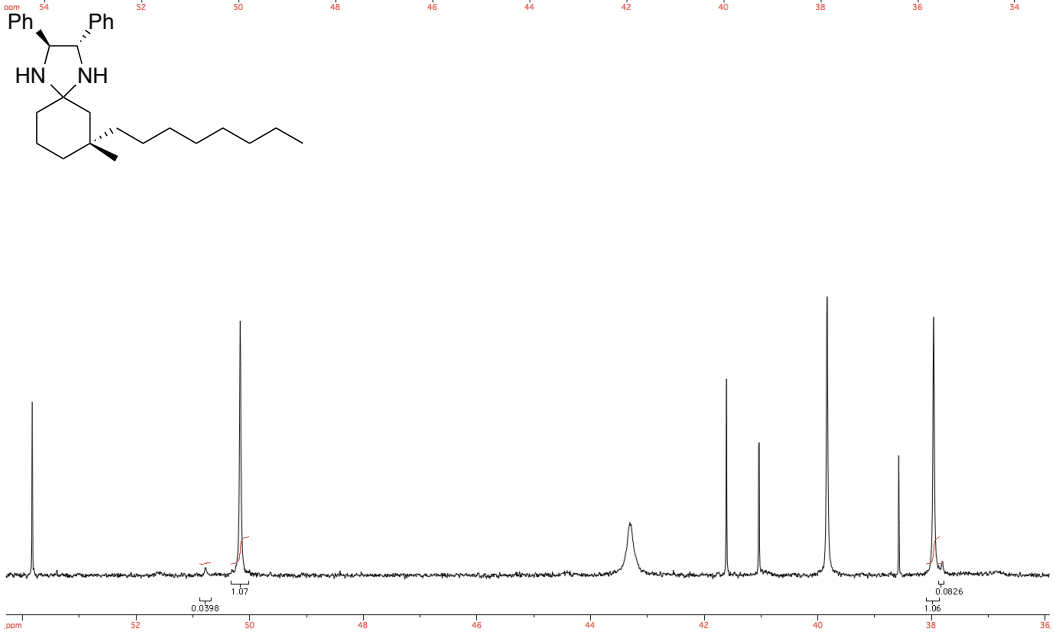
36
34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NH
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1.07
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1.06
ppm
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46
44
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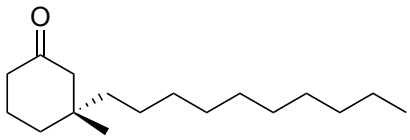
38
36

(+)-(*S*)-3-Decyl-3-methylcyclohexan-1-one (6)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*R*)-**L2** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in ^{t}BuOMe (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. $AgNTf_2$ (17.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred solution of *trans*-5-Decene (0.19 mL, 1.0 mmol, 2.5 eq) in THF (1 mL) under an argon atmosphere and heated at 60°C for 30 min until the hydrozirconation was complete (clear yellow solution). The THF was removed and the resulting oil was codistilled with CH_2Cl_2 before adding CH_2Cl_2 (0.4 mL). The stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the solution. The resulting black mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone (45 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (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. Flash column chromatography of the yellow residue (1:9 EtOAc/hexanes; SiO_2) gave (+)-(*S*)-3-Decyl-3-methylcyclohexan-1-one **6** (43 mg, 0.17 mmol, 43%) as a colorless oil. Enantiomeric excess (87% ee) was determined by integration of the diastereomeric mixture of the corresponding (+)-(*R*,*R*)-DPEN derivative by ^{13}C NMR spectroscopic analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 0.91 (t, *J*=6.8 Hz, 3 H), 0.94 (s, 3H), 1.24 - 1.33 (m, 18H), 1.53 - 1.60 (m, 1 H), 1.62 - 1.70 (m, 1 H), 1.86 - 1.92 (m, 2 H), 2.11 - 2.14 (m, 1 H), 2.19 - 2.23 (m, 1 H), 2.28 - 2.31 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 14.1, 22.1, 22.7, 23.3, 25.1, 29.3, 29.6 (2C), 30.3, 31.9, 35.8, 38.6, 41.0, 41.6, 53.8, 212.5.

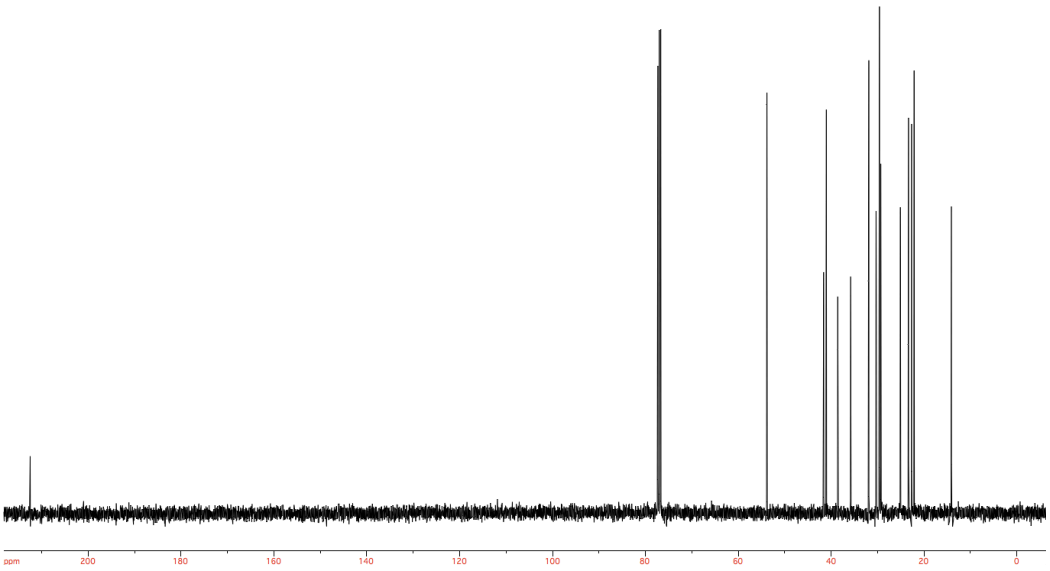
HRMS (EI) *m/z* calcd for $C_{16}H_{33}O$ $[M]^+$: 252.2453, found 252.2404.

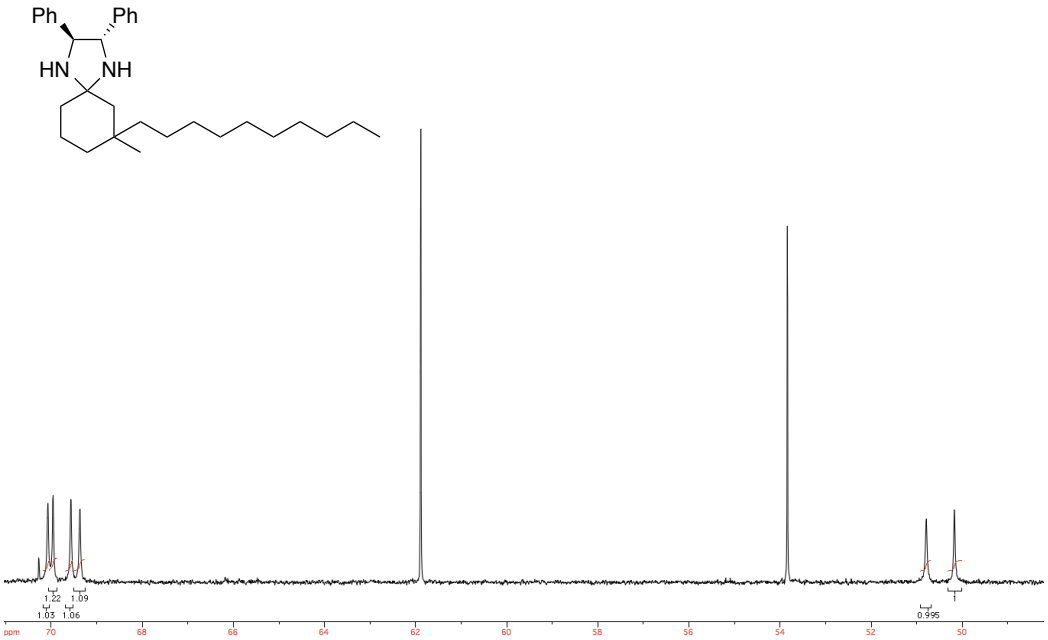
IR (ATR) ν (cm^{-1}): 2924, 2853, 1714, 1464, 1379, 1312, 1227, 722.

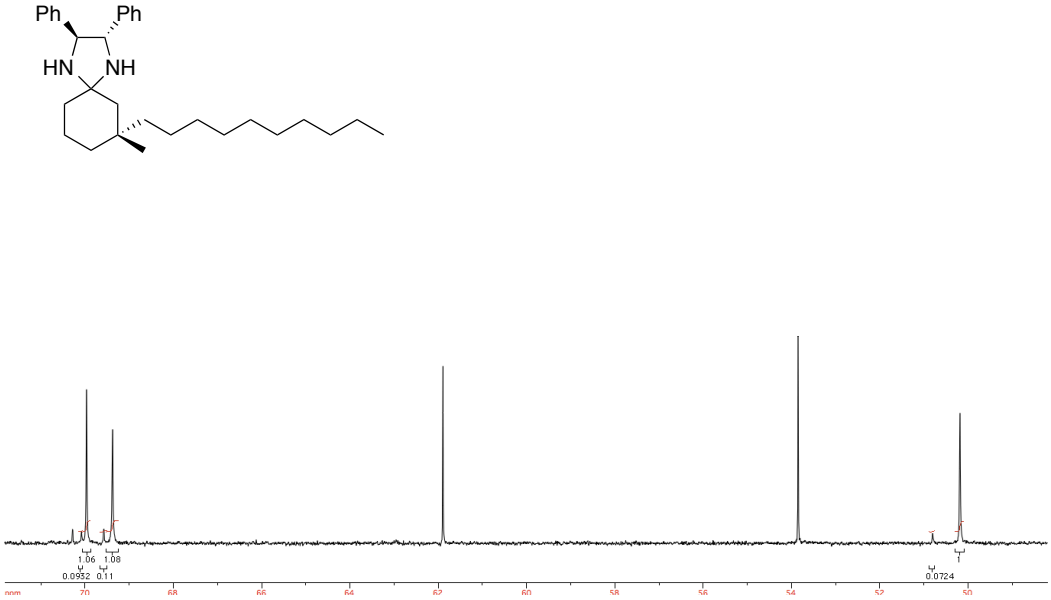
$[\alpha]^{20}_{589}$ = + 0.72 (*c* 1.02, $CHCl_3$).

^{1}H NMR:

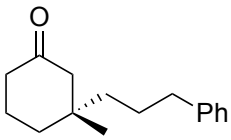
^{13}C NMR:







(+)-(*R*)-3-Methyl-3-(3-phenylpropyl)cyclohexan-1-one (7)



CuCl (3.6 mg, 0.04 mmol, 0.10 eq) and the phosphoramidite ligand (*R*)-**L2** (21.6 mg, 0.040 mmol, 0.10 eq) were dissolved in ^{t}BuOMe (2.0 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. $AgNTf_2$ (17.2 mg, 0.060 mmol, 0.15 eq) was added and the suspension was stirred for another 15 min. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred solution of *trans*-β-Methylstyrene (0.13 mL, 1.0 mmol, 2.5 eq) in THF (1 mL) under an argon atmosphere and

heated at 60°C for 30 min until the hydrozirconation was complete (clear red solution). The THF was removed and the resulting oil was codistilled with CH_2Cl_2 before adding CH_2Cl_2 (0.4 mL). The stirred solution containing the copper and ligand was transferred and filtered using a syringe filter to the solution. The resulting black mixture was allowed to stir for an additional 10 min before 3-methyl-2-cyclohexenone (45 µL, 0.40 mmol, 1.0 eq) was added dropwise *via* syringe. Stirring continued 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3mL) and then NH_4Cl (1M aq., *ca* 1.5mL). The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O (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. Flash column chromatography of the yellow residue (1:9 EtOAc/hexanes; SiO_2) gave (+)-(*R*)-3-Methyl-3-(3-phenylpropyl)cyclohexan-1-one **7** (28 mg, 0.12 mmol, 30%) as a yellow oil.

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IC; flow: 1 mL/min; hexane/^{i}PrOH: 98:2; λ = 210 nm; major enantiomer (+)-(R)-3-methyl-3-(3-phenylpropyl)cyclohexan-1-one, t_R = 15.9 min; minor enantiomer (-)-(*S*)-3-Methyl-3-(3-phenylpropyl)cyclohexan-1-one, t_R = 17.1 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 0.90 (s, 3 H), 1.29 - 1.34 (m, 2 H), 1.49 - 1.65 (m, 4 H), 1.80 - 1.89 (m, 2 H), 2.10 (d, *J*=13.5 Hz, 1 H), 2.18 (d, *J*=13.5 Hz, 1 H), 2.28 - 2.64 (m, 2 H), 2.56 - 2.60 (m, 2 H), 7.16 - 7.20 (m, 3 H), 7.26 - 7.30 (m, 2 H).

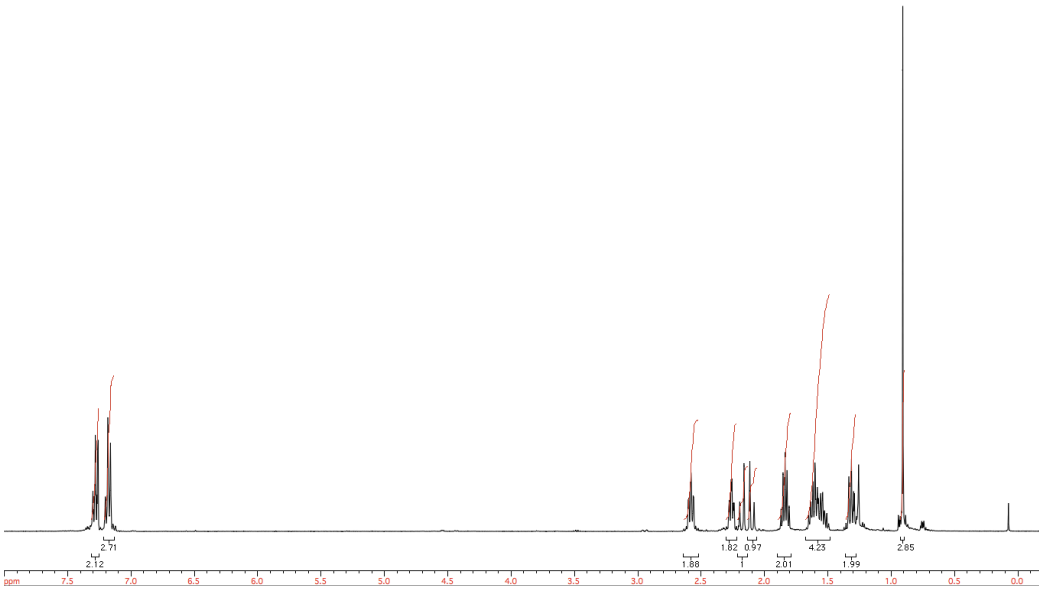
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 22.1, 25.0, 25.4, 35.7, 36.4, 38.5, 41.0, 41.2, 53.8, 125.7, 128.3, 142.3, 212.3.

HRMS (EI) *m/z* calcd for $C_{16}H_{22}O$ $[M]^+$: 230.1671, found 230.1671.

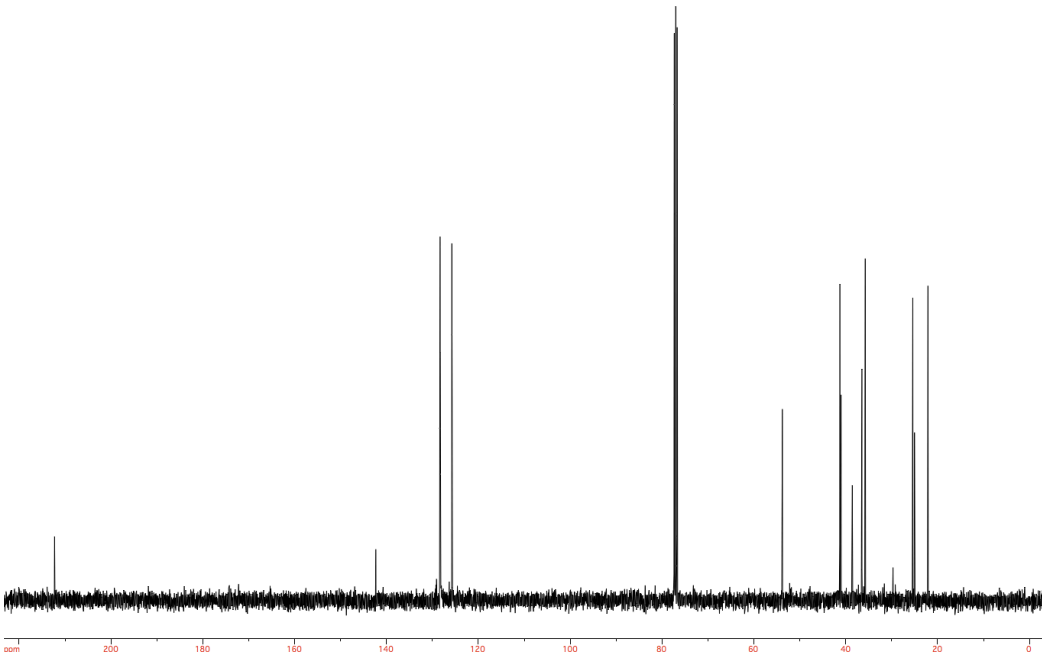
IR (ATR) ν (cm^{-1}): 2936, 1710, 1496, 1454, 1312, 1228, 1076, 749, 699.

$[\alpha]^{20}_{589}$ = –15.2 (*c* 0.99, $CHCl_3$) .

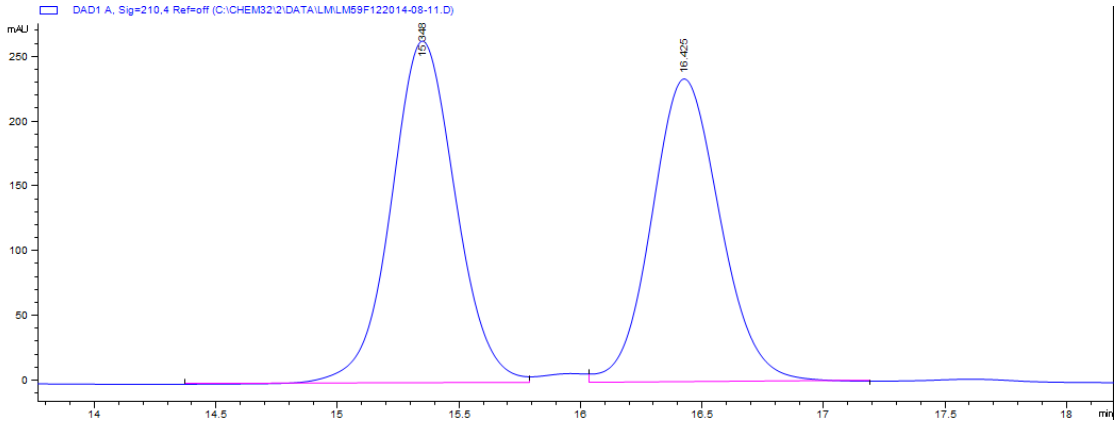
^{1}H NMR:

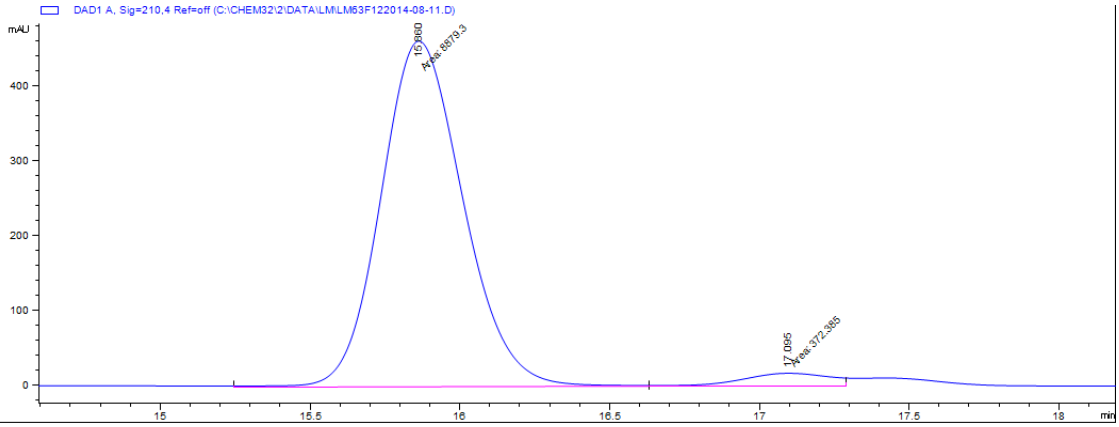


^{13}C NMR:

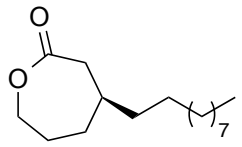


HPLC traces:





(–)-(*S*)-4-Decyloxepan-2-one (8)



Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq.) was added to a stirred, room temperature, solution of *trans*-5-Decene (0.19 mL, 1.0 mmol, 2.5 eq) in THF (1 mL) under an argon atmosphere and heated at 60°C for 30 min until the hydrozirconation was complete (clear yellow solution). The THF was removed and the resulting oil was codistilled with CH_2Cl_2 before adding CH_2Cl_2 (0.4 mL) and transferring *via* syringe over about 1 min to a clear colourless stirred solution of CuOTfl-**L2** complex (30.0 mg, 0.040 mmol, 0.10 eq.) in Et_2O (2.0 mL) under an argon atmosphere. The resulting dark mixture was allowed to stir for 10 min before 6,7-dihydrooxepin-2(5H)-one (45 µL, 0.40 mmol, 1.0 eq.) and then TMSCl (0.25 mL, 2.0 mmol, 5.0 eq.) were added via syringe. Stirring was continued for 12 h before the reaction was quenched by the addition of Et_2O (*ca* 3 mL) and then NH_4Cl (1 M aq., *ca* 1.5 mL). The mixture was partitioned between water and Et_2O and the aqueous phase was extracted with Et_2O (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. Flash column chromatography of the yellow residue (2:3 EtOAc/hexane; SiO2) gave (-)-(*S*)-4-Decyloxepan-2-one (40 mg, 0.16 mmol, 40%) as a pale yellow oil.

HPLC analysis of the derivative of **8** (see general procedures) indicated an enantiomeric excess of 84% [Chiralpak® IC; flow: 1 mL/min; hexane/^{i}PrOH: 80:20; λ = 210 nm; major enantiomer t_R = 7.8 min; minor enantiomer t_R = 8.9 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 0.87 (t, *J*=6.9 Hz, 3 H), 1.25 - 1.35 (m, 18 H), 1.42 - 1.47 (m, 2H), 1.72 - 1.78 (m, 2 H), 1.88 - 1.93 (m, 2 H), 2.52 (dd, *J*=13.5, 9.74 Hz, 1 H), 2.58 - 2.63 (m, 1 H), 4.15 – 4.23 (m, 2 H).

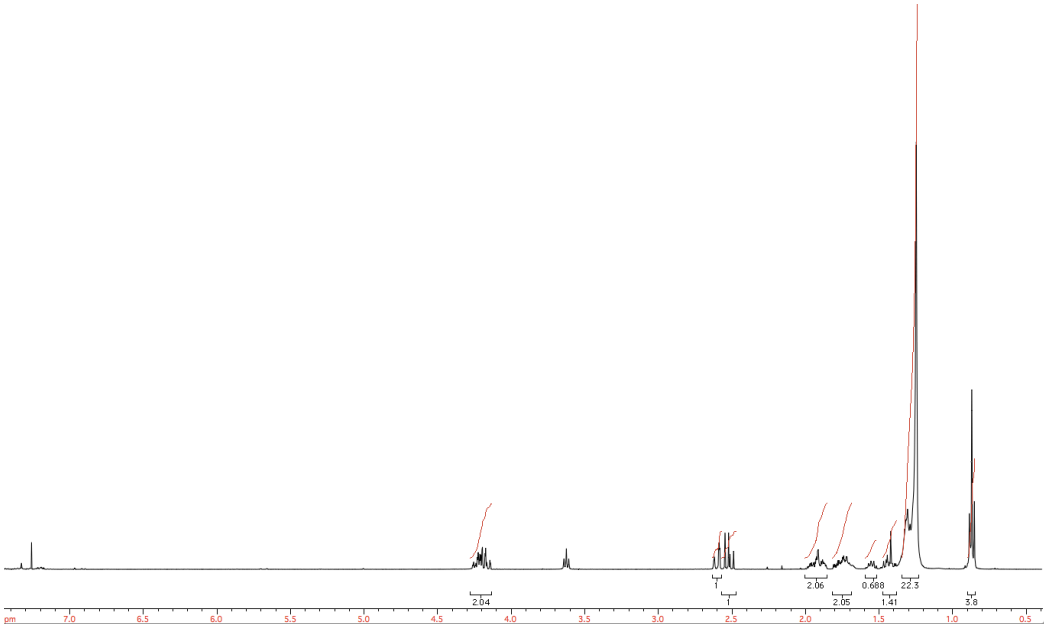
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 14.1, 22.6, 25.7, 26.7, 27.7, 29.3, 29.4, 29.5, 29.6, 31.7, 32.8, 34.0, 36.0, 40.1, 69.2, 175.2.

HRMS (ESI) *m/z* calcd for $C_{16}H_{31}O_2Na$ $[M+Na]^+$: 277.21347, found: 277.21380.

IR (ATR) ν (cm^{-1}): 2923, 2853, 1731, 1466, 1392, 1288, 1169, 1057, 722.

$[\alpha]^{20}_{589}$ = –22.0 (*c* 0.99, $CHCl_3$).

^{1}H NMR: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22.3
3.8
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6.5
6.0
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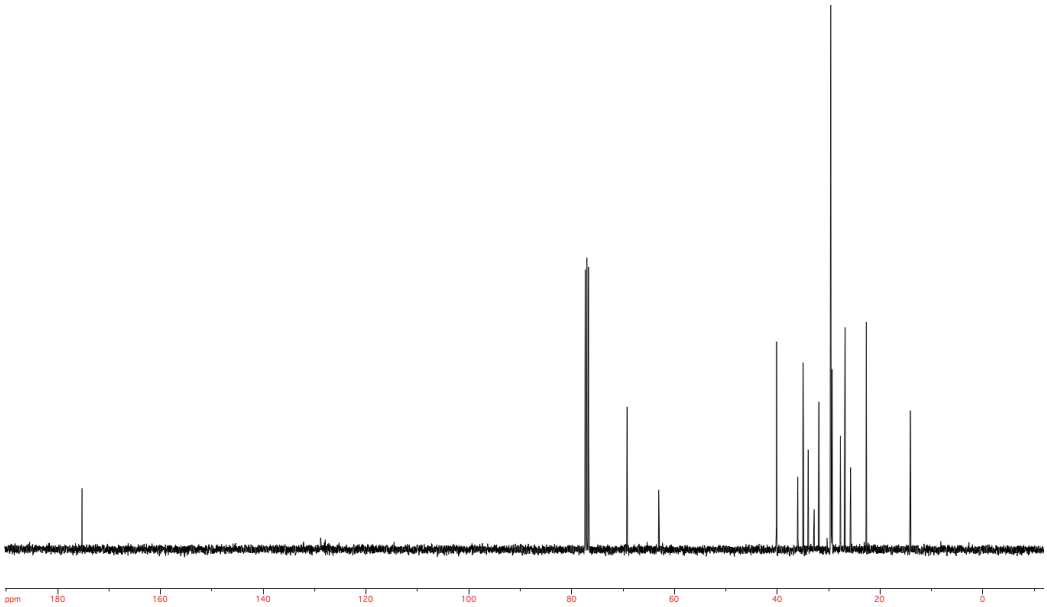
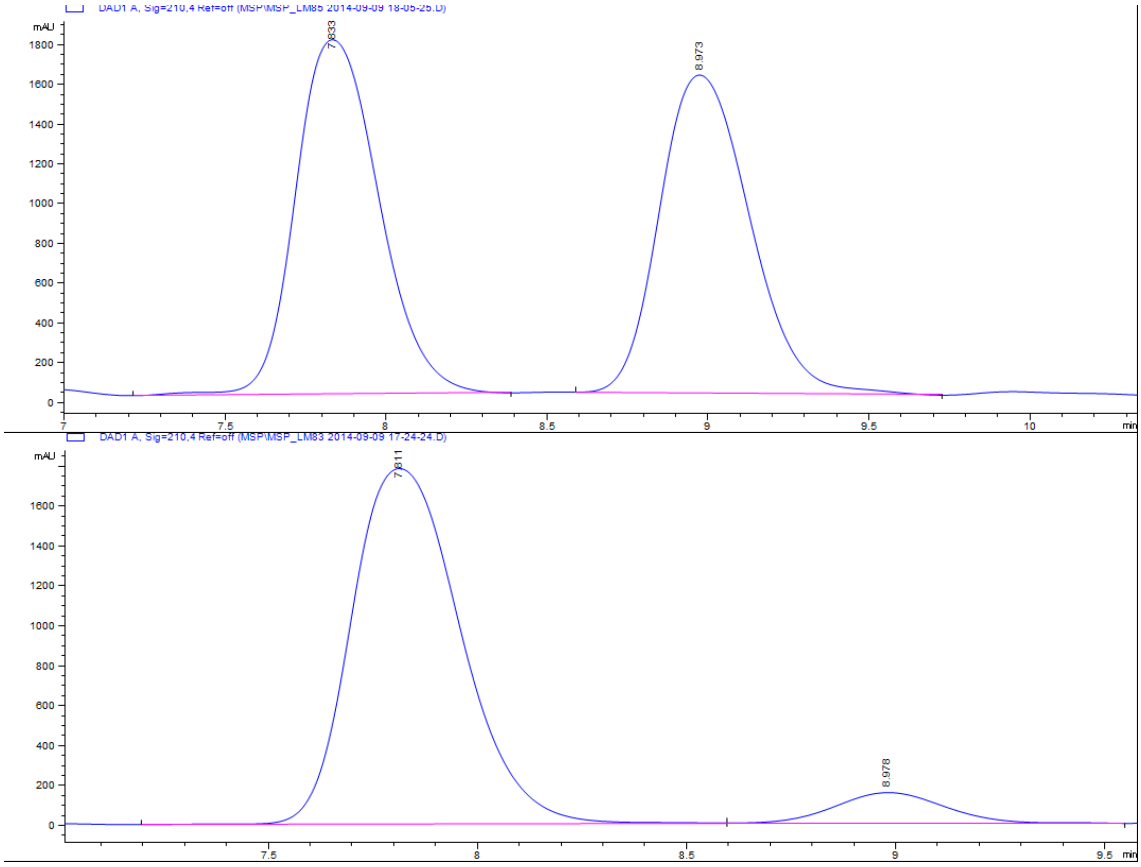
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

^{13}C NMR:


ppm
180
160
140
120
100
80
60
40
20
0

HPLC traces:



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