Supporting Information

Retooling Asymmetric Conjugate Additions for Sterically Demanding Substrates with an Iterative Data-Driven Approach

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Contents

I. Experimental Section

1. General Information

Procedures were all carried out in flame-dried flasks with anhydrous solvents under Argon atmosphere.

Analytical thin-layer chromatography (TLC) was conducted on precoated glass-backed plates (Silica Gel 60 F254, Merck). Visualization was performed by UV light (254nm), p-Anisaldehyde and aqueous basic potassium permanganate (KMnO4) stains as stated in the general methods.

Flash column chromatography was carried out using Apollo Scientific silica gel 60 (0.040 – 0.063 nm), VWR (40-63 μm) silica gel, Sigma Aldrich silica gel. SCX column chromatography was carried out using Isolute® flash SCX-2 columns from Biotage.

Reaction temperature at 0 °C was achieved using an ice-water bath. The reactions were regularly topped up with ice and wrapped with cotton in order to keep the reaction at 0 °C overnight. Light sensitive reactions were processed under Aluminium foil protection.

Preformed ligand-copper complexes were filtered under Argon atmosphere through polytetrafluorethane (PTFE) syringe filter (13 mm, 0.2 μm) from Camlab.

All NMR spectra were recorded at room temperature. ^{1}H, ^{13}C and ^{31}P nuclear magnetic resonance (NMR) experiments were carried out using “AVG-400” (Bruker AVIIIHD 400 nanobay 400/100 MHz) , “AVH-400” (Bruker AVIIIHD 400 nanobay 400/100 MHz) or “AVC-500” (Bruker AVII 500 with 13C cryoprobe 500/125 MHz) spectrometers. Quantitative ^{1}H NMR experiments were carried out using “AV700” (Bruker AVIII 700 with He cryoprobe). Chemical shifts (δ) were reported in part per million, referenced to the residual solvent peak. Scalar coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (p) or multiplet (m). Broad peaks are indicated as (br). Coupling constants (J) were quoted to one decimal place in hertz (Hz). Chemical shifts were quoted to two decimal places in ^{1}H NMR and one decimal place in ^{13}C NMR and ^{31}P NMR. HSQC, COSY and HMBC based experiments were performed to aid the assignment of spectra.

Chiral HPLC separations were achieved using an Agilent 1260 Infinity series normal phase HPLC unit and HP Chemstation software. Retention times (t_R) are given in min. Chiralpak® columns (250×4.6 mm), fitted with matching Chiralpak® Guard Cartridges (10×4 mm), were used as specified in the text. Chiral SFC (supercritical fluid chromatography) separations were conducted on a Waters Acquity UPC2 system using Waters Empower software. Chiralpak® columns (150 × 3 mm, particle size 3 μm) were used. Solvents used were of HPLC grade (Fisher Scientific, Sigma Aldrich or Rathburn). All eluent systems were isocratic, except stated otherwise.

Infra-red spectra were recorded on a Bruker Tensor 27 FTIR spectrometer equipped with a PIKE Miracle Attenuated Total Reflectance sampling accessory using a solid sample or thin film for liquid compounds. IR data was reported in wavenumbers (cm^{-1})

High Resolution Mass spectra were carried out by internal service at the University of Oxford. Electron spray ionisation (ESI^{+}) was recorded on a Fisons Platform II. Electron ionisation (EI)/Chemical ionisation (CI) was performed on an Agilent 7200 quadrupole time of flight (Q-ToF)

instrument equipped with a direct insertion probe supplied by Scientific instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using Agilent MassHunter software. The system was calibrated on the day of the analysis and its mass accuracy with external calibration (as used for these experiments) is better than 5ppm for 24 hours following calibration. Source conditions for both EI and CI were adjusted to maximise sensitivity, the reagent gas used in CI was either methane or ammonia. Atmospheric pressure chemical ionisation ($APCI^+$) was performed using a Thermo Exactive mass spectrometer equipped with Waters Acquity liquid chromatography system. Instrument control and data processing were performed using Thermo Xcalibur Software. The system was calibrated on the day of the analysis and its mass accuracy with external calibration (as used for these experiments) is better than 5ppm for 24 hours following calibration. The mass spec was operated using the APCI probe and resolution was set to 50,000. APCI source conditions were adjusted to maximise sensitivity. A mixture of 10% water, 89.9% methanol and 0.1% formic acid was used to transport samples to the mass spectrometer at a flow rate of 0.2 mL/min.

Chemical names were generated from CambridgeSoft ChemBioDraw Ultra 14.0 programme. Optical rotations ($[\alpha]^T_D$) were recorded from a Perkin Elmer 241 Polarimeter and are reported in degree·ml$(\cdot g \cdot dm)^{-1}$. Samples were prepared at concentration (c) measured in g·100 ml^{-1}.

2. Chemicals

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.

Deuterated solvents were purchased from Sigma-Aldrich ($CDCl_3$). The 99.99% purity CuCl was from Sigma-Aldrich and was used without any further purification. Dry Trimethylsilyl chloride (TMSCl) under inert atmosphere was used without further purification from Sigma-Aldrich, and was distilled fresh and stored in a Schlenk flask with CaH_2(s) under an argon atmosphere when stated differently in the text. PCl_3 from Sigma-Aldrich was freshly distilled every time before use. All phosphoramidite ligands were synthesized by the Fletcher group and were not commercial yet.

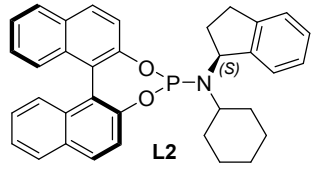
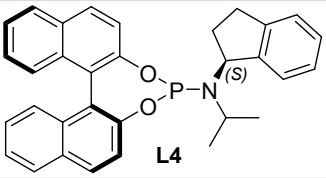
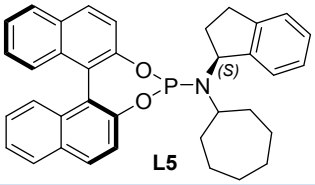
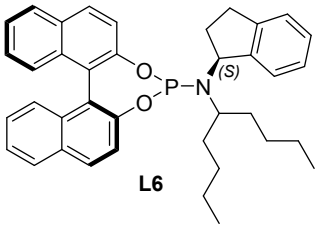
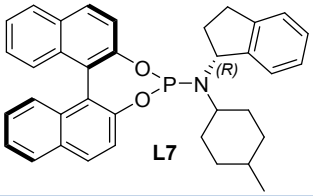
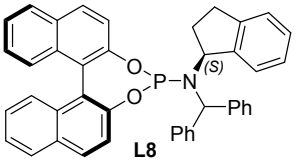
Anhydrous Et_2O, DCM and THF were obtained from mBraun SPS-800 solvent purification system equipped with anhydrous alumina columns. Anhydrous MeOH and other solvents were used as purchased. Anhydrous EtOH was dried onto 4 Å molecular sieves.

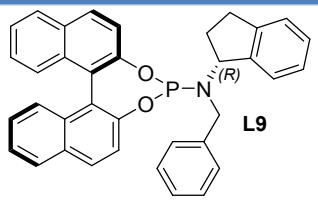
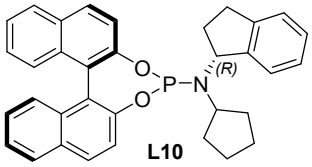
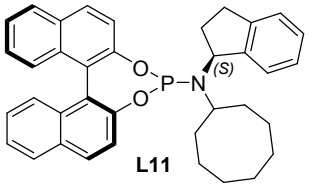
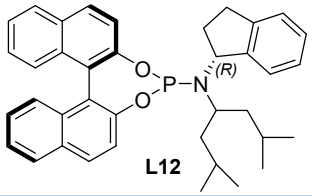
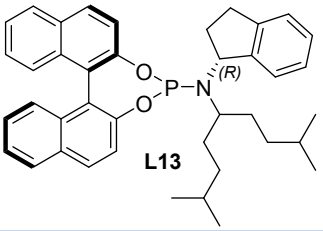
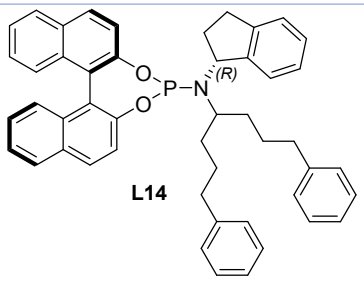
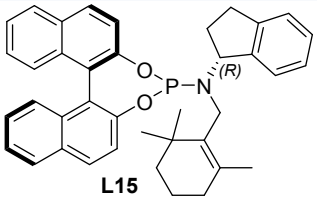
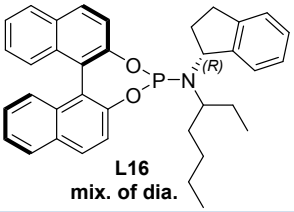
3. Reproducibility

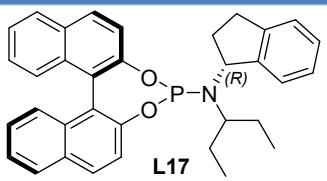
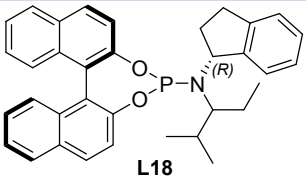
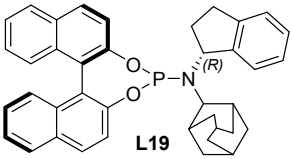
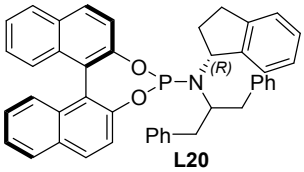
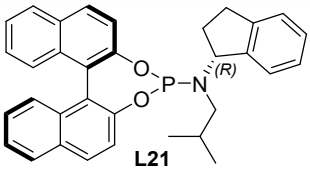
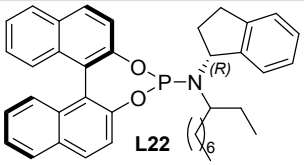
Multiple repeats (2 to 5) were carried out for all the ligands in order to verify the consistency of the results before realising statistical modelling with this data.

Inconsistent results can arise for different reasons. We have identified poor quality Schwartz reagent as a factor resulting in low yield and eroded ee. One should therefore always repeat a known reaction and check the reproducibility of results with the new batch (or an unused old batch) before screening new ligands. The quality of silver triflate, which is a bit hygroscopic, can also play a role. **Using high quality reagents should give yields within ±3% and ee within ±1% except in rare cases** as shown in Table S1.

Table S1. List of Ligands and their experimental results repeated at least twice. The yields were obtained by NMR spectroscopy using $MeNO_2$ as an external standard and calibrated. HPLC conditions were found to separate the enantiomers from impurities by comparing the isolated and filtered-crude product.

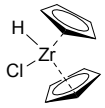
#	Ligands	Repeats	<Yield> (%)	STDEV Yield (%)	<|ee|> (%)	STDEV ee (%)
L02	 **L2**	3	69	12.5	69	3.2
L04	 **L4**	2	93	0.7	68	0.7
L05	 **L5**	2	89	4.2	77	0.7
L06	 **L6**	2	95	2.8	92	0.0
L07	 **L7**	2	79	1.4	74	0.0
L08	 **L8**	2	78	21.2	82	1.4

#	Ligands	Repeats	<Yield> (%)	STDEV Yield (%)	<|ee|> (%)	STDEV ee (%)
L09	 **L9**	3	94	3.6	26	1.0
L10	 **L10**	2	91	1.4	55	0.0
L11	 **L11**	2	94	4.9	83	4.9
L12	 **L12**	2	94	2.1	94	0.0
L13	 **L13**	2	91	0.7	92	0.0
L14	 **L14**	2	95	0.0	94	0.0
L15	 **L15**	2	97	0.0	75	0.0
L16	 **L16** mix. of dia.	2	92	1.4	92	0.7

#	Ligands	Repeats	<Yield> (%)	STDEV Yield (%)	<|ee|> (%)	STDEV ee (%)
L17	 **L17**	3	99	0.0	91	1.0
L18	 **L18** **mix. of dia.**	3	97	2.1	89	1.2
L19	 **L19**	2	51	7.1	75	1.4
L20	 **L20**	3	97	2.0	75	2.3
L21	 **L21**	3	83	5.0	24	0.6
L22	 **L22** **mix. of dia.**	2	78	0.7	92	0.0

4. General Methods

1. Preparation of the Schwartz reagent (Cp_2ZrHCl)



[Zirconium, chlorobis(η5-2,4-cyclopentadien-1-yl)hydro-]

Commercially available Schwartz reagent was not examined because it is expensive. It has previously been reported more consistent results are obtained when it was freshly prepared.[1] **In our hands, the quality of the Schwartz reagent is critical for experimental self-consistency.**

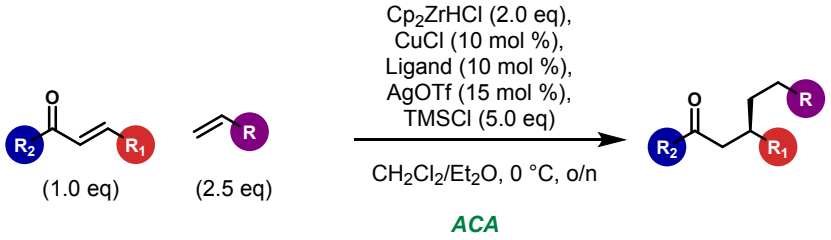
Schwartz reagent was prepared according to a literature procedure from Cp_2ZrCl_2.[2] The lithium aluminum hydride ($LiAlH_4$) reduction of zirconocene dichloride (Cp_2ZrCl_2) leads to over-reduction and give zirconocene dihydride (Cp_2ZrH_2). Treatment of Cp_2ZrH_2 with dichloromethane (DCM) converts the dihydride back into the Schwartz's Reagent.

Zirconocene dichloride (30.0 g, 0.103 mol) was added to a flame-dry 250 mL Schlenk flask wrapped with aluminium foil under argon. Dry THF (140 mL) was added and the suspension was stirred at 35 °C for 30 minutes. $LiAlH_4$ in Et_2O (2 M, 28.2 mmol) was added dropwise to the mixture over about 30 minutes with a vigorous (magnetic stirring bar) stirring. The resulting suspension was stirred at 35 °C for 3 additional hours. The red mixture was then Schlenk-filtered under argon and washed with tetrahydrofuran (300 mL in total), dichloromethane (250 mL in total), and diethyl ether (250 mL in total). The precipitate was dried under high vacuum for two hours to give a white powder (22.6 g, 85%) that was then stored under argon in a small flame-dried Aluminium foiled Schlenk flask.

Material obtained this way has an average purity better than 95% (zirconocene dihydride being the impurity). A known amount of Schwartz reagent was mixed with a known amount of excess acetone, and then diluted in an NMR tube in C_6D_6. The relative areas of the signal for the mono and diisopropoxides were determined by ^1H NMR corresponding to Cp_2ZrHCl and Cp_2ZrH_2, respectively.

The Schwartz reagent can be kept and remain pure for months under these storage conditions if flushed with Vacuum/Ar (x3) after each use.

2. Copper-catalysed conjugate addition of alkylzirconium nucleophiles



ACA

a. Racemic product

General Procedure A:

In a flamed dried round bottom flask was added CuCl (0.1 eq.), (*R,R*) Ligand **L17** (0.055 eq.) and (*S,S*) Ligand **L6** (0.055 eq.). The flask was purged 3 times with vacuum/Ar, foiled with aluminium to protect it from the light and 2.0 mL dry Et_2O was then added under an argon atmosphere. The resulting colourless clear solution was stirred for 1 h at room temperature.

In the meantime, Cp_2ZrHCl (2.0 eq) was added to a second flame dried round bottom flask, purged 3 times with vacuum/Ar, and foiled with Aluminium to protect it from the light. Addition of 0.5 mL dry CH_2Cl_2 under an argon atmosphere forms a milky solution. Alkene (2.5 eq) was rapidly added during the next minute as the Schwartz reagent is unstable with CH_2Cl_2 after about 10 min. After stirring for 15 min, the resulting yellow clear solution was manually agitated to remove the traces of Schwartz reagent on the sides of the flask and stirring was continued.

After stirring the foiled flask containing CuCl for 1 h, AgOTf (0.15 eq) was added, and the grey-brown cloudy solution was stirred for precisely 15 min (results become less reproducible if stirring continues for over 20 min). The mixture was then transferred over about 30 sec via syringe using a syringe filter to the yellow clear Zr-containing solution. The resulting dark mixture was then cooled with an ice bath and stirred for a further 5 min before the enone (1.0 eq) and then TMSCl (5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued overnight for about 15 h. The reaction was then quenched by the addition of NH_4Cl (1 M aq., *ca* 0.1 mL) and stirring was continued for 30 min. The mixture was concentrated in-vacuo then diluted with 1 mL hexane. The crude mixture was purified by flash column chromatography.

Note: These reactions require ligand to give product, as (S,S) ***L17*** *was not available we used (S,S) ligand* ***L6*** *as a pseudoenantiomer* for (R,R) ligand **L17**. *Using this procedure generally give products with ee's between 0% (rac) and ~30%.*

b. Asymmetric product

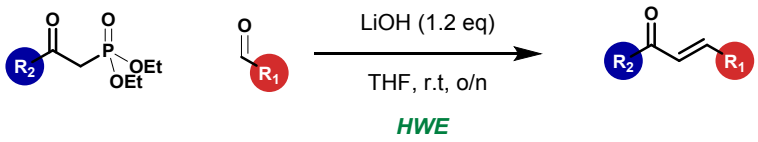
General Procedure B:

In a flame-dried round bottom flask was added CuCl (0.1 eq.) and (*R,R*) Ligand **L17** (0.11 eq.). The flask was purged 3 times with vacuum/Ar, foiled with aluminium to protect it from the light and 2.0 mL dry Et_2O was then added under an argon atmosphere. The resulting colourless clear solution was stirred for 1 h at room temperature.

In the meantime, Cp_2ZrHCl (2.0 eq) was added to a second flame dried round bottom flask, purged 3 times with vacuum/Ar, and foiled with Aluminium to protect it from the light. Addition of 0.5 mL dry CH_2Cl_2 under an argon atmosphere forms a milky solution. Alkene (2.5 eq) was rapidly added during the next minute as the Schwartz reagent is unstable with CH_2Cl_2 after about 10 min. After stirring for 15 min, the resulting yellow clear solution was manually leaned in order to remove the traces of Schwartz reagent on the sides of the flask and stirring was continued.

After stirring the foiled flask containing CuCl for 1 h, AgOTf (0.15 eq) was added, and the grey-brown cloudy solution was stirred for precisely 15 min. The mixture was then transferred over about 30 sec via syringe using a syringe filter to the yellow clear solution. The resulting dark mixture was then cooled with an ice bath and stirred for a further 5 min before the enone (1.0 eq) and then TMSCl (5.0 eq) were added dropwise via syringe. Stirring at 0 °C was continued overnight for about 15 h. The reaction was then quenched by the addition of NH_4Cl (1 M aq., *ca* 0.1 mL) and stirring was continued for 30 min. The mixture was concentrated in-vacuo then diluted with 1 mL hexane. The crude mixture was purified by flash column chromatography.

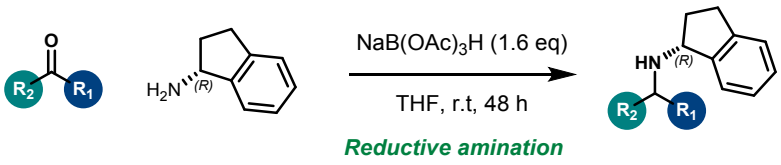
3. Preparation of enones



General Procedure C:

According to a procedure from Jacobson,[3] lithium hydroxide (1.2 eq) and the diethyl phosphonate (1.05 eq) were added sequentially to a solution of the aldehyde (1.0 eq) in THF (0.2 mmol·mL^{-1}). The reaction was stirred for 15 hours, and then concentrated *in vacuo*. The residue was dissolved in Et_2O, and washed twice with 1 M aqueous hydrochloric acid, twice with saturated aqueous sodium bicarbonate solution. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The (E)-enone was isolated after flash column chromatography.

4. Preparation of amines



General Procedure D:

According to a modified procedure from Abdel-Magid,[4] (R)-2,3-dihydro-1H-inden-1-aminium chloride (1.0 eq) was mixed with aq. NaOH (2M) (until pH = 12-14) and CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The ketone (1.0 eq) was then added to a stirring solution of the freshly concentrated (R)-2,3-dihydro-1H-inden-1-amine in dry THF (0.25 mmol·mL^{-1}) at rt. After 5min, $NaB(OAc)_3H$ (1.6 eq) was added into the reaction mixture at rt and the suspension was stirred for 48 h. The mixture was diluted with Et_2O (20 mL) and $NaHCO_3$ (aq. sat., *ca* 20 mL).

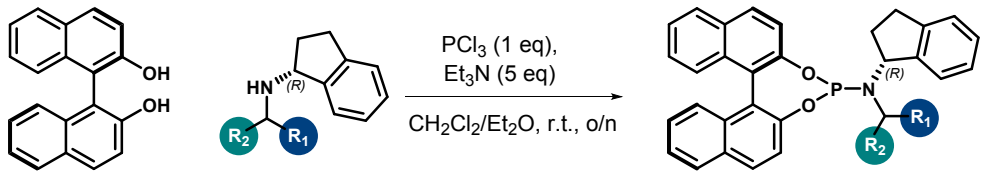
After 30 min, the organic and aqueous layers were partitioned and the aqueous phase was extracted with Et_2O (3 × 20 mL).

Acid-base purification: HCl (aq. 2.0 M) was added dropwise (until pH = 1). The mixture was partitioned between the aqueous and organic phases, and the organic phase was extracted with HCl (aq. 2.0 M). Then CH_2Cl_2 was added to the combined aqueous phases and NaOH (4 M) was added (until pH = 12-14). The mixture was partitioned between aqueous and organic phases. CH_2Cl_2 was used to extract residual product from the aqueous layer (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the desired product.

Although pure enough in practice to carry out the phosphoramidite synthesis, most amines remained impure after acid-base workup for characterisation. We therefore tried to precipitate the amines with several acids but it proved unsuccessful in our hands. The pure amine was therefore obtained after flash column chromatography.

For few cases, even the flash column chromatography was unsuccessful. The amine was therefore filtered through a strong cation exchange column ISOLUTE® SCX-2 (propylsulfonic acid) with MeOH to wash off non-basic component followed by ammonia solution in MeOH (2 M) to release the pure product. Final column chromatography is usually required to remove ammonia contaminant that will react faster in the phosphoramidite synthesis.

5. Preparation of phosphoramidite ligands



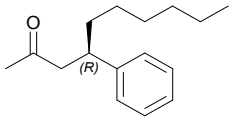
General Procedure E:

According to a procedure reported by our group,[5] triethylamine (5.0 eq.) was added dropwise to a stirred solution cooled at 0 °C of freshly distilled PCl_3 (1.0 eq.) in CH_2Cl_2 (20 mL). The ice bath was removed and the solution left to warm to room temperature before the (R)-amine (1.0 eq.) was added to the stirring solution. After 5 additional hours of stirring, (R)-binaphthol (1.0 eq.) was added to the suspension and the subsequent mixture was left to stir for an additional 18 h before the solution was then filtered on a small pad of celite® and rinsed with CH_2Cl_2 (*ca* 20 mL). The resulting solution was concentrated under reduced pressure to afford a yellow residue. The phosphoramidite was obtained as a foamy white solid after flash column chromatography.

5. Characterization of compounds

1. Copper-catalysed asymmetric conjugate addition products

(R)-4-phenyldecan-2-one 18



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), hex-1-ene (0.12 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-phenylbut-3-en-2-one (59 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-4-phenyldecan-2-one (93 mg, 0.400 mmol, 99%) as a slightly yellow oil.

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IB; flow: 0.8 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 7.9 min; major enantiomer, t_R = 8.3 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.17 (m, 2H), 7.16 – 7.06 (m, 3H), 3.03 (dtd, *J* = 9.3, 7.2, 5.5 Hz, 1H), 2.64 (dd, *J* = 7.2, 2.1 Hz, 2H), 1.94 (s, 3H), 1.59 – 1.43 (m, 2H), 1.25 – 0.95 (m, 8H), 0.77 (t, *J* = 7.0 Hz, 3H).

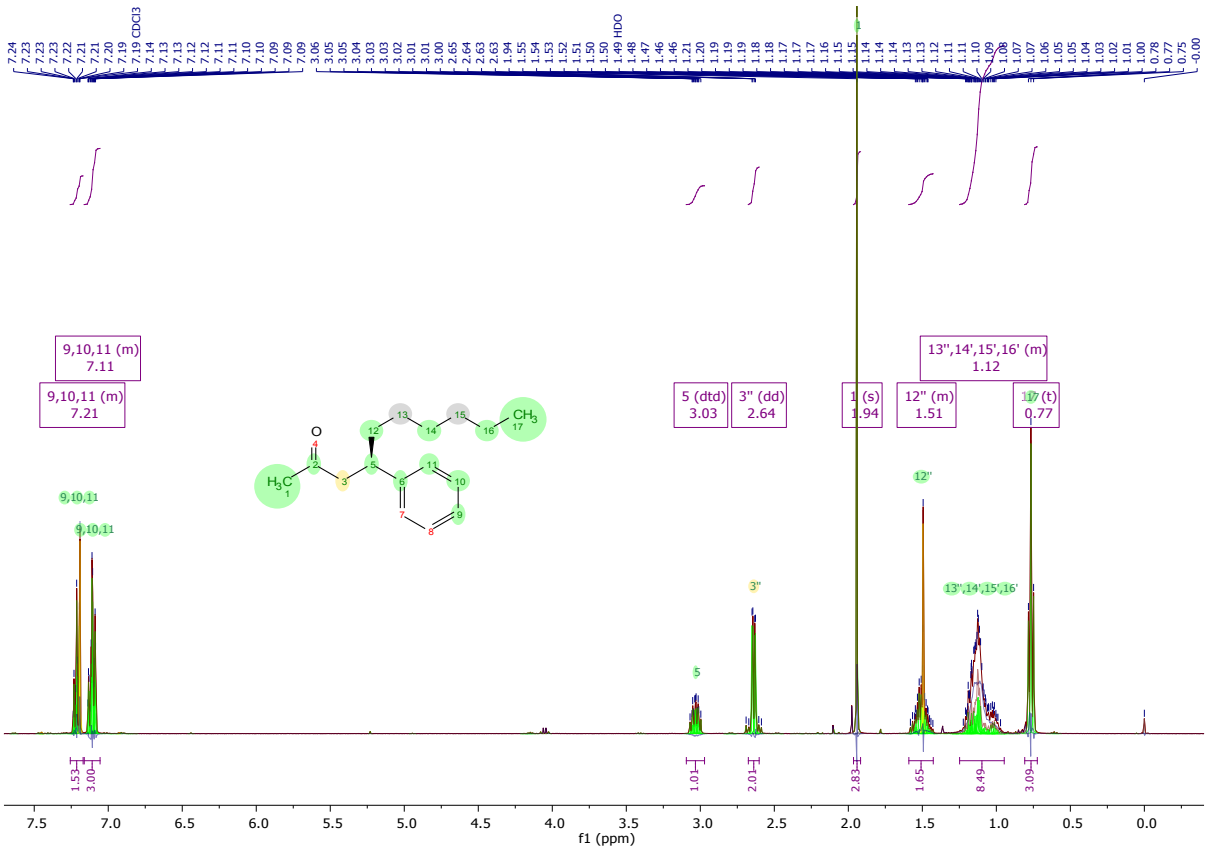
^{13}C NMR (101 MHz, Chloroform-*d*) δ 208.1, 144.6, 128.4 (2 C), 127.5 (2 C), 126.3, 51.0, 41.3, 36.5, 31.7, 30.7, 29.2, 27.4, 22.6, 14.1.

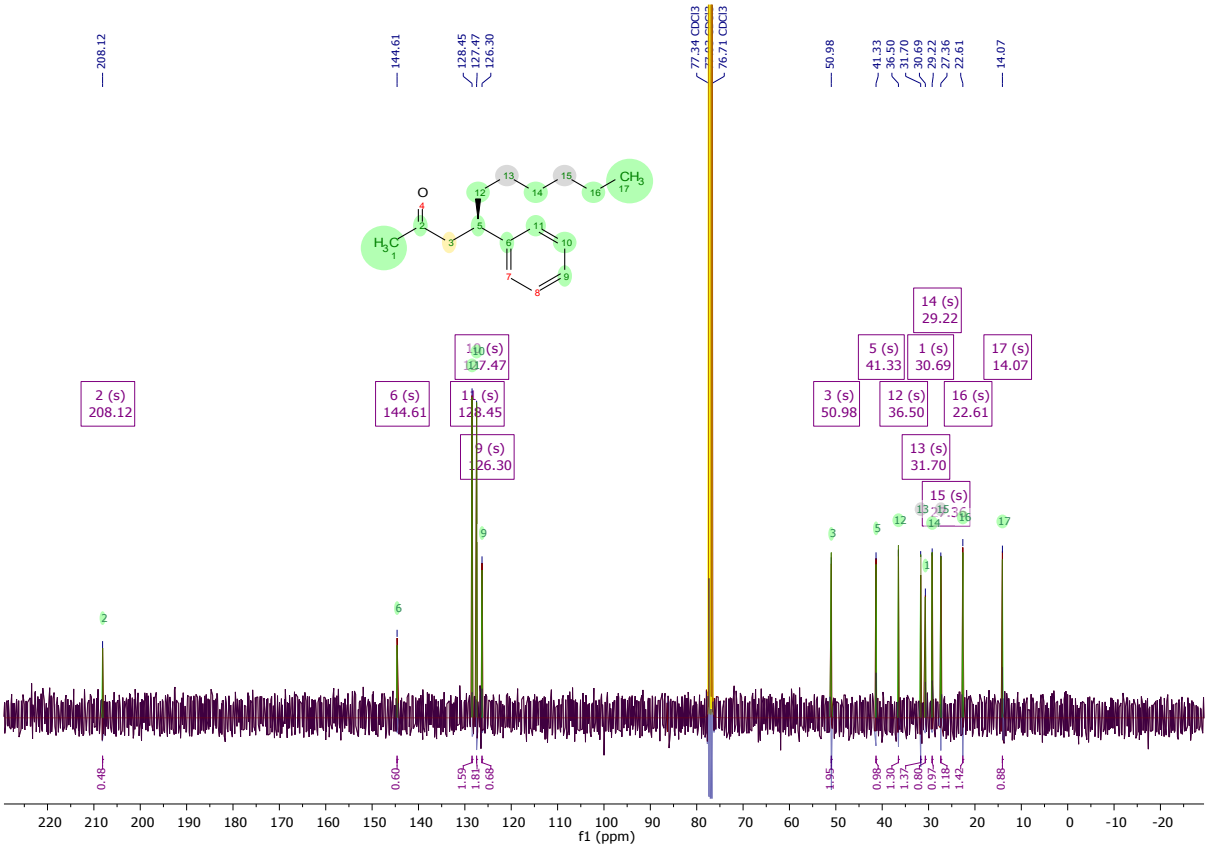
IR υ_{max} (film): 2926, 2855, 1717, 1453, 1356, 1159.

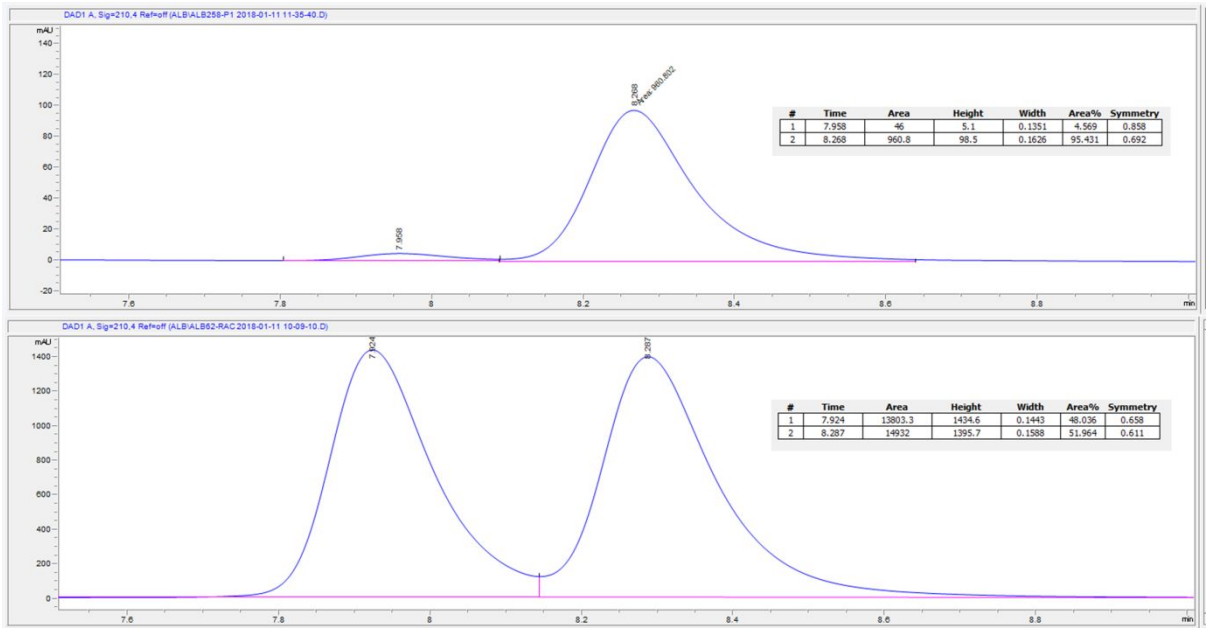
HRMS (GCMS Methane Cl) *m/z* calcd for $C_{16}H_{25}O$ $[M+H]^+$: 233.1900, found 233.1907.

$[\alpha]^{25}_{589}$ = +10.3 (*c* 1.2, $CHCl_3$) for 92% ee.

Analytical data are in agreement with the literature.[6]


9,10,11 (m)
7.11
9,10,11 (m)
7.21
5 (dtd)
3.03
3" (dd)
2.64
1 (s)
1.94
12" (m)
1.51
13",14',15',16' (m)
1.12
17 (t)
0.77
f1 (ppm)


2 (s)
208.12
6 (s)
144.61
14 (s)
29.22
5 (s)
41.33
1 (s)
30.69
17 (s)
14.07
3 (s)
50.98
12 (s)
36.50
16 (s)
22.61
13 (s)
31.70
15 (s)
f1 (ppm)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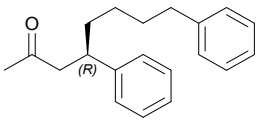
8.268
Area: 960.802
7.958
Time Area Height Width Area% Symmetry
1 7.958 46 5.1 0.1351 4.569 0.858
2 8.268 960.8 98.5 0.1626 95.431 0.692
min
DAD1 A, Sig=210,4 Ref=off (ALB\ALB62-RAC 2018-01-11 10-09-10.D)
mAU
7.924
8.287
Time Area Height Width Area% Symmetry
1 7.924 13803.3 1434.6 0.1443 48.036 0.658
2 8.287 14932 1395.7 0.1588 51.964 0.611
min

(R)-4,8-diphenyloctan-2-one 2



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-phenylbut-3-en-2-one (59 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-4,8-diphenyloctan-2-one (105 mg, 0.372 mmol, 92%) as a slightly yellow oil.

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IB; flow: 0.8 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 10.3 min; major enantiomer, t_R = 10.9 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

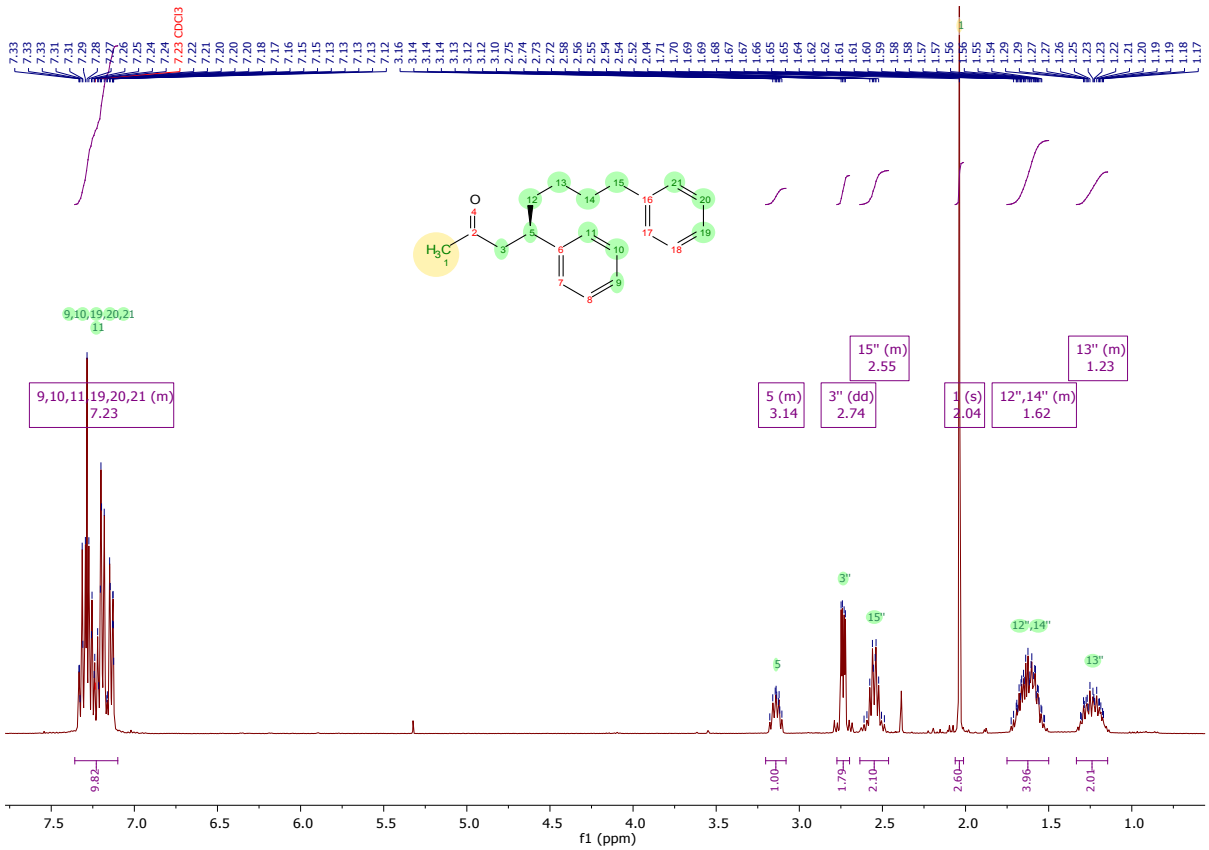
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.10 (m, 10H), 3.20 – 3.08 (m, 1H), 2.74 (dd, *J* = 7.2, 3.2 Hz, 2H), 2.64 – 2.46 (m, 2H), 2.04 (s, 3H), 1.75 – 1.50 (m, 4H), 1.33 – 1.15 (m, 2H).

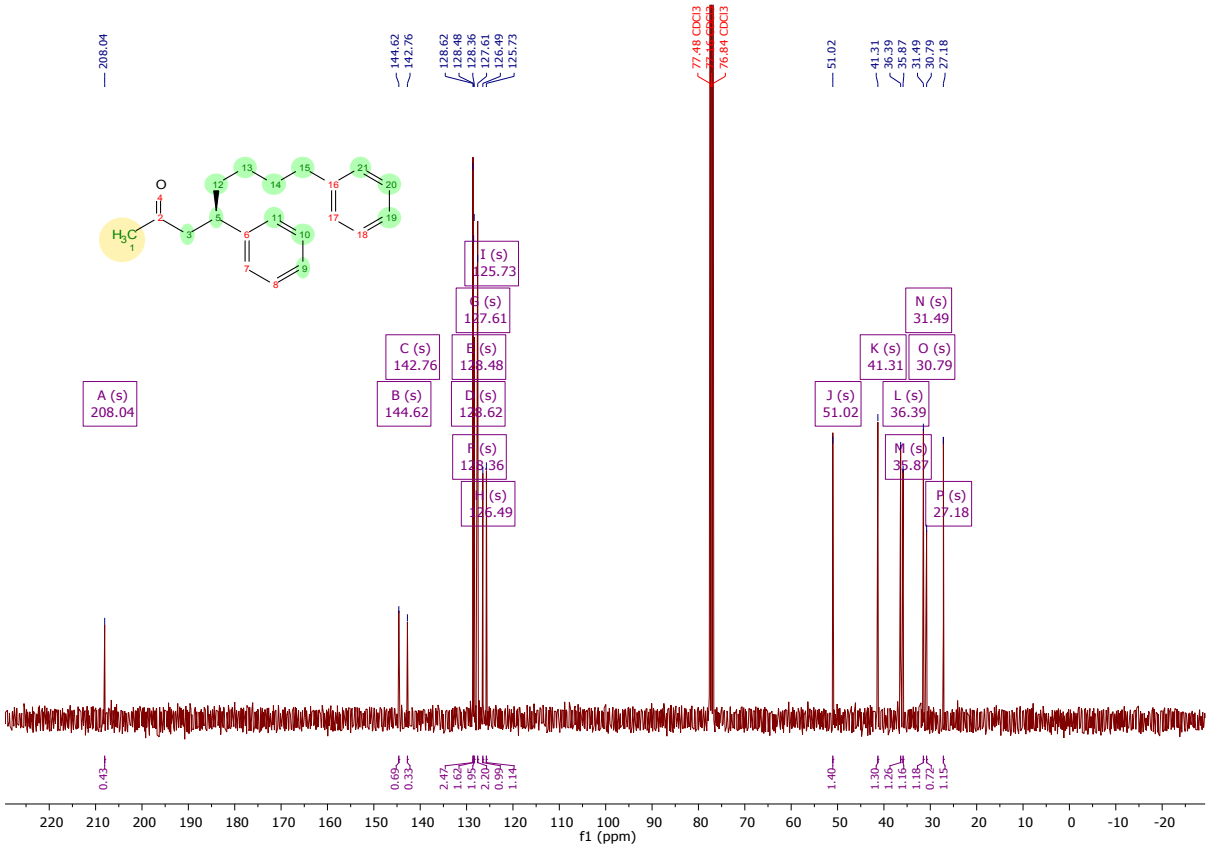
^{13}C NMR (126 MHz, Chloroform-*d*) δ 208.0, 144.6, 142.8, 128.6 (2 C), 128.5 (2 C), 128.4 (2 C), 127.6 (2 C), 126.5, 125.7, 51.0, 41.3, 36.4, 35.9, 31.5, 30.8, 27.2.

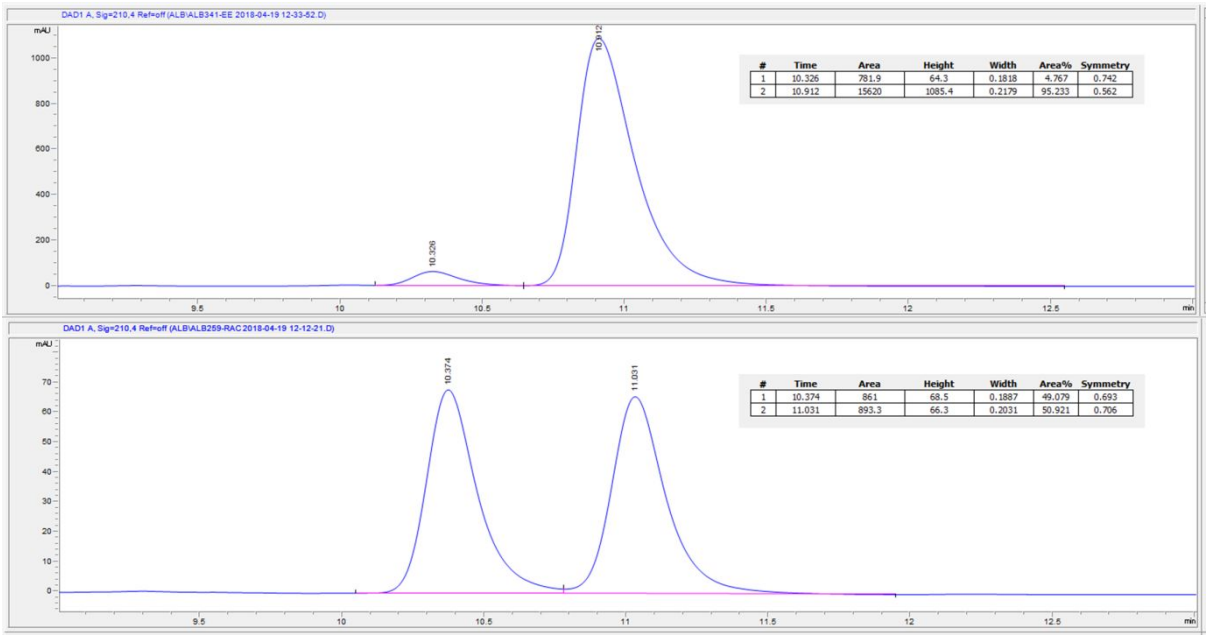
IR υ_{max} (film): 3026, 2929, 2361, 1716, 1494, 1453, 1356, 1160.

HRMS (APCI$^+$) *m/z* calcd for $C_{20}H_{25}O$ $[M+H]^+$: 281.1900, found 281.1898.

$[\alpha]^{25}_{589}$ = -4.8 (*c* 1.0, $CHCl_3$) for 91% ee.


9,10,11,19,20,21 (m)
7.23
5 (m)
3.14
3'' (dd)
2.74
15'' (m)
2.55
1 (s)
2.04
12'',14'' (m)
1.62
13'' (m)
1.23
f1 (ppm)

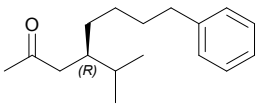

A (s)
208.04
B (s)
144.62
C (s)
142.76
I (s)
125.73
J (s)
51.02
K (s)
41.31
L (s)
36.39
N (s)
31.49
O (s)
30.79
P (s)
27.18
f1 (ppm)



#	Time	Area	Height	Width	Area%	Symmetry
1	10.326	781.9	64.3	0.1818	4.767	0.742
2	10.912	15620	1085.4	0.2179	95.233	0.562

#	Time	Area	Height	Width	Area%	Symmetry
1	10.374	861	68.5	0.1887	49.079	0.693
2	11.031	893.3	66.3	0.2031	50.921	0.706

(R)-4-isopropyl-8-phenyloctan-2-one 3



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-5-methylhex-3-en-2-one 75% from Aldrich (53 µL, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-4-isopropyl-8-phenyloctan-2-one (98.7 mg, 0.402 mmol, >99%) as a slightly yellow oil.

Note: Commercially available starting material was bought from Aldrich but was not pure. Yield obtained is higher than the actual purity because the impurity isomerizes to form the starting material in-situ, likely due to the copper species.

SFC analysis indicated an enantiomeric excess of 90% [Chiralpak® ID-3; 1500 psi, 30 °C, flow: 2.0 mL/min; 0.1% to 0.7% MeOH in 5 min; λ = 218 nm; major enantiomer, t_R = 4.20 min; minor enantiomer, t_R = 4.76 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.25 (m, 2H), 7.24 – 7.15 (m, 3H), 2.62 (t, J=7.5 Hz, 2H), 2.39 (dd, *J* = 16.2, 5.6 Hz, 1H), 2.25 (dd, *J* = 16.2, 7.4 Hz, 1H), 2.15 (s, 3H), 1.87 (ttd, *J* = 7.4, 5.6, 4.0 Hz, 1H), 1.78 – 1.65 (m, 1H), 1.69 – 1.56 (m, 2H), 1.42 – 1.25 (m, 3H), 1.19 (ddd, *J* = 14.2, 7.8, 4.0 Hz, 1H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

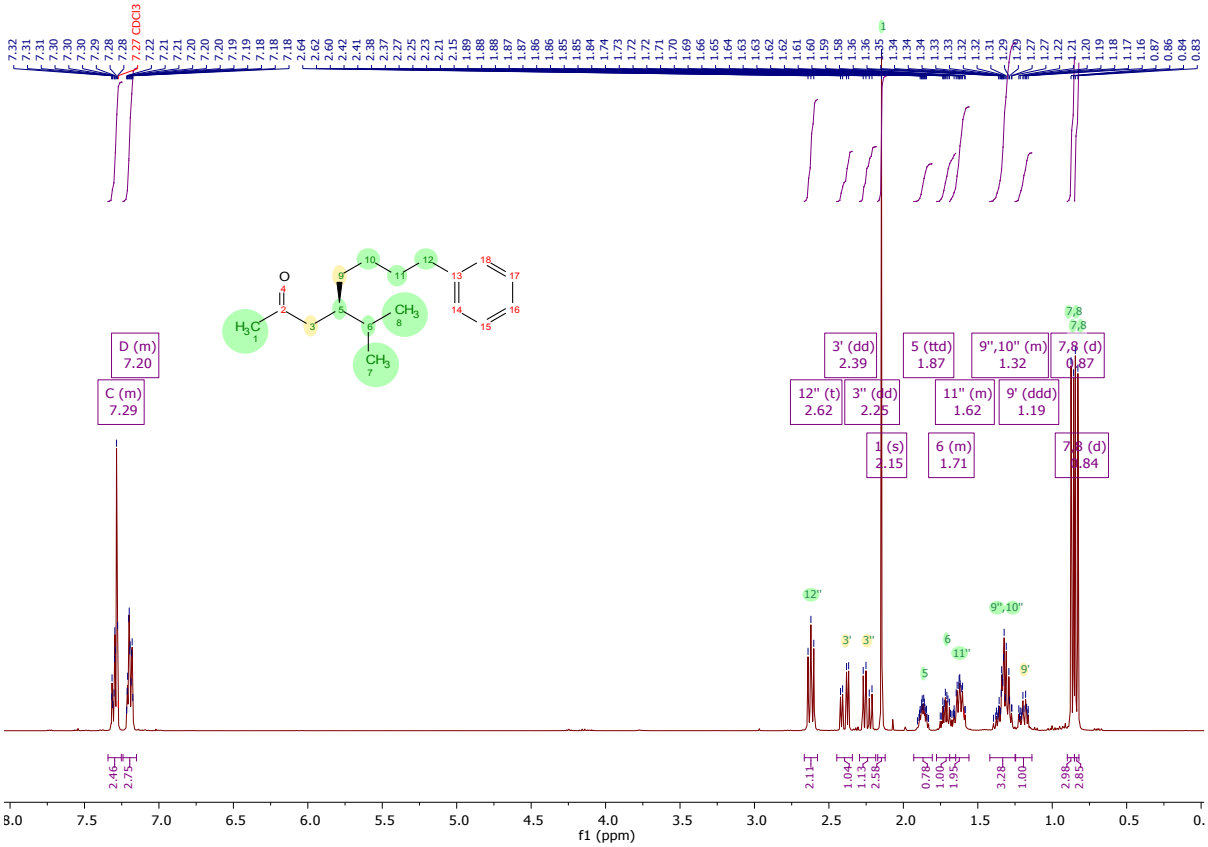
^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.6, 142.8, 128.5 (2 C), 128.4 (2 C), 125.7, 45.60, 39.5, 36.0, 31.8, 31.3, 30.5, 29.8, 27.1, 19.6, 18.6.

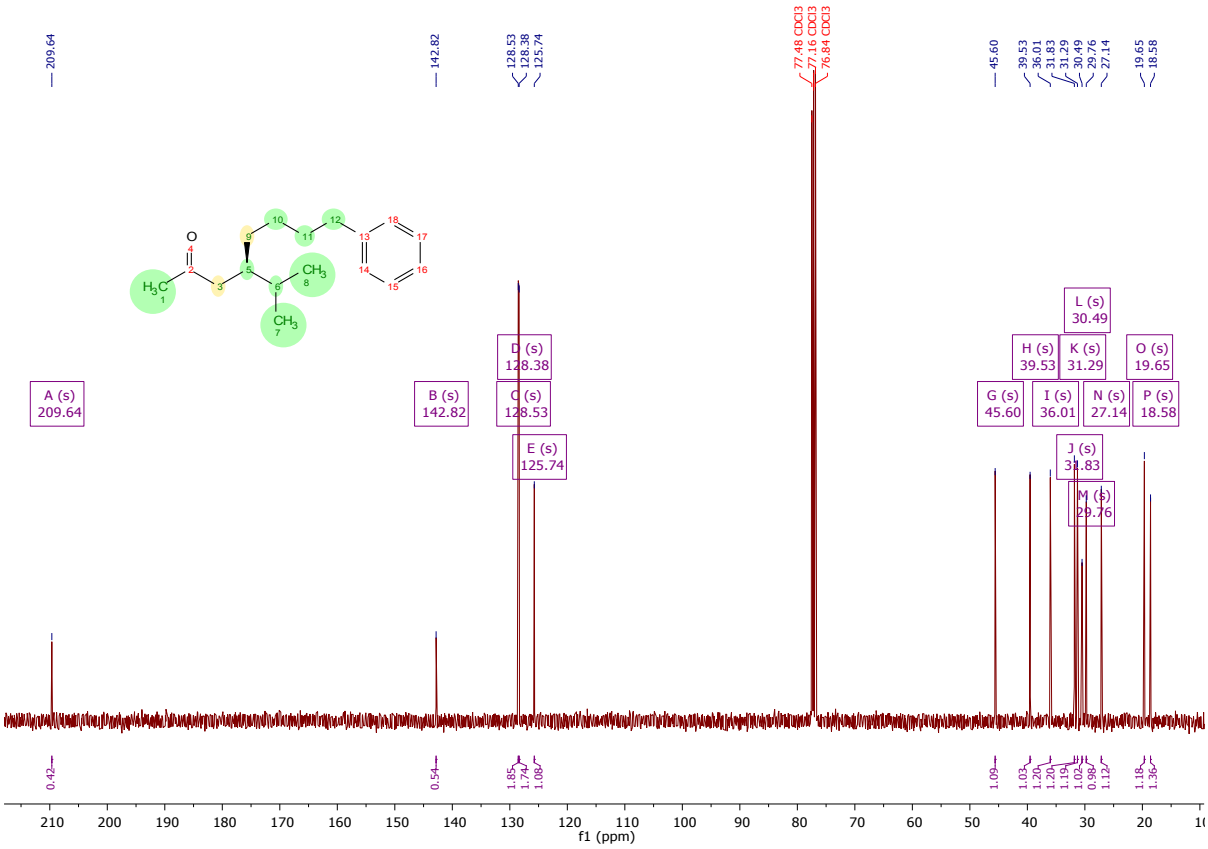
IR υ_{max} (film): 2980, 1715, 1462, 1383, 1251, 1154, 1072.

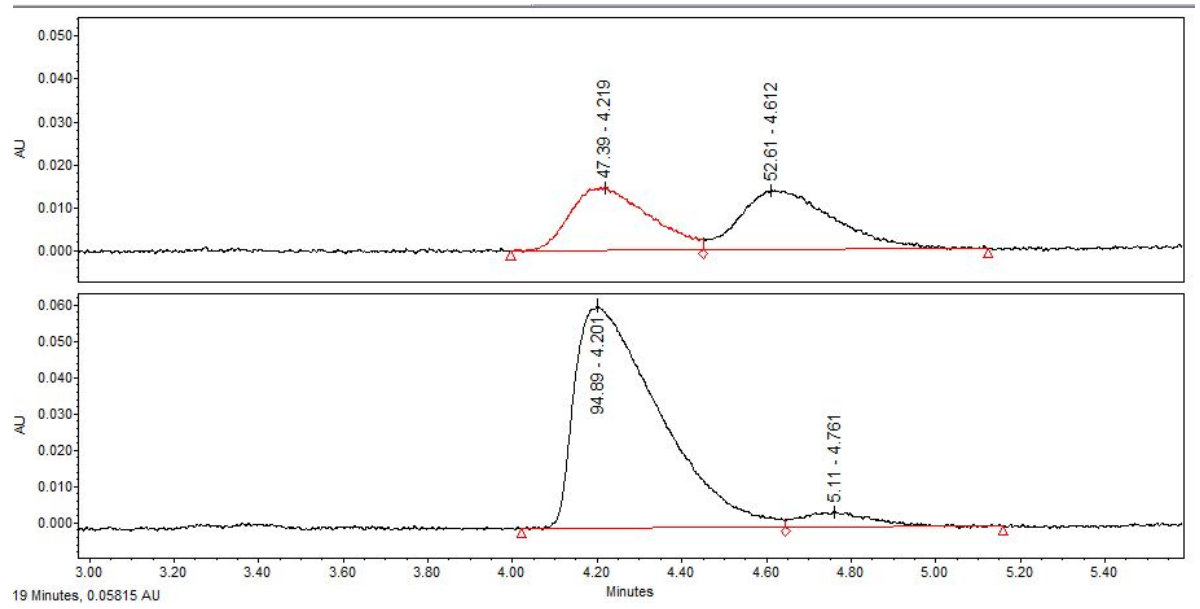
HRMS (APCI) *m/z* calcd for $C_{17}H_{27}O$ $[M+H]^+$: 247.2056, found 247.2058.

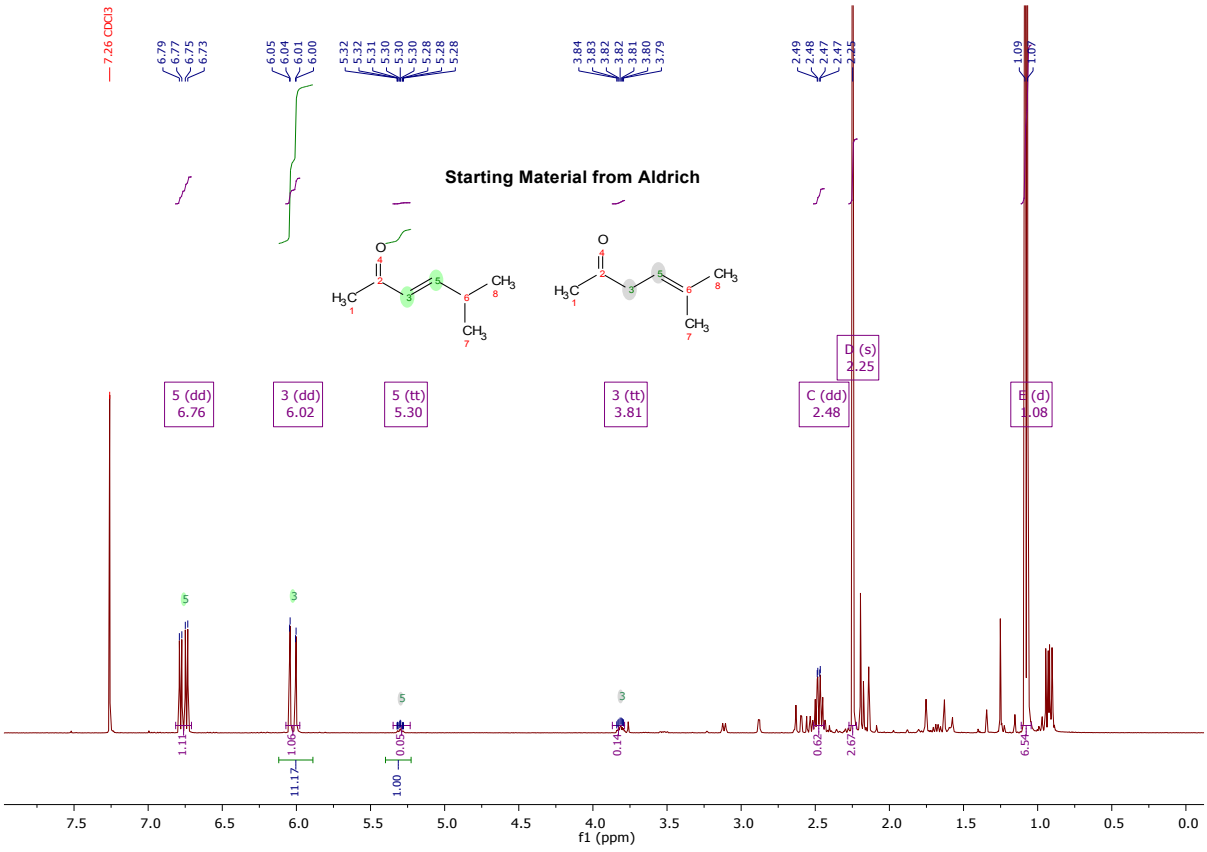
$[\alpha]^{25}_{589}$ = -0.9 (*c* 1.0, $CHCl_3$) for 90% ee.

Analytical data are in agreement with the literature.[6]

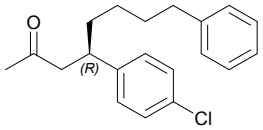

D (m)
7.20
C (m)
7.29
3' (dd)
2.39
5 (ttd)
1.87
9'',10'' (m)
1.32
7,8 (d)
0.87
12'' (t)
2.62
3'' (dd)
2.25
11'' (m)
1.62
9' (ddd)
1.19
1 (s)
2.15
6 (m)
1.71
7,8 (d)
0.84
f1 (ppm)


A (s)
209.64
B (s)
142.82
D (s)
128.38
C (s)
128.53
E (s)
125.74
G (s)
45.60
H (s)
39.53
I (s)
36.01
J (s)
31.83
K (s)
31.29
L (s)
30.49
M (s)
29.76
N (s)
27.14
O (s)
19.65
P (s)
18.58
f1 (ppm)


47.39 - 4.219
52.61 - 4.612
94.89 - 4.201
5.11 - 4.761
AU
Minutes
19 Minutes, 0.05815 AU


Starting Material from Aldrich
5 (dd) 6.76
3 (dd) 6.02
5 (tt) 5.30
3 (tt) 3.81
C (dd) 2.48
D (s) 2.25
E (d) 1.08
f1 (ppm)

(R)-4-(4-chlorophenyl)-8-phenyloctan-2-one 11



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-(4-chlorophenyl)but-3-en-2-one (73 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-4-(4-chlorophenyl)-8-phenyloctan-2-one (113.8 mg, 0.372 mmol, 89%) as a slightly yellow oil.

HPLC analysis indicated an enantiomeric excess of 81% [Chiralpak® ID; flow: 0.8 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 12.5 min; major enantiomer, t_R = 13.0 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

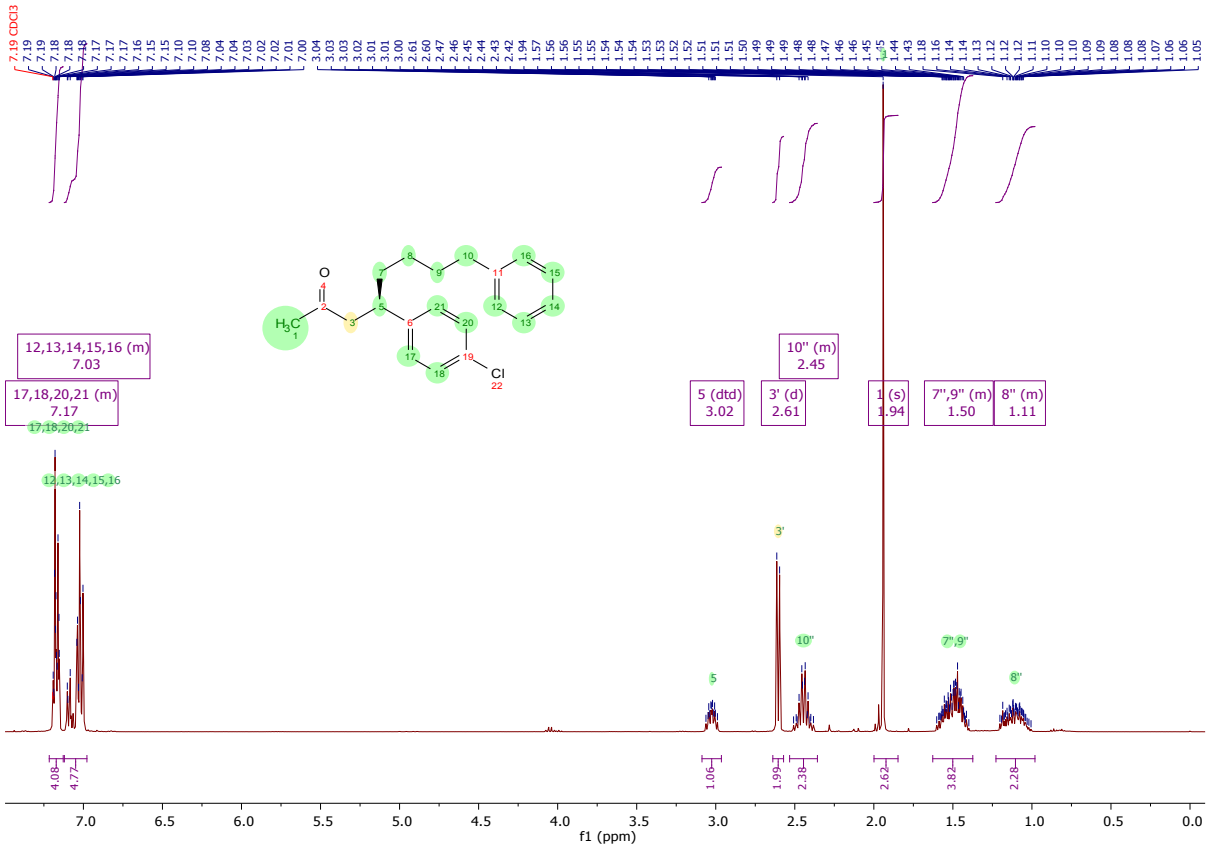
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 – 7.13 (m, 4H), 7.12 – 6.98 (m, 5H), 3.02 (dtd, *J* = 9.6, 7.1, 5.3 Hz, 1H), 2.61 (d, *J* = 7.1 Hz, 2H), 2.53 – 2.36 (m, 2H), 1.94 (s, 3H), 1.63 – 1.37 (m, 4H), 1.23 – 0.98 (m, 2H).

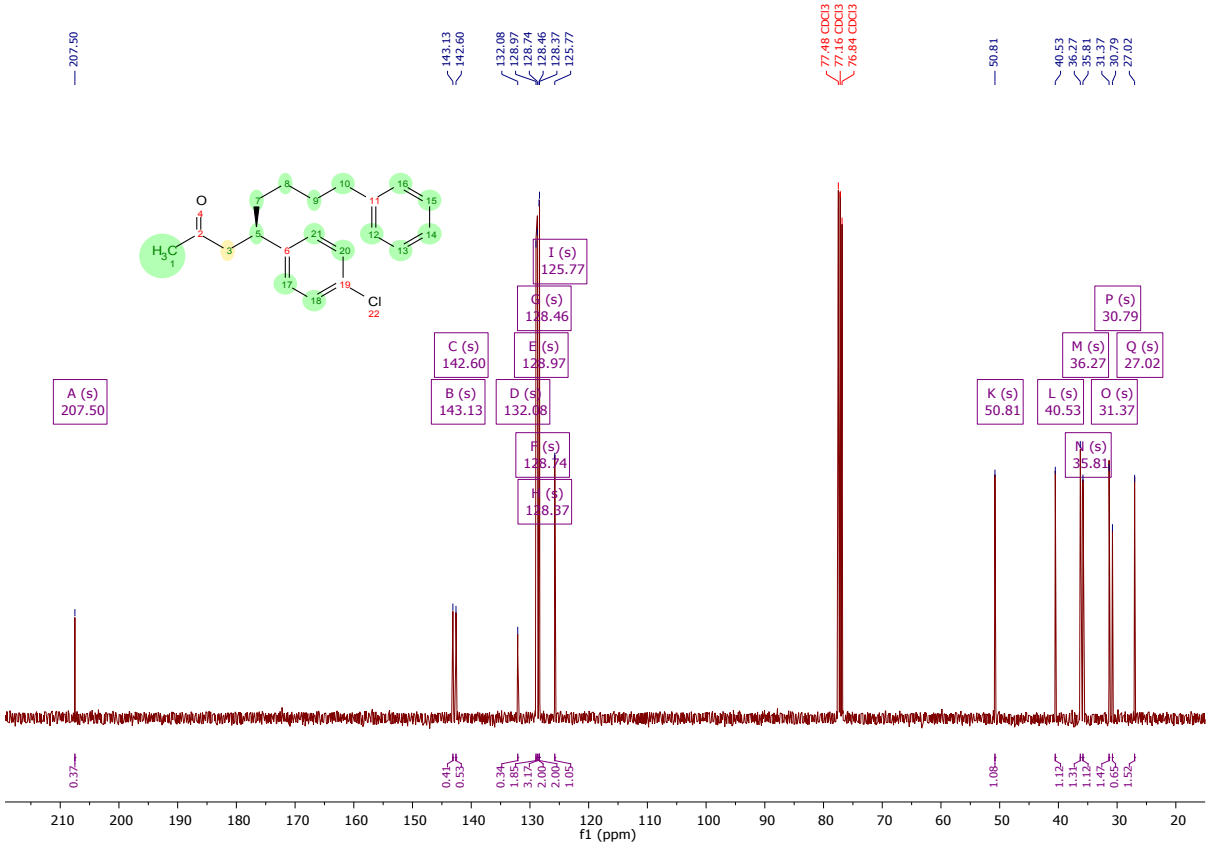
^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.5, 143.1, 142.6, 132.1, 129.0 (2 C), 128.7 (2 C), 128.5 (2 C), 128.4 (2 C), 125.8, 50.8, 40.5, 36.3, 35.8, 31.4, 30.8, 27.0.

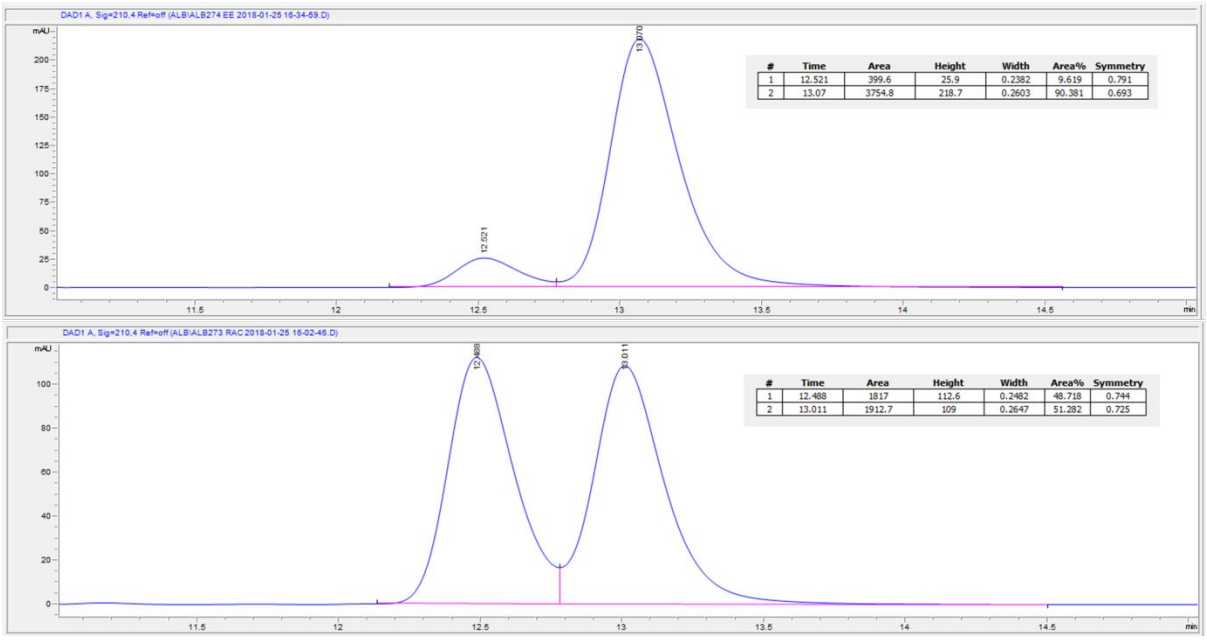
IR υ_{max} (film): 2980, 1716, 1492, 1382, 1251, 1155, 1089, 954.

HRMS (APCI$^+$) *m/z* calcd for $C_{20}H_{24}OCl$ $[M+H]^+$: 315.1510, found 315.1511.

$[\alpha]^{25}_{589}$ = -1.0 (*c* 1.0, $CHCl_3$) for 81% ee.


12,13,14,15,16 (m)
7.03
17,18,20,21 (m)
7.17
5 (dtd)
3.02
3' (d)
2.61
10'' (m)
2.45
1 (s)
1.94
7'',9'' (m)
1.50
8'' (m)
1.11
f1 (ppm)


A (s)
207.50
B (s)
143.13
C (s)
142.60
D (s)
132.08
E (s)
128.97
F (s)
128.74
G (s)
128.46
H (s)
128.37
I (s)
125.77
K (s)
50.81
L (s)
40.53
M (s)
36.27
N (s)
35.81
O (s)
31.37
P (s)
30.79
Q (s)
27.02
f1 (ppm)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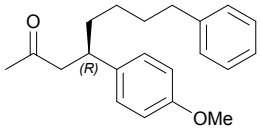
12.521
13.070
min
Time Area Height Width Area% Symmetry
1 12.521 399.6 25.9 0.2382 9.619 0.791
2 13.07 3754.8 218.7 0.2603 90.381 0.693
DAD1 A, Sig=210,4 Ref=off (ALB\ALB273 RAC 2018-01-25 16-02-46.D)
mAU
12.488
13.011
min
Time Area Height Width Area% Symmetry
1 12.488 1817 112.6 0.2482 48.718 0.744
2 13.011 1912.7 109 0.2647 51.282 0.725

(R)-4-(4-methoxyphenyl)-8-phenyloctan-2-one 8



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-(4-methoxyphenyl)but-3-en-2-one (71 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-4-(4-methoxyphenyl)-8-phenyloctan-2-one (69.1 mg, 0.214 mmol, 53%) as a slightly yellow oil.

HPLC analysis indicated an enantiomeric excess of 72% [Chiralpak® ID; flow: 1.0 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 19.4 min; major enantiomer, t_R = 22.1 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

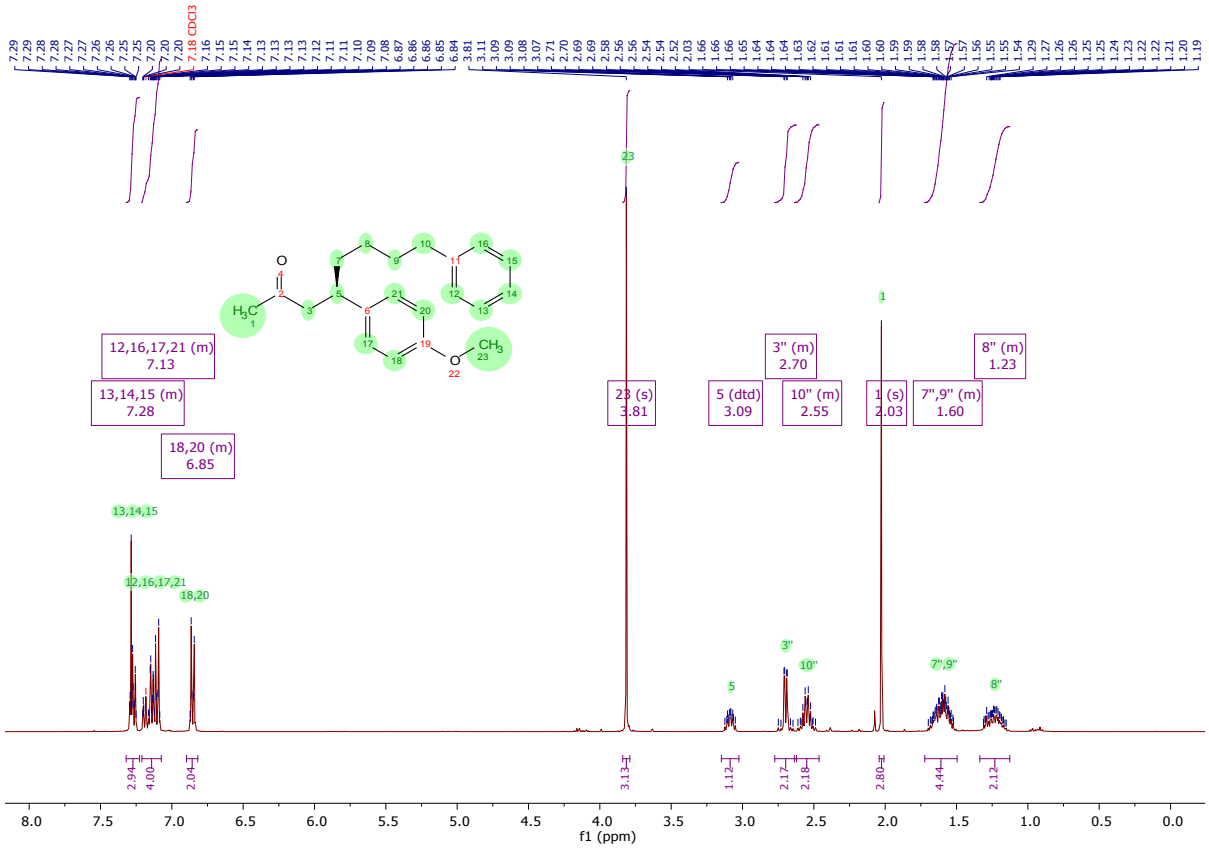
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.23 (m, 3H), 7.21 – 7.07 (m, 4H), 6.90 – 6.82 (m, 2H), 3.81 (s, 3H), 3.09 (dtd, *J* = 9.4, 7.2, 5.3 Hz, 1H), 2.77 – 2.62 (m, 2H), 2.64 – 2.46 (m, 2H), 2.03 (s, 3H), 1.72 – 1.50 (m, 4H), 1.34 – 1.13 (m, 2H).

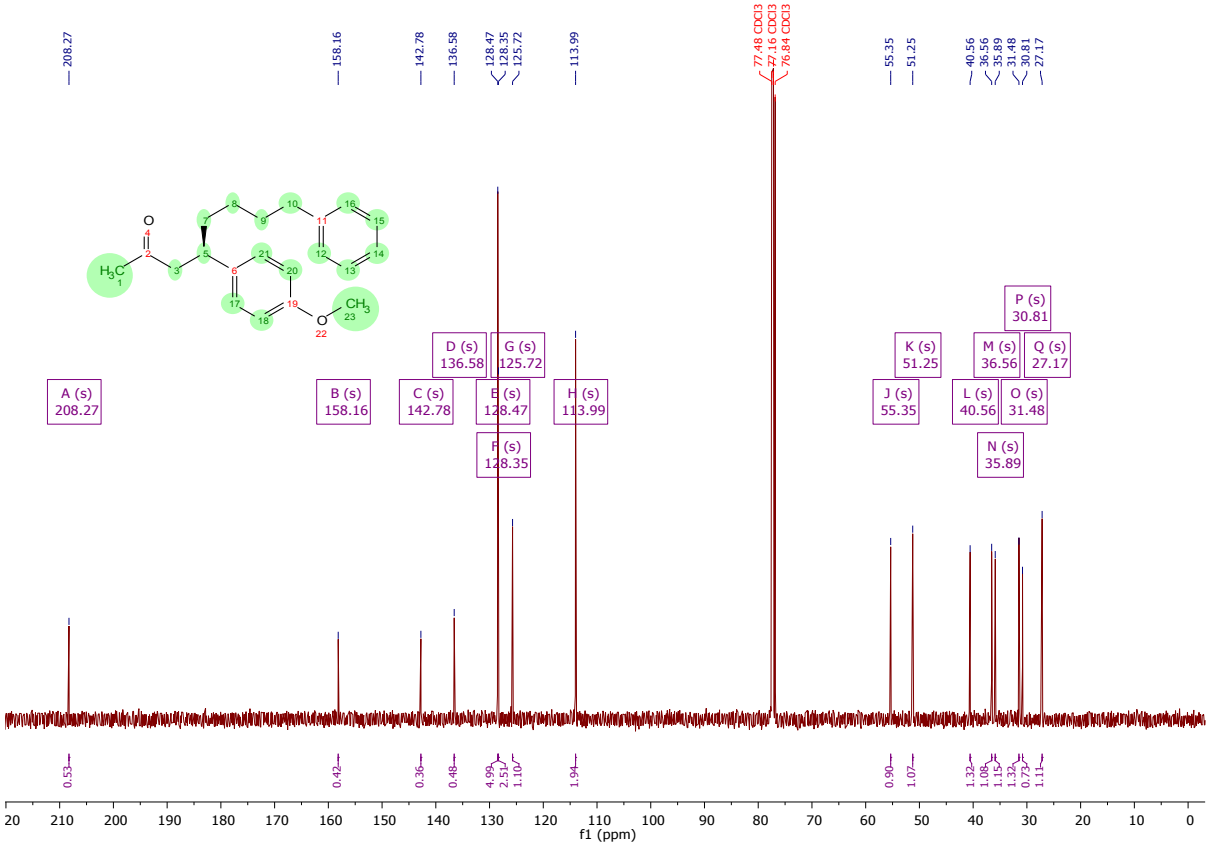
^{13}C NMR (101 MHz, Chloroform-*d*) δ 208.3, 158.2, 142.8, 136.6, 128.5 (4 C), 128.3 (2 C), 125.7, 114.0 (2 C), 55.3, 51.2, 40.6, 36.6, 35.9, 31.5, 30.8, 27.2.

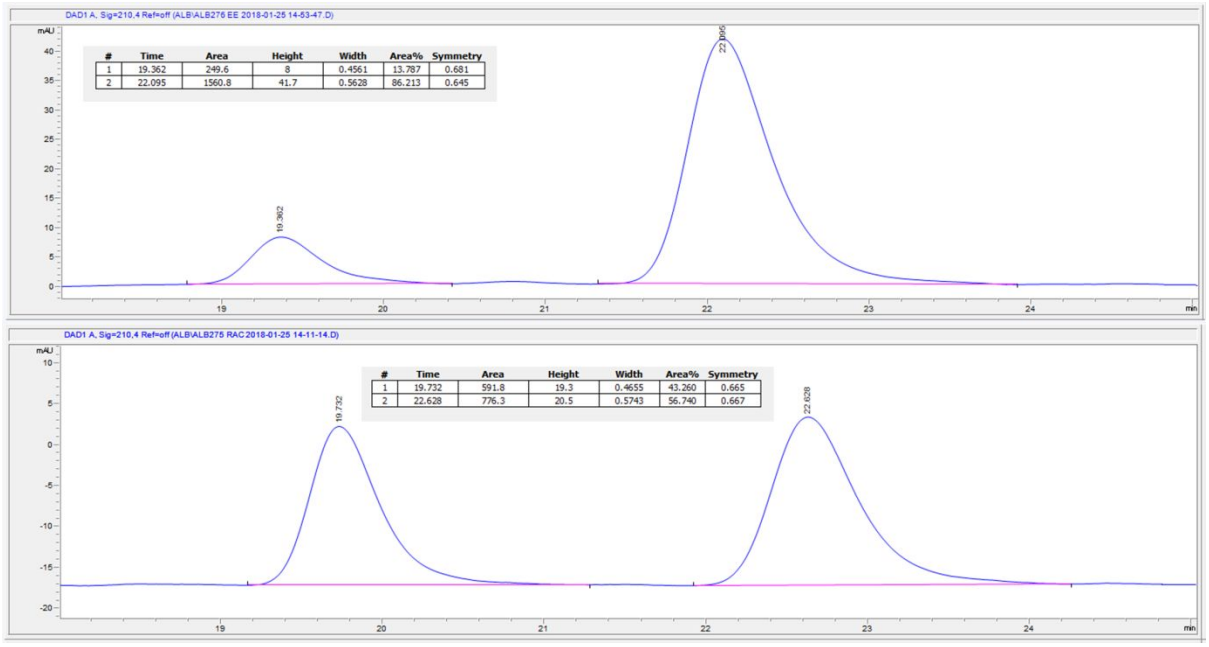
IR υ_{max} (film): 2980, 1714, 1610, 1512, 1382, 1249, 1155, 1072, 954.

HRMS (APCI$^+$) *m/z* calcd for $C_{21}H_{26}O_2Na$ $[M+Na]^+$: 333.1825, found 333.1826.

$[\alpha]^{25}_{589}$ = -3.4 (*c* 1.0, $CHCl_3$) for 72% ee.


12,16,17,21 (m)
7.13
13,14,15 (m)
7.28
18,20 (m)
6.85
23 (s)
3.81
5 (dtd)
3.09
3" (m)
2.70
10" (m)
2.55
1 (s)
2.03
8" (m)
1.23
7",9" (m)
1.60
f1 (ppm)

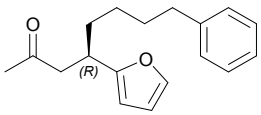

A (s)
208.27
B (s)
158.16
C (s)
142.78
D (s)
136.58
E (s)
128.47
F (s)
128.35
G (s)
125.72
H (s)
113.99
J (s)
55.35
K (s)
51.25
L (s)
40.56
M (s)
36.56
N (s)
35.89
O (s)
31.48
P (s)
30.81
Q (s)
27.17
f1 (ppm)



#	Time	Area	Height	Width	Area%	Symmetry
1	19.362	249.6	8	0.4561	13.787	0.681
2	22.095	1560.8	41.7	0.5628	86.213	0.645

#	Time	Area	Height	Width	Area%	Symmetry
1	19.732	591.8	19.3	0.4655	43.260	0.665
2	22.628	776.3	20.5	0.5743	56.740	0.667

(R)-4-(furan-2-yl)-8-phenyloctan-2-one 12



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-(furan-2-yl)but-3-en-2-one (55 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

Note: Commercially available (E)-4-(furan-2-yl)but-3-en-2-one was bought from Acros. Prior to use, the enone was dissolved in CH_2Cl_2, filtered to remove an unknown precipitate, and concentrated.^{1}H and ^{13}C NMR confirmed the structure of the enone.

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-4-(furan-2-yl)-8-phenyloctan-2-one (66.6 mg, 0.246 mmol, 61%) as a slightly yellow oil.

HPLC analysis indicated an enantiomeric excess of 88% [Chiralpak® IB; flow: 0.8 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 10.2 min; major enantiomer, t_R = 10.6 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

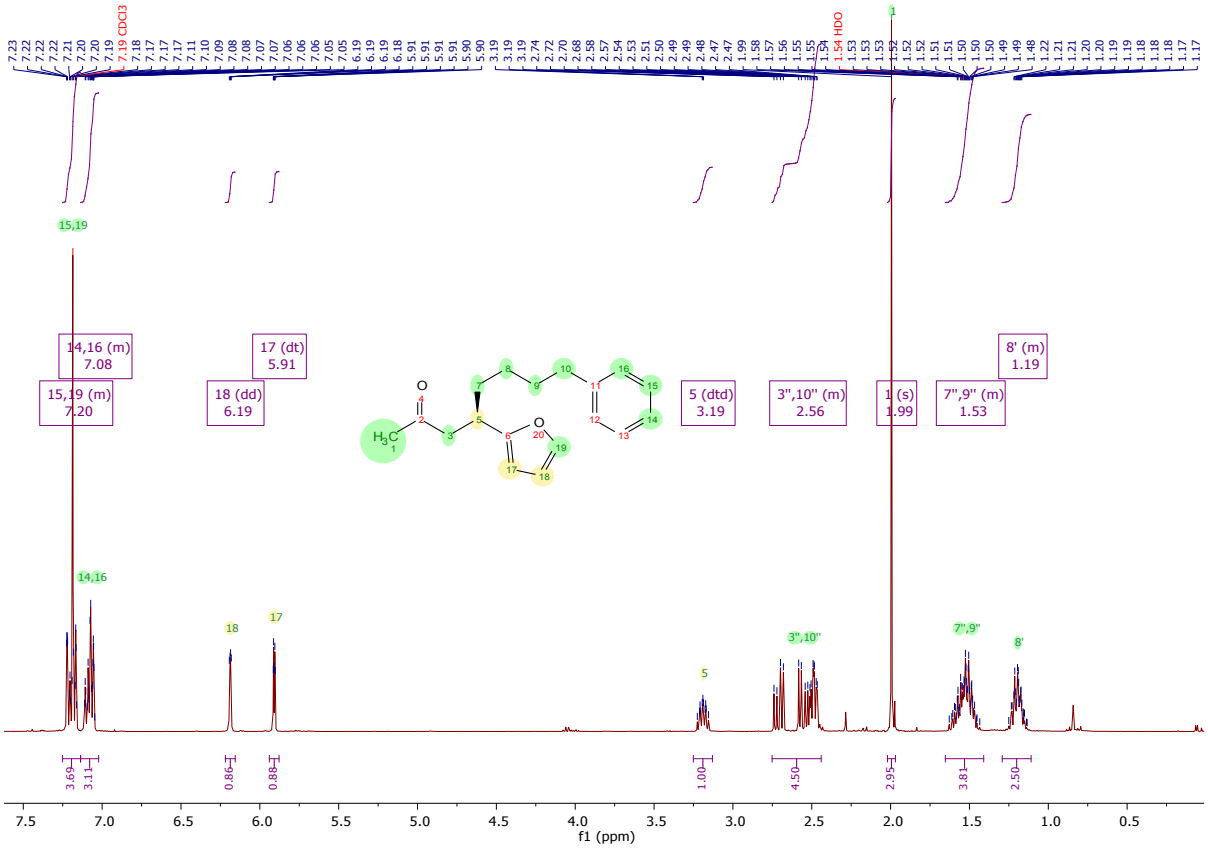
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.14 (m, 4H), 7.14 – 7.02 (m, 3H), 6.19 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.91 (dt, *J* = 3.2, 0.7 Hz, 1H), 3.19 (dtd, *J* = 8.7, 7.0, 5.6 Hz, 1H), 2.75 – 2.44 (m, 5H), 1.99 (s, 3H), 1.65 – 1.41 (m, 4H), 1.29 – 1.11 (m, 2H).

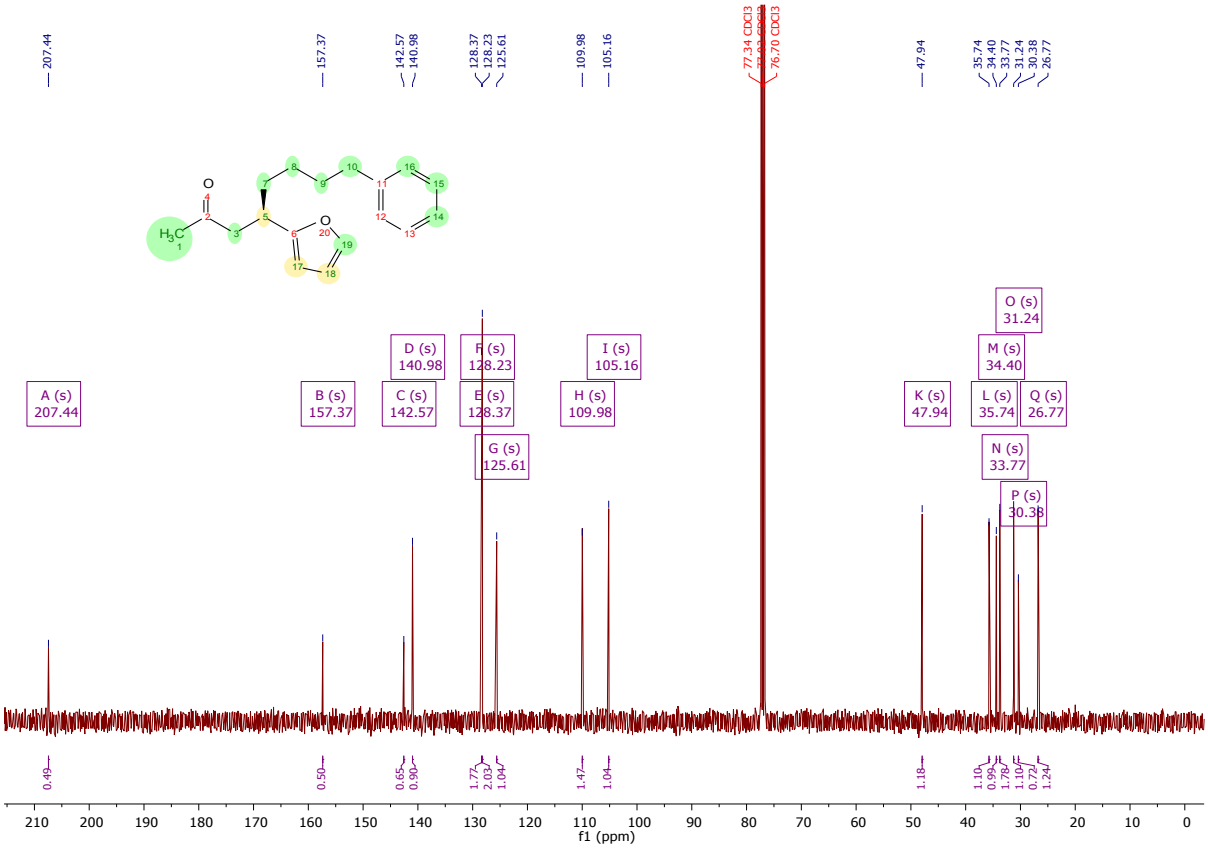
^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.4, 157.4, 142.6, 141.0, 128.4 (2 C), 128.2 (2 C), 125.6, 110.0, 105.2, 47.9, 35.7, 34.4, 33.8, 31.2, 30.4, 26.8.

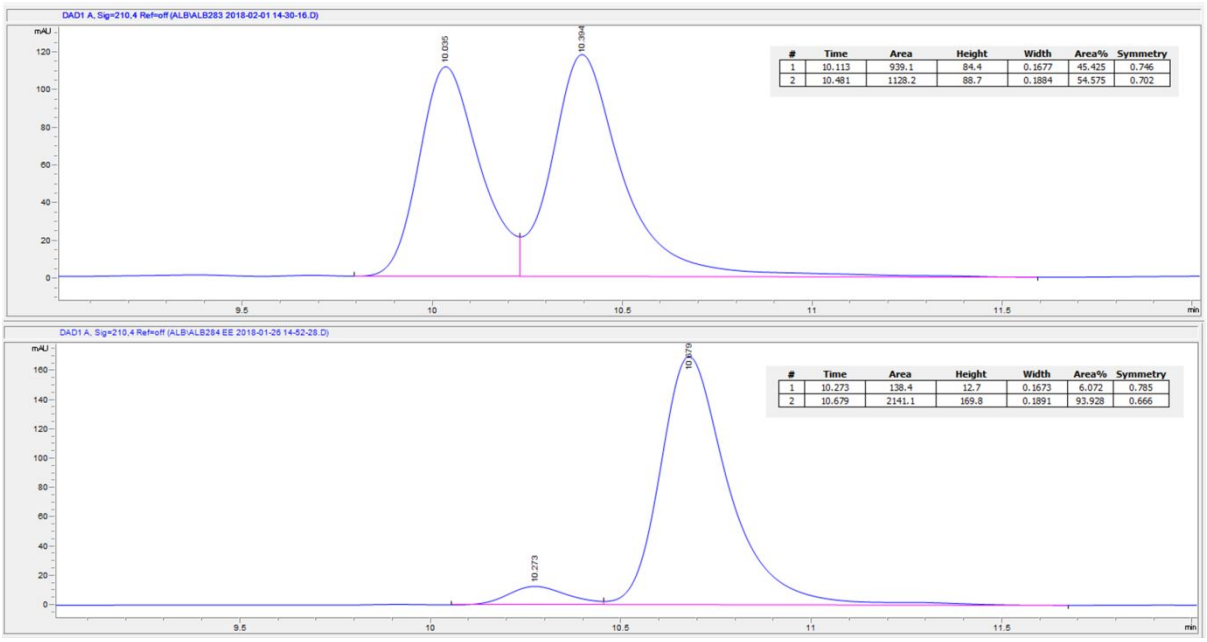
IR υ_{max} (film): 2980, 1717, 1461, 1382, 1251, 1151, 1073, 1009.

HRMS ($APCl^+$) *m/z* calcd for $C_{18}H_{23}O_2$ $[M+H]^+$: 271.1693, found 271.1695.

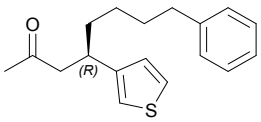
$[\alpha]^{25}_{589}$ = +3.6 (*c* 1.0, $CHCl_3$) for 88% ee.


14,16 (m)
7.08
15,19 (m)
7.20
17 (dt)
5.91
18 (dd)
6.19
5 (dtd)
3.19
3",10" (m)
2.56
1 (s)
1.99
7",9" (m)
1.53
8' (m)
1.19
f1 (ppm)


A (s)
207.44
B (s)
157.37
C (s)
142.57
D (s)
140.98
E (s)
128.37
F (s)
128.23
G (s)
125.61
H (s)
109.98
I (s)
105.16
K (s)
47.94
L (s)
35.74
M (s)
34.40
N (s)
33.77
O (s)
31.24
P (s)
30.38
Q (s)
26.77
f1 (ppm)


DAD1 A, Sig=210,4 Ref=off (ALB\ALB283 2018-02-01 14-30-16.D)
mAU
10.035
10.394
Time Area Height Width Area% Symmetry
1 10.113 939.1 84.4 0.1677 45.425 0.746
2 10.481 1128.2 88.7 0.1884 54.575 0.702
min
DAD1 A, Sig=210,4 Ref=off (ALB\ALB284 EE 2018-01-26 14-52-28.D)
mAU
10.273
10.679
Time Area Height Width Area% Symmetry
1 10.273 138.4 12.7 0.1673 6.072 0.785
2 10.679 2141.1 169.8 0.1891 93.928 0.666
min

(R)-8-phenyl-4-(thiophen-3-yl)octan-2-one 13



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-(thiophen-3-yl)but-3-en-2-one (61 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-8-phenyl-4-(thiophen-3-yl)octan-2-one (82.0 mg, 0.286 mmol, 71%) as a slightly yellow oil.

HPLC analysis indicated an enantiomeric excess of 76% [Chiralpak® IB; flow: 0.8 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 12.9 min; major enantiomer, t_R = 13.7 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

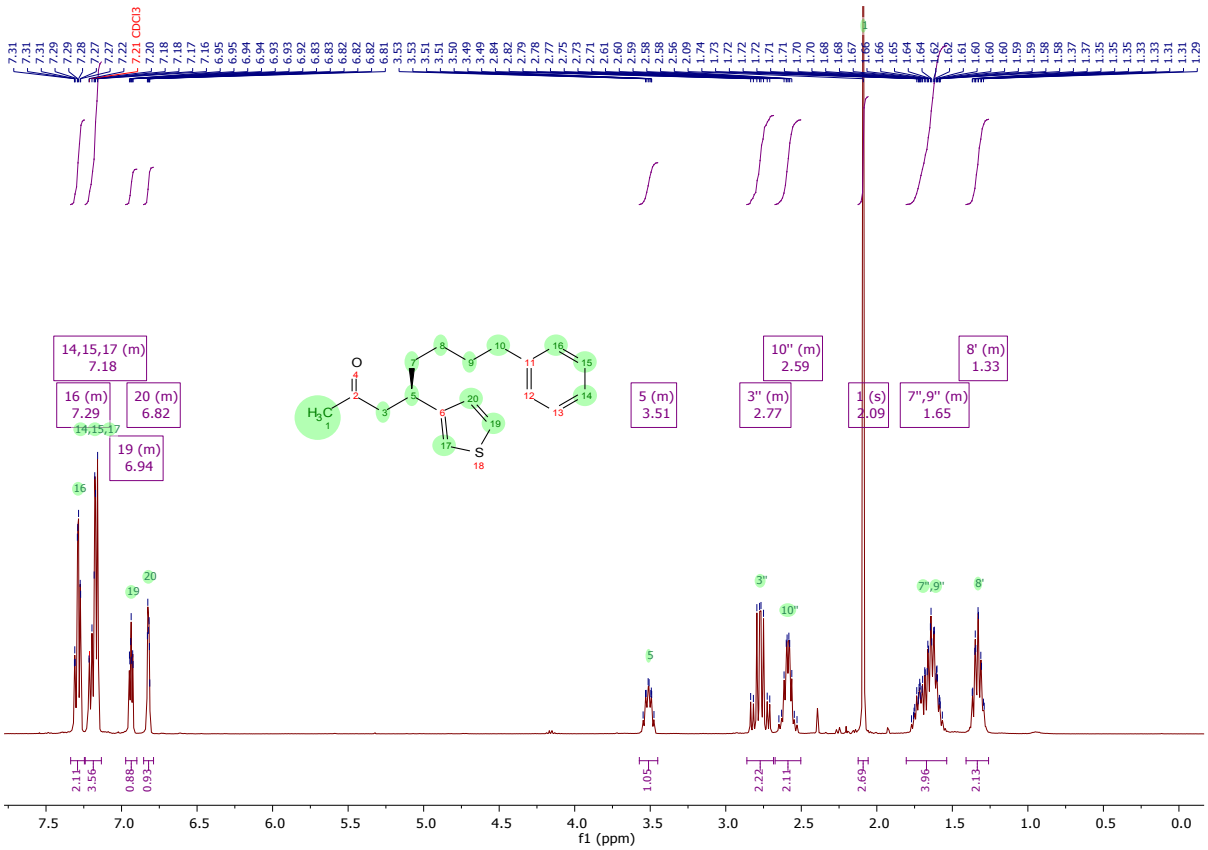
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.25 (m, 2H), 7.24 – 7.13 (m, 4H), 6.97 – 6.90 (m, 1H), 6.85 – 6.79 (m, 1H), 3.57 – 3.45 (m, 1H), 2.86 – 2.68 (m, 2H), 2.67 – 2.50 (m, 2H), 2.09 (s, 3H), 1.81 – 1.54 (m, 4H), 1.41 – 1.26 (m, 2H).

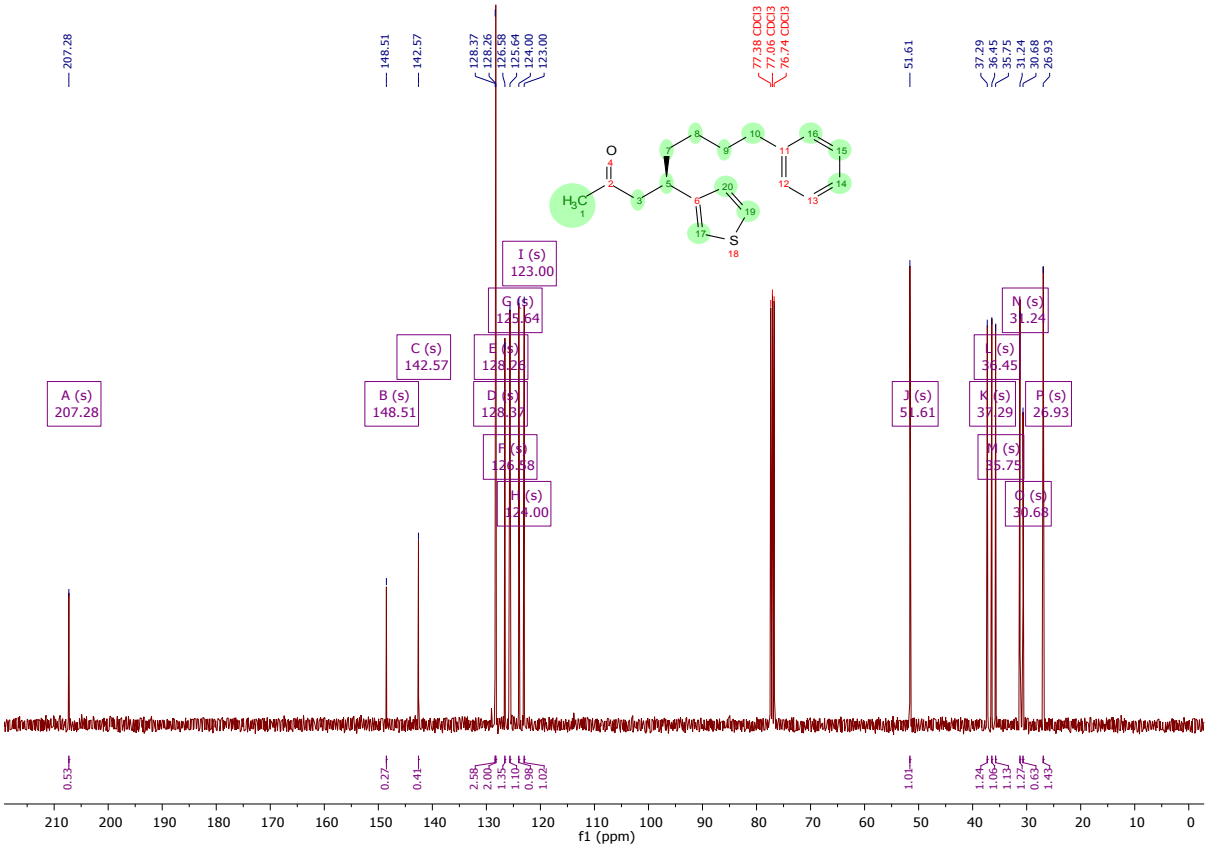
^{13}C NMR (126 MHz, Chloroform-*d*) δ 207.3, 148.5, 142.6, 128.4 (2 C), 128.3 (2 C), 126.6, 125.6, 124.0, 123.0, 51.6, 37.3, 36.4, 35.7, 31.2, 30.7, 26.9.

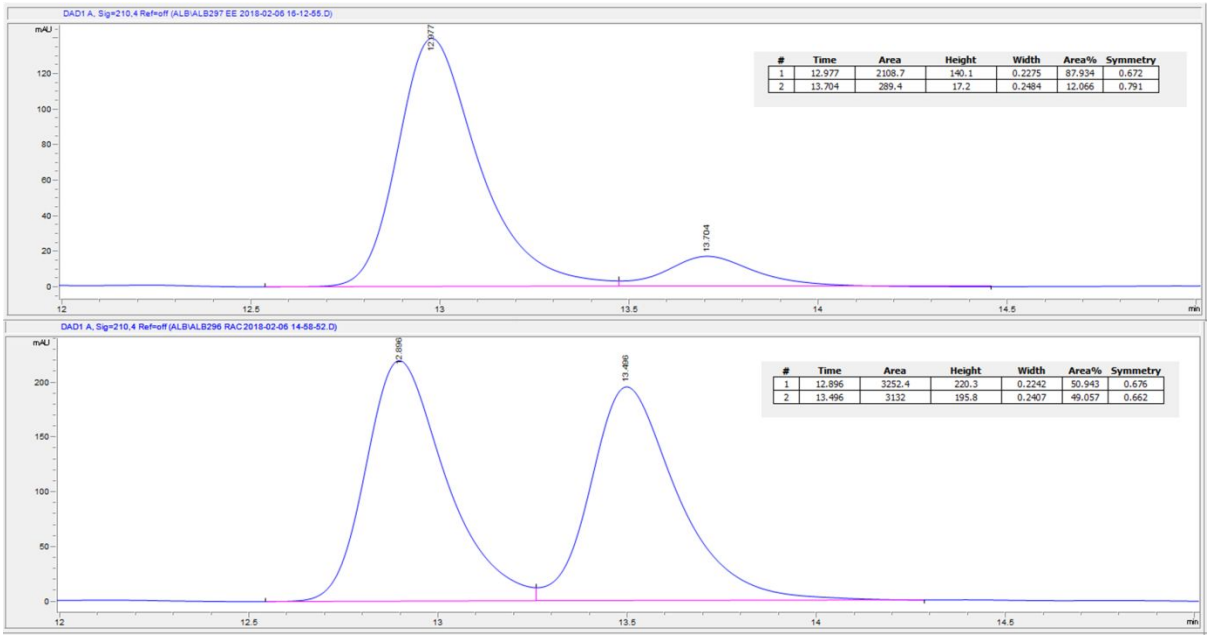
IR υ_{max} (film): 2930, 1716, 1495, 1453, 1357, 1158.

HRMS (APCI$^+$) *m/z* calcd for C_{18} H_{23} O S $[M+H]^+$: 287.1464, found 287.1461.

$[\alpha]^{25}_{589}$ = -4.6 (*c* 1.0, $CHCl_3$) for 76% ee.


14,15,17 (m)
7.18
16 (m)
7.29
20 (m)
6.82
19 (m)
6.94
5 (m)
3.51
10'' (m)
2.59
3'' (m)
2.77
1 (s)
2.09
7'',9'' (m)
1.65
8' (m)
1.33
f1 (ppm)

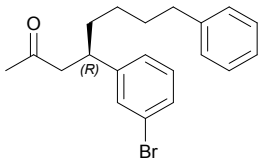

A (s)
207.28
B (s)
148.51
C (s)
142.57
D (s)
128.37
E (s)
128.26
F (s)
126.58
G (s)
125.64
H (s)
124.00
I (s)
123.00
J (s)
51.61
K (s)
37.29
L (s)
36.45
M (s)
35.75
N (s)
31.24
O (s)
30.68
P (s)
26.93
f1 (ppm)



#	Time	Area	Height	Width	Area%	Symmetry
1	12.977	2108.7	140.1	0.2275	87.934	0.672
2	13.704	289.4	17.2	0.2484	12.066	0.791

#	Time	Area	Height	Width	Area%	Symmetry
1	12.896	3252.4	220.3	0.2242	50.943	0.676
2	13.496	3132	195.8	0.2407	49.057	0.662

(R)-4-(3-bromophenyl)-8-phenyloctan-2-one 9



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-(3-bromophenyl)but-3-en-2-one (91 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-4-(3-bromophenyl)-8-phenyloctan-2-one (132.4 mg, 0.367 mmol, 91%) as a slightly yellow oil.

HPLC analysis indicated an enantiomeric excess of 95% [Chiralpak® ID; flow: 0.8 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 11.7 min; major enantiomer, t_R = 12.3 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

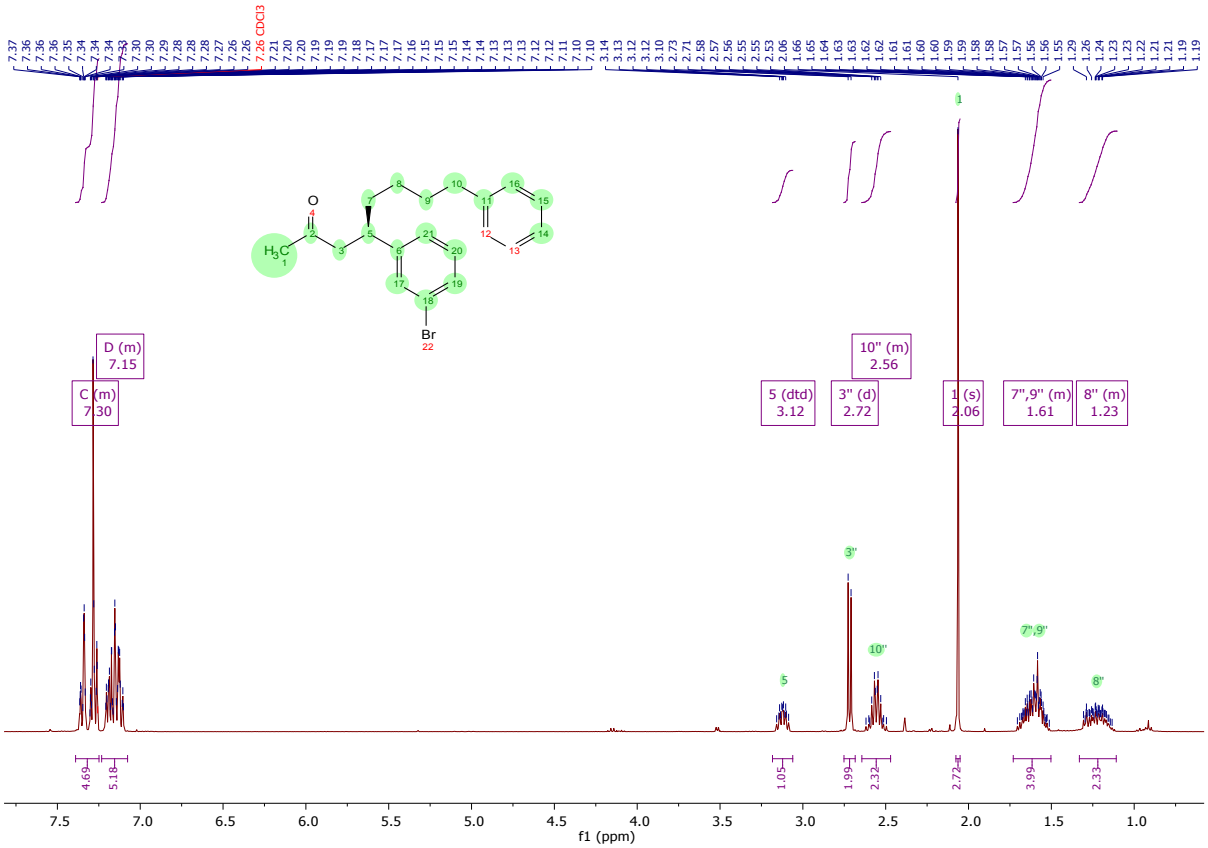
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.25 (m, 4H), 7.23 – 7.08 (m, 5H), 3.12 (dtd, *J* = 9.4, 7.1, 5.3 Hz, 1H), 2.72 (d, *J* = 7.1 Hz, 2H), 2.64 – 2.47 (m, 2H), 2.06 (s, 3H), 1.73 – 1.50 (m, 4H), 1.33 – 1.11 (m, 2H).

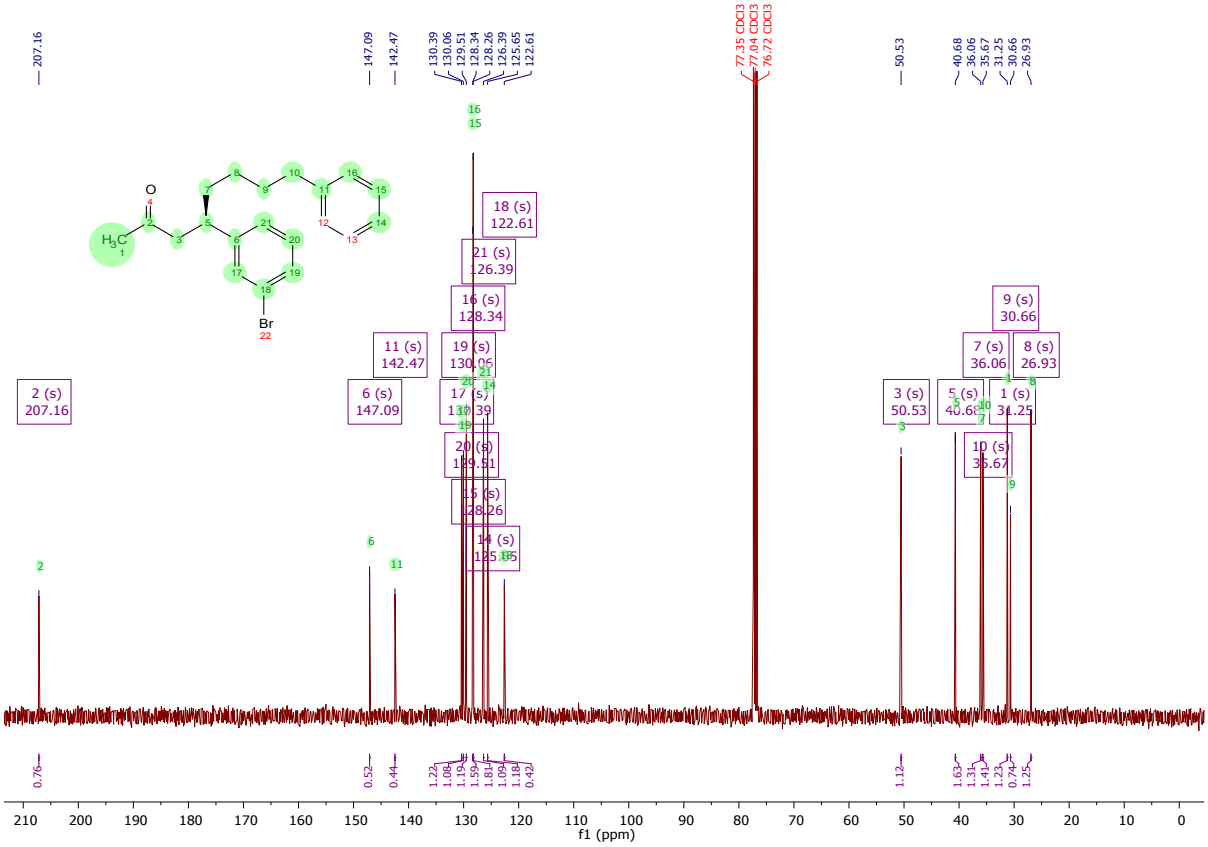
^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.2, 147.1, 142.5, 130.4, 130.1, 129.5, 128.3 (2 C), 128.3 (2 C), 126.4, 125.6, 122.6, 50.5, 40.7, 36.1, 35.7, 31.2, 30.7, 26.9.

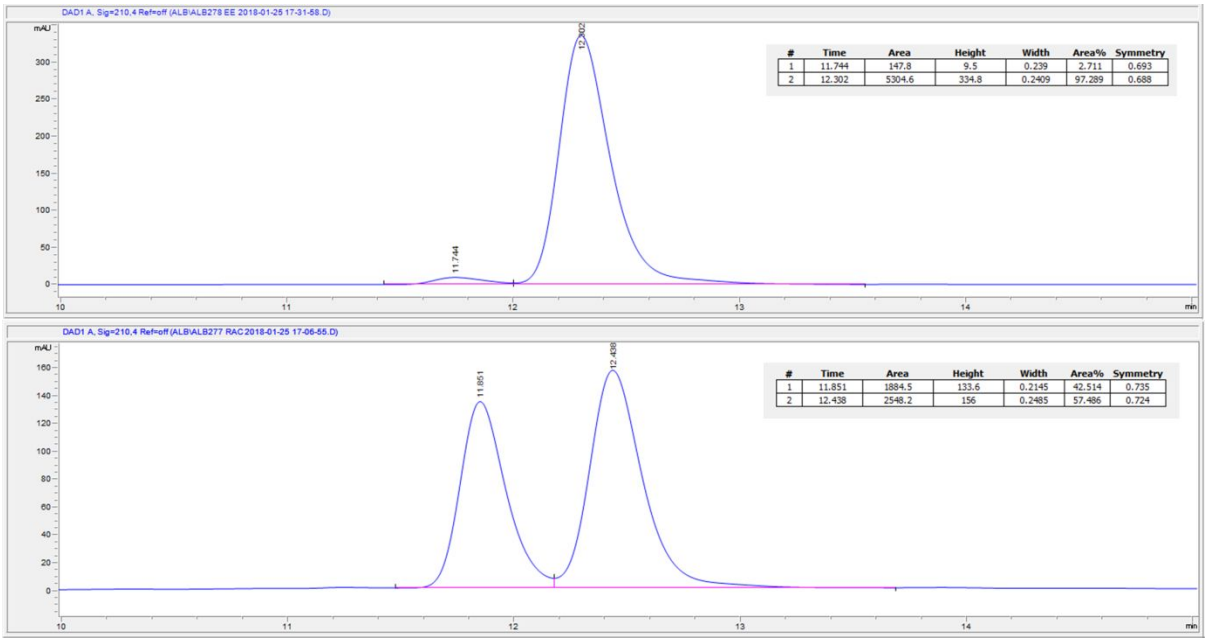
IR υ_{max} (film): 2930, 1716, 1593, 1566, 1427, 1358, 1161.

HRMS (APCI$^+$) *m/z* calcd for $C_{20}H_{24}OBr$ $[M+H]^+$: 359.1005, found 359.1000.

$[\alpha]^{25}_{589}$ = -0.3 (*c* 1.0, $CHCl_3$) for 95% ee.


D (m)
7.15
C (m)
7.30
5 (dtd)
3.12
3" (d)
2.72
10" (m)
2.56
1 (s)
2.06
7",9" (m)
1.61
8" (m)
1.23
f1 (ppm)

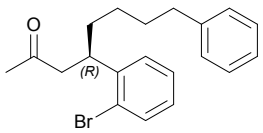

2 (s)
207.16
6 (s)
147.09
11 (s)
142.47
18 (s)
122.61
21 (s)
126.39
16 (s)
128.34
19 (s)
130.06
9 (s)
30.66
7 (s)
36.06
8 (s)
26.93
3 (s)
50.53
1 (s)
f1 (ppm)



#	Time	Area	Height	Width	Area%	Symmetry
1	11.744	147.8	9.5	0.239	2.711	0.693
2	12.302	5304.6	334.8	0.2409	97.289	0.688

#	Time	Area	Height	Width	Area%	Symmetry
1	11.851	1884.5	133.6	0.2145	42.514	0.735
2	12.438	2548.2	156	0.2485	57.486	0.724

(R)-4-(2-bromophenyl)-8-phenyloctan-2-one 10



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-(2-bromophenyl)but-3-en-2-one (91 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-4-(2-bromophenyl)-8-phenyloctan-2-one (104.5 mg, 0.291 mmol, 72%) as a slightly yellow oil.

HPLC analysis indicated an enantiomeric excess of 82% [Chiralpak® IB; flow: 0.8 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 14.4 min; major enantiomer, t_R = 16.6 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

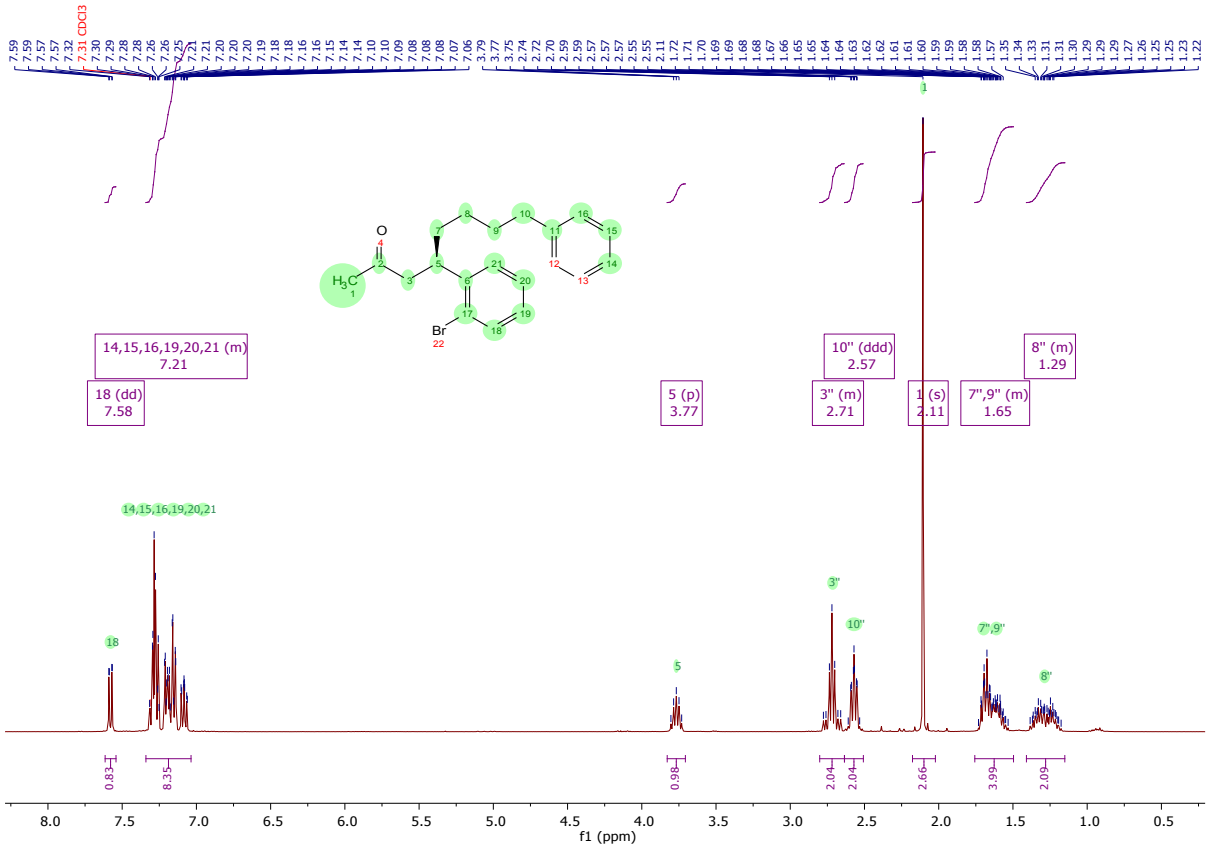
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.34 – 7.04 (m, 8H), 3.77 (p, *J* = 7.2 Hz, 1H), 2.80 – 2.64 (m, 2H), 2.57 (ddd, *J* = 8.5, 7.2, 1.7 Hz, 2H), 2.11 (s, 3H), 1.76 – 1.50 (m, 4H), 1.41 – 1.15 (m, 2H).

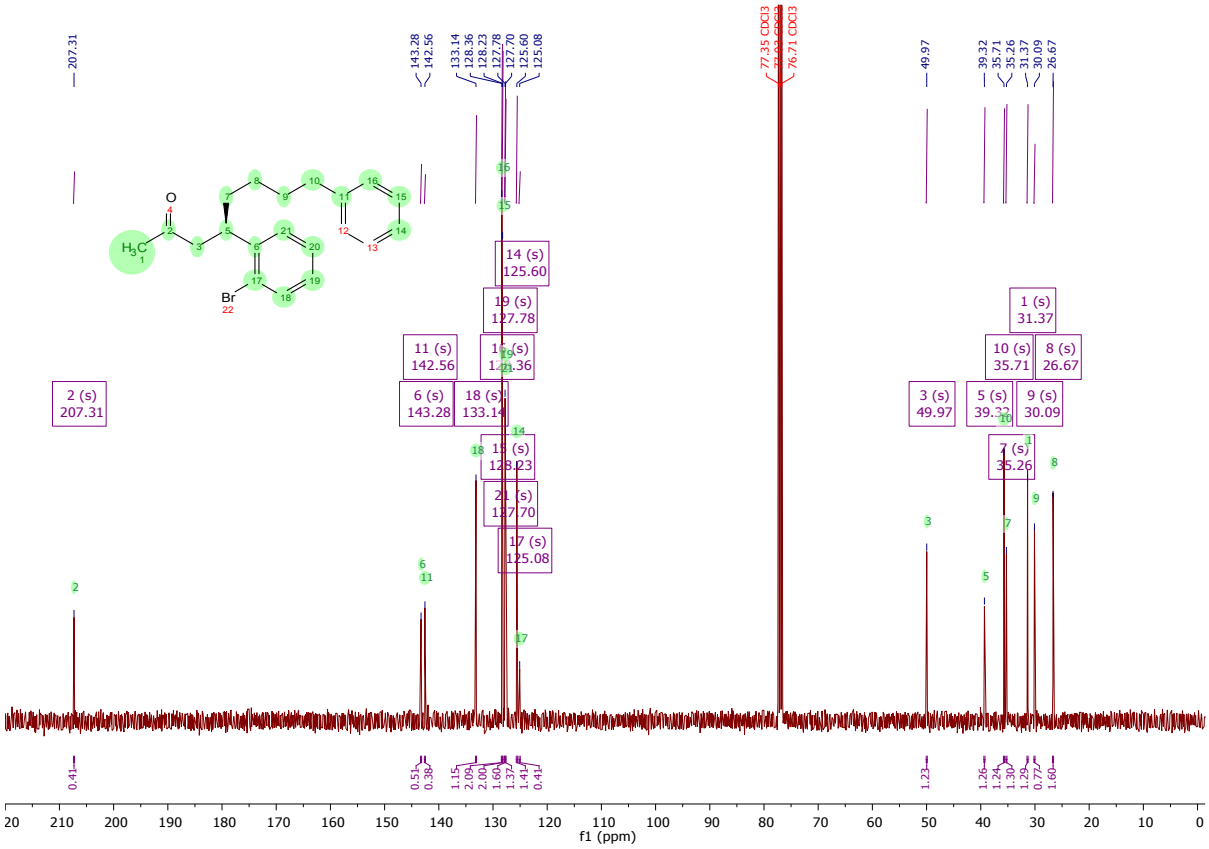
^{13}C NMR (126 MHz, Chloroform-*d*) δ 207.3, 143.3, 142.6, 133.1, 128.4 (2 C), 128.2 (2 C), 127.8, 127.7, 125.6, 125.1, 50.0, 39.3, 35.7, 35.3, 31.4, 30.1, 26.7.

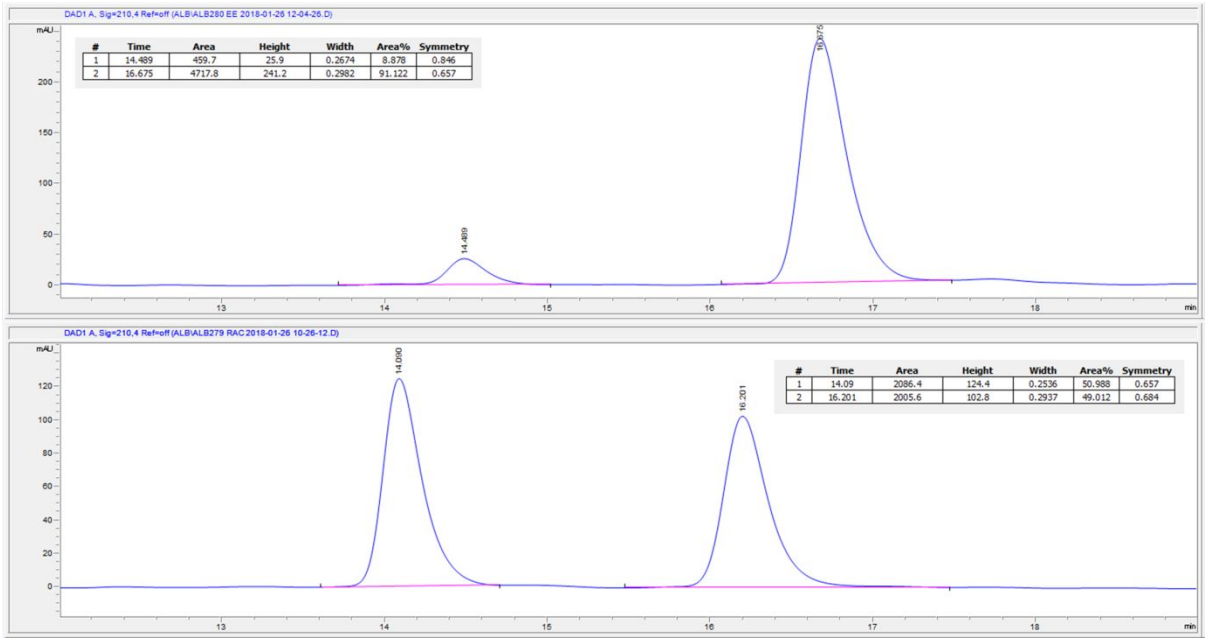
IR υ_{max} (film): 2930, 1715, 1470, 1356, 1161, 1021.

HRMS (APCI$^+$) *m/z* calcd for $C_{20}H_{24}OBr$ $[M+H]^+$: 359.1005, found 359.1000.

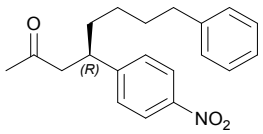
$[\alpha]^{25}_{589}$ = -3.5 (*c* 1.0, $CHCl_3$) for 82% ee.


14,15,16,19,20,21 (m)
7.21
18 (dd)
7.58
5 (p)
3.77
10'' (ddd)
2.57
3'' (m)
2.71
1 (s)
2.11
8'' (m)
1.29
7'',9'' (m)
1.65
f1 (ppm)


2 (s)
207.31
6 (s)
143.28
11 (s)
142.56
18 (s)
133.14
14 (s)
125.60
19 (s)
127.78
1 (s)
31.37
10 (s)
35.71
8 (s)
26.67
3 (s)
49.97
5 (s)
39.32
9 (s)
30.09
7 (s)
35.26
f1 (ppm)


DAD1 A, Sig=210,4 Ref=off (ALB\ALB280 EE 2018-01-26 12-04-26.D)
mAU
Time Area Height Width Area% Symmetry
1 14.489 459.7 25.9 0.2674 8.878 0.846
2 16.675 4717.8 241.2 0.2982 91.122 0.657
14.489
16.675
min
DAD1 A, Sig=210,4 Ref=off (ALB\ALB279 RAC 2018-01-26 10-26-12.D)
mAU
Time Area Height Width Area% Symmetry
1 14.09 2086.4 124.4 0.2536 50.988 0.657
2 16.201 2005.6 102.8 0.2937 49.012 0.684
14.090
16.201
min

(R)-4-(4-nitrophenyl)-8-phenyloctan-2-one 7



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-(4-nitrophenyl)but-3-en-2-one (77 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-4-(4-nitrophenyl)-8-phenyloctan-2-one (93.3 mg, 0.286 mmol, 71%) as a slightly yellow oil.

SFC analysis indicated an enantiomeric excess of 91% [Chiralpak® ID-3; 1500 psi, 30 °C, flow: 1.5 mL/min; 1.0% to 30.0% MeOH in 5 min; λ = 218 nm; major enantiomer, tR = 3.57 min; minor enantiomer, tR = 3.83 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

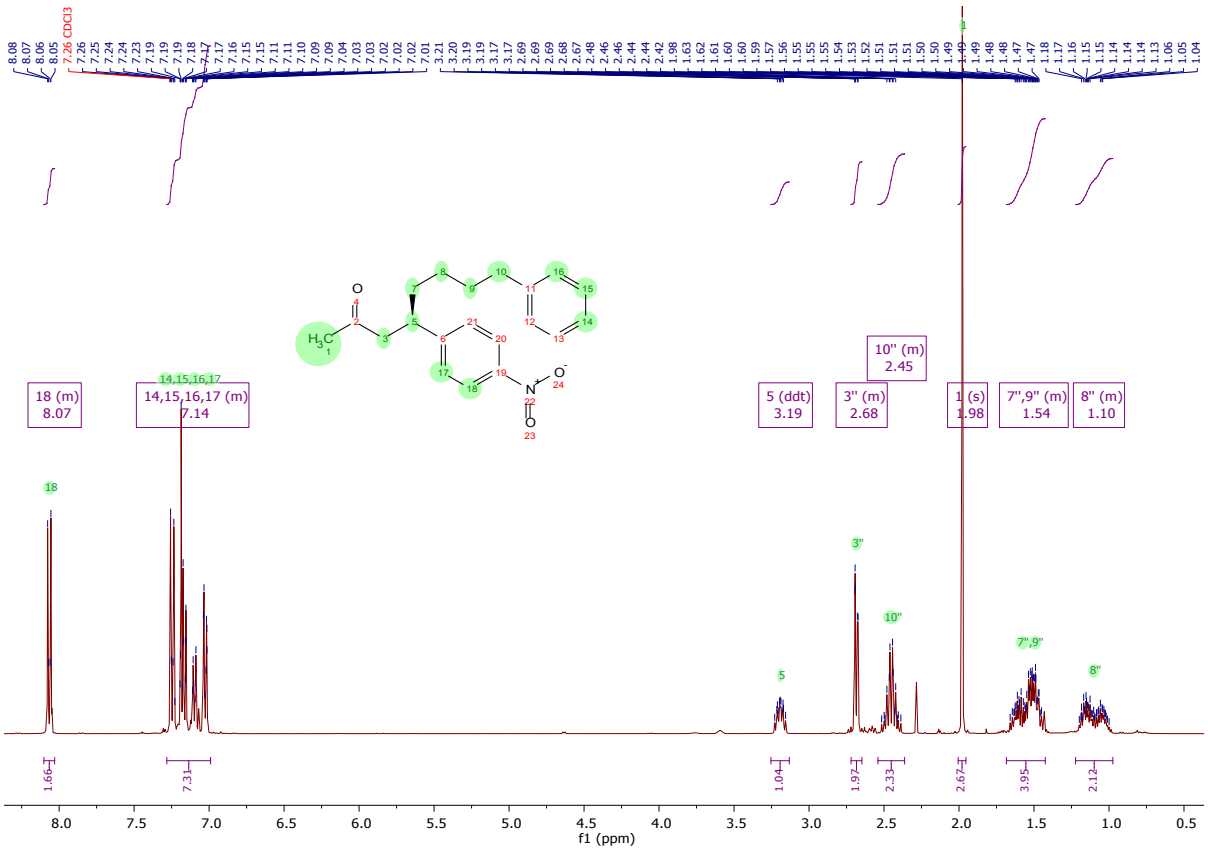
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.10 – 8.03 (m, 2H), 7.28 – 6.99 (m, 7H), 3.19 (ddt, *J* = 12.4, 9.4, 6.2 Hz, 1H), 2.72 – 2.65 (m, 2H), 2.54 – 2.36 (m, 2H), 1.98 (s, 3H), 1.68 – 1.42 (m, 4H), 1.22 – 0.97 (m, 2H).

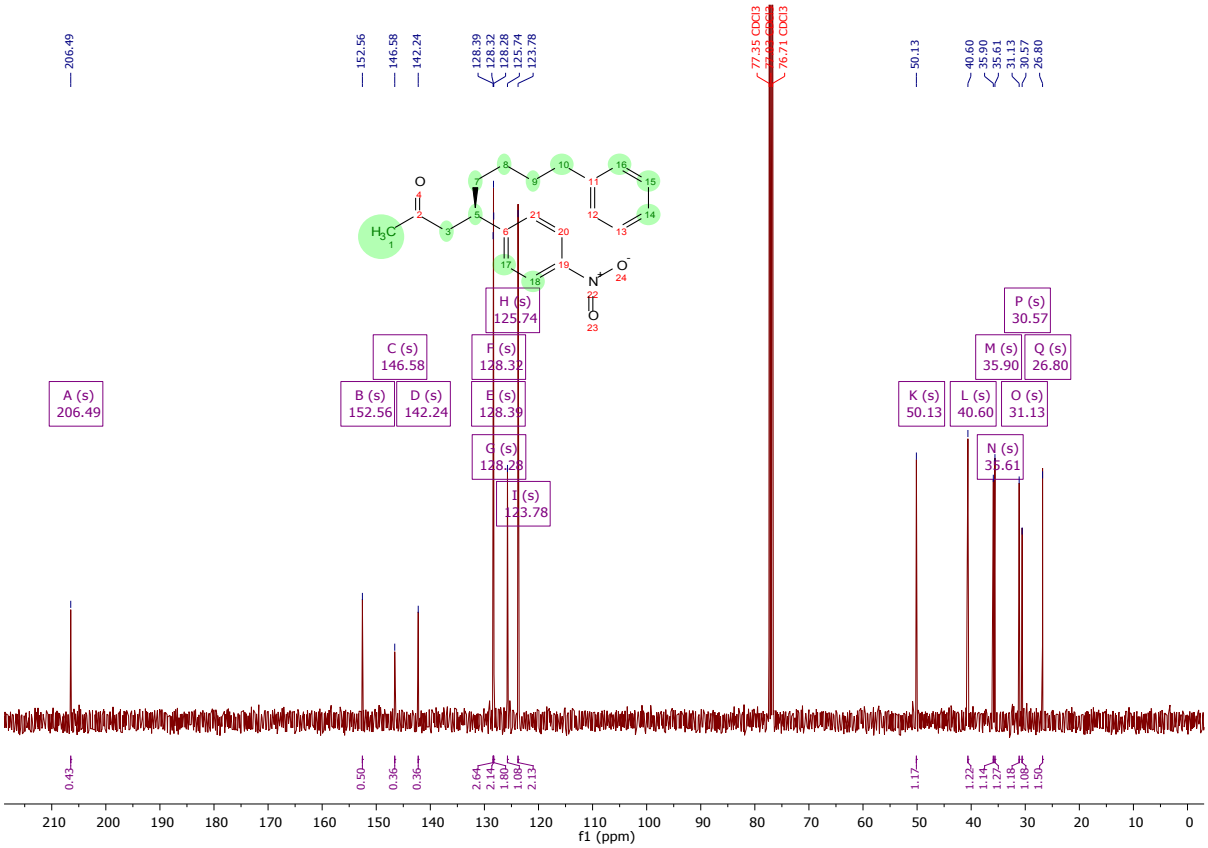
^{13}C NMR (126 MHz, Chloroform-*d*) δ 206.5, 152.6, 146.6, 142.2, 128.4 (2 C), 128.3 (2 C), 128.3 (2 C), 125.7, 123.8 (2 C), 50.1, 40.6, 35.9, 35.6, 31.1, 30.6, 26.8.

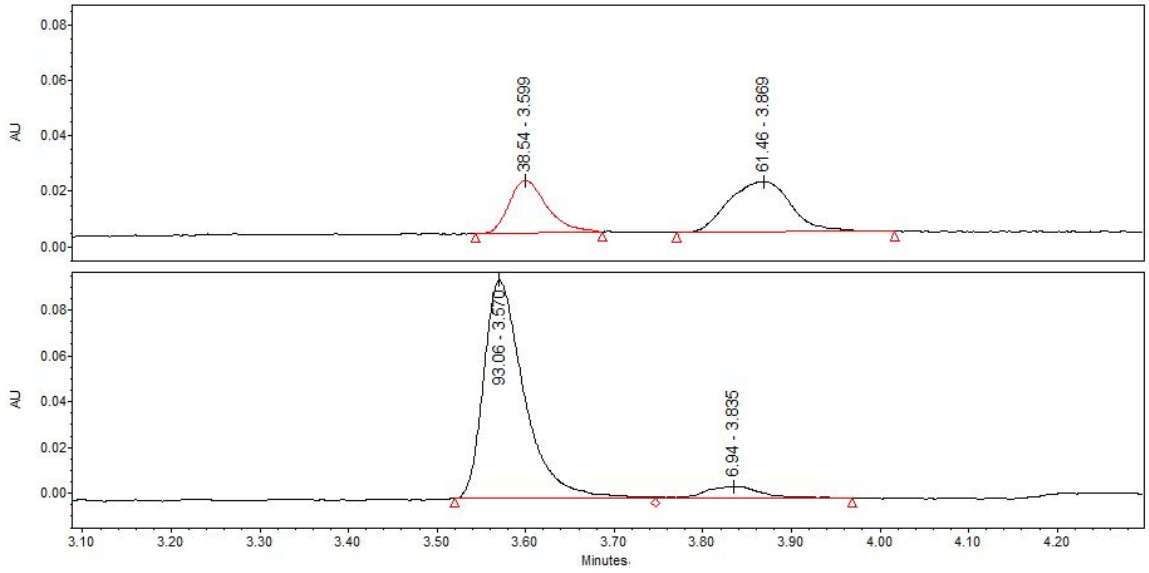
IR υ_{max} (film): 2931, 1716, 1603, 1517, 1345, 856, 699.

HRMS (APCI$^+$) *m/z* calcd for $C_{20}H_{24}O_3N$ $[M+H]^+$: 326.1751, found 326.1754.

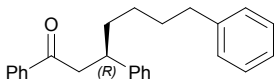
$[\alpha]^{25}_{589}$ = +5.9 (*c* 1.0, $CHCl_3$) for 91% ee.


18 (m)
8.07
14,15,16,17 (m)
7.14
5 (ddt)
3.19
3" (m)
2.68
10" (m)
2.45
1 (s)
1.98
7",9" (m)
1.54
8" (m)
1.10
f1 (ppm)


A (s)
206.49
B (s)
152.56
C (s)
146.58
D (s)
142.24
E (s)
128.39
F (s)
128.32
G (s)
128.28
H (s)
125.74
I (s)
123.78
K (s)
50.13
L (s)
40.60
M (s)
35.90
N (s)
35.61
O (s)
31.13
P (s)
30.57
Q (s)
26.80
f1 (ppm)


AU
0.08
0.06
0.04
0.02
0.00
38.54 - 3.599
61.46 - 3.869
AU
0.08
0.06
0.04
0.02
0.00
93.06 - 3.570
6.94 - 3.835
3.10
3.20
3.30
3.40
3.50
3.60
3.70
3.80
3.90
4.00
4.10
4.20
Minutes

(R)-1,3,7-triphenylheptan-1-one 17



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-chalcone (84 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-1,3,7-triphenylheptan-1-one (132.8 mg, 0.388 mmol, 96%) as a slightly yellow oil.

HPLC analysis indicated an enantiomeric excess of 78% [Chiralpak® ID; flow: 0.8 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 13.5 min; major enantiomer, t_R = 15.6 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

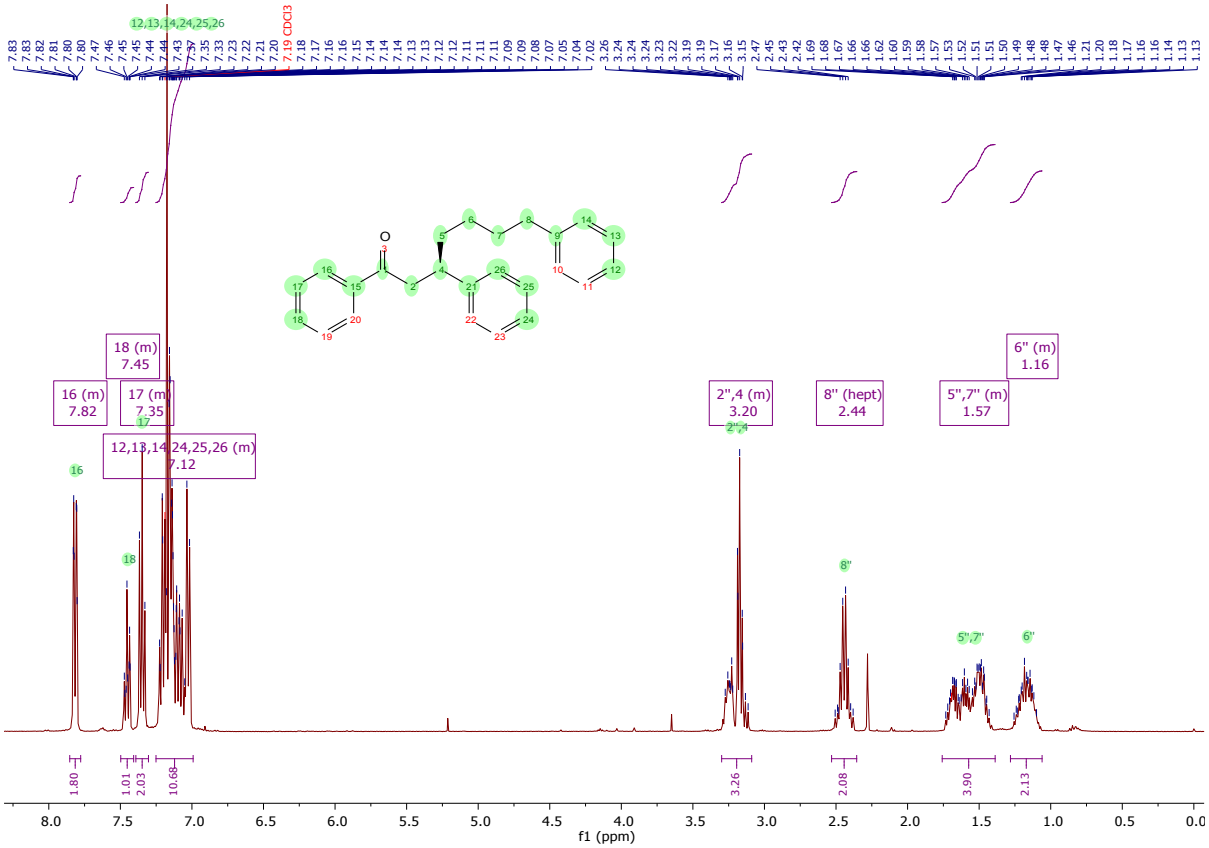
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 2H), 7.50 – 7.41 (m, 1H), 7.39 – 7.30 (m, 2H), 7.25 – 6.99 (m, 11H), 3.30 – 3.09 (m, 3H), 2.44 (hept, *J* = 7.1 Hz, 2H), 1.76 – 1.39 (m, 4H), 1.28 – 1.06 (m, 2H).

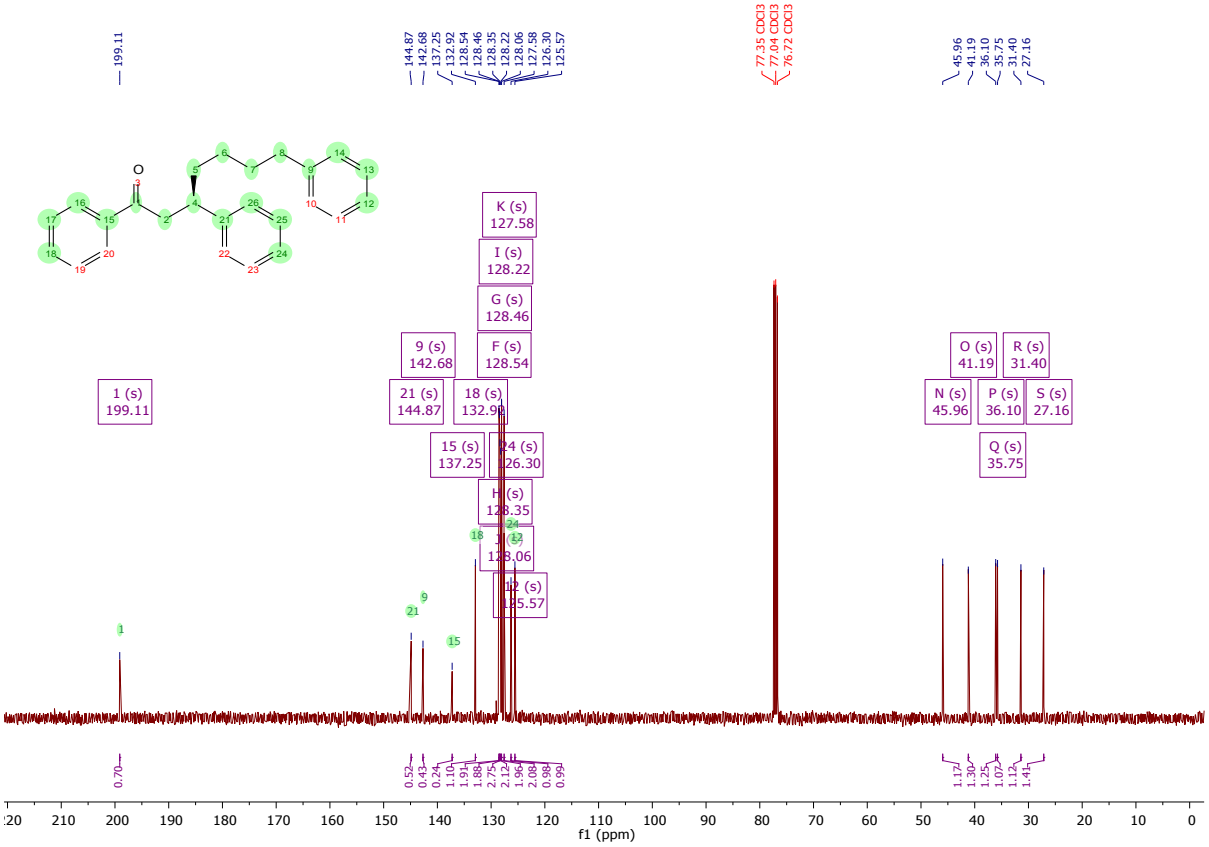
^{13}C NMR (126 MHz, Chloroform-*d*) δ 199.1, 144.9, 142.7, 137.2, 132.9, 128.5 (2 C), 128.5 (2 C), 128.3 (2 C), 128.2 (2 C), 128.1 (2 C), 127.6 (2 C), 126.3, 125.6, 46.0, 41.2, 36.1, 35.7, 31.4, 27.2.

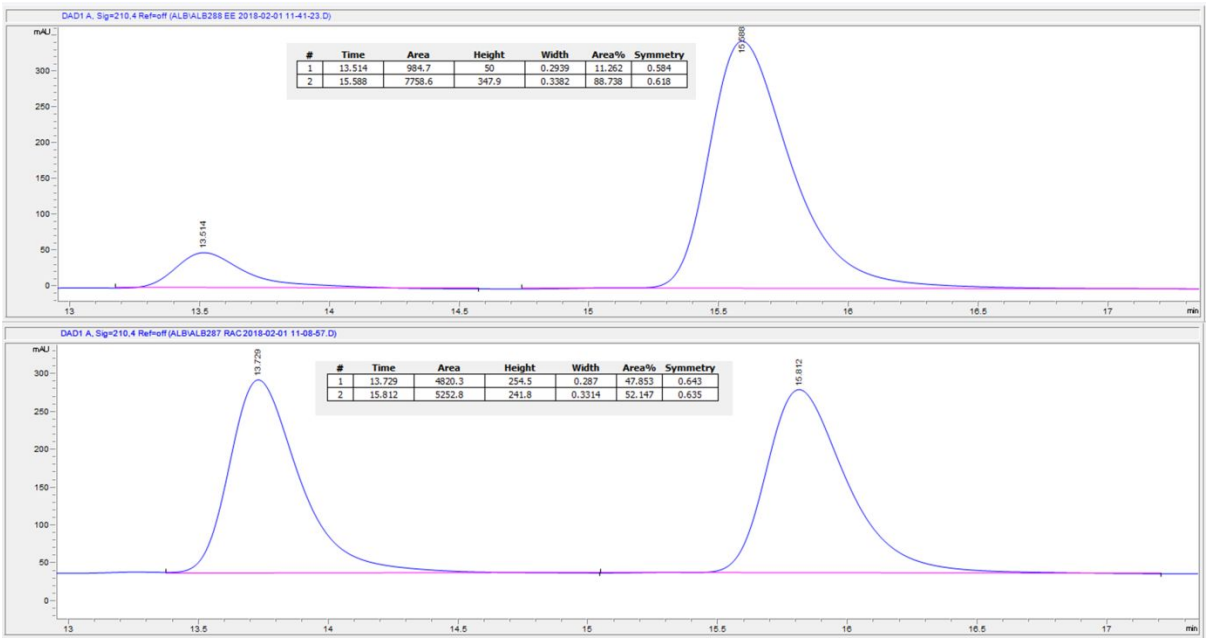
IR υ_{max} (film): 2980, 1685, 1494, 1382, 1251, 1153, 1073.

HRMS (APCI$^+$) *m/z* calcd for C_{25} H_{27} O $[M+H]^+$: 343.2056, found 343.2057.

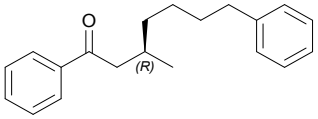
$[\alpha]^{25}_{589}$ = +4.2 (*c* 1.0, $CHCl_3$) for 78% ee.


18 (m)
7.45
16 (m)
7.82
17 (m)
7.35
12,13,14,24,25,26 (m)
7.12
2",4 (m)
3.20
8" (hept)
2.44
5",7" (m)
1.57
6" (m)
1.16
f1 (ppm)


K (s)
127.58
I (s)
128.22
G (s)
128.46
9 (s)
142.68
F (s)
128.54
21 (s)
144.87
18 (s)
132.98
15 (s)
137.25
24 (s)
126.30
H (s)
128.35
1 (s)
199.11
O (s)
41.19
R (s)
31.40
N (s)
45.96
P (s)
36.10
S (s)
27.16
Q (s)
35.75
f1 (ppm)


DAD1 A, Sig=210,4 Ref=off (ALB\ALB288 EE 2018-02-01 11-41-23.D)
mAU
13.514
15.588
min
Time Area Height Width Area% Symmetry
1 13.514 984.7 50 0.2939 11.262 0.584
2 15.588 7758.6 347.9 0.3382 88.738 0.618
DAD1 A, Sig=210,4 Ref=off (ALB\ALB287 RAC 2018-02-01 11-08-57.D)
mAU
13.729
15.812
min
Time Area Height Width Area% Symmetry
1 13.729 4820.3 254.5 0.287 47.853 0.643
2 15.812 5252.8 241.8 0.3314 52.147 0.635

(R)-3-methyl-1,7-diphenylheptan-1-one 16



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-1-phenylbut-2-en-1-one (58 µL, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-3-methyl-1,7-diphenylheptan-1-one (112.5 mg, 0.401 mmol, >99%) as a slightly yellow oil.

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IB; flow: 0.8 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 9.6 min; major enantiomer, t_R = 10.5 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

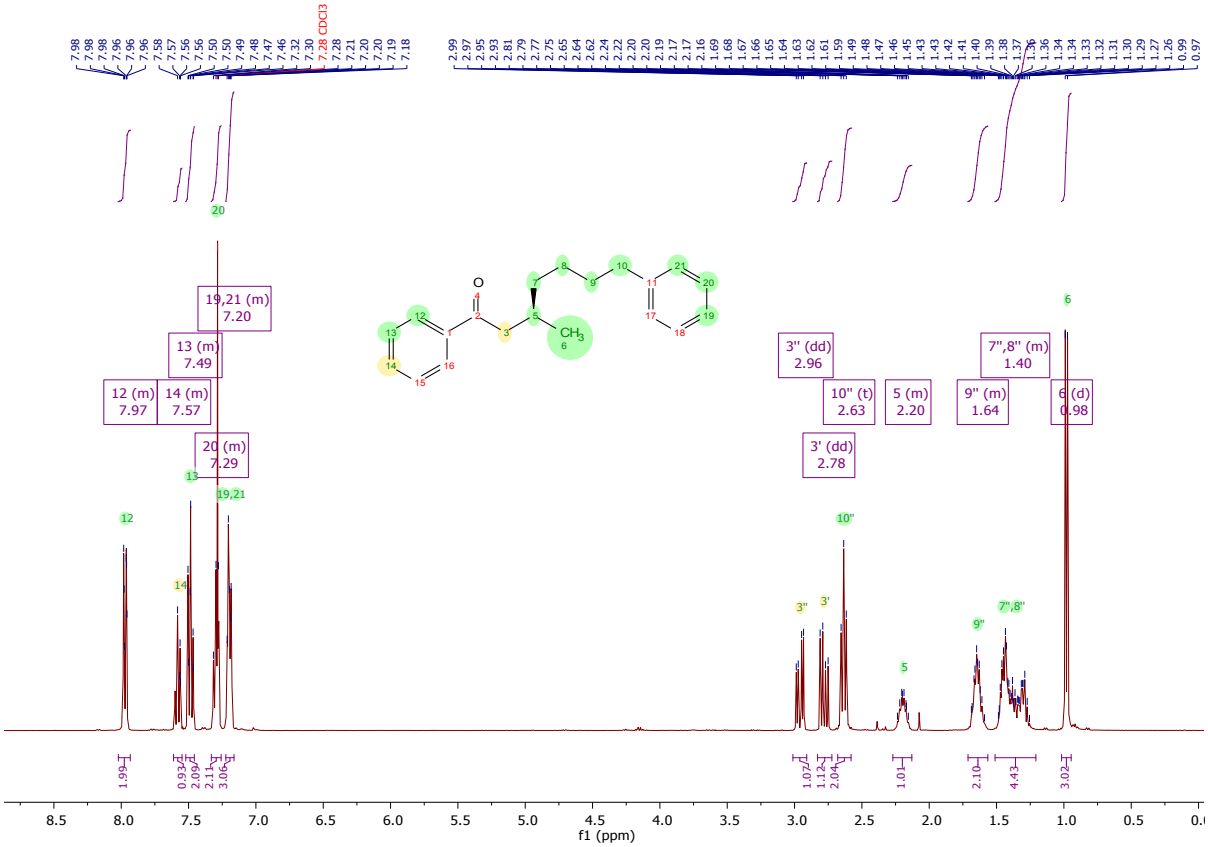
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 – 7.93 (m, 2H), 7.61 – 7.55 (m, 1H), 7.52 – 7.46 (m, 2H), 7.33 – 7.26 (m, 2H), 7.22 – 7.16 (m, 3H), 2.96 (dd, *J* = 15.8, 5.7 Hz, 1H), 2.78 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.27 – 2.13 (m, 1H), 1.71 – 1.56 (m, 2H), 1.51 – 1.21 (m, 4H), 0.98 (d, *J* = 6.7 Hz, 3H).

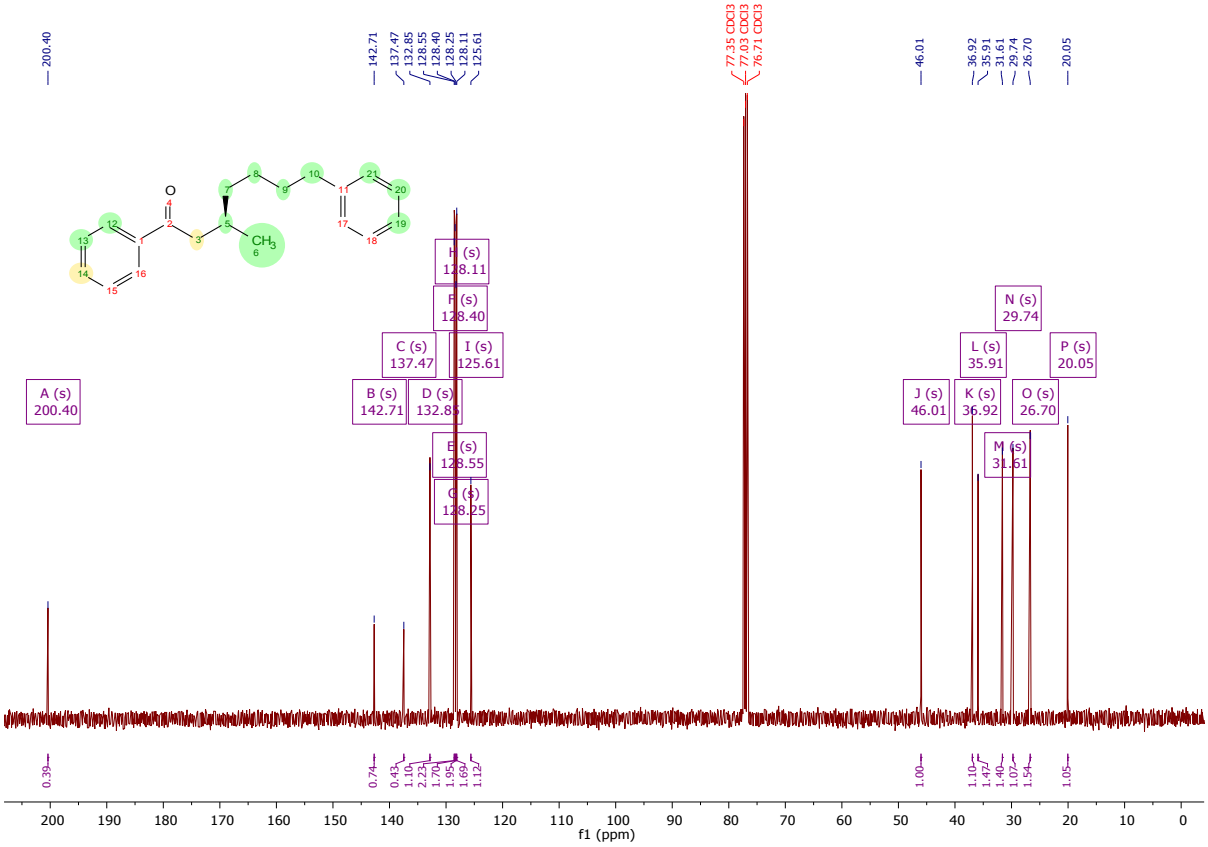
^{13}C NMR (126 MHz, Chloroform-*d*) δ 200.4, 142.7, 137.5, 132.8, 128.5 (2 C), 128.4 (2 C), 128.2 (2 C), 128.1 (2 C), 125.6, 46.0, 36.9, 35.9, 31.6, 29.7, 26.7, 20.0.

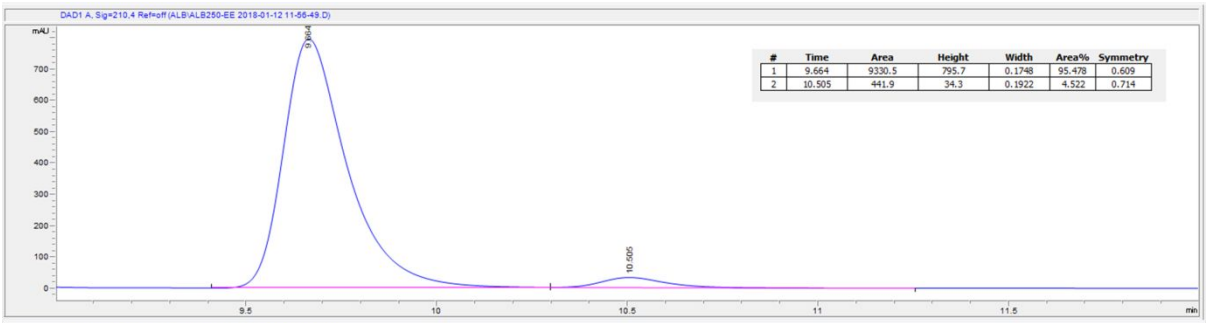
IR υ_{max} (film): 2980, 1685, 1449, 1379, 1252, 1155.

HRMS (APCI$^+$) *m/z* calcd for $C_{20}H_{25}O$ $[M+H]^+$: 281.1899, found 281.1900.

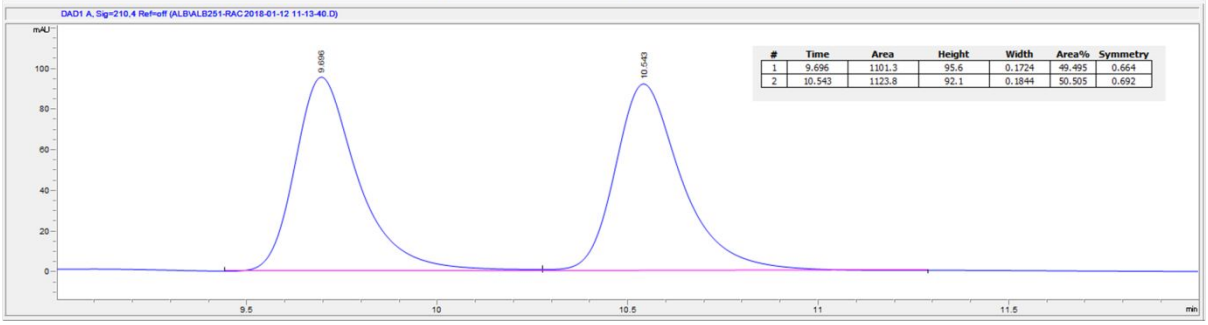
$[\alpha]^{25}_{589}$ = -0.5 (*c* 1.0, $CHCl_3$) for 91% ee.


19,21 (m)
7.20
13 (m)
7.49
12 (m)
7.97
14 (m)
7.57
20 (m)
7.29
3'' (dd)
2.96
10'' (t)
2.63
5 (m)
2.20
3' (dd)
2.78
9'' (m)
1.64
7'',8'' (m)
1.40
6 (d)
0.98
f1 (ppm)


A (s)
200.40
B (s)
142.71
C (s)
137.47
D (s)
132.85
E (s)
128.55
F (s)
128.40
G (s)
128.25
H (s)
128.11
I (s)
125.61
J (s)
46.01
K (s)
36.92
L (s)
35.91
M (s)
31.61
N (s)
29.74
O (s)
26.70
P (s)
20.05
f1 (ppm)

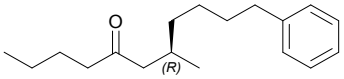


#	Time	Area	Height	Width	Area%	Symmetry
1	9.664	9330.5	795.7	0.1748	95.478	0.609
2	10.505	441.9	34.3	0.1922	4.522	0.714



#	Time	Area	Height	Width	Area%	Symmetry
1	9.696	1101.3	95.6	0.1724	49.495	0.664
2	10.543	1123.8	92.1	0.1844	50.505	0.692

(R)-7-methyl-11-phenylundecan-5-one 14



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-oct-2-en-4-one (60 µL, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-7-methyl-11-phenylundecan-5-one (102.1 mg, 0.392 mmol, 97%) as a slightly yellow oil.

HPLC analysis indicated an enantiomeric excess of 95% [Chiralpak® IC; flow: 1.0 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 6.9 min; major enantiomer, t_R = 7.3 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.26 (m, 2H), 7.24 – 7.15 (m, 3H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.43 – 2.33 (m, 3H), 2.22 (dd, *J* = 15.8, 8.0 Hz, 1H), 2.02 (hept, *J* = 6.6, 6.1 Hz, 1H), 1.71 – 1.51 (m, 4H), 1.46 – 1.14 (m, 6H), 0.98 – 0.86 (m, 6H).

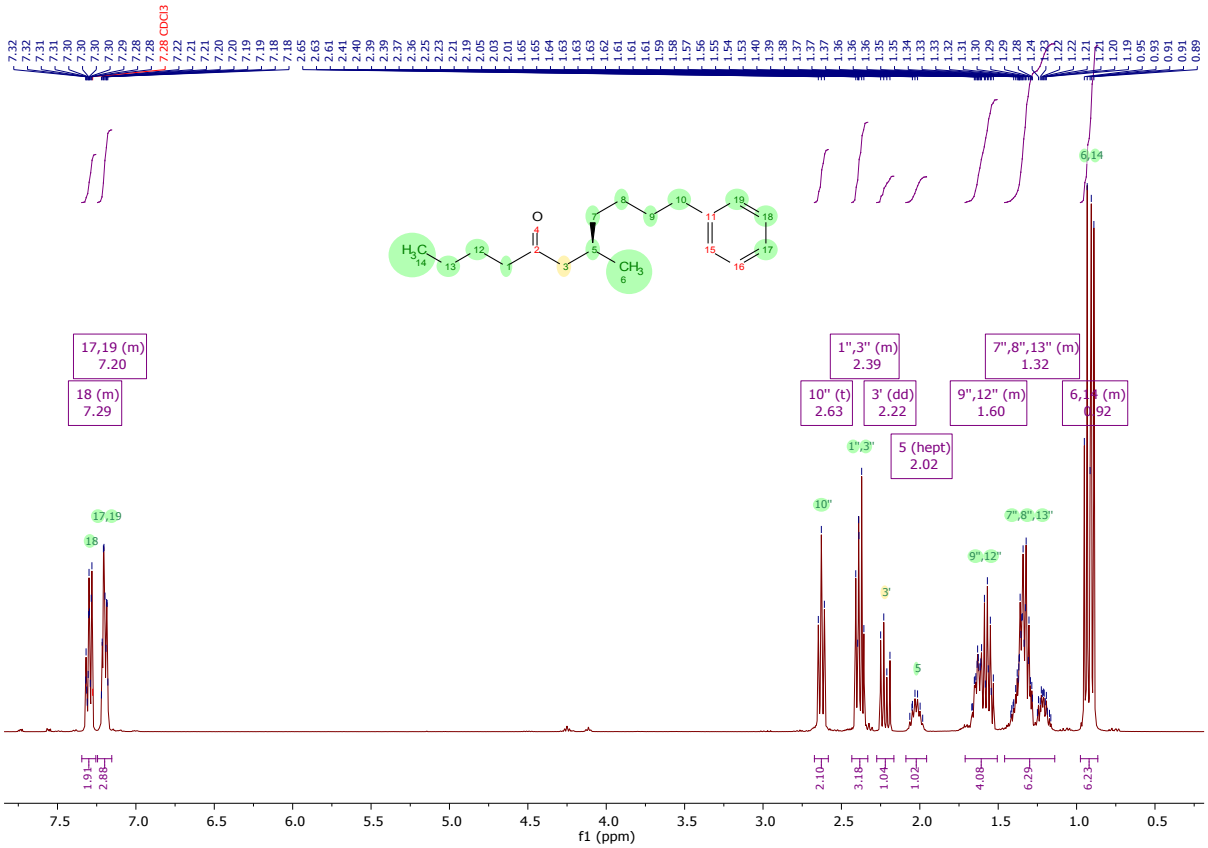
^{13}C NMR (126 MHz, Chloroform-*d*) δ 211.4, 142.7, 128.4 (2 C), 128.2 (2 C), 125.6, 50.3, 43.1, 36.8, 35.9, 31.6, 29.2, 26.6, 25.9, 22.4, 19.9, 13.9.

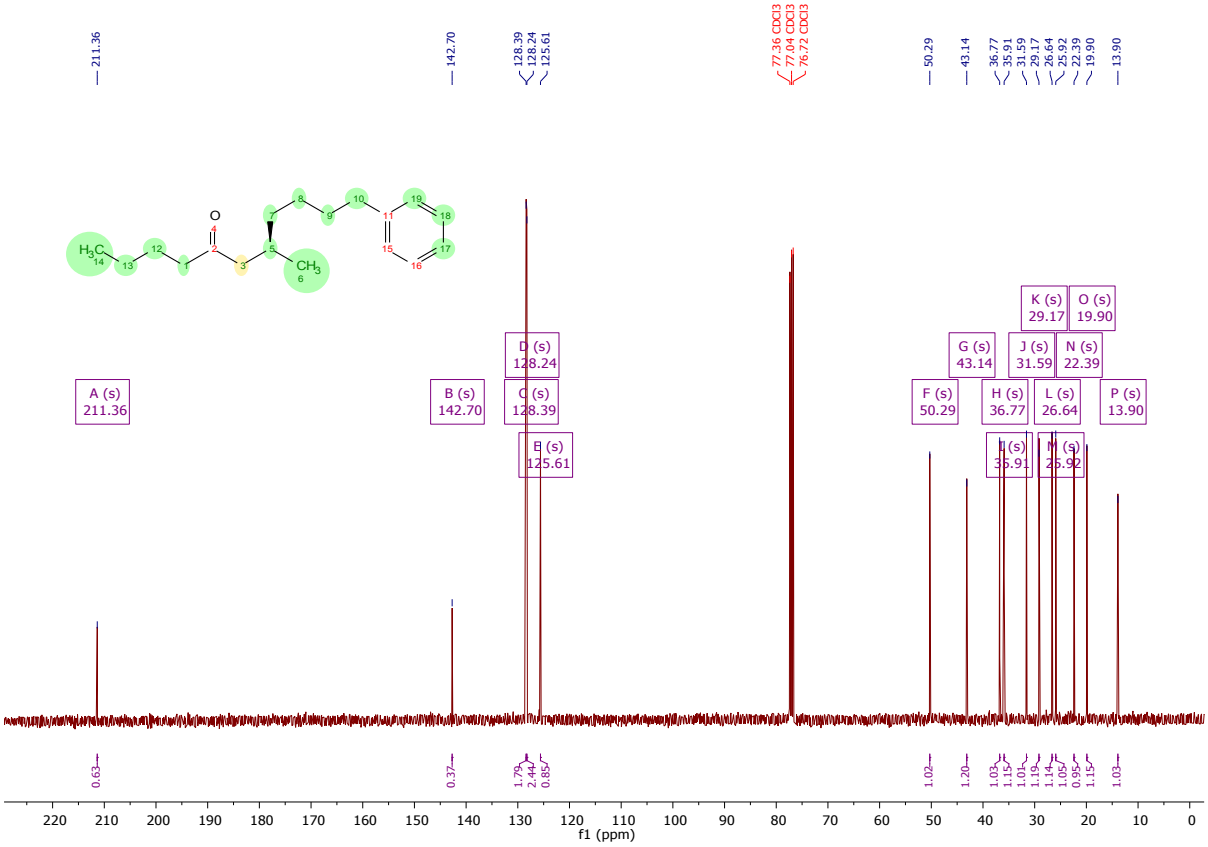
IR υ_{max} (film): 2930, 1712, 1454, 1377.

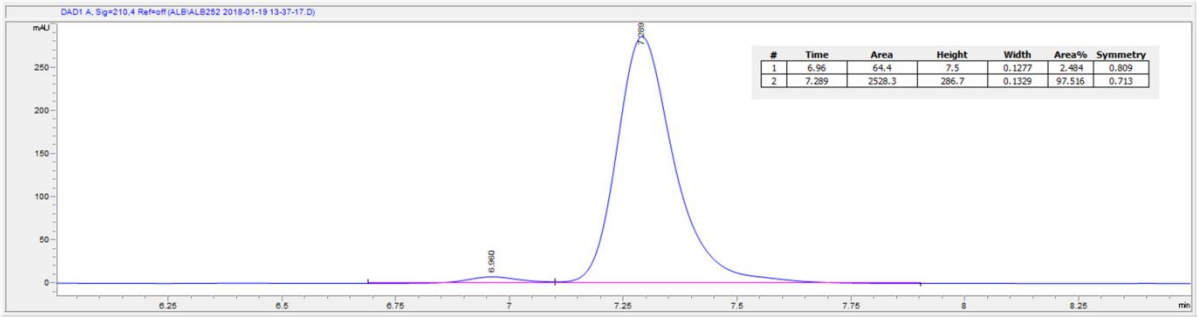
HRMS (APCI$^+$) *m/z* calcd for $C_{18}H_{29}O$ $[M+H]^+$: 261.2212, found 261.2212.

$[\alpha]^{25}_{589}$ = +6.5 (*c* 1.0, $CHCl_3$) for 95% ee.

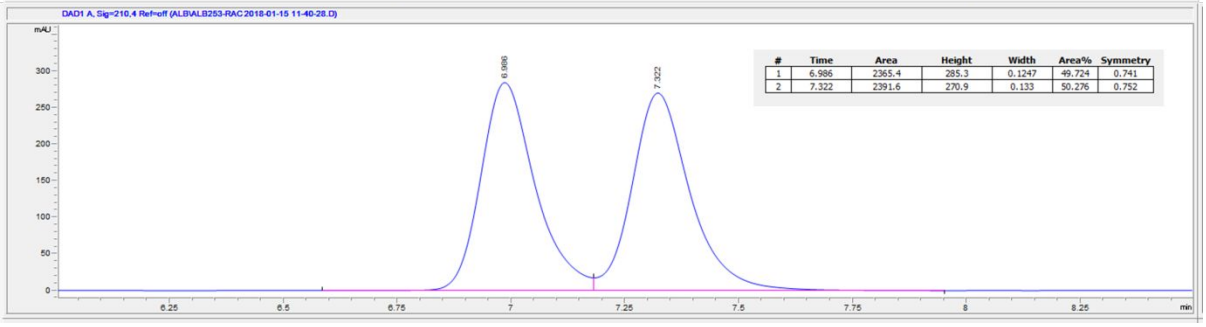
Analytical data are in agreement with the literature.[6]


17,19 (m)
7.20
18 (m)
7.29
1",3" (m)
2.39
10" (t)
2.63
3' (dd)
2.22
5 (hept)
2.02
9",12" (m)
1.60
7",8",13" (m)
1.32
6,14 (m)
0.92
f1 (ppm)


A (s)
211.36
B (s)
142.70
C (s)
128.39
D (s)
128.24
E (s)
125.61
F (s)
50.29
G (s)
43.14
H (s)
36.77
I (s)
35.91
J (s)
31.59
K (s)
29.17
L (s)
26.64
M (s)
25.92
N (s)
22.39
O (s)
19.90
P (s)
13.90
f1 (ppm)

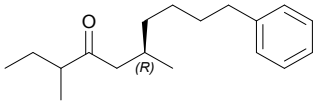


#	Time	Area	Height	Width	Area%	Symmetry
1	6.96	64.4	7.5	0.1277	2.484	0.809
2	7.289	2528.3	286.7	0.1329	97.516	0.713



#	Time	Area	Height	Width	Area%	Symmetry
1	6.986	2365.4	285.3	0.1247	49.724	0.741
2	7.322	2391.6	270.9	0.133	50.276	0.752

(6R)-3,6-dimethyl-10-phenyldecan-4-one 15



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-5-methylhept-2-en-4-one (60 µL, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford a mixture of inseparable diastereoisomers (6R)-3,6-dimethyl-10-phenyldecan-4-one (83.4 mg, 0.322 mmol, 80%) as a slightly yellow oil.

Quantitative ^{1}H NMR experiment analysis indicated a diastereomeric ratio of 1:1.4.

Diastereoisomer 1: SFC analysis indicated an enantiomeric excess of 96% [Chiralpak® IF-3; 1500 psi, 30 °C, flow: 1.5 mL/min; 1.0% to 30.0% MeOH in 5 min; λ = 218 nm; major enantiomer, t_R = 2.02 min; minor enantiomer, t_R = 2.28 min].

Diastereoisomer 2: SFC analysis indicated an enantiomeric excess of 91% [Chiralpak® IF-3; 1500 psi, 30 °C, flow: 1.5 mL/min; 1.0% to 30.0% MeOH in 5 min; λ = 218 nm; major enantiomer, t_R = 2.02 min; minor enantiomer, t_R = 2.36 min].

Racemic product was realised using *General Procedure A*. Absolute configuration was assigned by comparison to literature data.[6]

Mixture of diastereoisomers:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 – 7.19 (m, 2H), 7.19 – 7.09 (m, 3H), 2.57 (t, *J* = 7.7 Hz, 2H), 2.45 – 2.29 (m, 2H), 2.22 (ddd, *J* = 16.5, 7.8, 6.4 Hz, 1H), 2.06 – 1.92 (m, 1H), 1.73 – 1.49 (m, 3H), 1.41 – 1.22 (m, 4H), 1.21 – 1.09 (m, 1H), 1.01 (dd, *J* = 6.9, 1.2 Hz, 3H), 0.88 – 0.81 (m, 7H).

Diastereoisomer 1:

^{13}C NMR (101 MHz, Chloroform-*d*) δ 214.7, 142.8, 128.5 (2 C), 128.4 (2 C), 125.7, 48.9, 48.3, 36.9, 36.0, 31.7, 28.9, 26.8, 26.0, 20.1, 16.0, 11.9.

Diastereoisomer 2:

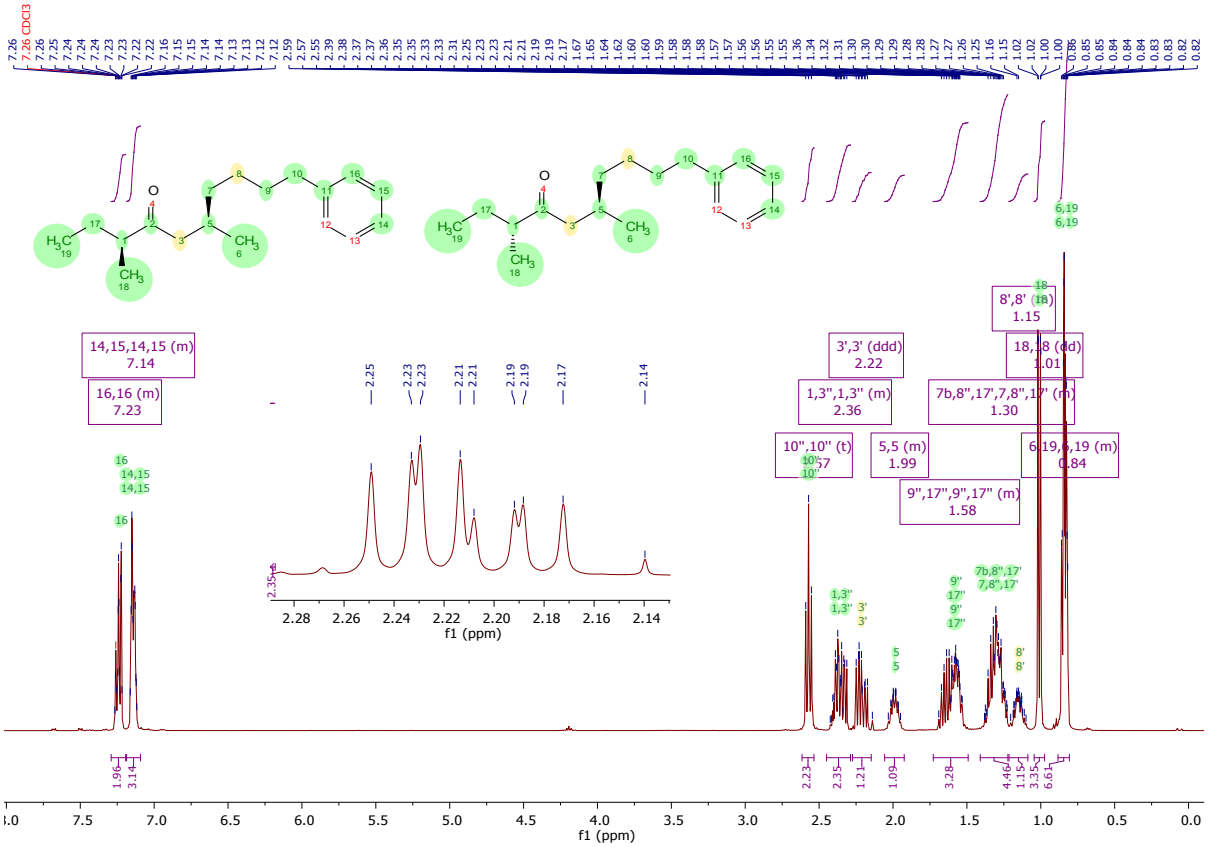
^{13}C NMR (101 MHz, Chloroform-*d*) δ 214.7, 142.8, 128.5 (2 C), 128.4 (2 C), 125.7, 48.9, 48.2, 36.9, 36.0, 31.7, 28.8, 26.8, 25.9, 20.0, 15.9, 11.8.

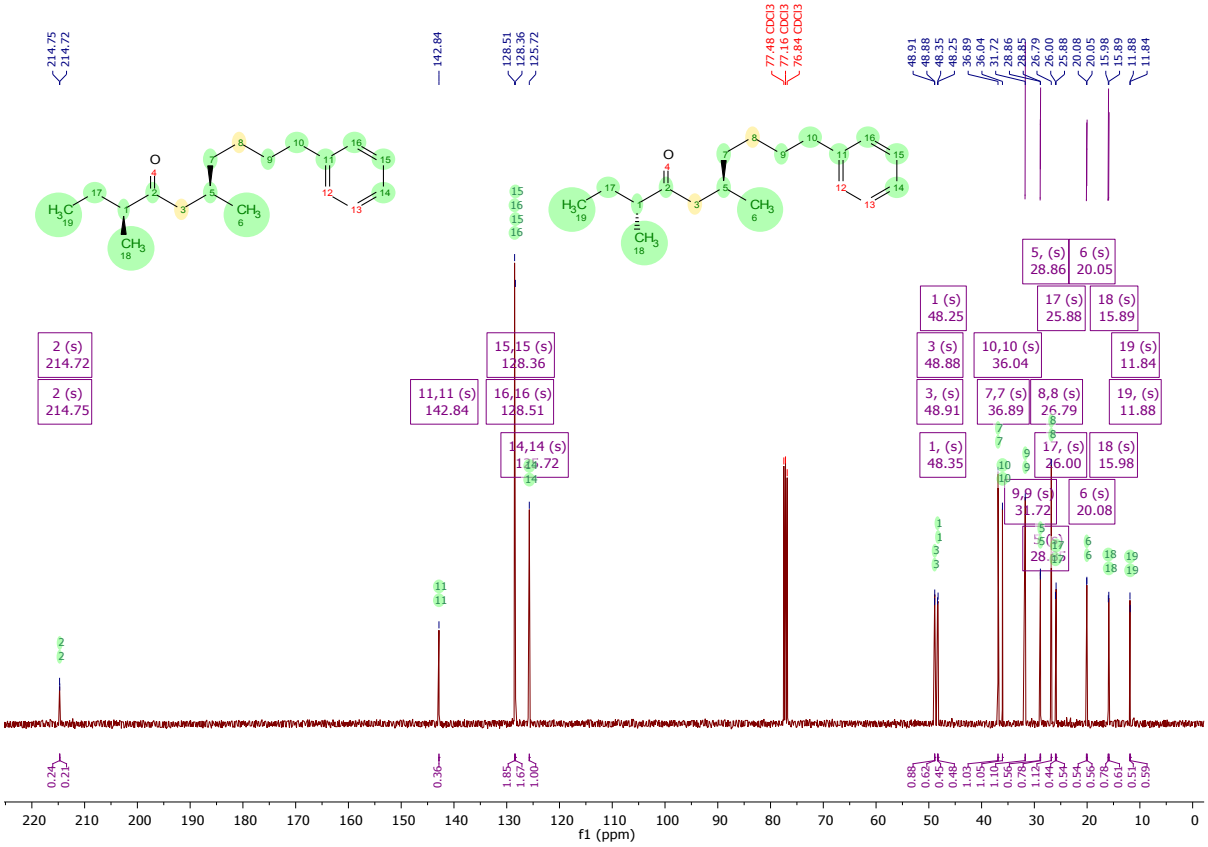
***Mixture of diastereoisomers*:**

IR υ_{max} (film): 2930, 2857, 1709, 1455, 1376.

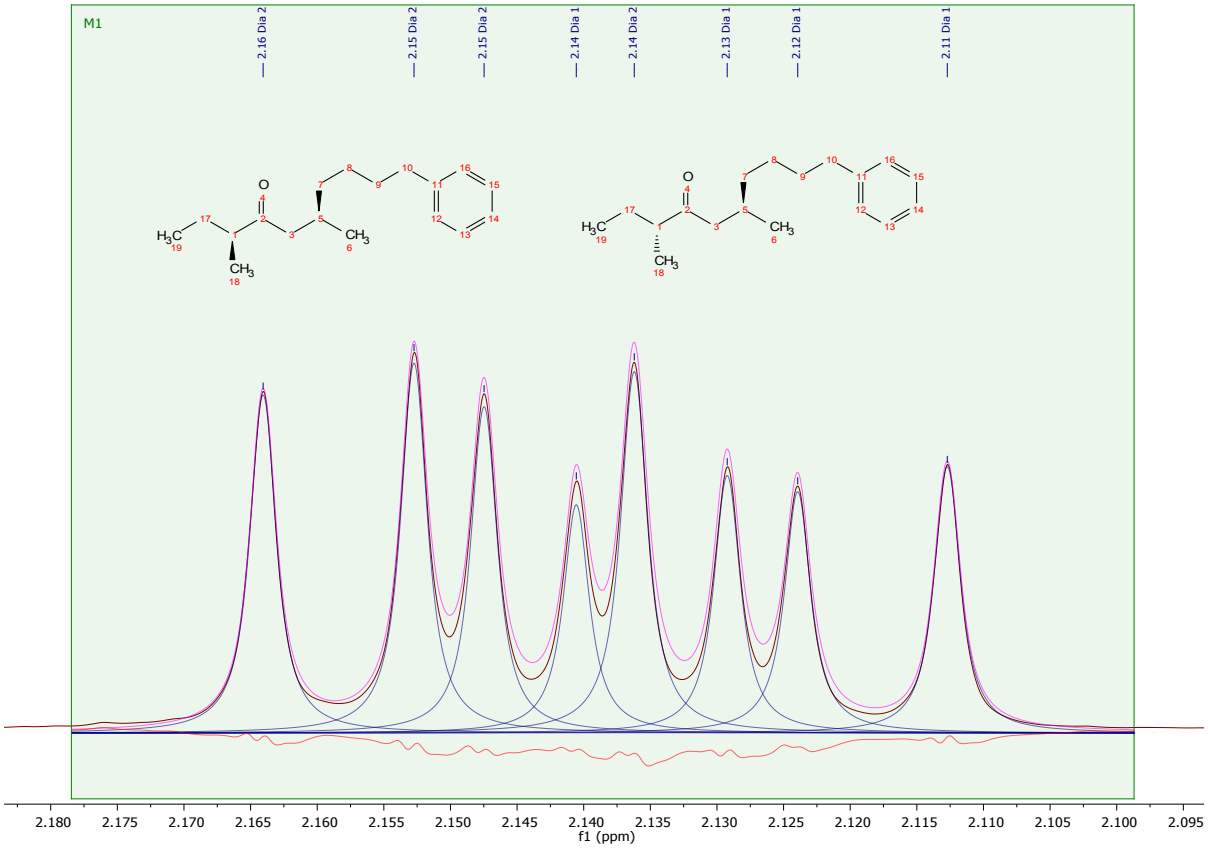
HRMS (APCI$^+$) *m/z* calcd for $C_{18}H_{29}O$ $[M+H]^+$: 261.2213, found 261.2212.

$[\alpha]^{25}_{589}$ = +6.5 (*c* 1.0, $CHCl_3$) for 96% ee and 91% ee.


14,15,14,15 (m)
7.14
16,16 (m)
7.23
3',3' (ddd)
2.22
1,3",1,3" (m)
2.36
10",10" (t)
2.57
5,5 (m)
1.99
9",17",9",17" (m)
1.58
7b,8",17',7,8",17" (m)
1.30
8',8' (dd)
1.15
18,18 (dd)
1.01
6,19,6,19 (m)
0.84
f1 (ppm)


2 (s)
214.72
2 (s)
214.75
11,11 (s)
142.84
15,15 (s)
128.36
16,16 (s)
128.51
14,14 (s)
125.72
1 (s)
48.25
3 (s)
48.88
3, (s)
48.91
1, (s)
48.35
10,10 (s)
36.04
7,7 (s)
36.89
8,8 (s)
26.79
17, (s)
26.00
9,9 (s)
31.72
5, (s)
28.86
6 (s)
20.05
17 (s)
25.88
18 (s)
15.89
19 (s)
11.84
19, (s)
11.88
18 (s)
15.98
6 (s)
20.08
f1 (ppm)

Diastereomeric ratio Experiment (quantitative ^{1}H NMR)

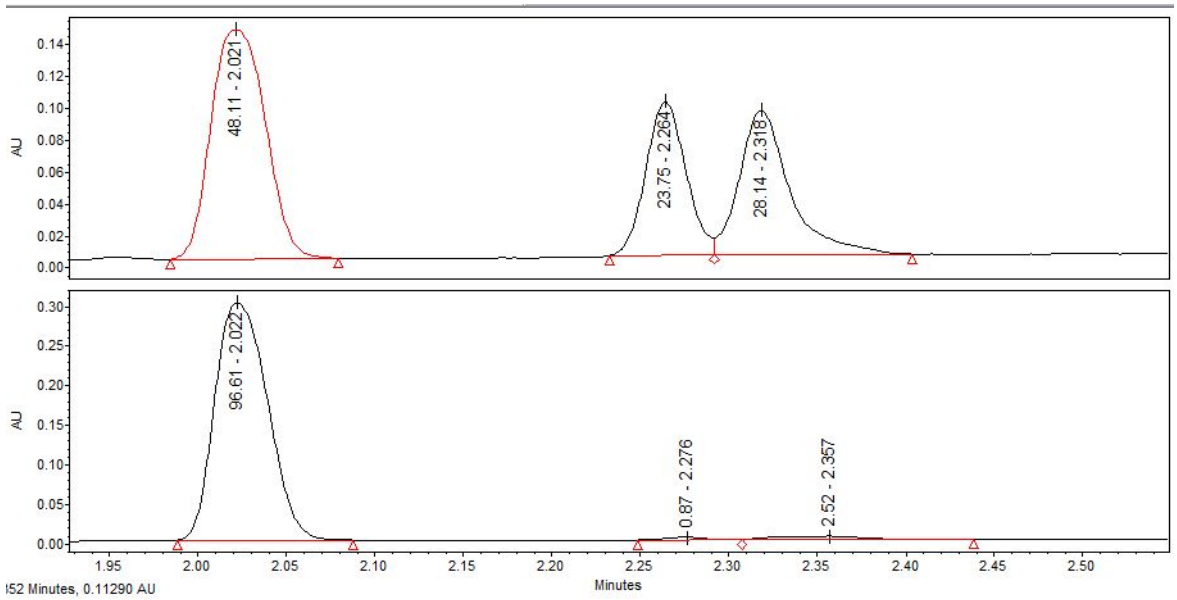


	ppm	Hz	Intensity	Width	Area	Compound
1	2.16	1514.8	302.4	1.66	14234.07	Dia 2
2	2.15	1506.9	330.9	1.66	15683.46	Dia 2
3	2.15	1503.2	291.9	1.66	13720.93	Dia 2
4	2.14	1498.4	204.3	1.64	9751.01	Dia 1
5	2.14	1495.3	323.3	1.7	15752.65	Dia 2
6	2.13	1490.4	230.4	1.66	10899.97	Dia 1
7	2.12	1486.7	216	1.66	10377.72	Dia 1
8	2.11	1478.9	238.3	1.66	11162.19	Dia 1

Total AUC Dia 2	59391.11	% Dia 2	**58%**
Total AUC Dia 1	42190.89	% Dia 1	**42%**

	Dia 1	**:**	**Dia 2**
Ratio	**1**	**:**	**1.4**

Enantiomeric excess calculation



Thus, solving this system of equations:

$R_1 + R_2 = 96.61\%$

$1.4 \times (R_1 + S_1) = (R_2 + S_2)$

$S_1 = 0.87\%$

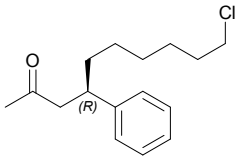
$S_2 = 2.52\%$

Leads to

S_1	0.87%
R_1	40.80%
S_2	2.52%
R_2	55.81%

Corresponding to 96% *ee* for “Dia 1” and 91% *ee* for “Dia 2”.

(R)-10-chloro-4-phenyldecan-2-one 20



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), (R,R) Ligand **L17** (23.3 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 6-chlorohex-1-ene (0.13 mL, 1.009 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-phenylbut-3-en-2-one (59 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-10-chloro-4-phenyldecan-2-one (94.8 mg, 0.355 mmol, 88%) as a slightly yellow oil.

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IB; flow: 0.8 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; major enantiomer, t_R = 9.8 min; minor enantiomer, t_R = 10.6 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

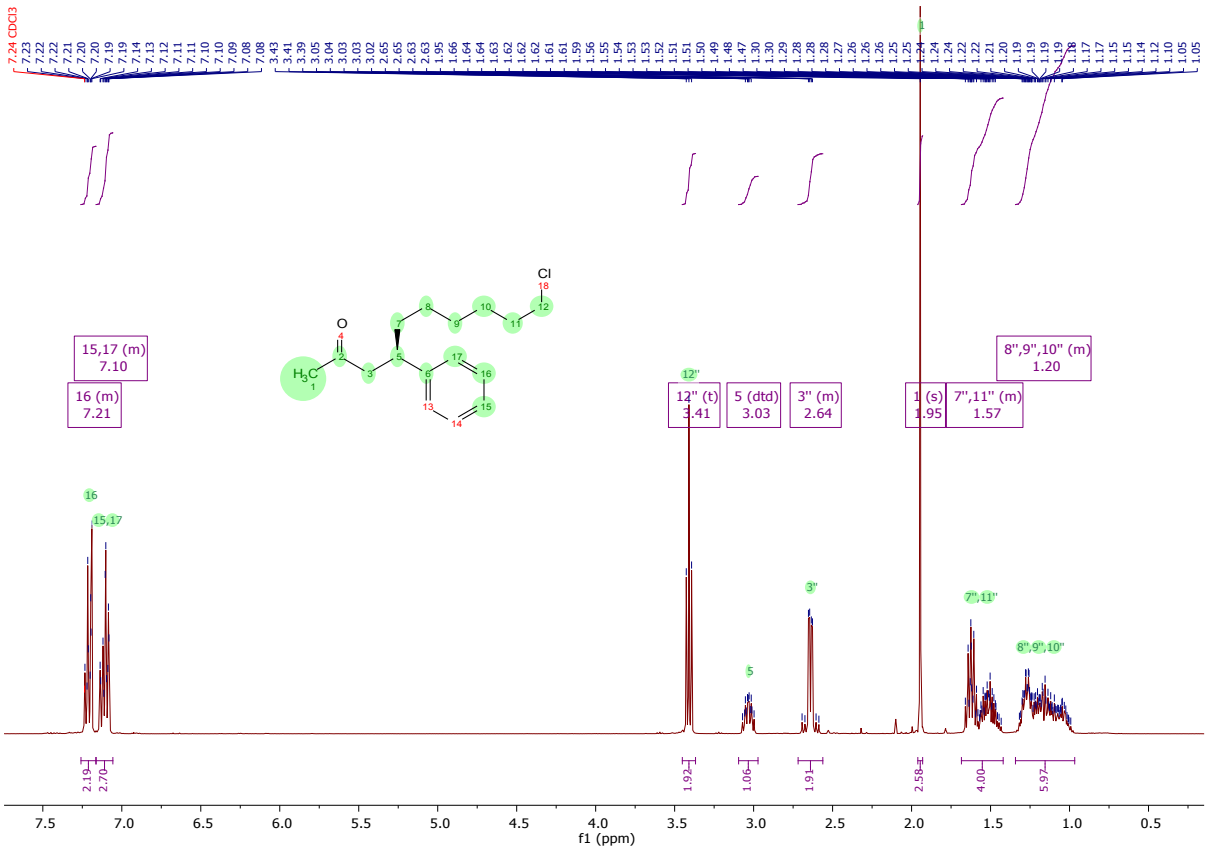
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.16 (m, 2H), 7.16 – 7.06 (m, 3H), 3.41 (t, *J* = 6.7 Hz, 2H), 3.03 (dtd, *J* = 9.5, 7.2, 5.3 Hz, 1H), 2.72 – 2.56 (m, 2H), 1.95 (s, 3H), 1.68 – 1.42 (m, 4H), 1.34 – 0.97 (m, 6H).

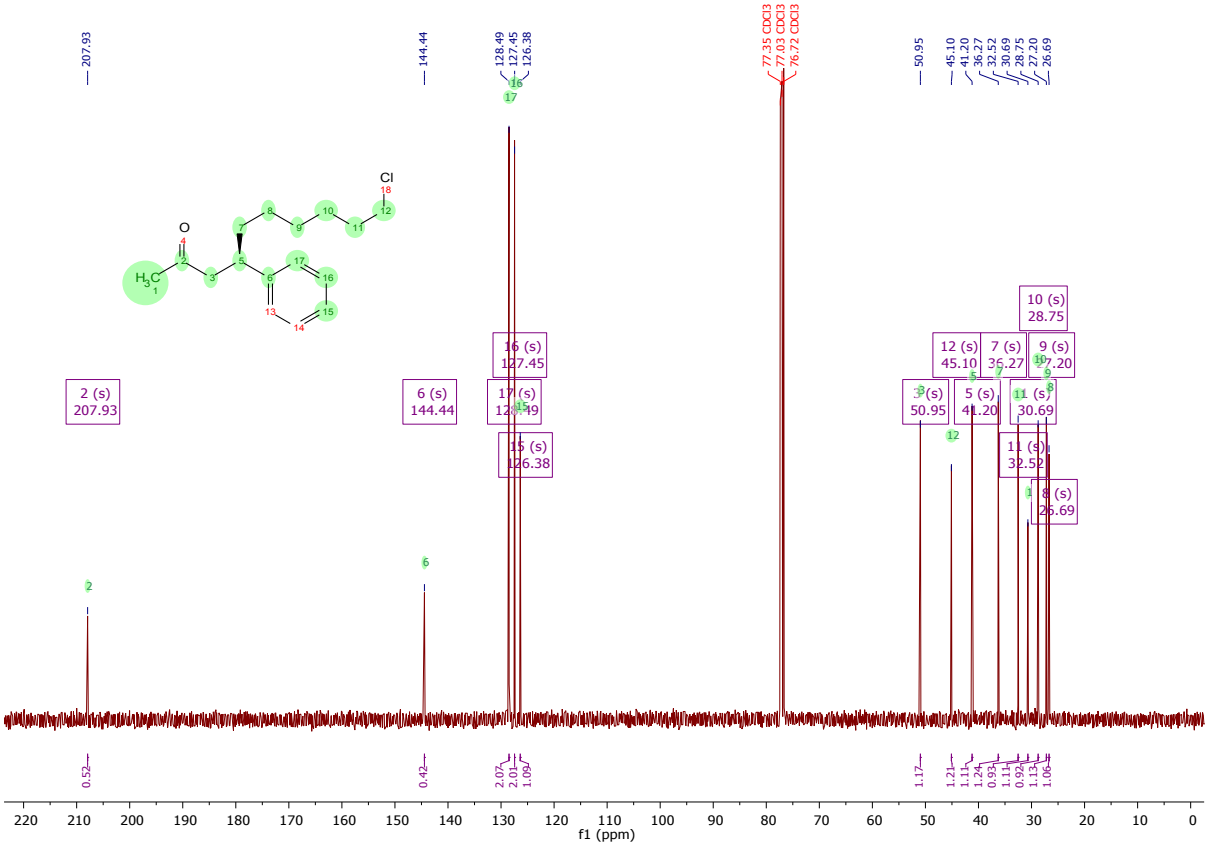
^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.9, 144.4, 128.5 (2 C), 127.4 (2 C), 126.4, 50.9, 45.1, 41.2, 36.3, 32.5, 30.7, 28.7, 27.2, 26.7.

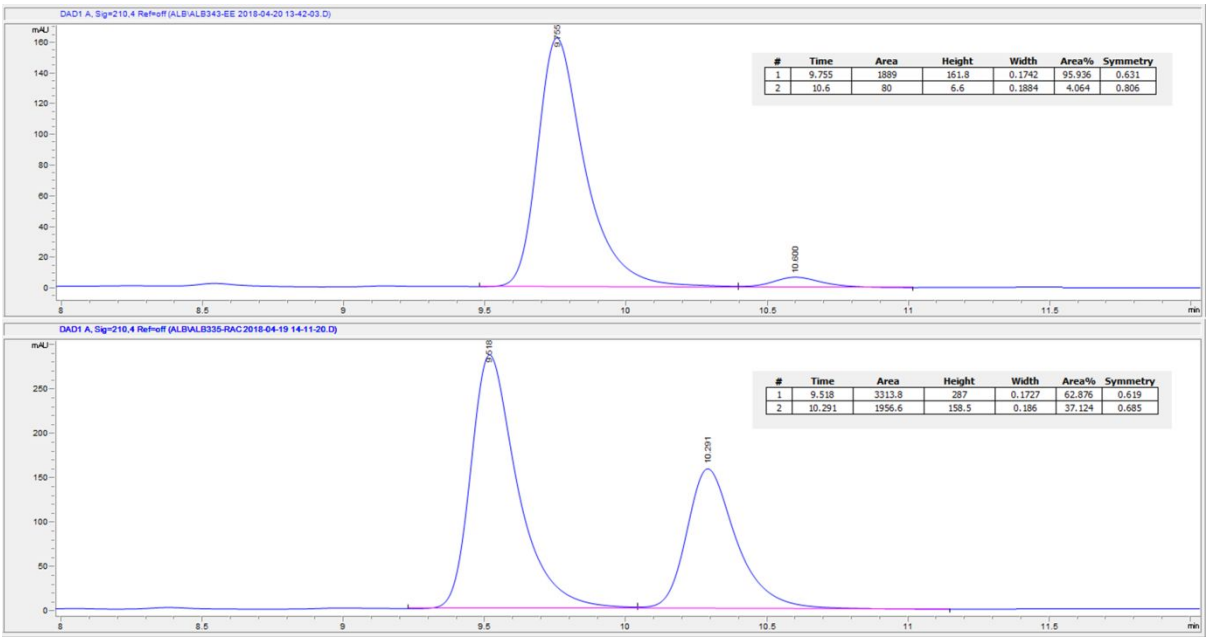
IR υ_{max} (film): 2980, 2930, 1715, 1494, 1453, 1357, 1159.

HRMS (APCI$^+$) *m/z* calcd for $C_{16}H_{24}OCl$ $[M+H]^+$: 267.1510, found 267.1510.

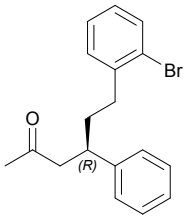
$[\alpha]^{25}_{589}$ = +9.5 (*c* 1.0, $CHCl_3$) for 92% ee.


15,17 (m)
7.10
16 (m)
7.21
12'' (t)
3.41
5 (dtd)
3.03
3'' (m)
2.64
1 (s)
1.95
7'',11'' (m)
1.57
8'',9'',10'' (m)
1.20
f1 (ppm)


2 (s)
207.93
6 (s)
144.44
16 (s)
127.45
17 (s)
15 (s)
126.38
10 (s)
28.75
12 (s)
45.10
7 (s)
9 (s)
5 (s)
11 (s)
30.69
11 (s)
32.52
f1 (ppm)


DAD1 A, Sig=210,4 Ref=off (ALB\ALB343-EE 2018-04-20 13-42-03.D)
mAU
9.755
10.600
min
Time Area Height Width Area% Symmetry
1 9.755 1889 161.8 0.1742 95.936 0.631
2 10.6 80 6.6 0.1884 4.064 0.806
DAD1 A, Sig=210,4 Ref=off (ALB\ALB335-RAC 2018-04-19 14-11-20.D)
mAU
9.518
10.291
min
Time Area Height Width Area% Symmetry
1 9.518 3313.8 287 0.1727 62.876 0.619
2 10.291 1956.6 158.5 0.186 37.124 0.685

(R)-6-(2-bromophenyl)-4-phenylhexan-2-one 19



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), (R,R) Ligand **L17** (23.5 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 1-bromo-2-vinylbenzene (0.13 mL, 1.009 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-phenylbut-3-en-2-one (59 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-6-(2-bromophenyl)-4-phenylhexan-2-one (120.4 mg, 0.364 mmol, 90%) as a slightly brown oil.

HPLC analysis indicated an enantiomeric excess of 93% [Chiralpak® IB; flow: 0.8 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; major enantiomer, t_R = 12.3 min; minor enantiomer, t_R = 13.0 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

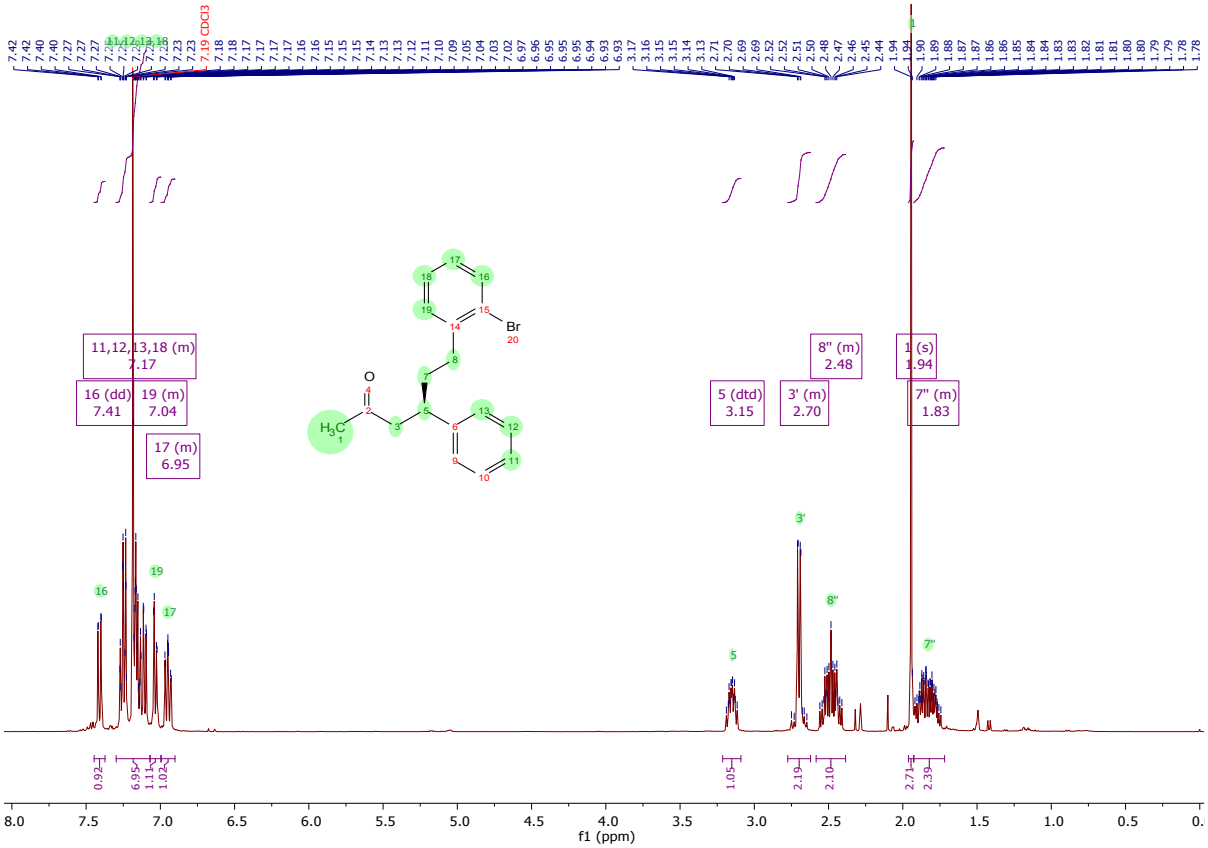
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.30 – 7.07 (m, 6H), 7.07 – 7.00 (m, 1H), 6.99 – 6.90 (m, 1H), 3.15 (dtd, *J* = 9.5, 7.1, 5.2 Hz, 1H), 2.77 – 2.62 (m, 2H), 2.58 – 2.39 (m, 2H), 1.94 (s, 3H), 1.92 – 1.72 (m, 2H).

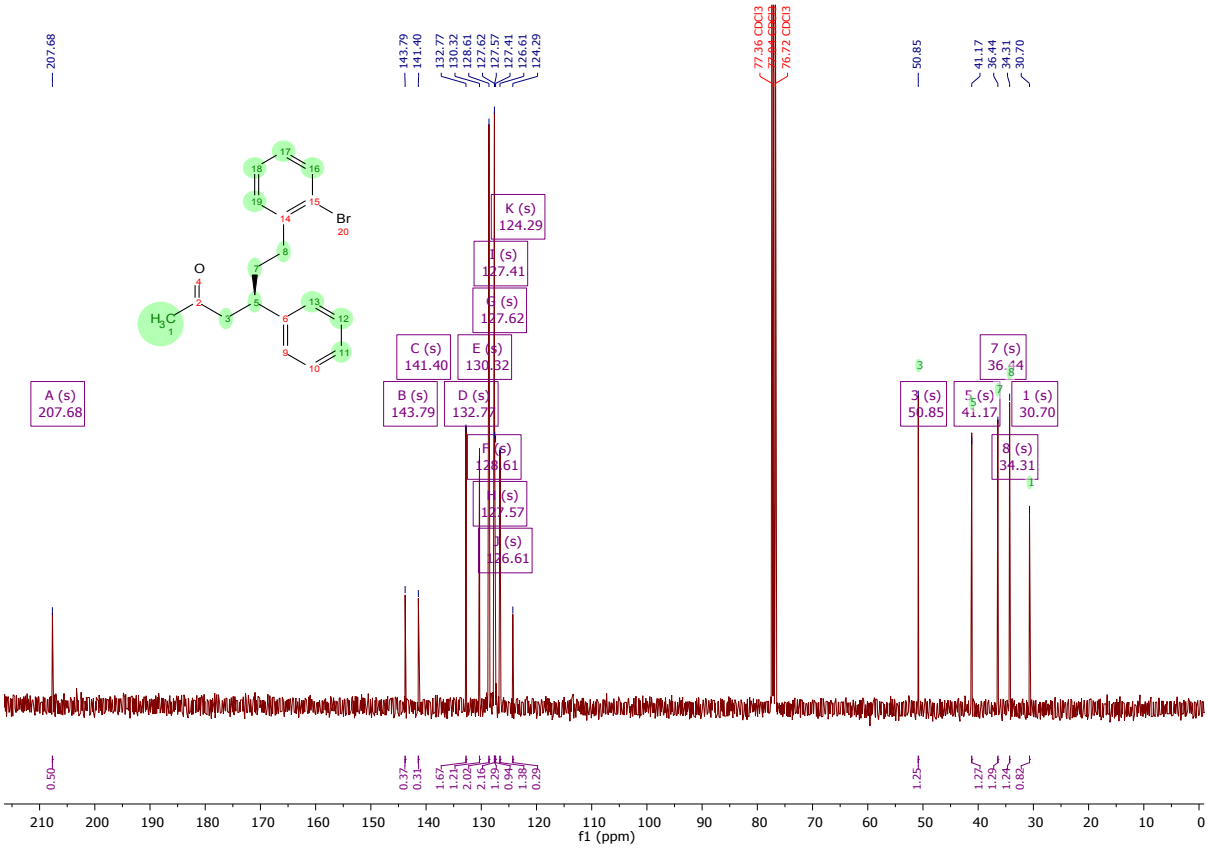
^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.7, 143.8, 141.4, 132.8, 130.3, 128.6 (2 C), 127.6 (2 C), 127.6, 127.4, 126.6, 124.3, 50.8, 41.2, 36.4, 34.3, 30.7.

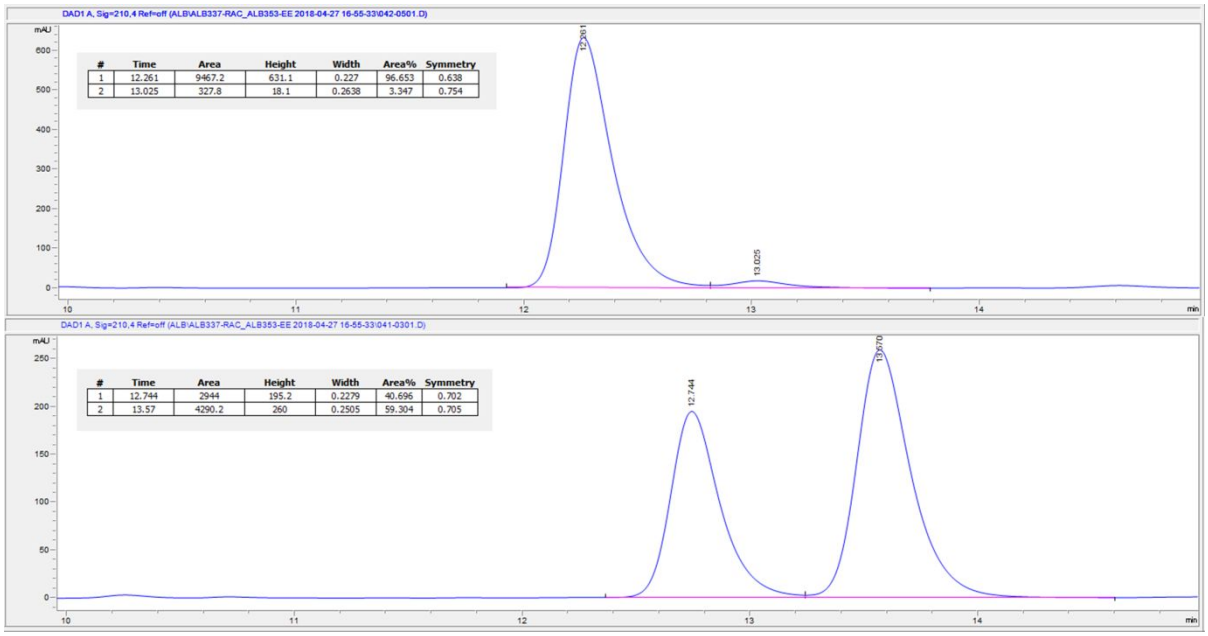
IR υ_{max} (film): 2980, 1715, 1493, 1358, 1250, 1157, 1022.

HRMS (APCI$^+$) *m/z* calcd for C_{18} H_{20} O Br $[M+H]^+$: 331.0692, found 331.0692.

$[\alpha]^{25}_{589}$ = -6.6 (*c* 1.0, $CHCl_3$) for 93% ee.


11,12,13,18 (m)
7.17
16 (dd)
7.41
19 (m)
7.04
17 (m)
6.95
5 (dtd)
3.15
3' (m)
2.70
8" (m)
2.48
1 (s)
1.94
7" (m)
1.83
f1 (ppm)


A (s)
207.68
B (s)
143.79
C (s)
141.40
D (s)
132.77
E (s)
130.32
F (s)
128.61
G (s)
127.62
H (s)
127.57
I (s)
127.41
J (s)
126.61
K (s)
124.29
1 (s)
30.70
3 (s)
50.85
5 (s)
41.17
7 (s)
36.44
8 (s)
34.31
f1 (ppm)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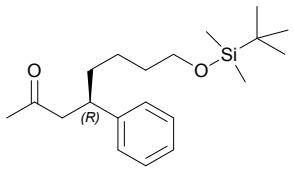
mAU
600
500
400
300
200
100
0
12.261
13.025
10
11
12
13
14
min
Time Area Height Width Area% Symmetry
1 12.261 9467.2 631.1 0.227 96.653 0.638
2 13.025 327.8 18.1 0.2638 3.347 0.754
DAD1 A, Sig=210,4 Ref=off (ALB\ALB337-RAC_ALB353-EE 2018-04-27 16-55-33\041-0301.D)
mAU
250
200
150
100
50
0
12.744
13.570
10
11
12
13
14
min
Time Area Height Width Area% Symmetry
1 12.744 2944 195.2 0.2279 40.696 0.702
2 13.57 4290.2 260 0.2505 59.304 0.705

(R)-8-((tert-butyldimethylsilyl)oxy)-4-phenyloctan-2-one 21



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), (R,R) Ligand **L17** (23.5 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), (but-3-en-1-yloxy)(tert-butyl)dimethylsilane (188.0 mg, 1.009 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-phenylbut-3-en-2-one (59 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

Note: Freshly distilled TMSCl stored in a Schlenk flask with CaH_2 under an argon atmosphere is of critical importance to keep protected the hydroxyl group in a fairly good amount. Carrying out the work up below also helps.

The reaction was quenched by the addition of NH_4Cl (sat. aq.) and followed by Et_2O (2 mL). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-8-((tert-butyldimethylsilyl)oxy)-4-phenyloctan-2-one (83.8 mg, 0.250 mmol, 62%) as a colourless clear oil.

HPLC analysis indicated an enantiomeric excess of 93% [Chiralpak® IB; flow: 0.8 mL/min; hexane/i-PrOH: 99:1; λ = 210 nm; minor enantiomer, t_R = 7.2 min; major enantiomer, t_R = 7.6 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

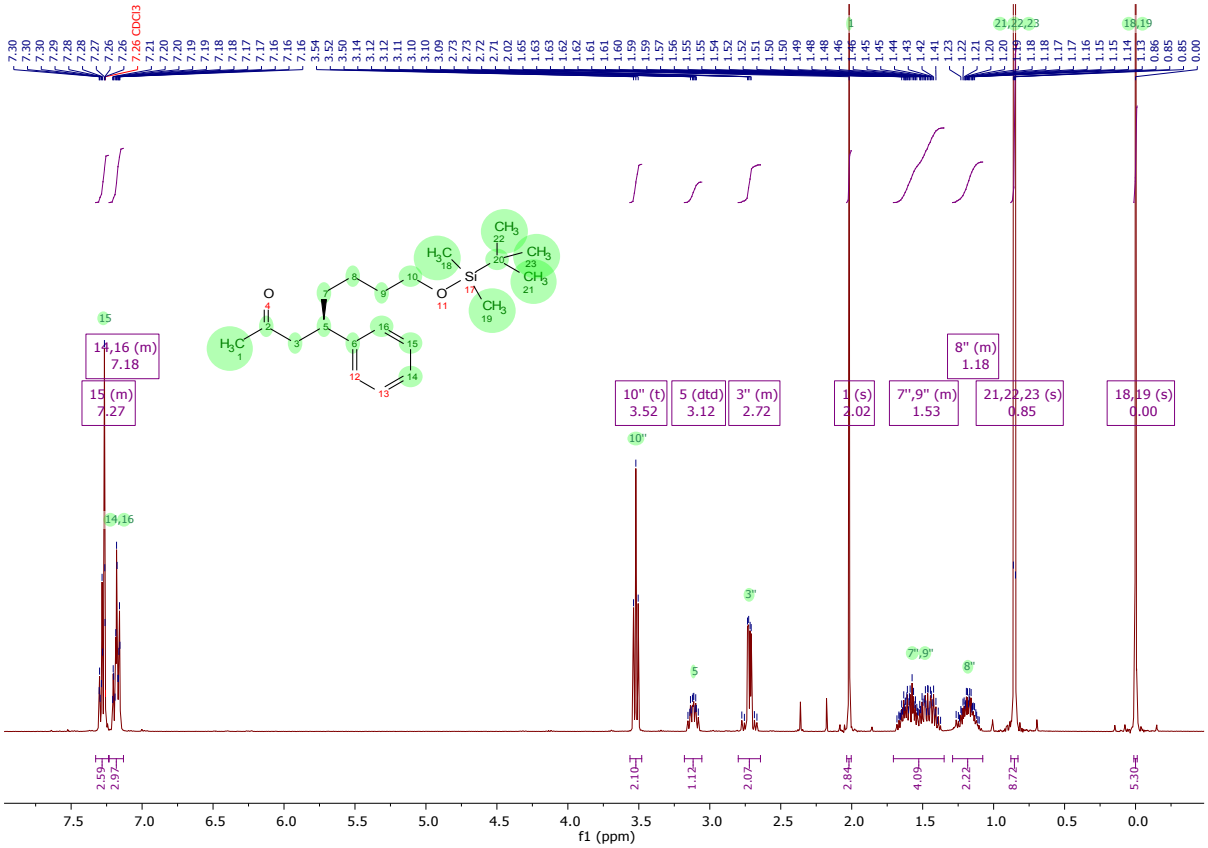
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.24 (m, 3H), 7.23 – 7.13 (m, 3H), 3.52 (t, *J* = 6.6 Hz, 2H), 3.12 (dtd, *J* = 9.4, 7.2, 5.4 Hz, 1H), 2.80 – 2.64 (m, 2H), 2.02 (s, 3H), 1.71 – 1.35 (m, 4H), 1.29 – 1.08 (m, 2H), 0.85 (s, 9H), 0.00 (s, 6H).

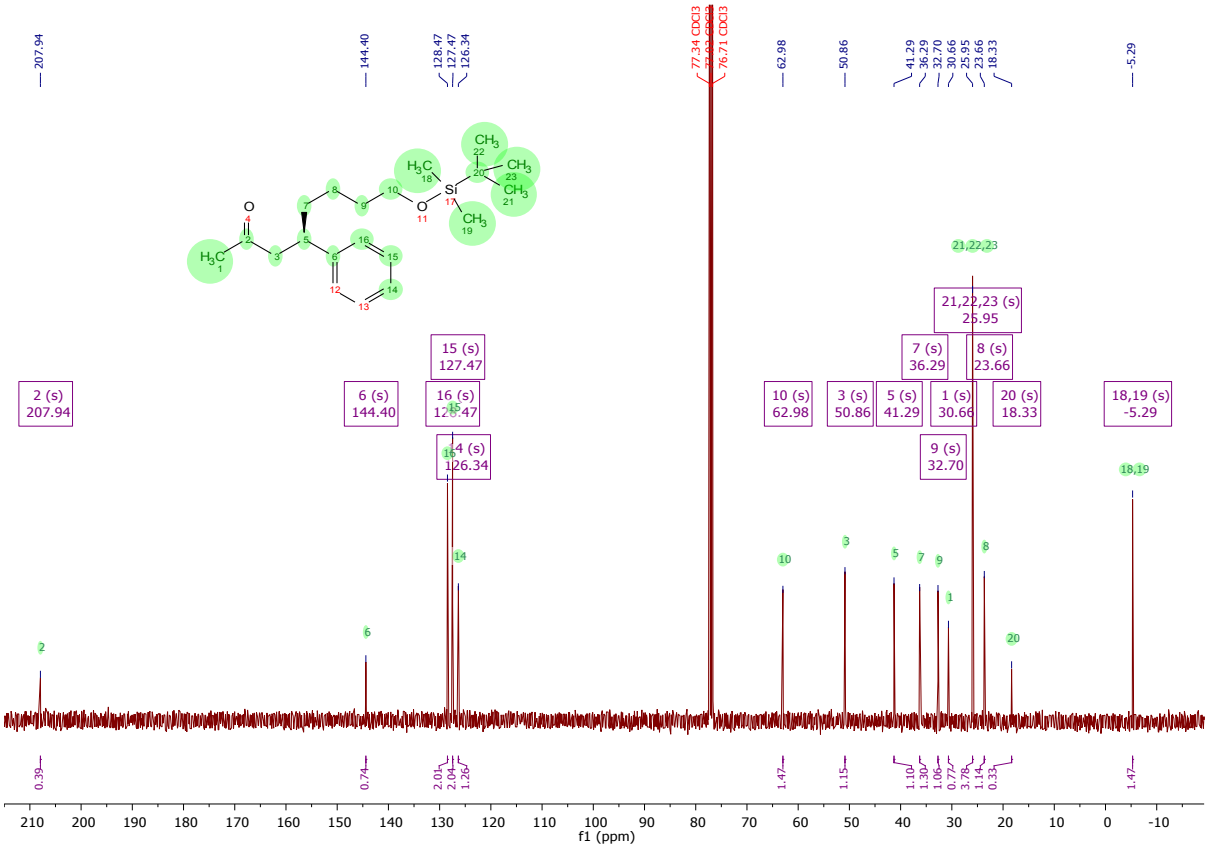
^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.9, 144.4, 128.5 (2 C), 127.5 (2 C), 126.3, 63.0, 50.9, 41.3, 36.3, 32.7, 30.7, 25.9 (3 C), 23.7, 18.3, -5.3 (2 C).

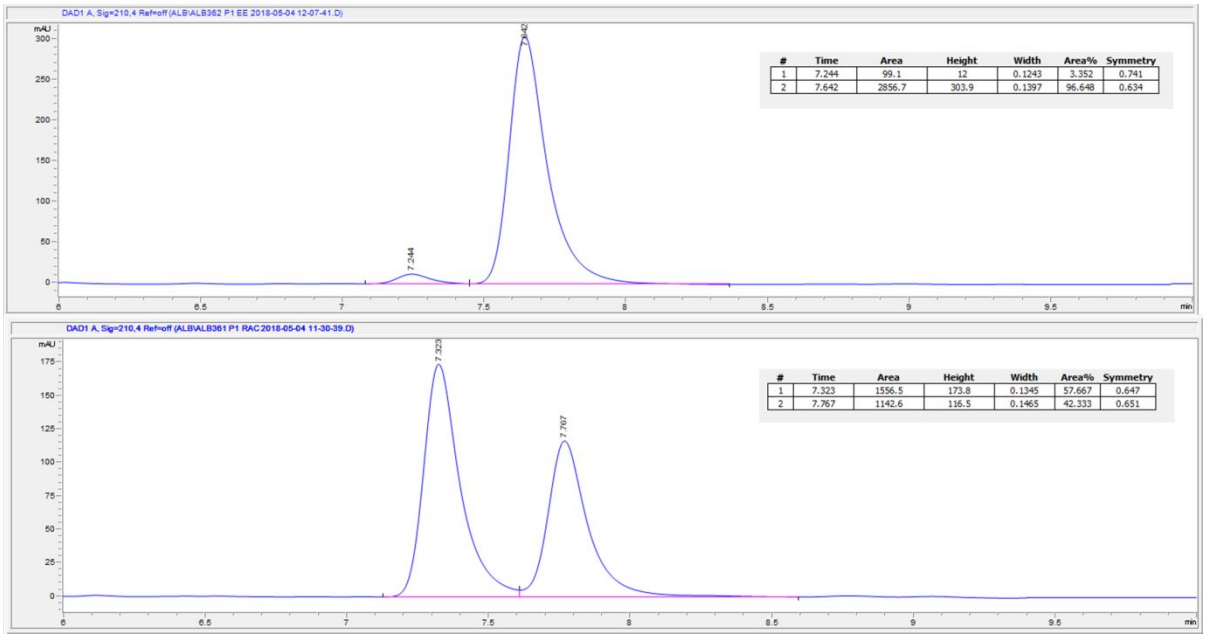
IR υ_{max} (film): 2980, 1719, 1472, 1383, 1253, 1155, 1093.

HRMS (APCI$^+$) *m/z* calcd for $C_{20}H_{35}O_2Si$ $[M+H]^+$: 335.2401, 335.2401.

$[\alpha]^{25}_{589}$ = -5.8 (*c* 1.0, $CHCl_3$) for 93% ee.


14,16 (m)
7.18
15 (m)
7.27
10" (t)
3.52
5 (dtd)
3.12
3" (m)
2.72
1 (s)
2.02
7",9" (m)
1.53
8" (m)
1.18
21,22,23 (s)
0.85
18,19 (s)
0.00
f1 (ppm)


2 (s)
207.94
6 (s)
144.40
15 (s)
127.47
16 (s)
127.47
14 (s)
126.34
10 (s)
62.98
3 (s)
50.86
5 (s)
41.29
1 (s)
30.66
9 (s)
32.70
7 (s)
36.29
8 (s)
23.66
20 (s)
18.33
21,22,23 (s)
25.95
18,19 (s)
-5.29
f1 (ppm)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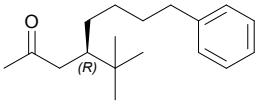
mAU
7.642
7.244
min
Time Area Height Width Area% Symmetry
1 7.244 99.1 12 0.1243 3.352 0.741
2 7.642 2856.7 303.9 0.1397 96.648 0.634
DAD1 A, Sig=210,4 Ref=off (ALB\ALB361 P1 RAC 2018-05-04 11-30-39.D)
mAU
7.323
7.767
min
Time Area Height Width Area% Symmetry
1 7.323 1556.5 173.8 0.1345 57.667 0.647
2 7.767 1142.6 116.5 0.1465 42.333 0.651

(R)-4-(tert-butyl)-8-phenyloctan-2-one 4



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-5,5-dimethylhex-3-en-2-one (51 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-4-(tert-butyl)-8-phenyloctan-2-one (74.2 mg, 0.287 mmol, 71%) as a slightly yellow oil.

SFC analysis indicated an enantiomeric excess of 83% [Chiralpak® IF-3; 1500 psi, 30 °C, flow: 1.5 mL/min; 1.0% to 30.0% MeOH in 5 min; λ = 218 nm; major enantiomer, tR = 1.76 min; minor enantiomer, tR = 1.84 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

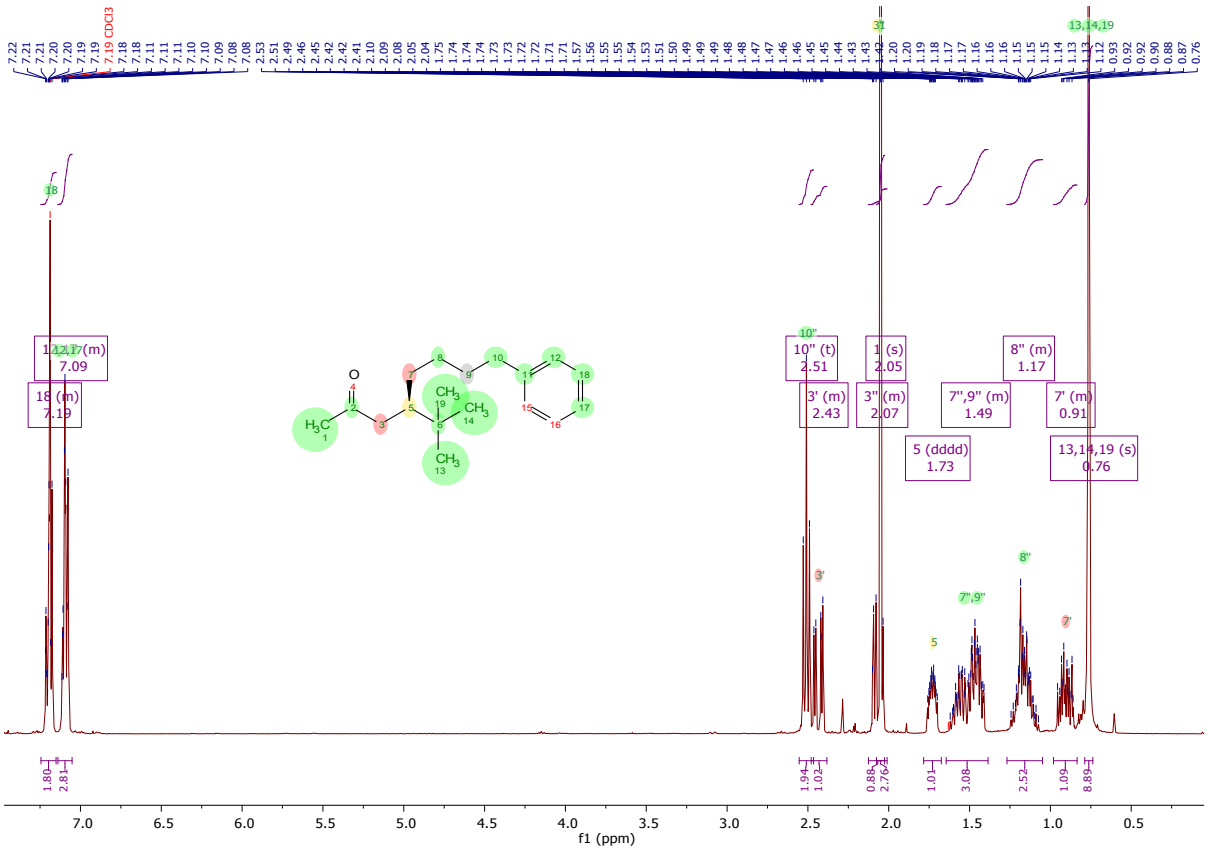
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 – 7.15 (m, 2H), 7.14 – 7.05 (m, 3H), 2.51 (t, *J* = 7.7 Hz, 2H), 2.48 – 2.38 (m, 1H), 2.13 – 2.01 (m, 1H), 2.05 (s, 3H), 1.73 (dddd, *J* = 9.1, 6.0, 4.8, 2.9 Hz, 1H), 1.64 – 1.39 (m, 3H), 1.27 – 1.05 (m, 2H), 0.98 – 0.83 (m, 1H), 0.76 (s, 9H).

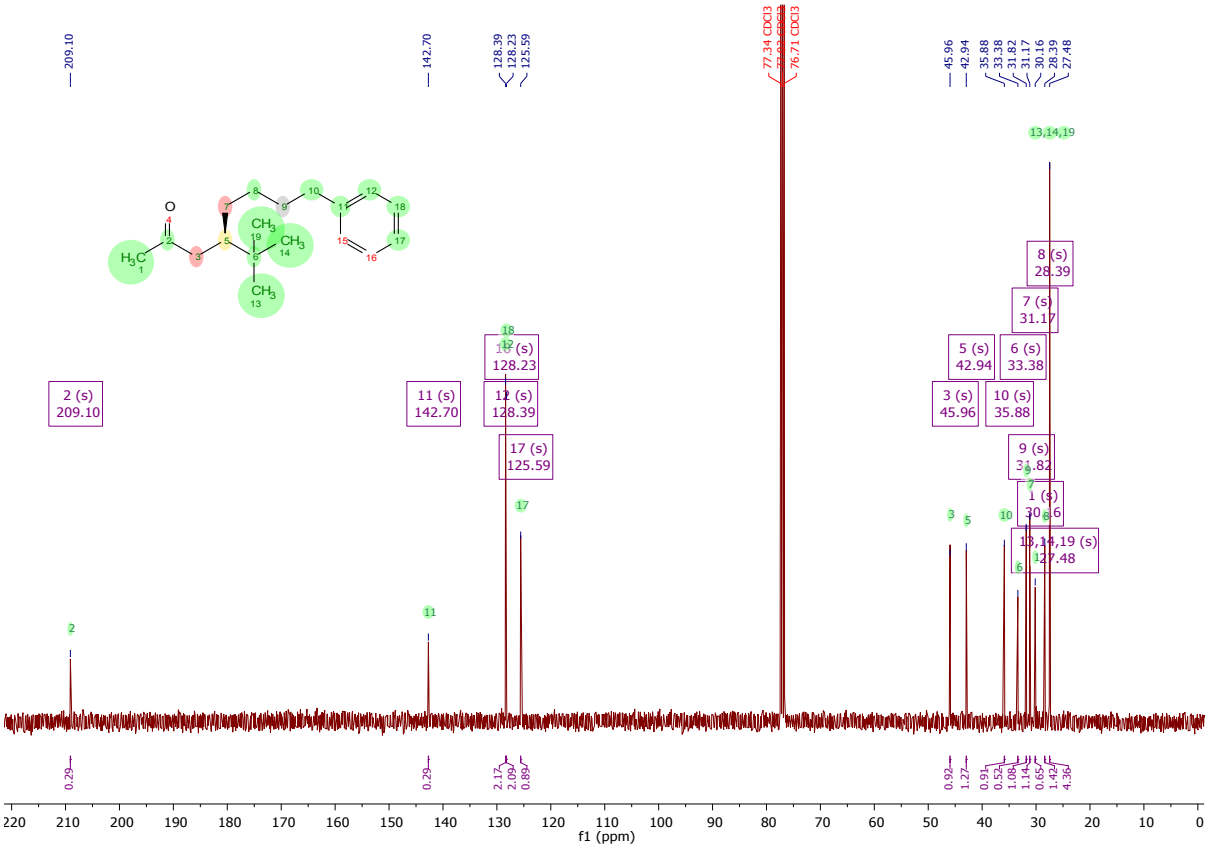
^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.1, 142.7, 128.4 (2 C), 128.2 (2 C), 125.6, 46.0, 42.9, 35.9, 33.4, 31.8, 31.2, 30.2, 28.4, 27.5.

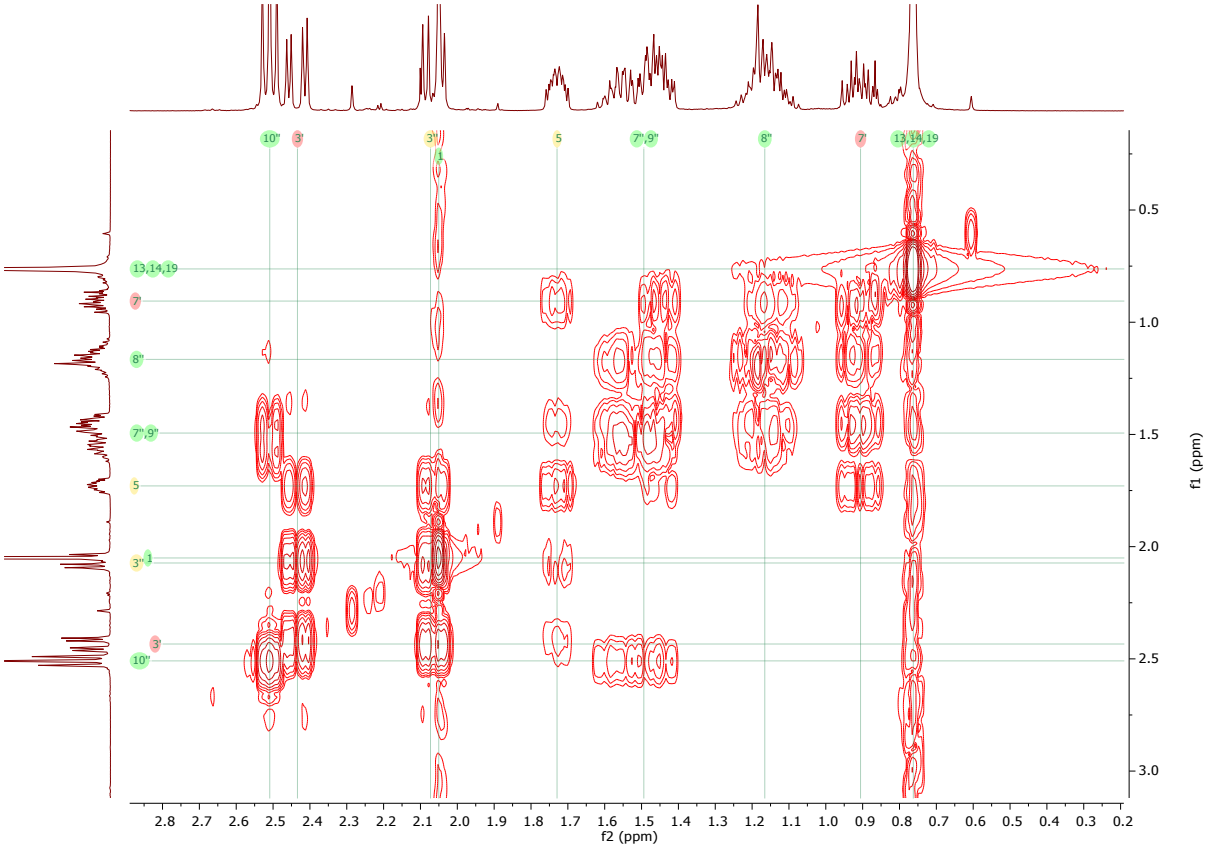
IR υ_{max} (film): 2980, 2889, 1717, 1472, 1382, 1251, 1156, 1073.

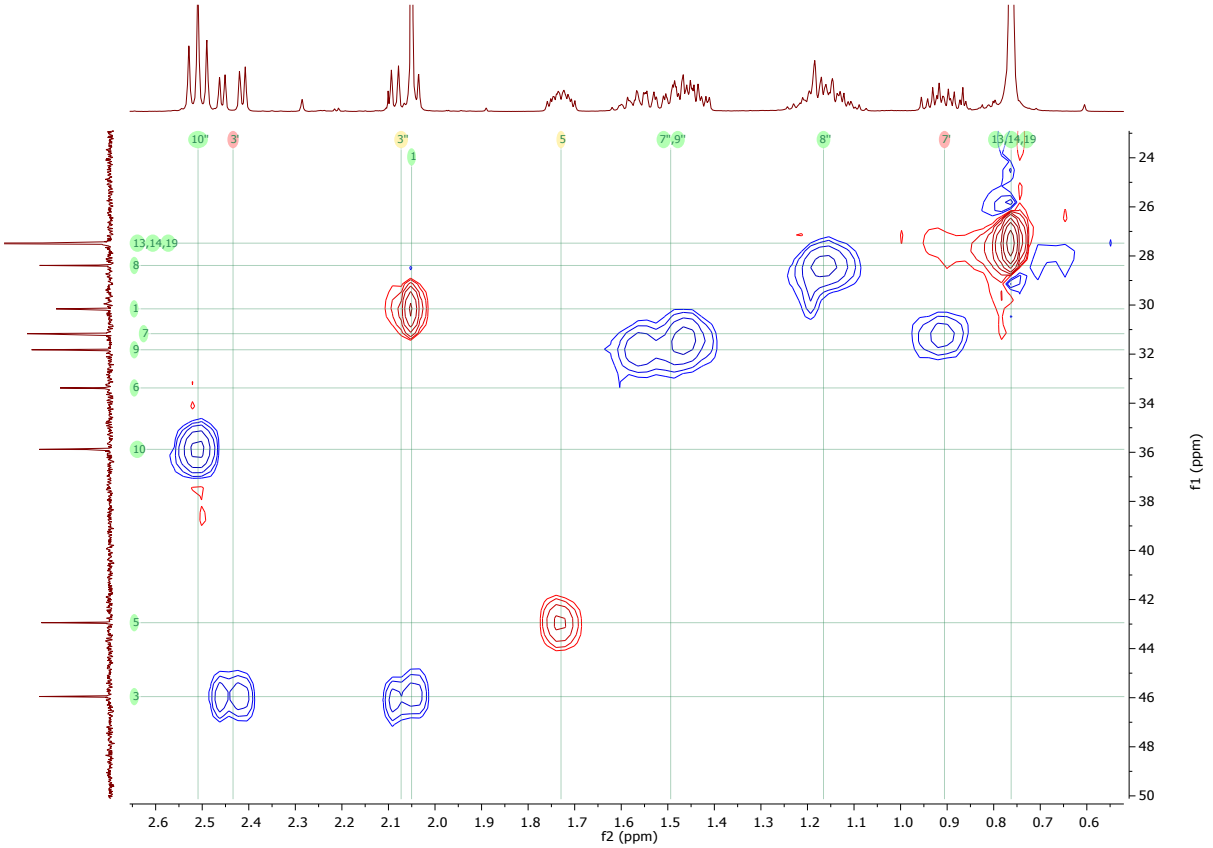
HRMS (APCI$^+$) *m/z* calcd for $C_{18}H_{29}O$ $[M+H]^+$: 261.2213, found 261.2215.

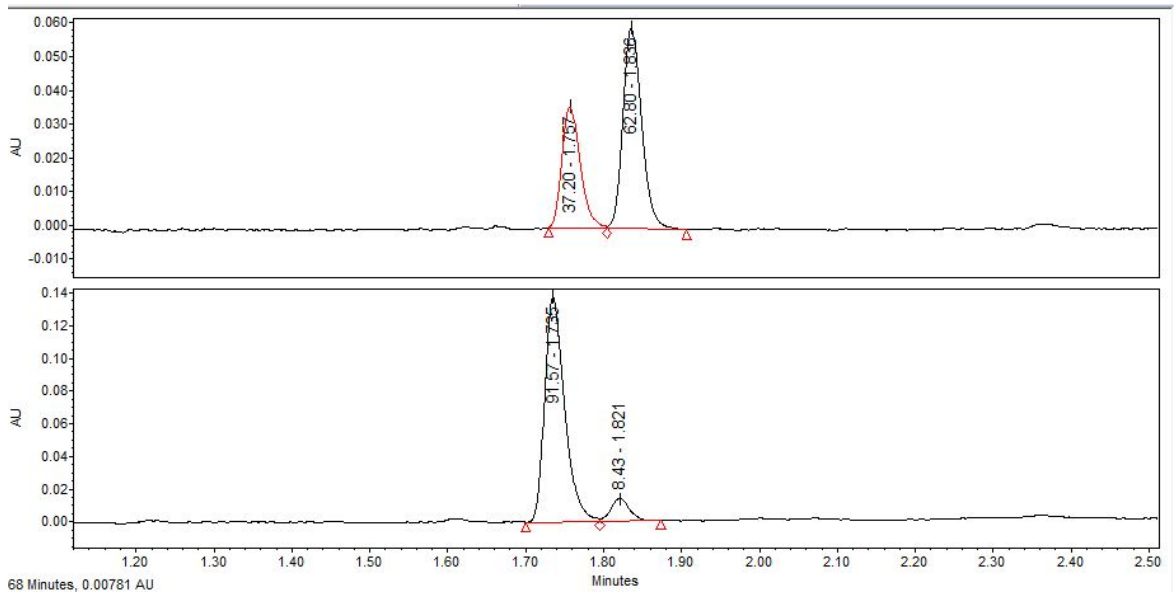
$[\alpha]^{25}_{589}$ = -12.0 (*c* 1.0, $CHCl_3$) for 83% ee.


1,12,17(m)
7.09
18 (m)
7.19
10" (t)
2.51
1 (s)
2.05
8" (m)
1.17
3' (m)
2.43
3" (m)
2.07
7",9" (m)
1.49
7' (m)
0.91
5 (dddd)
1.73
13,14,19 (s)
0.76
f1 (ppm)

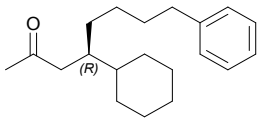

2 (s)
209.10
11 (s)
142.70
12 (s)
128.39
17 (s)
125.59
3 (s)
45.96
5 (s)
42.94
6 (s)
33.38
10 (s)
35.88
8 (s)
28.39
7 (s)
31.17
9 (s)
31.82
1 (s)
30.16
13,14,19 (s)
27.48
f1 (ppm)


10''
3'
3''
5
7',9''
8''
7'
13,14,19
f2 (ppm)
f1 (ppm)


10''
3'
3''
5
7',9''
8''
7'
13,14,19
f2 (ppm)
f1 (ppm)


AU
0.060
0.050
0.040
0.030
0.020
0.010
0.000
-0.010
37.20 - 1.757
62.80 - 1.835
AU
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
91.57 - 1.735
8.43 - 1.821
1.20
1.30
1.40
1.50
1.60
1.70
1.80
1.90
2.00
2.10
2.20
2.30
2.40
2.50
Minutes
68 Minutes, 0.00781 AU

(R)-4-cyclohexyl-8-phenyloctan-2-one 5



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-4-cyclohexylbut-3-en-2-one (61 mg, 0.401 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (R)-4-cyclohexyl-8-phenyloctan-2-one (80.5 mg, 0.283 mmol, 70%) as a slightly yellow oil.

SFC analysis indicated an enantiomeric excess of 89% [Chiralpak® IG-3; 1500 psi, 30 °C, flow: 1.5 mL/min; 1.0% to 30.0% MeOH in 5 min; λ = 218 nm; minor enantiomer, t_R = 3.34 min; major enantiomer, t_R = 3.50 min]. Racemic product was realised using *General Procedure A*.

Absolute configuration was assigned by comparison to literature data.[6]

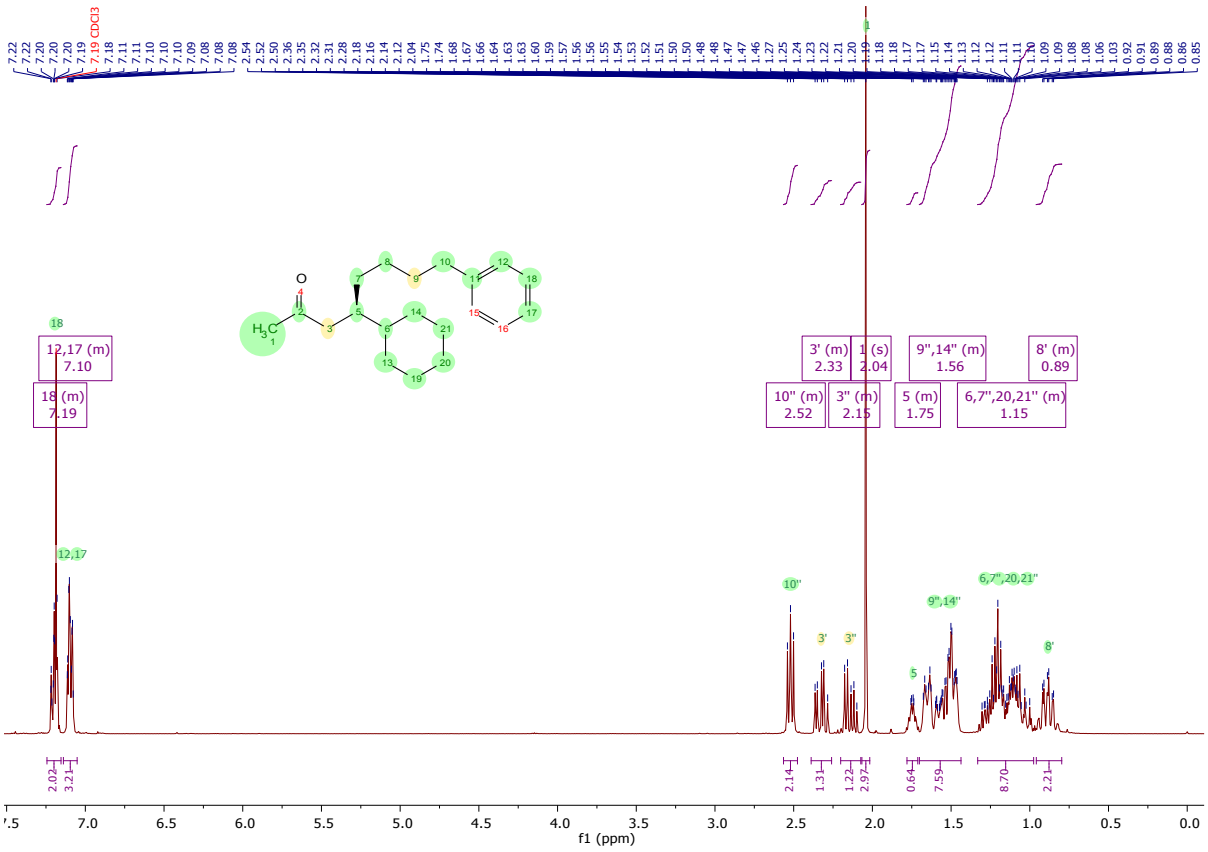
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 – 7.15 (m, 2H), 7.14 – 7.05 (m, 3H), 2.56 – 2.48 (m, 2H), 2.39 – 2.26 (m, 1H), 2.20 – 2.07 (m, 1H), 2.04 (s, 3H), 1.78 – 1.71 (m, 1H), 1.70 – 1.44 (m, 6H), 1.33 – 0.98 (m, 9H), 0.96 – 0.80 (m, 2H).

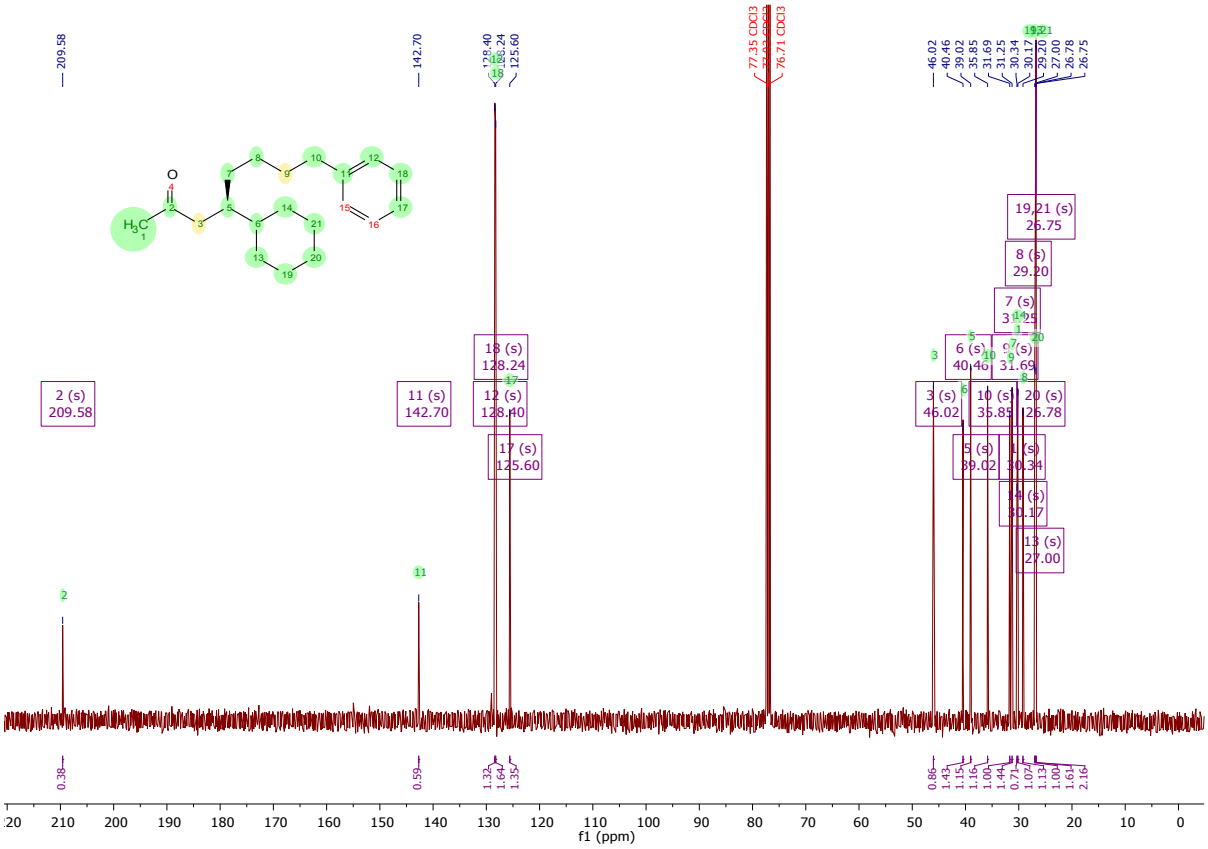
^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.6, 142.7, 128.4 (2 C), 128.2 (2 C), 125.6, 46.0, 39.0, 40.5, 35.8, 31.7, 31.2, 30.3, 30.2, 29.2, 27.0, 26.8, 26.7 (2 C).

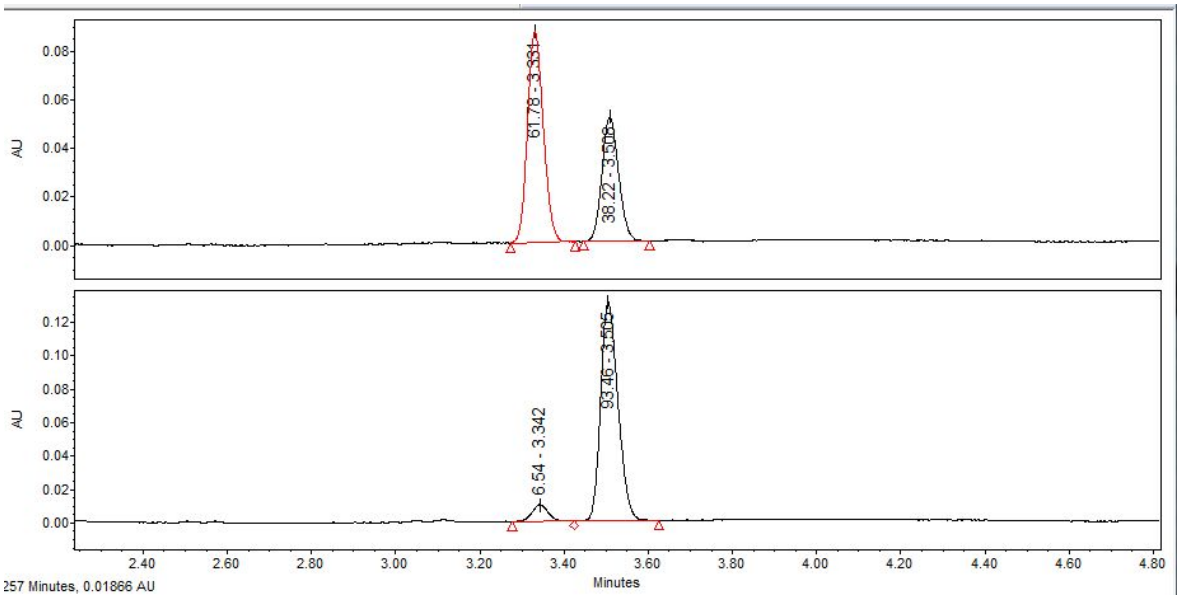
IR υ_{max} (film): 2980, 2927, 1716, 1461, 1382, 1251, 1153, 1073.

HRMS ($APCI^+$) *m/z* calcd for $C_{20}H_{31}O$ $[M+H]^+$: 287.2369, found 287.2370.

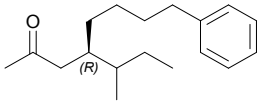
$[\alpha]^{25}_{589}$ = -0.8 (*c* 1.0, $CHCl_3$) for 89% ee.


12,17 (m)
7.10
18 (m)
7.19
3' (m)
2.33
1 (s)
2.04
9'',14'' (m)
1.56
8' (m)
0.89
10'' (m)
2.52
3'' (m)
2.15
5 (m)
1.75
6,7'',20,21'' (m)
1.15
f1 (ppm)


2 (s)
209.58
11 (s)
142.70
19 (s)
128.24
12 (s)
128.40
17 (s)
125.60
19,21 (s)
26.75
8 (s)
29.20
6 (s)
40.46
3 (s)
46.02
10 (s)
35.85
20 (s)
26.78
5 (s)
39.02
f1 (ppm)


AU
0.08
0.06
0.04
0.02
0.00
61.78 - 3.331
38.22 - 3.508
AU
0.12
0.10
0.08
0.06
0.04
0.02
0.00
6.54 - 3.342
93.46 - 3.505
2.40
2.60
2.80
3.00
3.20
3.40
3.60
3.80
4.00
4.20
4.40
4.60
4.80
Minutes
257 Minutes, 0.01866 AU

(4R)-4-(sec-butyl)-8-phenyloctan-2-one 6



General Procedure B: CuCl (4.0 mg, 0.040 mmol, 0.1 eq.), Ligand **L17** (23.2 mg, 0.040 mmol, 0.1 eq.), Et_2O (2.0 mL), Cp_2ZrHCl (208 mg, 0.807 mmol, 2.0 eq), CH_2Cl_2 (0.5 mL), 4-phenyl-1-butene (0.15 mL, 1.010 mmol, 2.5 eq), AgOTf (15.6 mg, 0.061 mmol, 0.15 eq), (E)-5-methylhept-3-en-2-one (51 mg, 0.404 mmol, 1.0 eq), TMSCl (0.26 mL, 2.018 mmol, 5.0 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (EtOAc/Hexane 5:100, SiO_2) to afford (4R)-4-(sec-butyl)-8-phenyloctan-2-one (74.7 mg, 0.287 mmol, 71%) as a slightly yellow oil.

Quantitative ^{1}H NMR experiment analysis indicated a diastereomeric ratio of 1:1.2.

Diastereoisomer 1: **HPLC and SFC analysis** indicated an enantiomeric excess of 89% [SFC: Chiralpak® IG-3; 1500 psi, 30 °C, flow: 1.5 mL/min; 1.0% to 30.0% MeOH in 5 min; λ = 218 nm; minor enantiomer, t_R = 2.05 min; major enantiomer, t_R = 2.12 min. HPLC: Chiralpak® AY-H; flow: 1.0 mL/min; hexane/i-PrOH: 99.2:0.8; λ = 210 nm; major enantiomer, t_R = 7.4 min; minor enantiomer, t_R = 9.6 min].

Diastereoisomer 2: **HPLC and SFC analysis** indicated an enantiomeric excess of 92% [SFC: Chiralpak® IG-3; 1500 psi, 30 °C, flow: 1.5 mL/min; 1.0% to 30.0% MeOH in 5 min; λ = 218 nm; minor enantiomer, t_R = 2.05 min; major enantiomer, t_R = 2.12 min. HPLC: Chiralpak® AY-H; flow: 1.0 mL/min; hexane/i-PrOH: 99.2:0.8; λ = 210 nm; major enantiomer, t_R = 7.8 min; minor enantiomer, t_R = 7.8 min].

Absolute configuration was assigned by comparison to literature data.[6]

Mixture of Diastereoisomers:

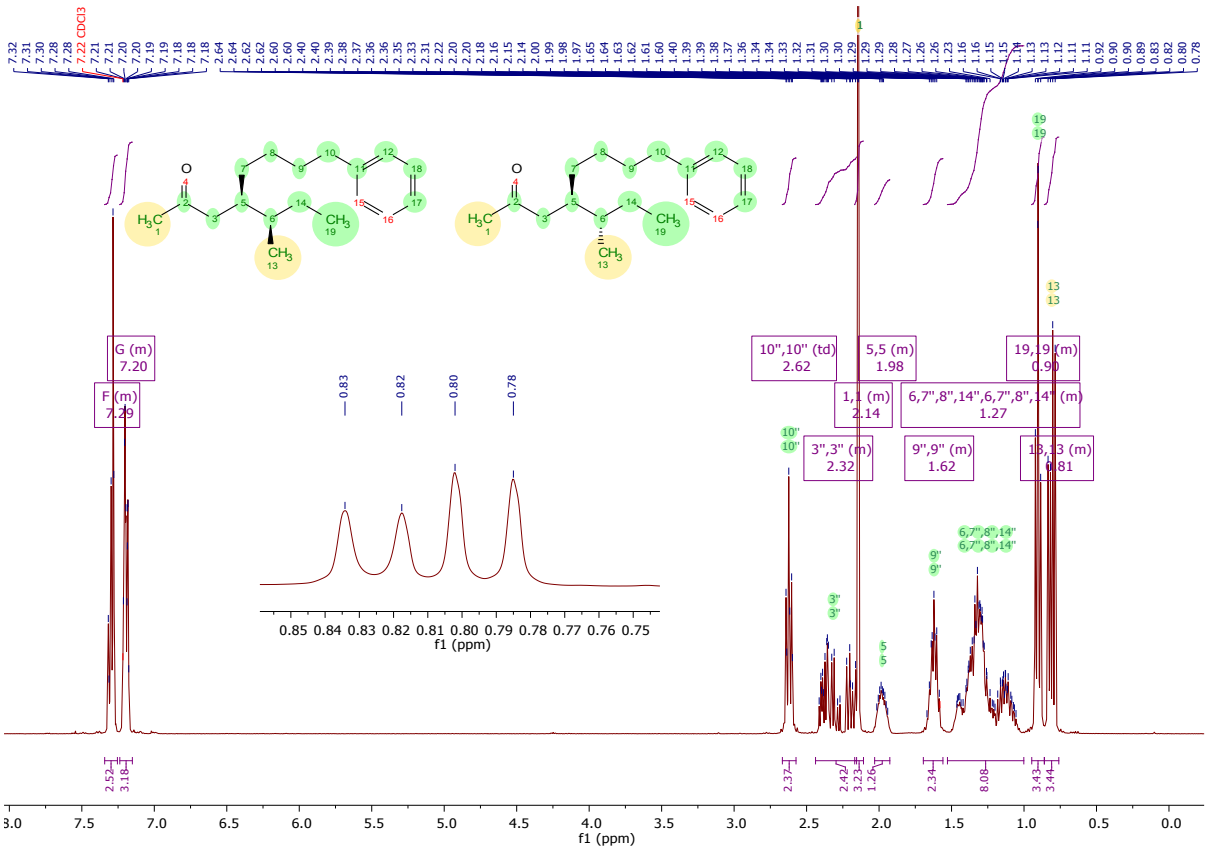
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.25 (m, 2H), 7.24 – 7.15 (m, 3H), 2.62 (td, *J* = 7.5, 2.1 Hz, 2H), 2.44 – 2.16 (m, 2H), 2.17 – 2.11 (m, 3H), 2.03 – 1.93 (m, 1H), 1.69 – 1.56 (m, 2H), 1.53 – 1.00 (m, 7H), 0.95 – 0.86 (m, 3H), 0.86 – 0.76 (m, 3H).

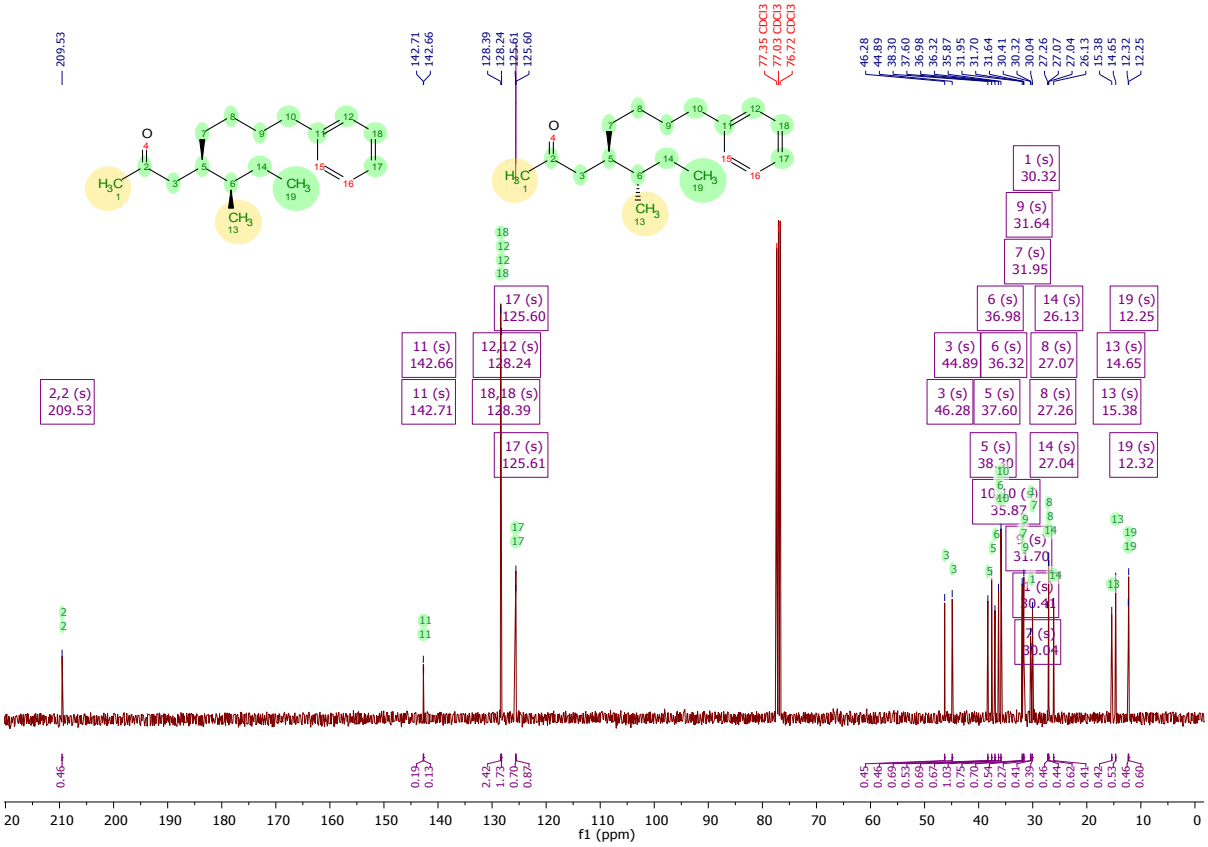
^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.5 (2 C), 142.7, 142.7, 128.4 (4 C), 128.2 (4 C), 125.6, 125.6, 46.3, 44.9, 38.3, 37.6, 37.0, 36.3, 35.9 (2 C), 31.9, 31.7, 31.6, 30.4, 30.3, 30.0, 27.3, 27.1, 27.0, 26.1, 15.4, 14.6, 12.3, 12.2.

IR υ_{max} (film): 2980, 1716, 1461, 1381, 1251, 1154, 1073.

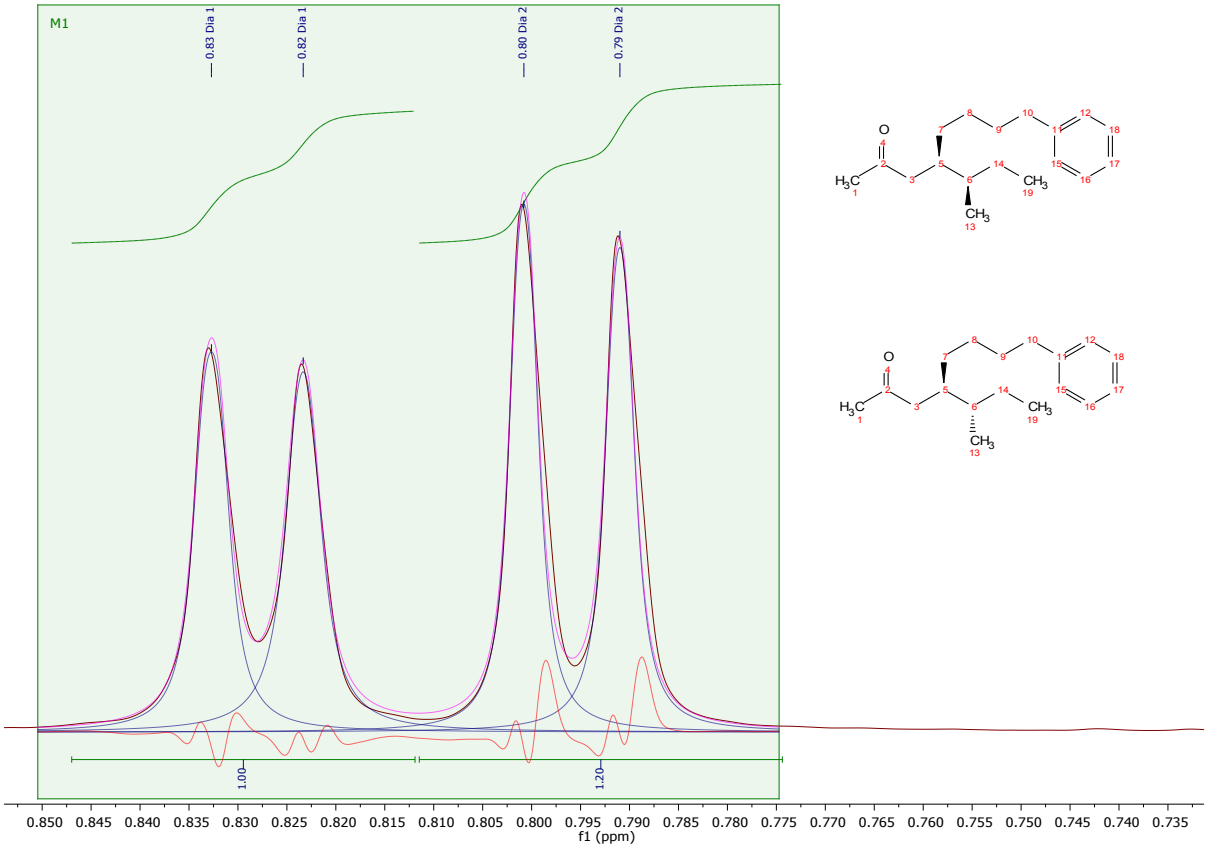
HRMS (APCI$^+$) *m/z* calcd for $C_{18}H_{29}O$ $[M+H]^+$: 261.2213, found 261.2215.

$[\alpha]^{25}_{589}$ = -0.8 (*c* 1.0, $CHCl_3$) for 89% ee and 92% ee.


G (m)
7.20
F (m)
7.29
10",10" (td)
2.62
5,5 (m)
1.98
19,19 (m)
0.90
1,1 (m)
2.14
6,7",8",14",6,7",8",14" (m)
1.27
3",3" (m)
2.32
9",9" (m)
1.62
13,13 (m)
0.81
f1 (ppm)

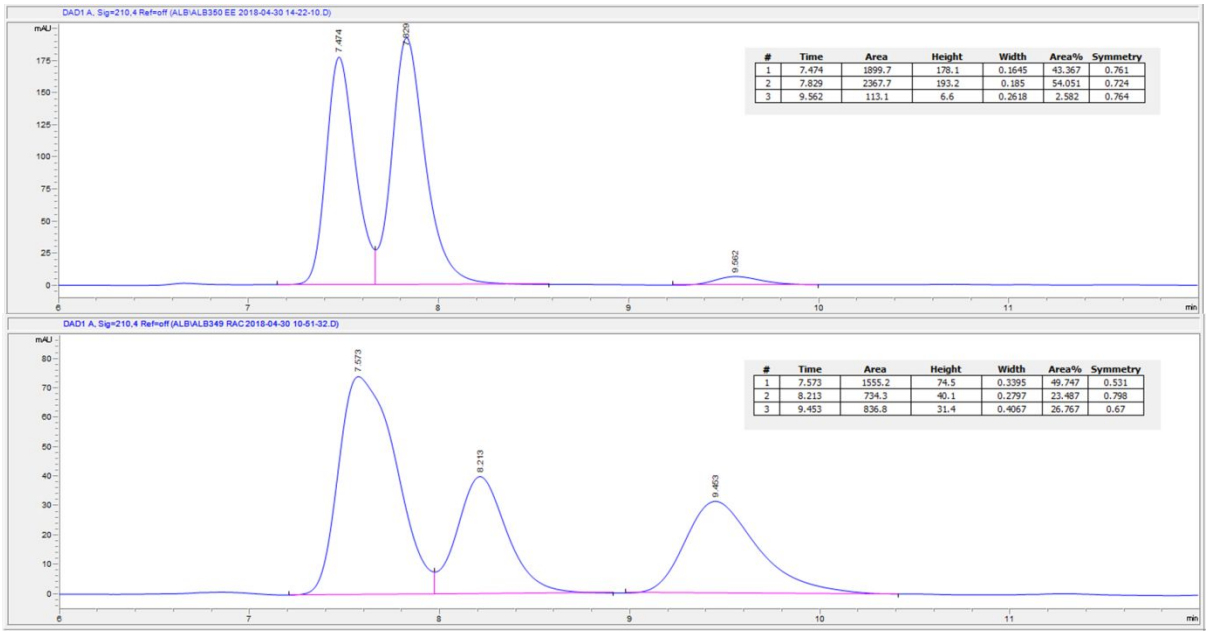

2,2 (s)
209.53
11 (s)
142.66
11 (s)
142.71
12,12 (s)
128.24
18,18 (s)
128.39
17 (s)
125.60
17 (s)
125.61
1 (s)
30.32
9 (s)
31.64
7 (s)
31.95
6 (s)
36.98
14 (s)
26.13
19 (s)
12.25
3 (s)
44.89
6 (s)
36.32
8 (s)
27.07
13 (s)
14.65
3 (s)
46.28
5 (s)
37.60
8 (s)
27.26
13 (s)
15.38
5 (s)
38.20
14 (s)
27.04
19 (s)
12.32
f1 (ppm)

Diastereomeric ratio Experiment (quantitative ^{1}H NMR)



Enantiomeric excess calculation

HPLC:



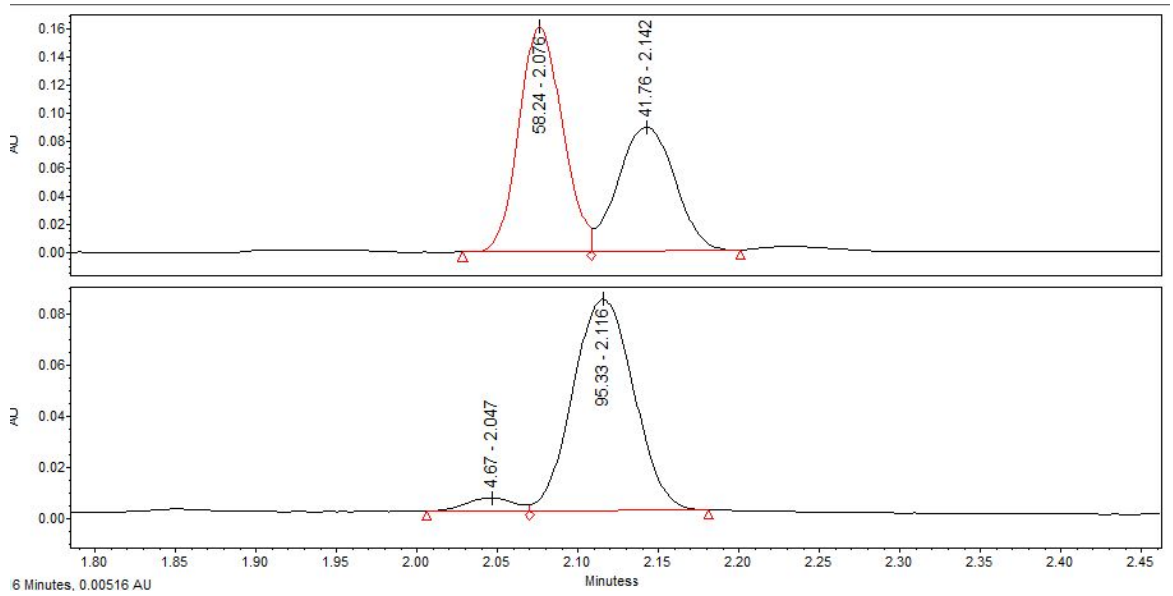
The only combination which correlates the diastereomeric ratio is by assigning the first and third signals to one diastereoisomer (“Dia 1”) and the second signal to the other one (“Dia 2”).

Ret time (min)	7.474	7.829	9.562
AUC	43.367%	54.051%	2.582%
	Dia 1	***Dia 2***	***Dia 1***

Dia 1	45.949%	**1**
Dia 2	54.051%	**1.18**

Leading to an enantiomeric excess of 89% ee for the minor diastereoisomer “Dia 1”. The enantiomers of “Dia 2” were unfortunately not separated.

SFC:



The SFC could only separate the enantiomers but not the diastereoisomers. Thus, solving this system of equations:

$R_1 + R_2 = 95.33\%$
$S_1 + S_2 = 4.67\%$
$1.2 \times (R_1 + S_1) = (R_2 + S_2)$
$(R_1 - S_1) / (R_1 + S_1) = 89\%$

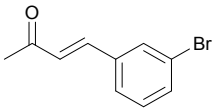
Leads to

S_1	2.50%
R_1	42.95%
S_2	2.17%
R_2	52.38%

Corresponding to 89% *ee* for “Dia 1” and 92% *ee* for “Dia 2”.

2. Enones

(E)-4-(3-bromophenyl)but-3-en-2-one



General Procedure C: Lithium hydroxide (68.8 mg, 2.789 mmol, 1.2 eq), Diethyl (2-oxopropyl)phosphonate (0.47 mL, 2.440 mmol, 1.05 eq), 3-bromobenzaldehyde (430 mg, 2.324 mmol, 1.0 eq), THF (10 mL).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane:EtOAc, 90:10, SiO_2) to afford (E)-4-(3-bromophenyl)but-3-en-2-one (394 mg, 1.748 mmol, 75%) as a pale yellow oil.

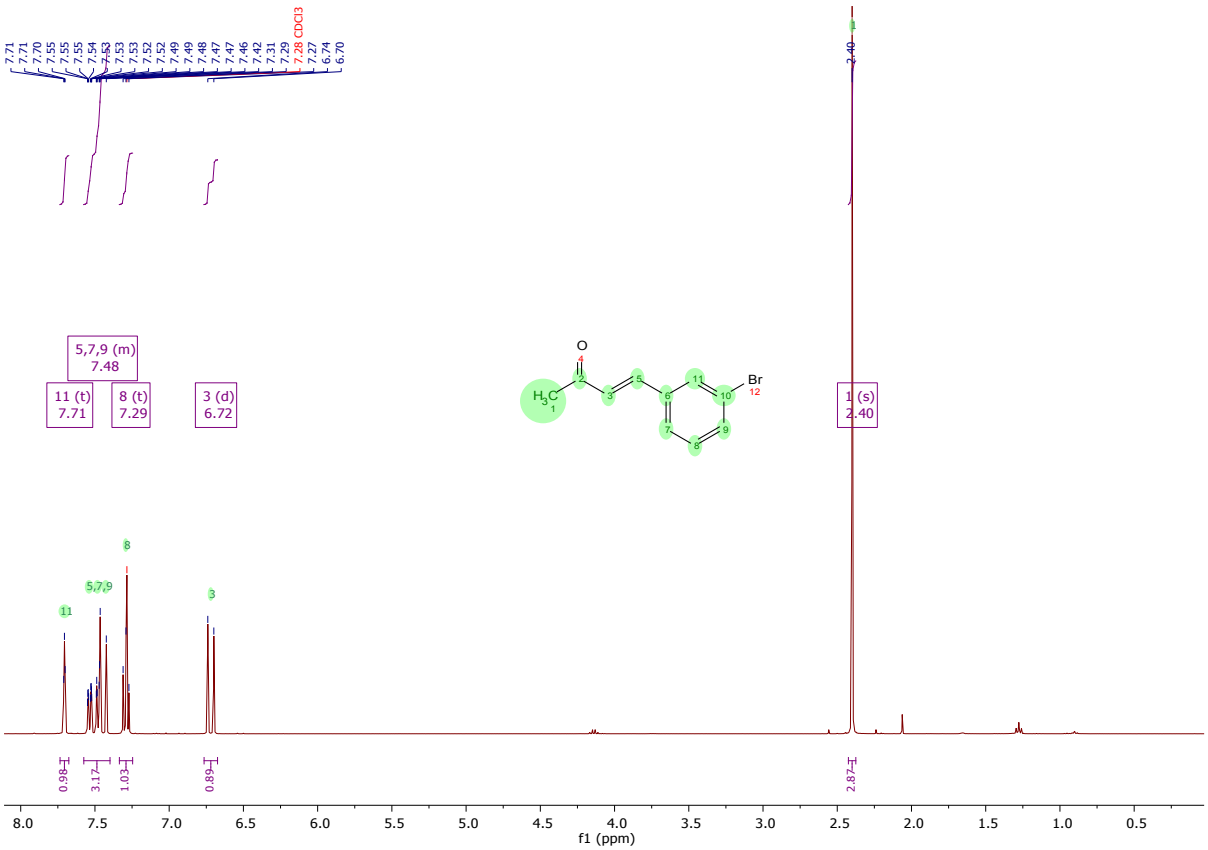
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.71 (t, *J* = 1.8 Hz, 1H), 7.58 – 7.40 (m, 3H), 7.29 (t, *J* = 7.9 Hz, 1H), 6.72 (d, *J* = 16.3 Hz, 1H), 2.40 (s, 3H).

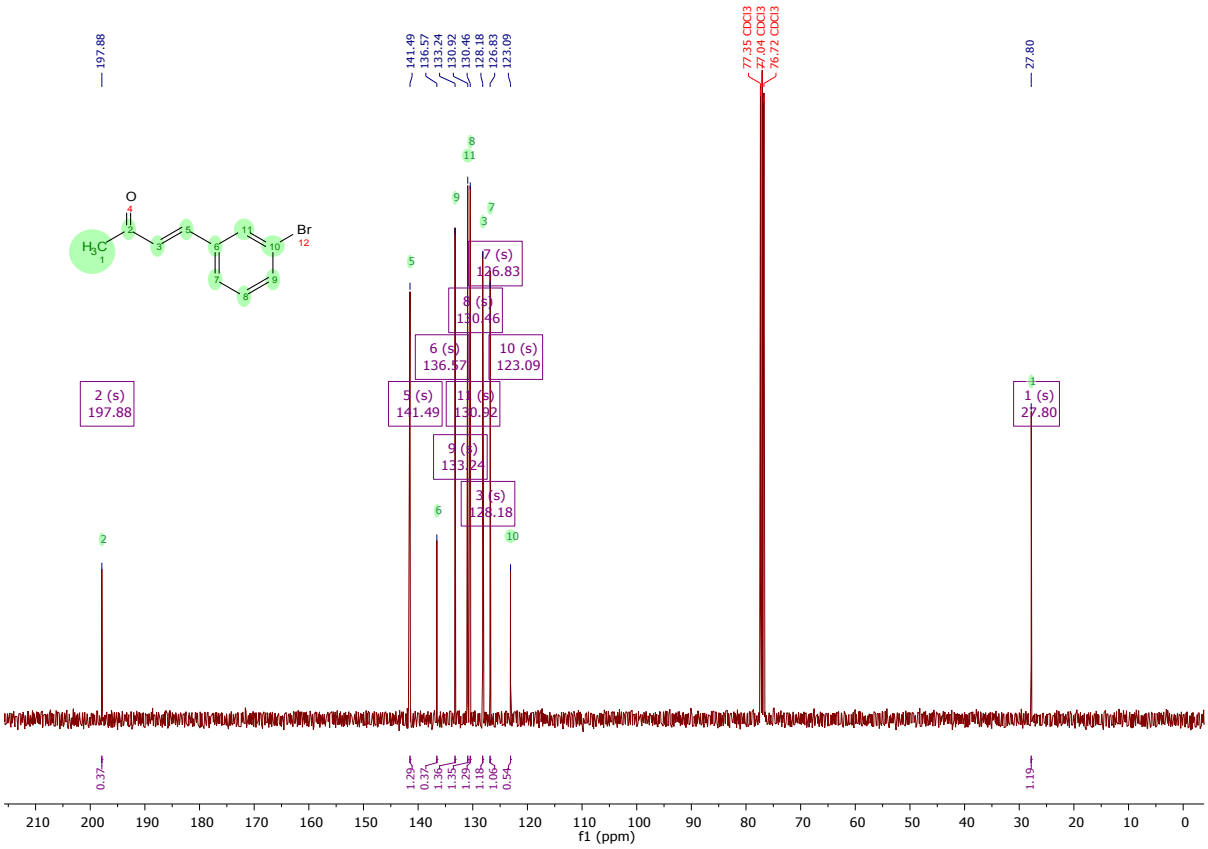
^{13}C NMR (126 MHz, Chloroform-*d*) δ 197.9, 141.5, 136.6, 133.2, 130.9, 130.5, 128.2, 126.8, 123.1, 27.8.

IR υ_{max} (film): 3059, 1692, 1670, 1611, 1359, 1257, 1179.

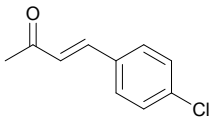
HRMS (APCI) *m/z* calcd for C_{10} H_{10} O Br $[M+H]^+$: 224.9909, found 224.9912.

Analytical data are in agreement with the literature.[7]


7.71
7.71
7.70
7.55
7.55
7.54
7.53
7.53
7.52
7.49
7.49
7.48
7.47
7.47
7.46
7.42
7.31
7.29
7.28 CDCl3
7.27
6.74
6.70
2.40
5,7,9 (m)
7.48
11 (t)
7.71
8 (t)
7.29
3 (d)
6.72
1 (s)
2.40
O
Br
H3C
0.98
3.17
1.03
0.89
2.87
f1 (ppm)


197.88
141.49
136.57
133.24
130.92
130.46
128.18
126.83
123.09
77.35 CDCl3
77.04 CDCl3
76.72 CDCl3
27.80
O
Br
H3C
2 (s)
197.88
5 (s)
141.49
11 (s)
130.92
9 (s)
133.24
3 (s)
128.18
6 (s)
136.57
10 (s)
123.09
8 (s)
130.46
7 (s)
126.83
1 (s)
27.80
0.37
1.29
0.37
1.36
1.35
1.29
1.18
1.06
0.54
1.19
f1 (ppm)

(E)-4-(4-chlorophenyl)but-3-en-2-one



General Procedure C: Lithium hydroxide (57.5 mg, 2.399 mmol, 1.2 eq), Diethyl (2-oxopropyl)phosphonate (0.40 mL, 2.099 mmol, 1.05 eq), 4-chlorobenzaldehyde (281 mg, 1.999 mmol, 1.0 eq), THF (10 mL).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane:EtOAc, 90:10, SiO_2) to afford (E)-4-(4-chlorophenyl)but-3-en-2-one (319 mg, 1.759 mmol, 88%) as a pale yellow solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 – 7.40 (m, 3H), 7.40 – 7.33 (m, 2H), 6.68 (d, *J* = 16.3 Hz, 1H), 2.37 (s, 3H).

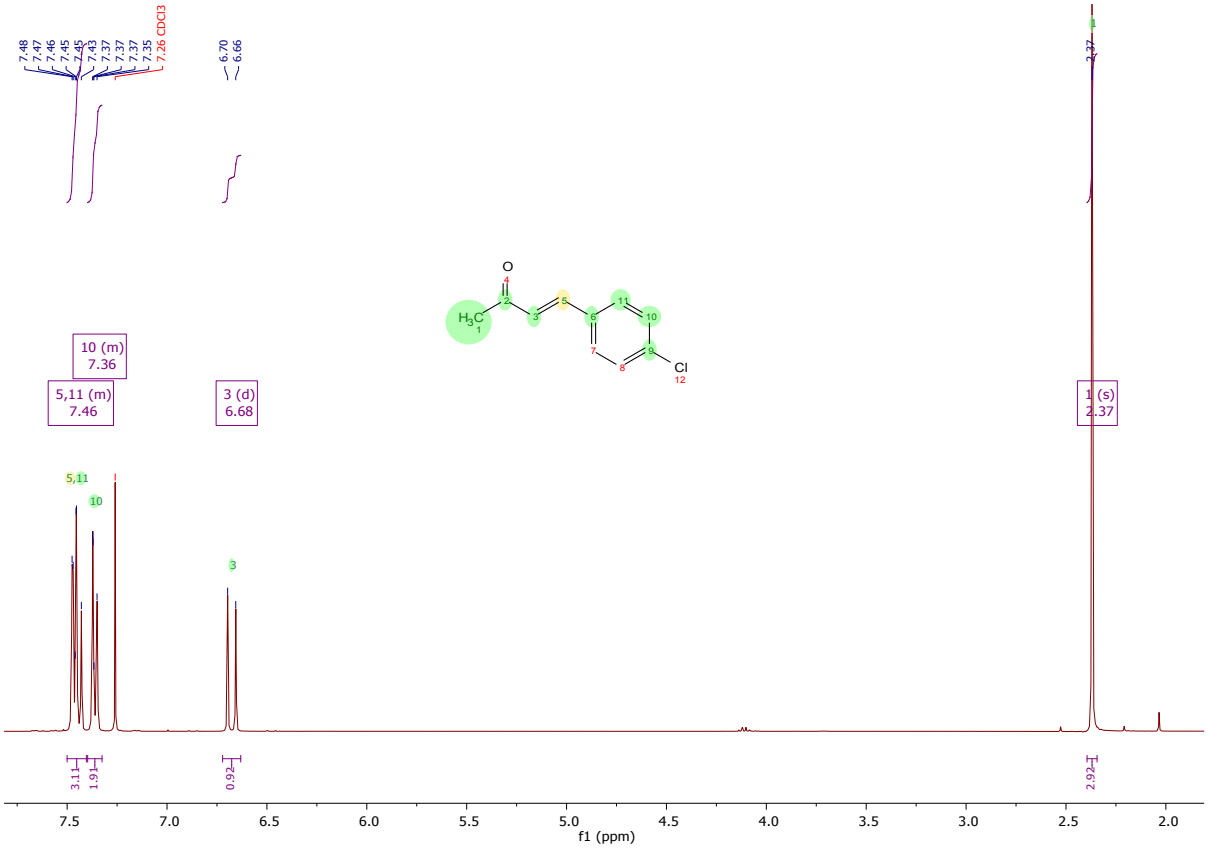
^{13}C NMR (126 MHz, Chloroform-*d*) δ 198.1, 142.0, 136.5, 133.0, 129.5 (2 C), 129.4 (2 C), 127.6, 27.8.

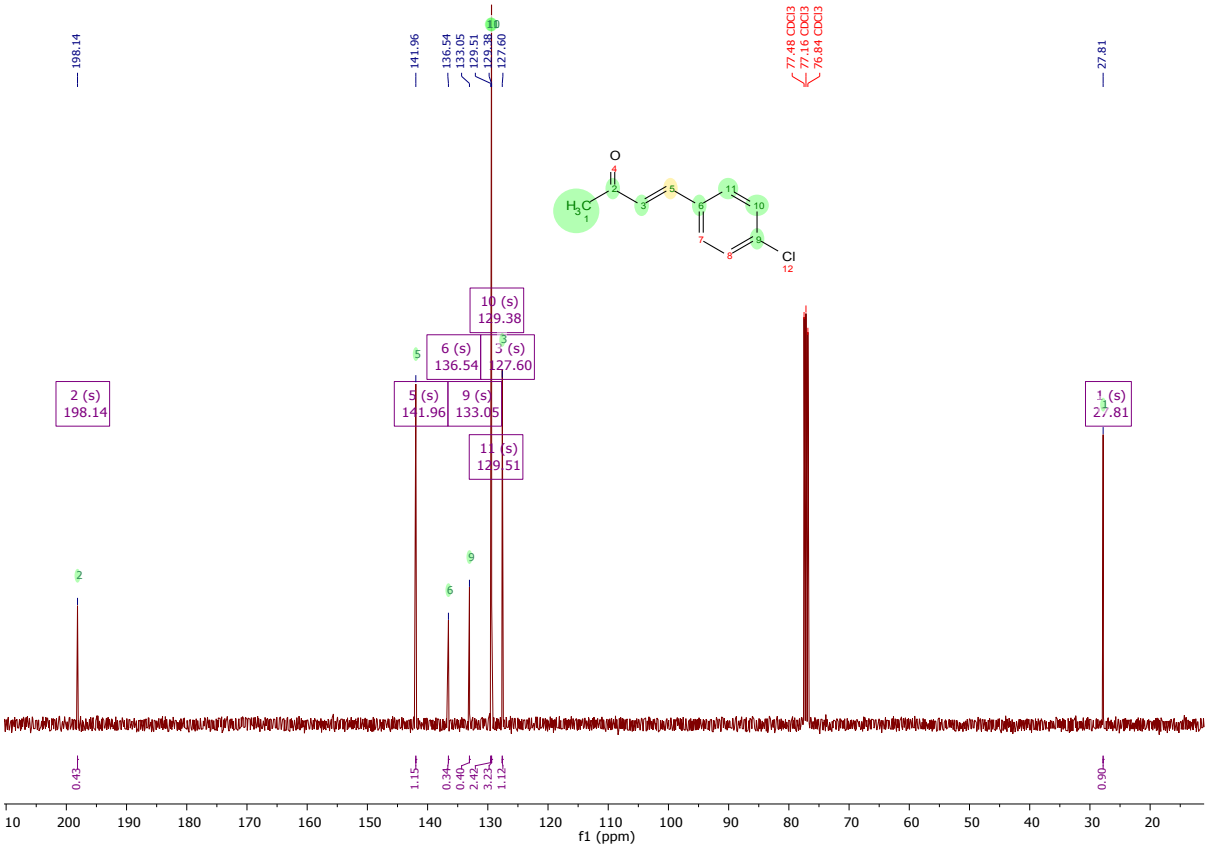
IR υ_{max} (film): 2981, 2361, 1691, 1669, 1610, 1491, 1359, 1256, 1090.

HRMS (APCI) *m/z* calcd for C_{10} H_{10} O Cl $[M+H]^+$: 181.0415, found 181.0416.

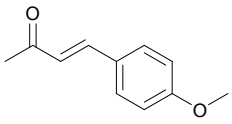
MP: 56.8 °C.

Analytical data are in agreement with the literature.[8]


7.48
7.47
7.46
7.45
7.43
7.37
7.37
7.35
7.26 CDCl3
6.70
6.66
2.37
10 (m)
7.36
5,11 (m)
7.46
3 (d)
6.68
1 (s)
2.37
3.11
1.91
0.92
2.92
f1 (ppm)


198.14
141.96
136.54
133.05
129.51
129.38
127.60
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
27.81
10 (s)
129.38
6 (s)
136.54
3 (s)
127.60
5 (s)
141.96
9 (s)
133.05
11 (s)
129.51
2 (s)
198.14
1 (s)
27.81
0.43
1.15
0.34
0.40
2.42
3.23
1.12
0.90
f1 (ppm)

(E)-4-(4-methoxyphenyl)but-3-en-2-one



General Procedure C: Lithium hydroxide (89.9 mg, 3.755 mmol, 1.2 eq), Diethyl (2-oxopropyl)phosphonate (0.63 mL, 3.285 mmol, 1.05 eq), 4-methoxybenzaldehyde (426 mg, 3.129 mmol, 1.0 eq), THF (20 mL).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane:EtOAc, 90:10, SiO_2) to afford (E)-4-(4-methoxyphenyl)but-3-en-2-one (257 mg, 1.471 mmol, 47%) as a pale yellow solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 – 7.43 (m, 3H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 16.2 Hz, 1H), 3.84 (s, 3H), 2.36 (s, 3H).

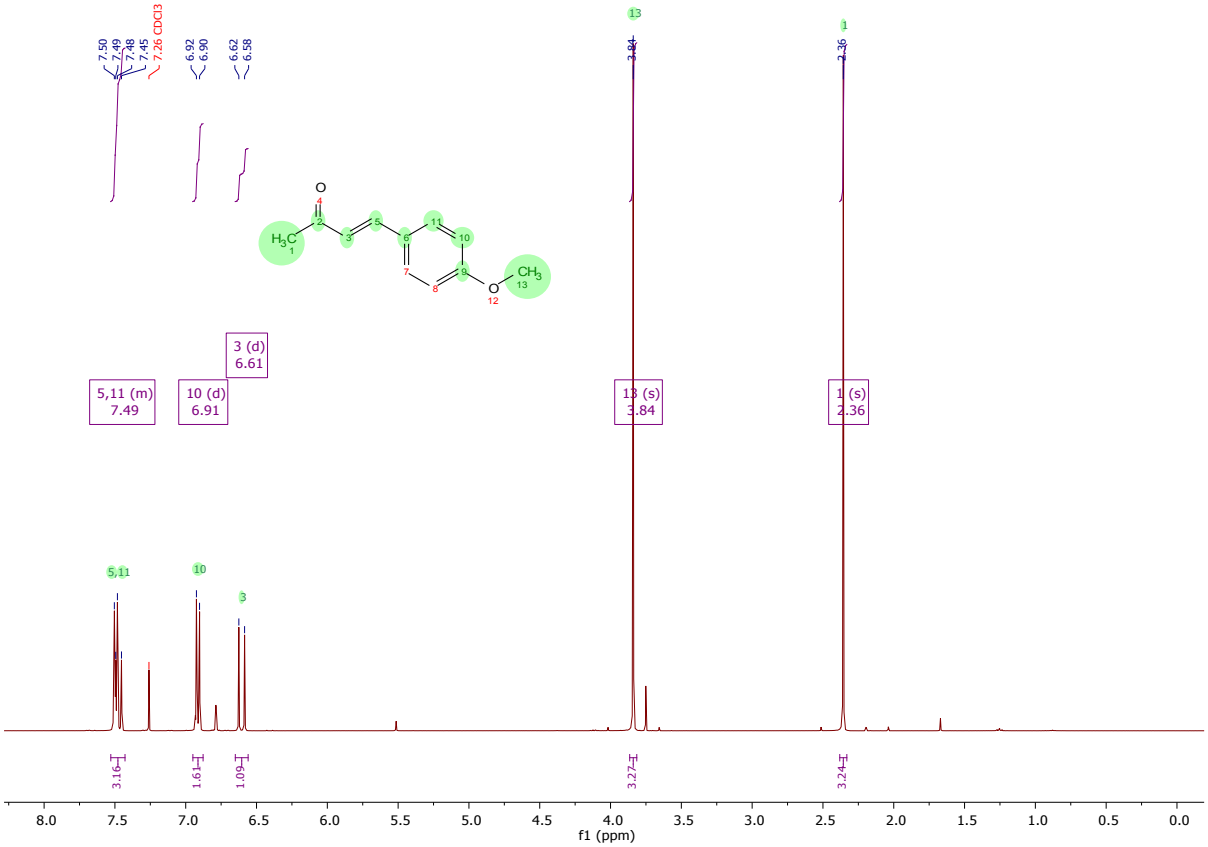
^{13}C NMR (126 MHz, Chloroform-*d*) δ 198.5, 161.7, 143.4, 130.1 (2 C), 127.2, 125.2, 114.6 (2 C), 55.5, 27.5.

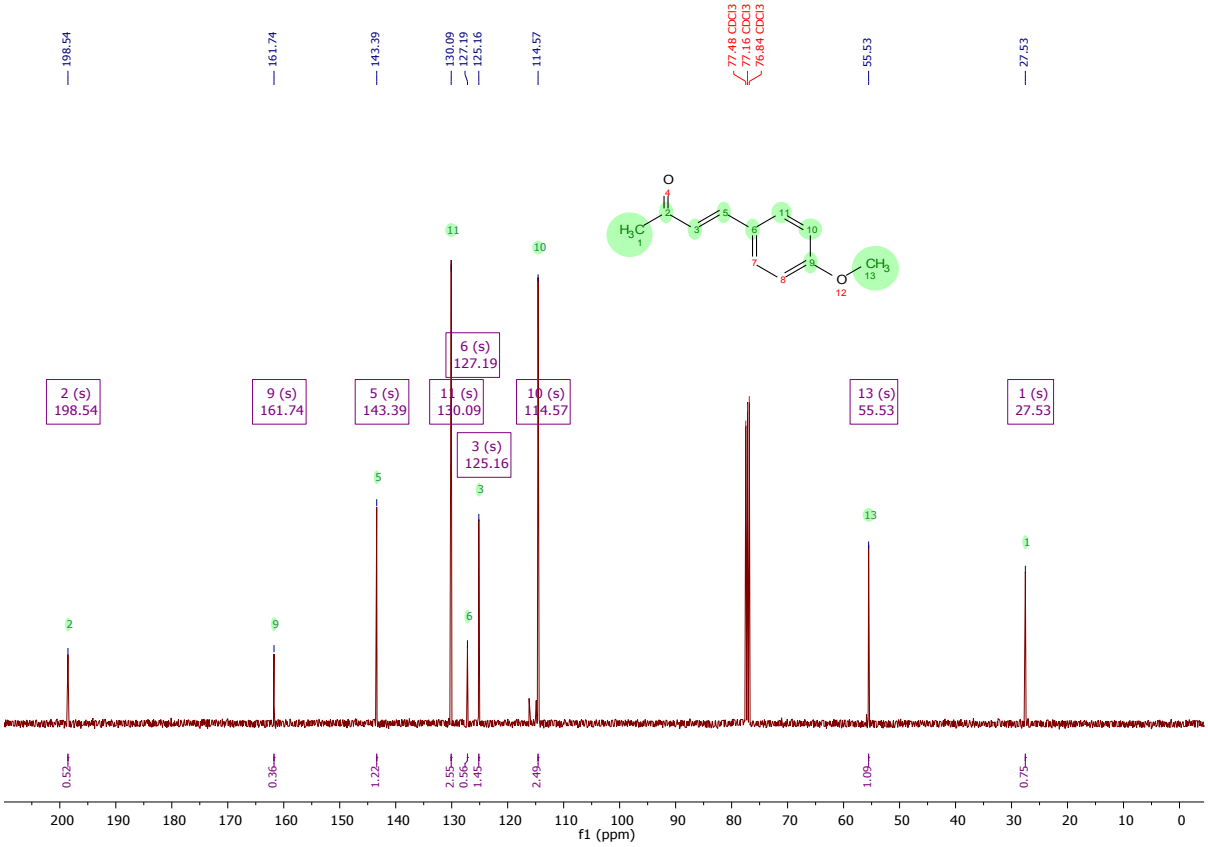
IR υ_{max} (film): 2979, 2360, 1681, 1600, 1513, 1359, 1264, 1176, 1021.

HRMS (APCI) *m/z* calcd for $C_{11}H_{13}O_2$ $[M+H]^+$: 177.0910, found 177.0912.

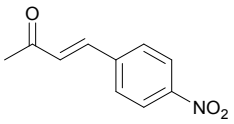
MP: 67 °C.

Analytical data are in agreement with the literature.[8]


7.50
7.49
7.48
7.45
7.26 CDCl3
6.92
6.90
6.62
6.58
3.84
2.36
5,11 (m)
7.49
10 (d)
6.91
3 (d)
6.61
13 (s)
3.84
1 (s)
2.36
3.16
1.61
1.09
3.27
3.24
f1 (ppm)


198.54
161.74
143.39
130.09
127.19
125.16
114.57
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.53
27.53
2 (s)
198.54
9 (s)
161.74
5 (s)
143.39
11 (s)
130.09
6 (s)
127.19
3 (s)
125.16
10 (s)
114.57
13 (s)
55.53
1 (s)
27.53
0.52
0.36
1.22
2.55
0.56
1.45
2.49
1.09
0.75
f1 (ppm)

(E)-4-(4-nitrophenyl)but-3-en-2-one



General Procedure C: Lithium hydroxide (26.6 mg, 1.112 mmol, 1.2 eq), Diethyl (2-oxopropyl)phosphonate (0.19 mL, 0.973 mmol, 1.05 eq), 4-nitrobenzaldehyde (140 mg, 0.926 mmol, 1.0 eq), THF (5 mL).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane:EtOAc, 90:10, SiO_2) to (E)-4-(4-nitrophenyl)but-3-en-2-one (139 mg, 0.731 mmol, 79%) as a pale yellow solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.30 – 8.21 (m, 2H), 7.74 – 7.65 (m, 2H), 7.53 (d, *J* = 16.3 Hz, 1H), 6.81 (d, *J* = 16.3 Hz, 1H), 2.42 (s, 3H).

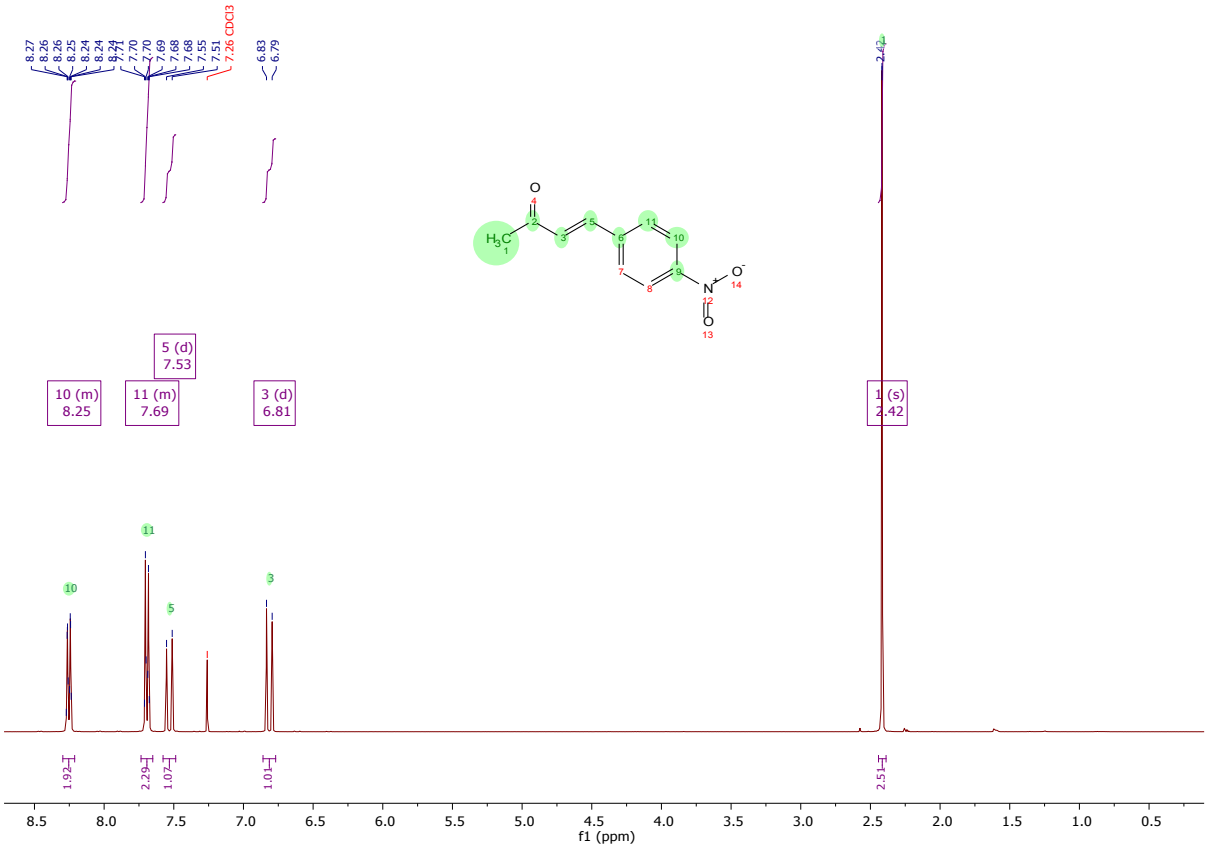
^{13}C NMR (126 MHz, Chloroform-*d*) δ 197.6, 148.7, 140.8, 140.2, 130.5, 128.9 (2 C), 124.3 (2 C), 28.2.

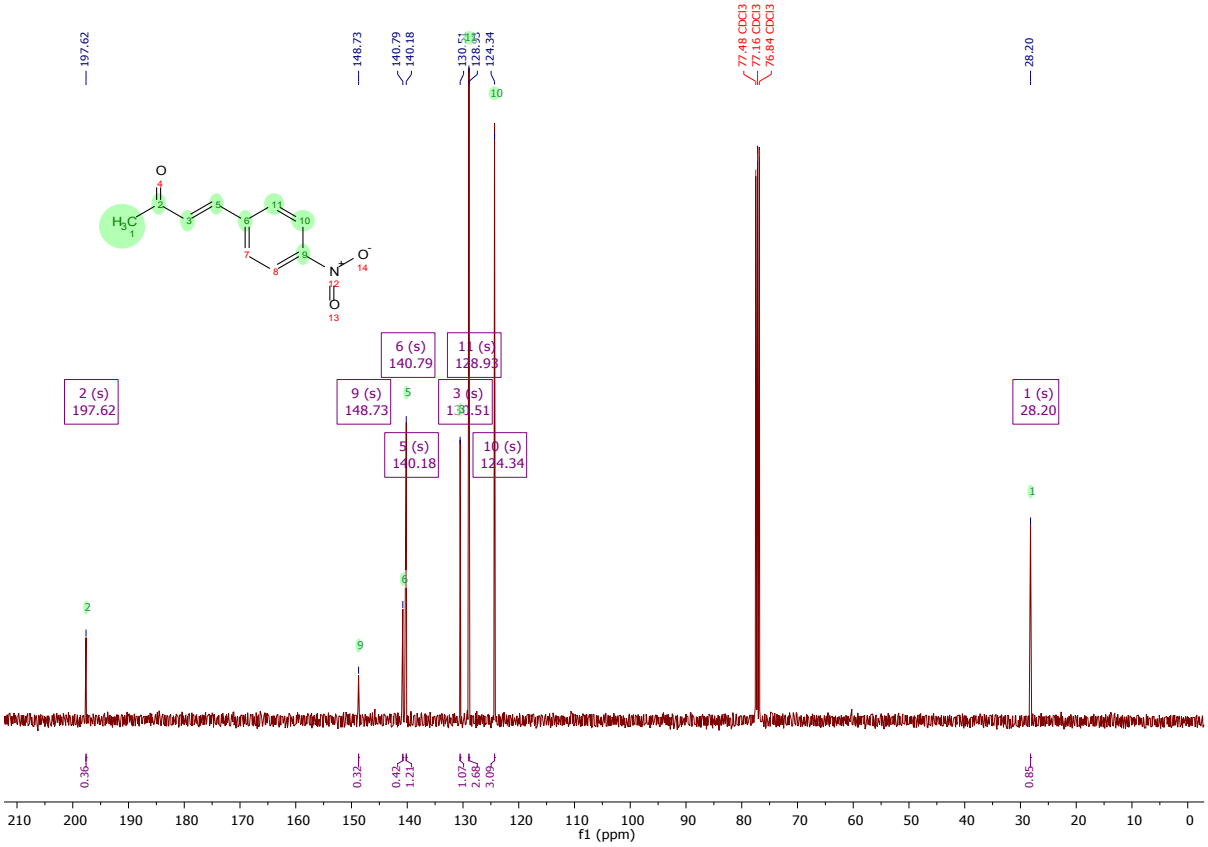
IR υ_{max} (film): 3112, 2360, 1692, 1668, 1614, 1593, 1510, 1337, 1187.

HRMS (APCI) *m/z* calcd for $C_{10}H_{10}O_3N$ $[M+H]^+$: 192.0655, found 192.0658.

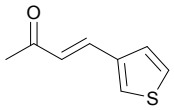
MP: 105 °C.

Analytical data are in agreement with the literature.[8]


8.27
8.26
8.26
8.25
8.24
8.24
8.24
7.71
7.70
7.70
7.69
7.68
7.68
7.55
7.51
7.26 CDCl3
6.83
6.79
2.42
5 (d)
7.53
10 (m)
8.25
11 (m)
7.69
3 (d)
6.81
1 (s)
2.42
1.92
2.29
1.07
1.01
2.51
f1 (ppm)


197.62
148.73
140.79
140.18
130.51
128.93
124.34
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
28.20
2 (s)
197.62
9 (s)
148.73
6 (s)
140.79
5 (s)
140.18
11 (s)
128.93
3 (s)
130.51
10 (s)
124.34
1 (s)
28.20
0.36
0.32
0.42
1.21
1.07
2.68
3.09
0.85
f1 (ppm)

(E)-4-(thiophen-3-yl)but-3-en-2-one



General Procedure C: Lithium hydroxide (164.0 mg, 6.848 mmol, 1.2 eq), Diethyl (2-oxopropyl)phosphonate (1.15 mL, 5.992 mmol, 1.05 eq), thiophene-3-carbaldehyde (0.50 mL, 5.707 mmol, 1.0 eq), THF (25 mL).

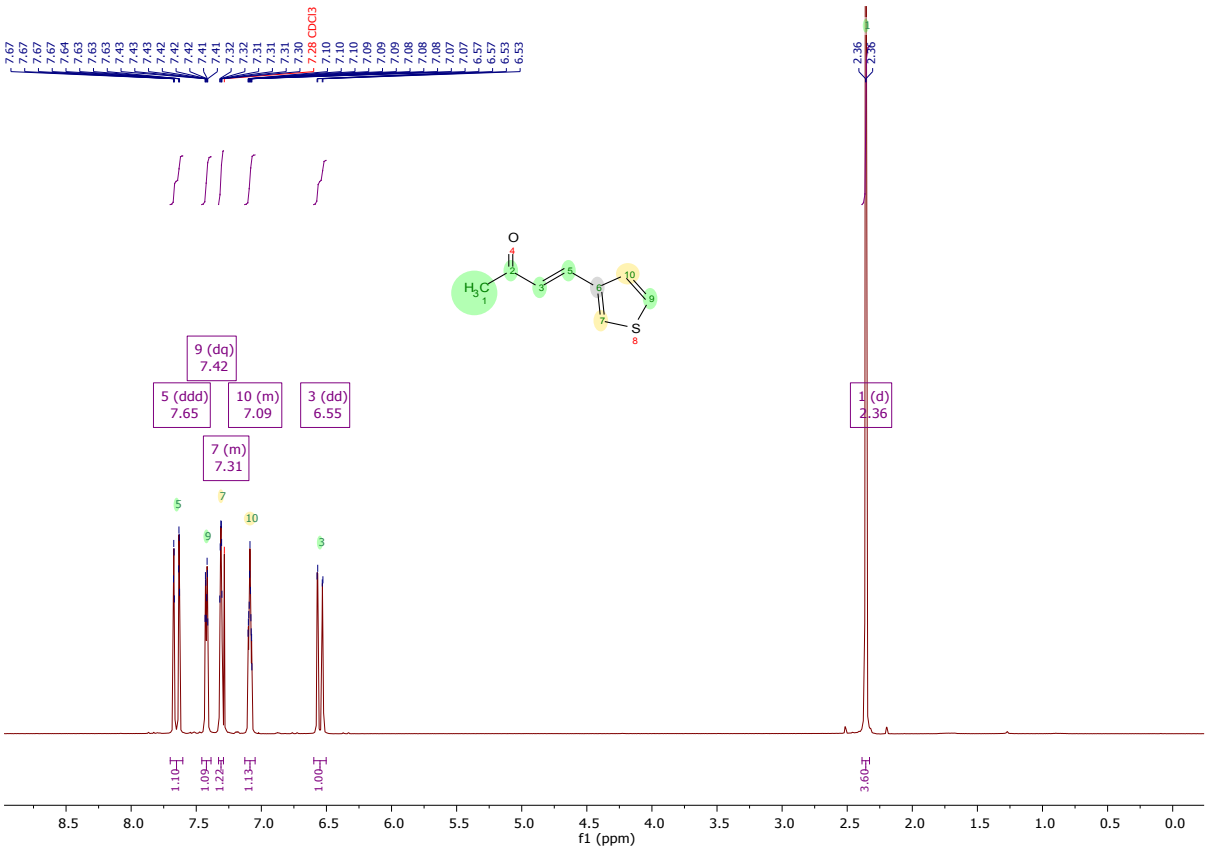
The crude mixture was treated as described above and was purified by flash column chromatography (Hexane:EtOAc, 90:10, SiO_2) to afford (E)-4-(thiophen-3-yl)but-3-en-2-one (352 mg, 2.311 mmol, 40%) as a pale yellow oil.

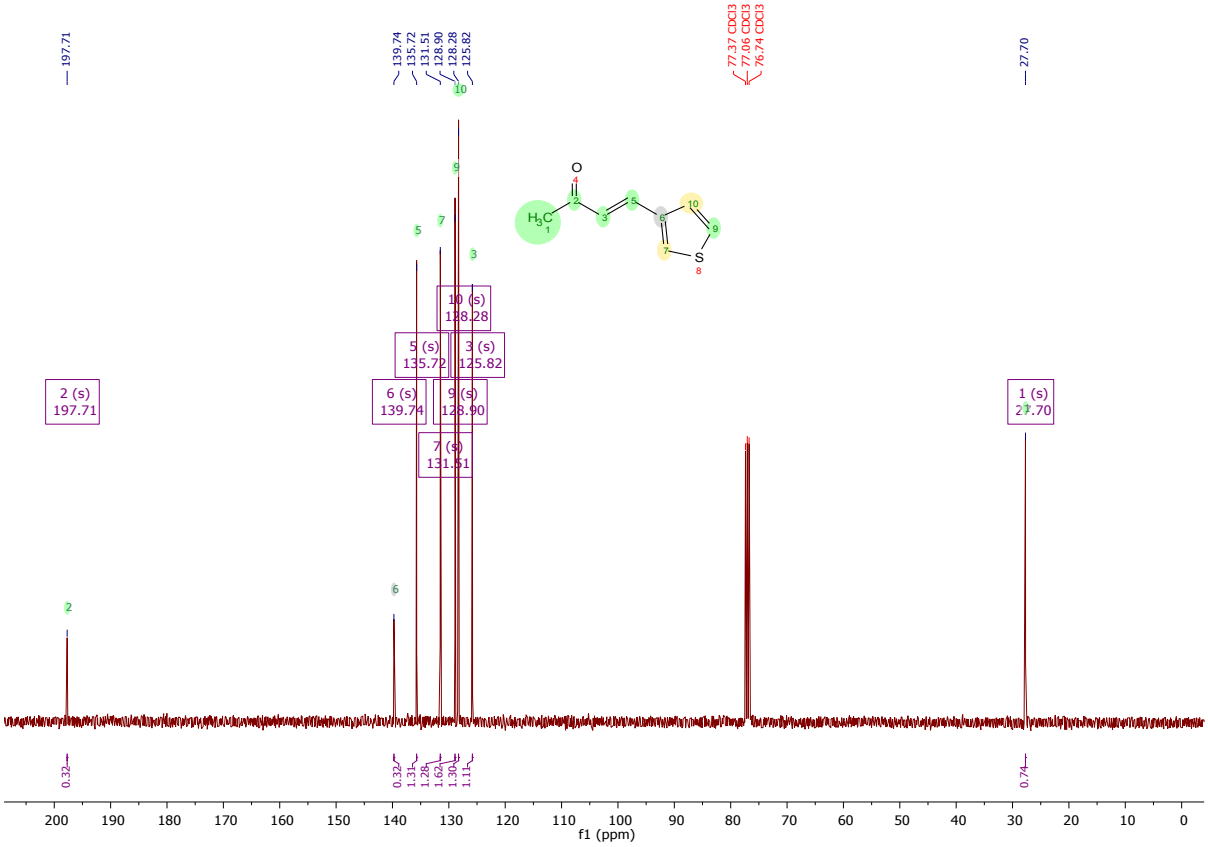
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (ddd, *J* = 15.9, 1.8, 0.9 Hz, 1H), 7.42 (dq, *J* = 5.0, 1.0 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.13 – 7.05 (m, 1H), 6.55 (dd, *J* = 16.0, 2.0 Hz, 1H), 2.36 (d, *J* = 1.2 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 197.7, 139.7, 135.7, 131.5, 128.9, 128.3, 125.8, 27.7.

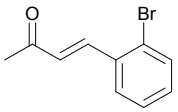
IR υ_{max} (film): 3104, 1663, 1594, 1423, 1358, 1254, 1200.

HRMS (APCI) *m/z* calcd for $C_8 H_9 O S [M+H]^+$: 153.0369, found 153.0369.


9 (dq)
7.42
5 (ddd)
7.65
10 (m)
7.09
3 (dd)
6.55
7 (m)
7.31
1 (d)
2.36
f1 (ppm)


2 (s)
197.71
10 (s)
128.28
5 (s)
135.72
3 (s)
125.82
6 (s)
139.74
9 (s)
128.90
7 (s)
131.51
1 (s)
27.70
f1 (ppm)

(E)-4-(2-bromophenyl)but-3-en-2-one



General Procedure C: Lithium hydroxide (41.0 mg, 1.713 mmol, 1.2 eq), Diethyl (2-oxopropyl)phosphonate (0.35 mL, 1.799 mmol, 1.05 eq), 2-bromobenzaldehyde (0.20 mL, 1.713 mmol, 1.0 eq), THF (10 mL).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane:EtOAc, 90:10, SiO_2) to afford (E)-4-(2-bromophenyl)but-3-en-2-one (222.1 mg, 0.993 mmol, 58%) as a pale brown oil.

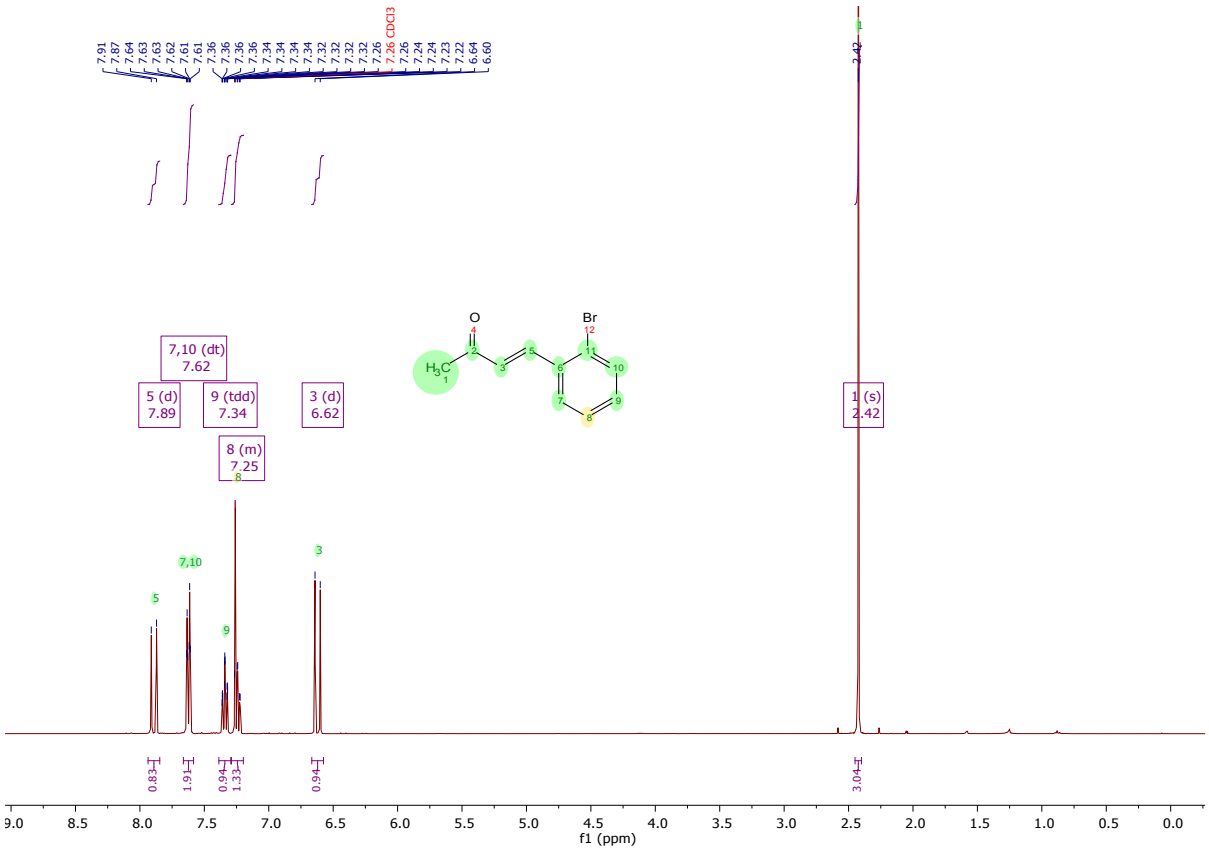
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 16.3 Hz, 1H), 7.62 (dt, *J* = 7.8, 1.7 Hz, 2H), 7.34 (tdd, *J* = 7.9, 1.3, 0.7 Hz, 1H), 7.29 – 7.20 (m, 1H), 6.62 (d, *J* = 16.3 Hz, 1H), 2.42 (s, 3H).

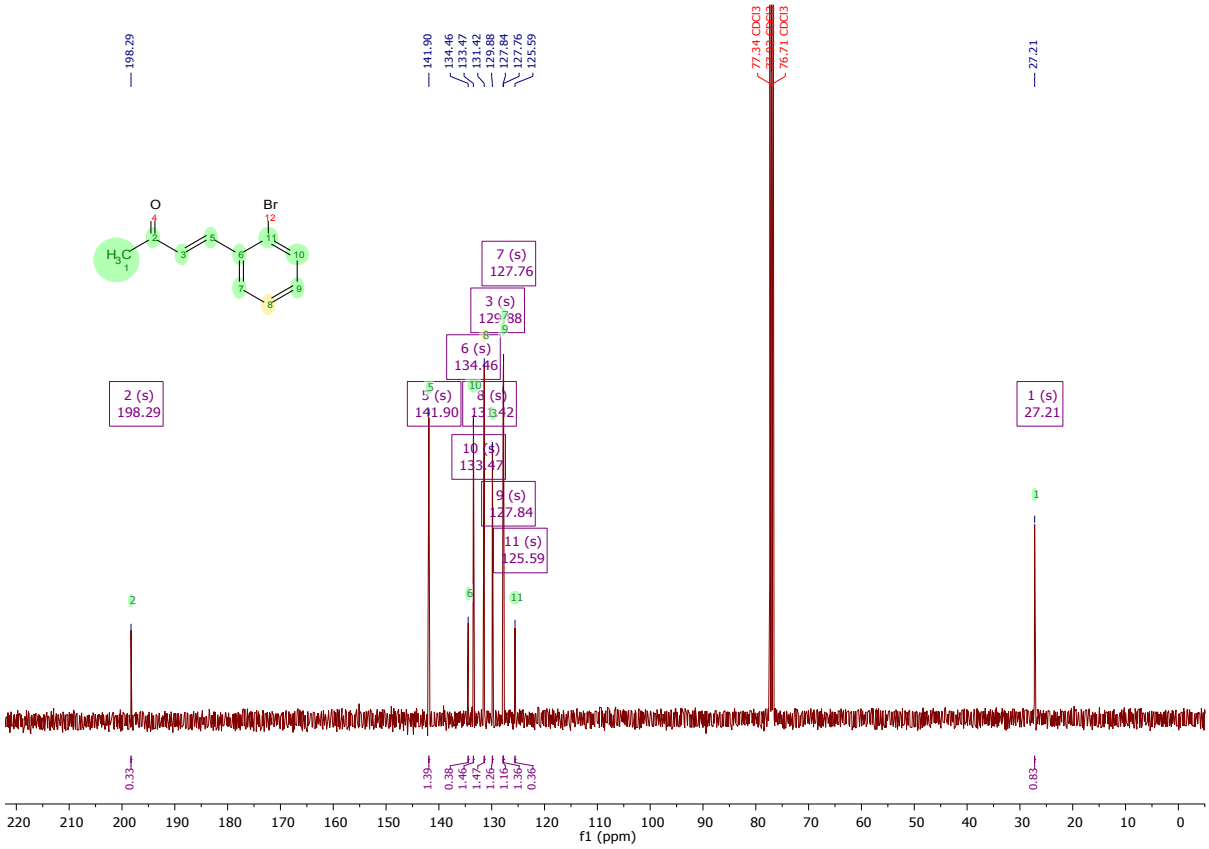
^{13}C NMR (126 MHz, Chloroform-*d*) δ 198.3, 141.9, 134.5, 133.5, 131.4, 129.9, 127.8, 127.8, 125.6, 27.2.

IR υ_{max} (film): 2980, 1671, 1607, 1437, 1358, 1257, 1026.

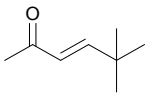
HRMS (APCI$^+$) *m/z* calcd for C_{10} H_{10} O Br $[M+H]^+$: 224.9909, found 224.9912.

Analytical data are in agreement with the literature.[9]


7,10 (dt)
7.62
5 (d)
7.89
9 (tdd)
7.34
3 (d)
6.62
8 (m)
7.25
1 (s)
2.42
f1 (ppm)


2 (s)
198.29
7 (s)
127.76
3 (s)
129.88
6 (s)
134.46
5 (s)
141.90
10 (s)
133.47
9 (s)
127.84
11 (s)
125.59
1 (s)
27.21
f1 (ppm)

(E)-5,5-dimethylhex-3-en-2-one



General Procedure C: Lithium hydroxide (185.2 mg, 7.734 mmol, 1.2 eq), Diethyl (2-oxopropyl)phosphonate (1.30 mL, 6.767 mmol, 1.05 eq), pivalaldehyde (0.70 mL, 6.445 mmol, 1.0 eq), THF (30 mL).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane:EtOAc, 90:10, SiO_2) to afford (E)-5,5-dimethylhex-3-en-2-one (356.2 mg, 2.836 mmol, 44%) as a colourless oil.

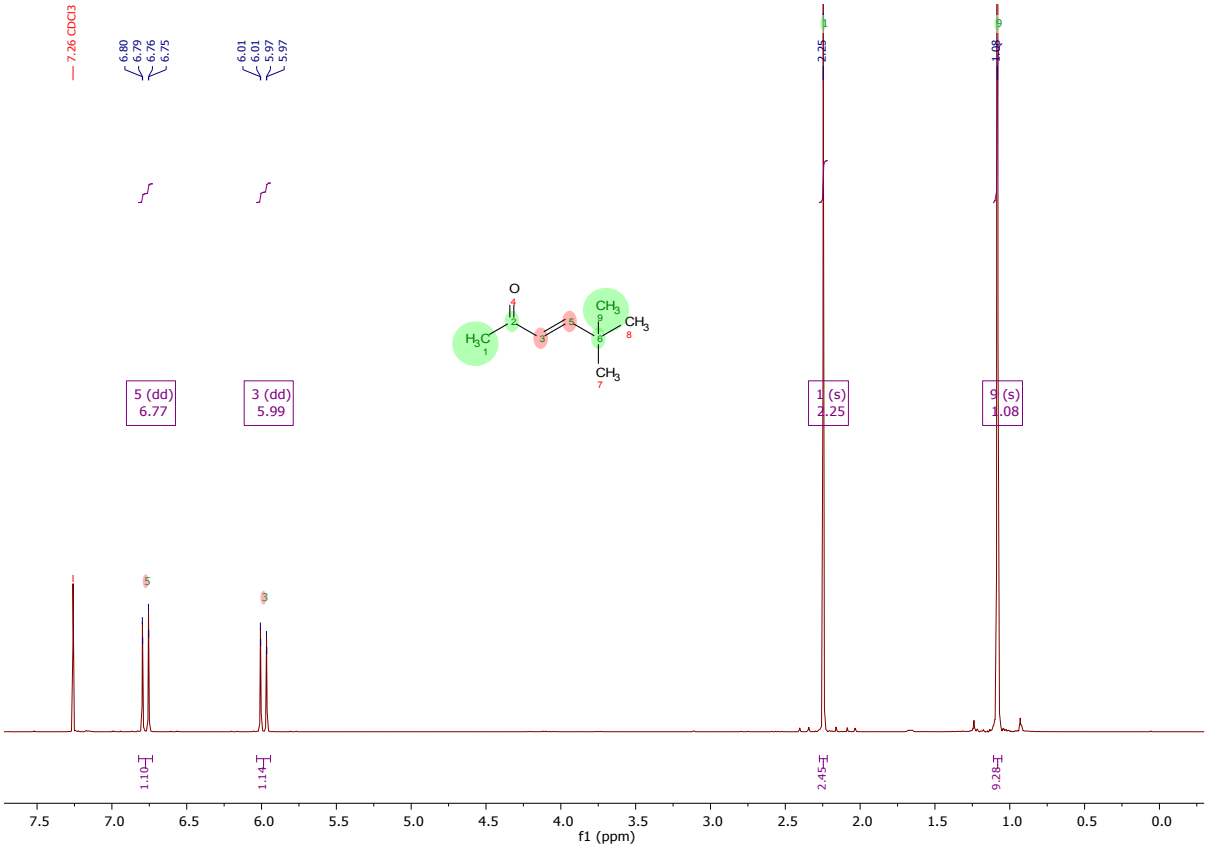
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.78 (dd, *J* = 16.3, 0.7 Hz, 1H), 5.99 (dd, *J* = 16.3, 0.7 Hz, 1H), 2.25 (s, 3H), 1.08 (s, 9H).

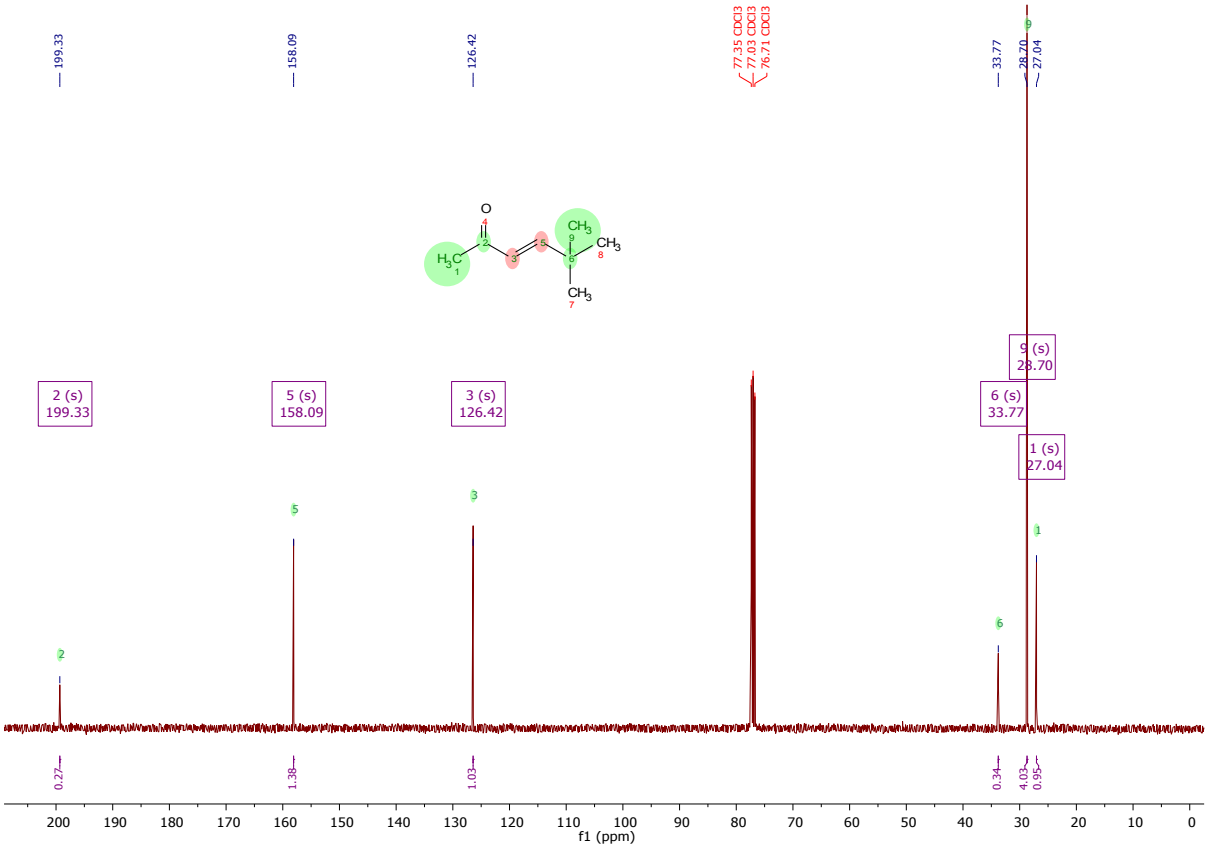
^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.3, 158.1, 126.4, 33.8, 28.7 (3 C), 27.0.

IR υ_{max} (film):3659, 2980, 1472, 1461, 1251, 1152, 1073.

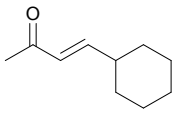
HRMS (APCI$^+$) *m/z* calcd for $C_8H_{15}O$ $[M+H]^+$: 127.1117, found 127.1116.

Analytical data are in agreement with the literature.[10]


7.26 CDCl3
6.80
6.79
6.76
6.75
6.01
6.01
5.97
5.97
2.25
1.08
5 (dd)
6.77
3 (dd)
5.99
1 (s)
2.25
9 (s)
1.08
1.10
1.14
2.45
9.28
f1 (ppm)


199.33
158.09
126.42
77.35 CDCl3
77.03 CDCl3
76.71 CDCl3
33.77
28.70
27.04
2 (s)
199.33
5 (s)
158.09
3 (s)
126.42
9 (s)
28.70
6 (s)
33.77
1 (s)
27.04
0.27
1.38
1.03
0.34
4.03
0.95
f1 (ppm)

(E)-4-cyclohexylbut-3-en-2-one



General Procedure C: Lithium hydroxide (177.9 mg, 7.430 mmol, 1.2 eq), Diethyl (2-oxopropyl)phosphonate (1.25 mL, 6.501 mmol, 1.05 eq), cyclohexanecarbaldehyde (0.75 mL, 6.191 mmol, 1.0 eq), THF (30 mL).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane:EtOAc, 90:10, SiO_2) to afford (E)-4-cyclohexylbut-3-en-2-one (399 mg, 2.600 mmol, 42%) as a pale yellow oil.

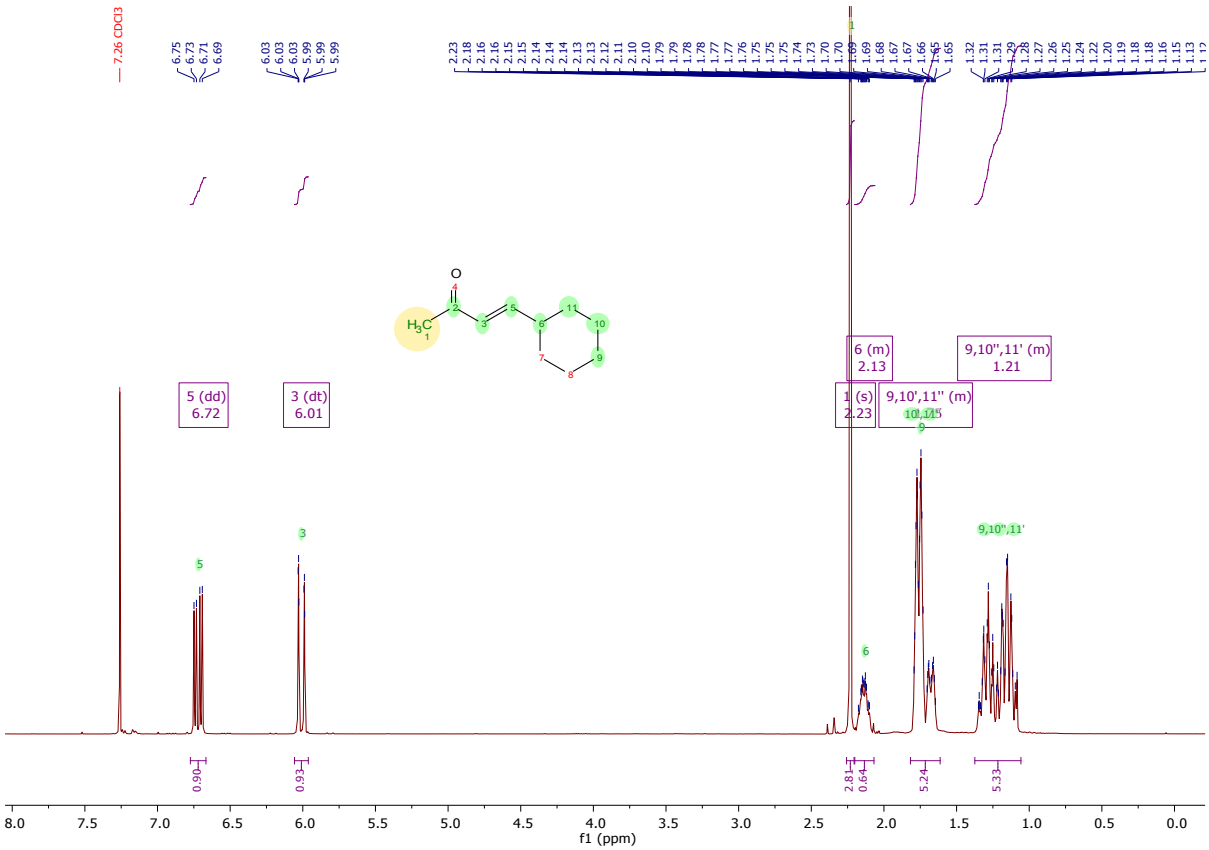
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.72 (dd, *J* = 16.1, 6.8 Hz, 1H), 6.01 (dt, *J* = 16.1, 1.0 Hz, 1H), 2.23 (s, 3H), 2.20 – 2.07 (m, 1H), 1.82 – 1.61 (m, 5H), 1.37 – 1.06 (m, 5H).

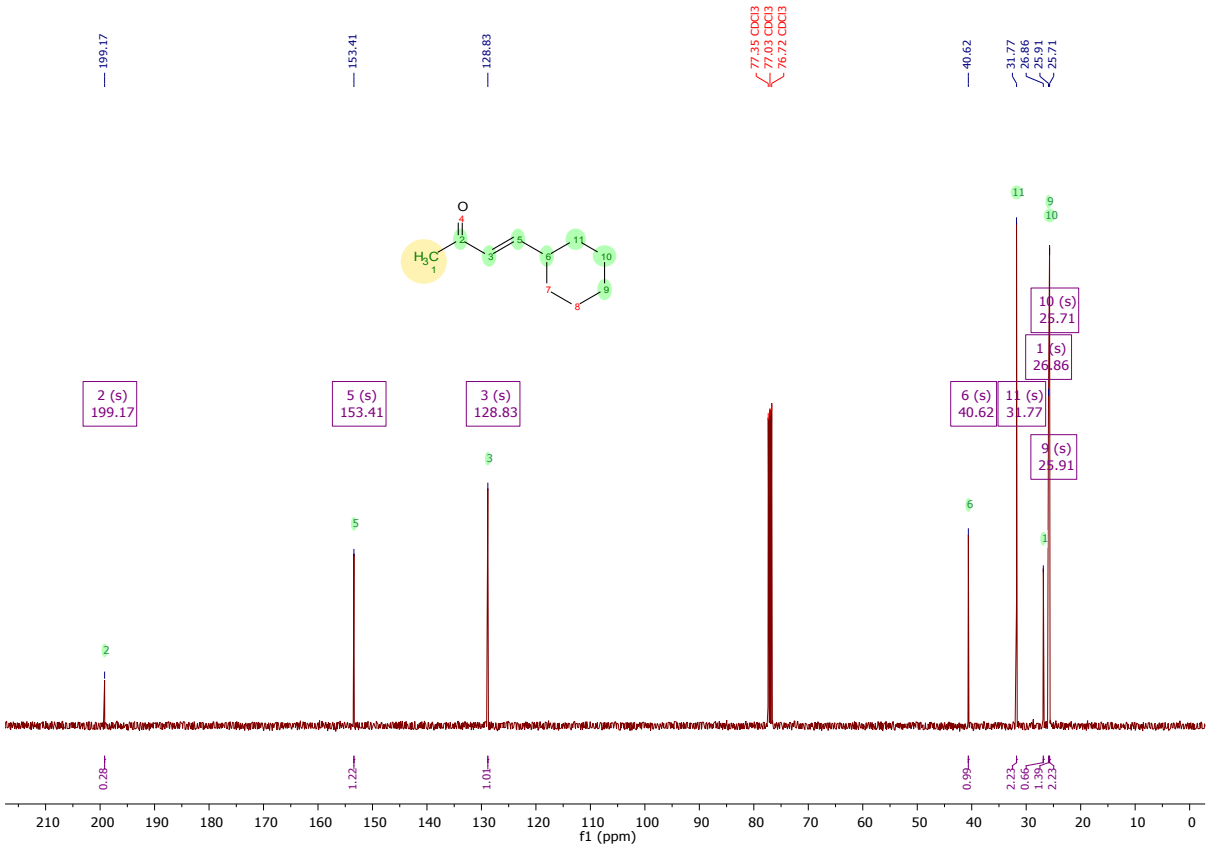
^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.2, 153.4, 128.8, 40.6, 31.8 (2 C), 26.9, 25.9, 25.7 (2 C).

IR υ_{max} (film): 2924, 2852, 1673, 1623, 1448, 1357, 1252.

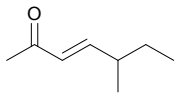
HRMS (APCI) *m/z* calcd for $C_{10}H_{17}O$ $[M+H]^+$: 153.1274, found 153.1273.

Analytical data are in agreement with the literature.[10]


7.26 CDCl3
5 (dd)
6.72
3 (dt)
6.01
6 (m)
2.13
1 (s)
2.23
9,10'',11' (m)
1.21
9,10',11'' (m)
f1 (ppm)


199.17
153.41
128.83
77.35 CDCl3
77.03 CDCl3
76.72 CDCl3
40.62
31.77
26.86
25.91
25.71
2 (s)
199.17
5 (s)
153.41
3 (s)
128.83
6 (s)
40.62
11 (s)
31.77
10 (s)
25.71
1 (s)
26.86
9 (s)
25.91
f1 (ppm)

(E)-5-methylhept-3-en-2-one



General Procedure C: Lithium hydroxide (201.2 mg, 8.402 mmol, 1.2 eq), Diethyl (2-oxopropyl)phosphonate (1.41 mL, 7.351 mmol, 1.05 eq), methylbutyraldehyde (0.75 mL, 7.001 mmol, 1.0 eq), THF (25 mL).

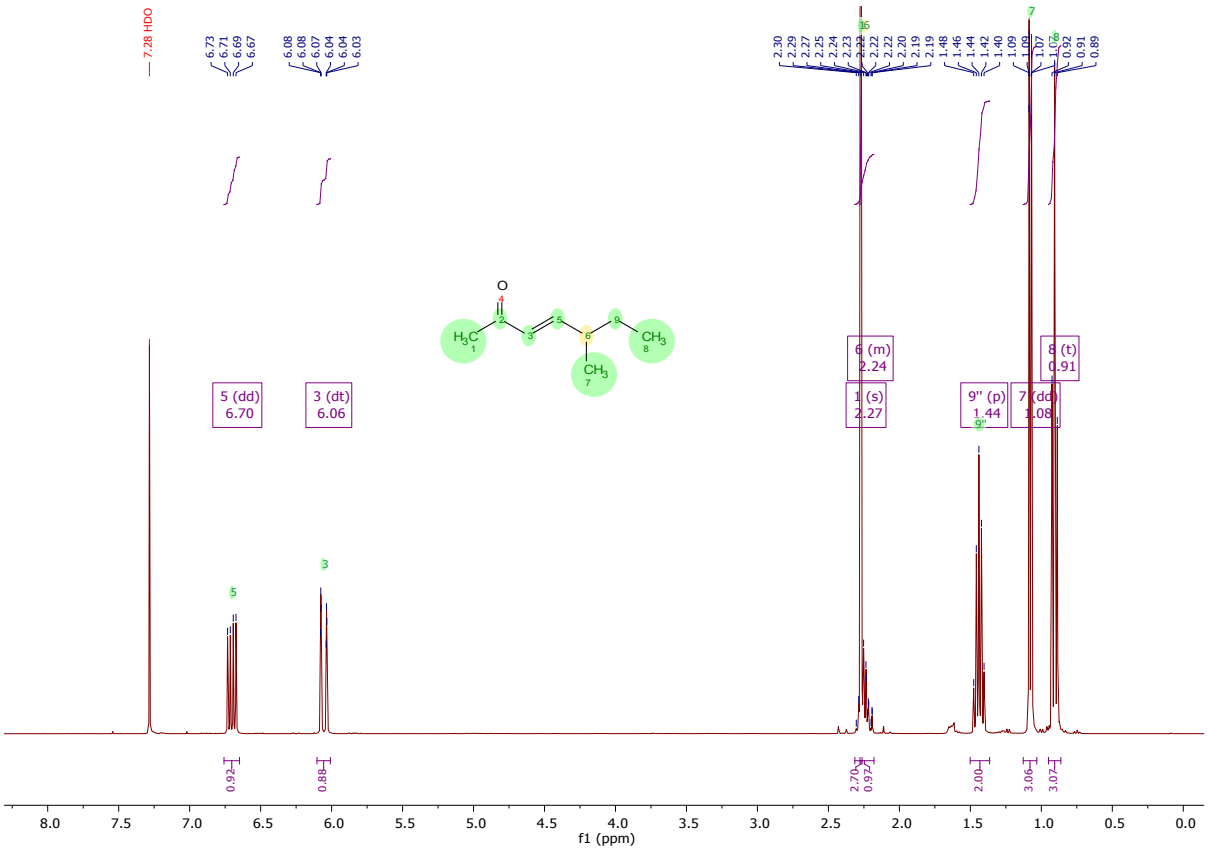
The crude mixture was treated as described above and was purified by flash column chromatography (Hexane:EtOAc, 90:10, SiO_2) to afford (E)-5-methylhept-3-en-2-one (514.3 mg, 4.075 mmol, 58%) as a pale yellow oil.

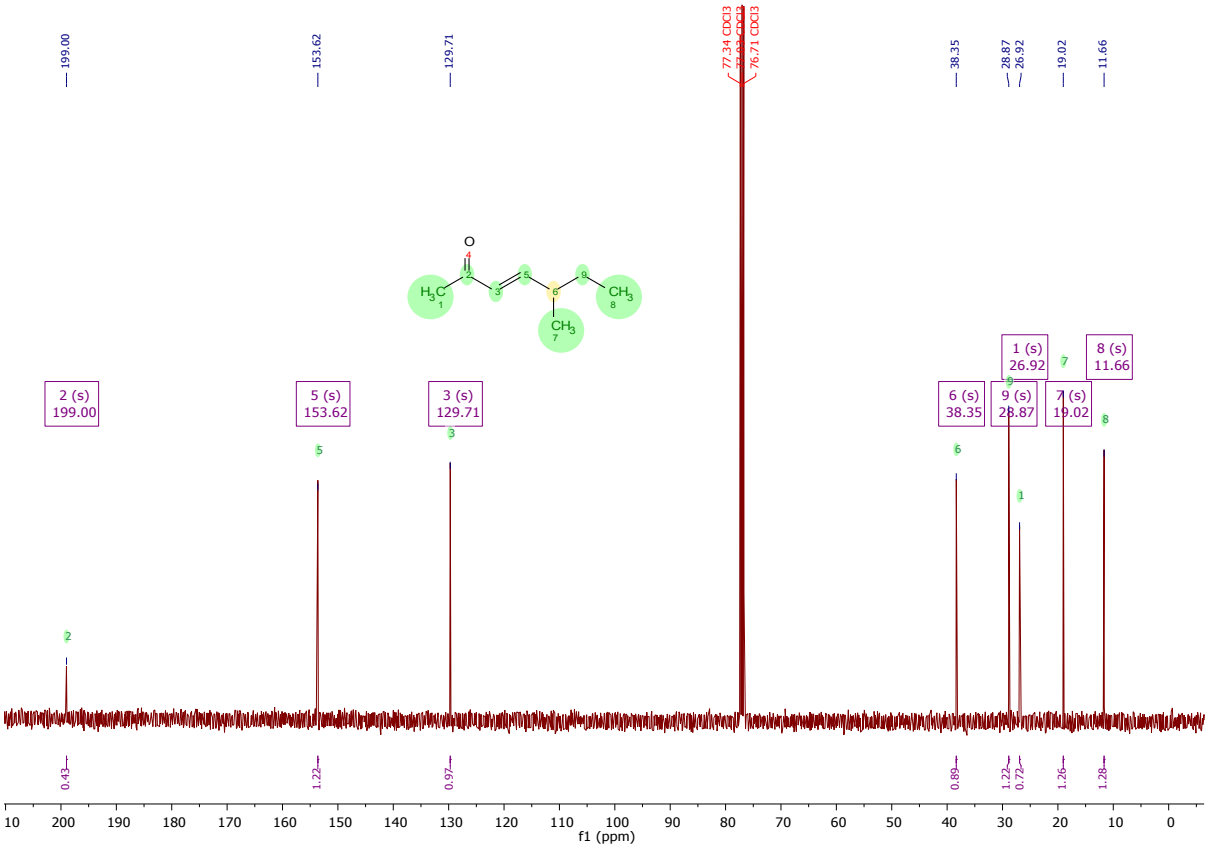
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.70 (dd, *J* = 16.0, 7.7 Hz, 1H), 6.06 (dt, *J* = 16.0, 0.9 Hz, 1H), 2.27 (s, 3H), 2.31 – 2.18 (m, 1H), 1.44 (p, *J* = 7.3 Hz, 2H), 1.08 (dd, *J* = 6.7, 0.6 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.0, 153.6, 129.7, 38.3, 28.9, 26.9, 19.0, 11.7.

IR υ_{max} (film): 2980, 1548, 1462, 1381, 1251, 1151, 1074.

HRMS (APCI) *m/z* calcd for $C_8H_{15}O$ $[M+H]^+$: 127.1117, found 127.1117.

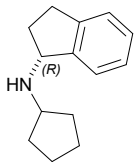

7.28 HDO
6.73
6.71
6.69
6.67
6.08
6.08
6.07
6.04
6.04
6.03
2.30
2.29
2.27
2.25
2.24
2.23
2.22
2.22
2.20
2.19
1.48
1.46
1.44
1.42
1.40
1.09
1.09
1.07
0.92
0.91
0.89
5 (dd) 6.70
3 (dt) 6.06
6 (m) 2.24
1 (s) 2.27
9'' (p) 1.44
7 (dd) 1.08
8 (t) 0.91
0.92
0.88
2.70
0.92
2.00
3.06
3.07
f1 (ppm)


199.00
153.62
129.71
77.34 CDCl3
76.71 CDCl3
38.35
28.87
26.92
19.02
11.66
2 (s) 199.00
5 (s) 153.62
3 (s) 129.71
1 (s) 26.92
8 (s) 11.66
6 (s) 38.35
9 (s) 28.87
7 (s) 19.02
0.43
1.22
0.97
0.89
1.22
0.72
1.26
1.28
f1 (ppm)

3. Amines

Note: All the amines were put under high-vacuum for at least 5 h, even though some retained solvent due to their viscosity.

(R)-N-cyclopentyl-2,3-dihydro-1H-inden-1-amine



General Procedure D: cyclopentanone (0.10 mL, 1.091 mmol, 1.4 eq), (R)-2,3-dihydro-1H-inden-1-amine (0.1 mL, 0.779 mmol, 1.0 eq), dry THF (10 mL), $NaB(OAc)_3H$ (264.3 mg, 1.247 mmol, 1.6 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (CH_2Cl_2:Hexane, 70:30, SiO_2) to afford (R)-N-cyclopentyl-2,3-dihydro-1H-inden-1-amine (46.8 mg, 0.234 mmol, 30%) as a pale yellow oil.

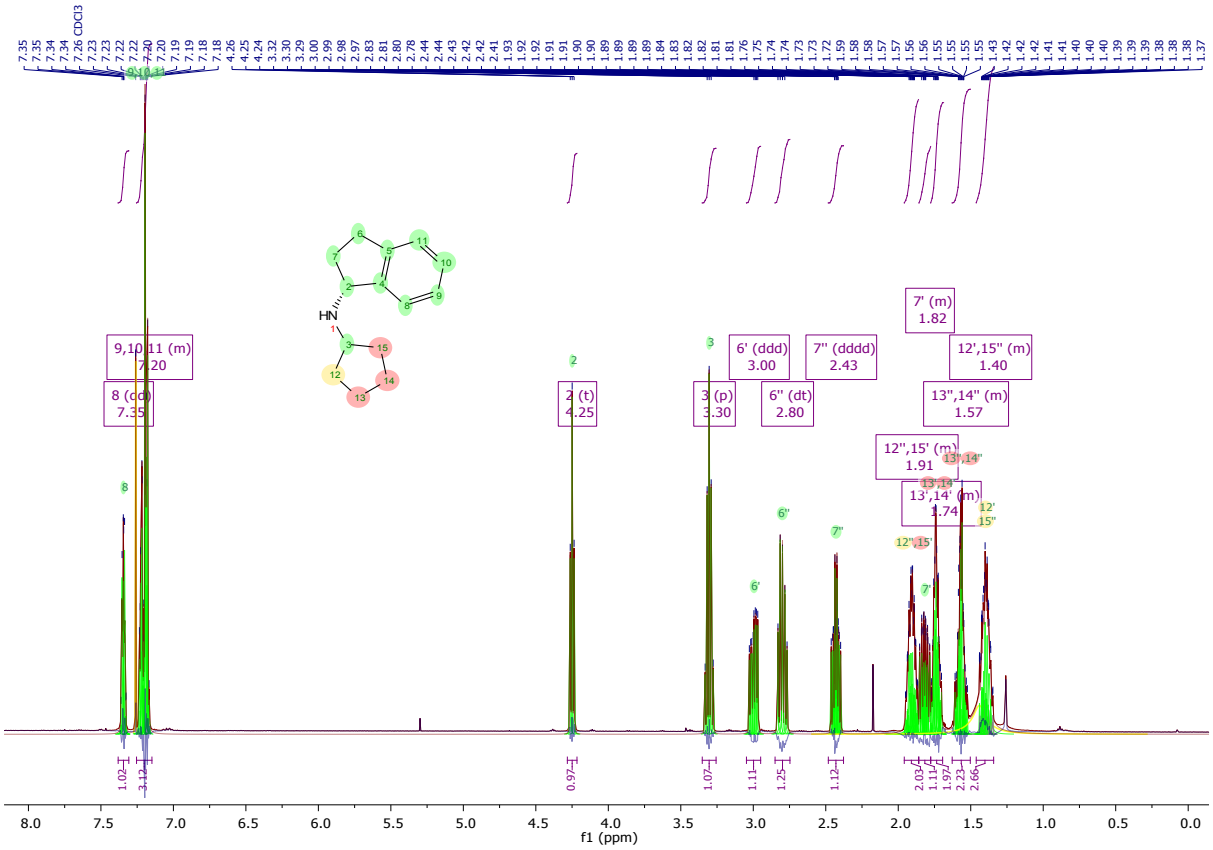
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.35 (dd, *J* = 4.9, 3.7 Hz, 1H), 7.25 – 7.15 (m, 3H), 4.25 (t, *J* = 6.6 Hz, 1H), 3.30 (p, *J* = 6.9 Hz, 1H), 3.00 (ddd, *J* = 15.9, 8.5, 4.7 Hz, 1H), 2.80 (dt, *J* = 15.9, 7.8 Hz, 1H), 2.43 (dddd, *J* = 12.8, 8.5, 6.6, 4.7 Hz, 1H), 1.96 – 1.86 (m, 2H), 1.86 – 1.78 (m, 1H), 1.78 – 1.69 (m, 2H), 1.63 – 1.50 (m, 2H), 1.46 – 1.34 (m, 2H).

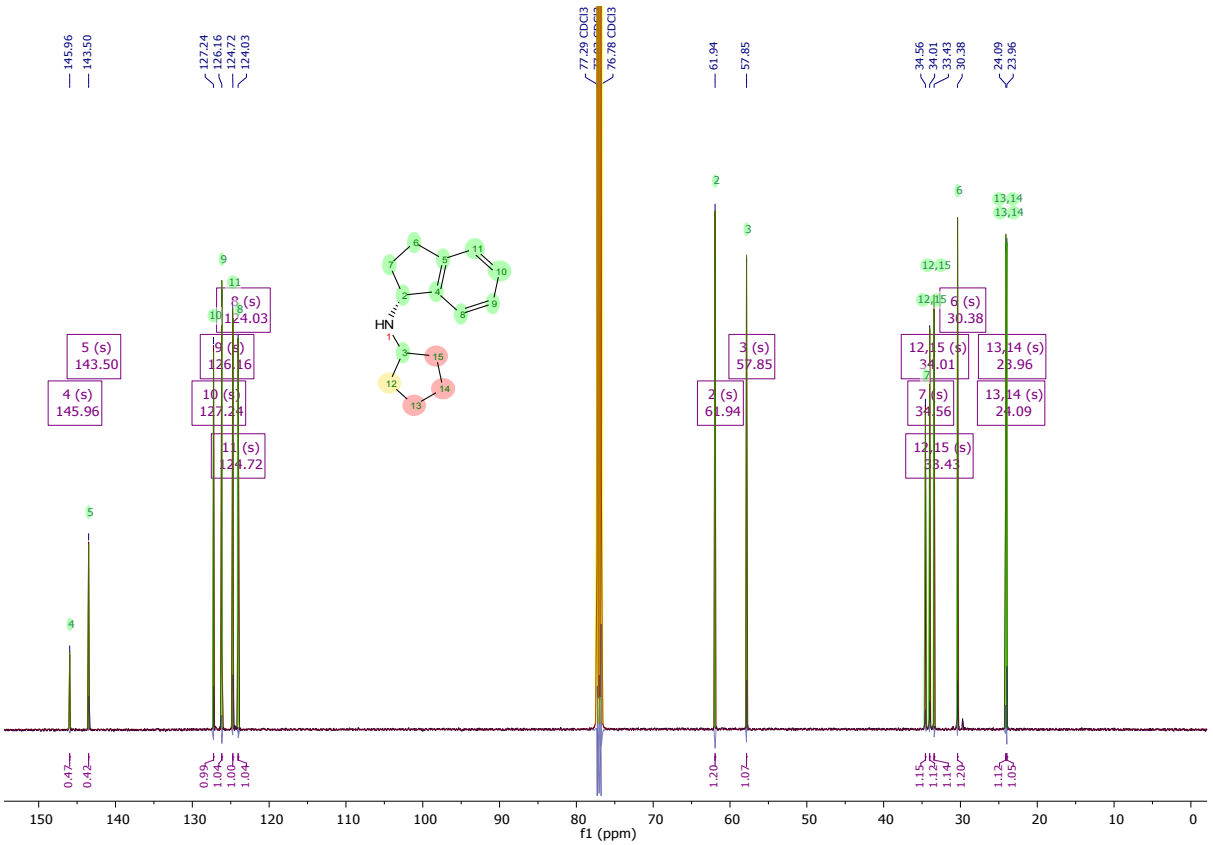
^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.0, 143.5, 127.2, 126.2, 124.7, 124.0, 61.9, 57.8, 34.6, 34.0, 33.4, 30.4, 24.1, 24.0.

IR υ_{max} (film): 2950, 2860, 1456, 1354, 1153, 1126.

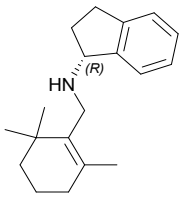
HRMS (EI^+) *m/z* calcd for C_{14} H_{20} N $[M+H]^+$: 202.1590, found 202.1591.

$[\alpha]^{25}_{589}$= -19.1 (*c* 1.2, $CHCl_3$) for 99% ee.


9,10,11 (m)
7.20
8 (dd)
7.35
2 (t)
4.25
3 (p)
3.30
6' (ddd)
3.00
6'' (dt)
2.80
7'' (dddd)
2.43
7' (m)
1.82
12',15'' (m)
1.40
13'',14'' (m)
1.57
12'',15' (m)
1.91
13',14' (m)
1.74
f1 (ppm)


5 (s)
143.50
4 (s)
145.96
9 (s)
126.16
10 (s)
127.24
11 (s)
124.72
8 (s)
124.03
3 (s)
57.85
2 (s)
61.94
6 (s)
30.38
12,15 (s)
34.01
7 (s)
34.56
12,15 (s)
33.43
13,14 (s)
23.96
13,14 (s)
24.09
f1 (ppm)

(R)-N-((2,6,6-trimethylcyclohex-1-en-1-yl)methyl)-2,3-dihydro-1H-inden-1-amine



General Procedure D: 2,6,6-trimethylcyclohex-1-ene-1-carbaldehyde (0.15 mL, 0.935 mmol, 1.2 eq), (R)-2,3-dihydro-1H-inden-1-amine (0.1 mL, 0.779 mmol, 1.0 eq), THF (10 mL), $NaB(OAc)_3H$ (264.3 mg, 1.247 mmol, 1.6 eq)

The crude mixture was treated as described above and was purified by flash column chromatography (CH_2Cl_2:Hexane, 70:30, SiO_2) then filtered through a strong cation exchange column ISOLUTE® SCX-2 with MeOH to wash off non-basic component followed by ammonia solution in MeOH (2 M) to afford (R)-N-((2,6,6-trimethylcyclohex-1-en-1-yl)methyl)-2,3-dihydro-1H-inden-1-amine (203 mg, 0.748 mmol, 96%) as a pale yellow oil.

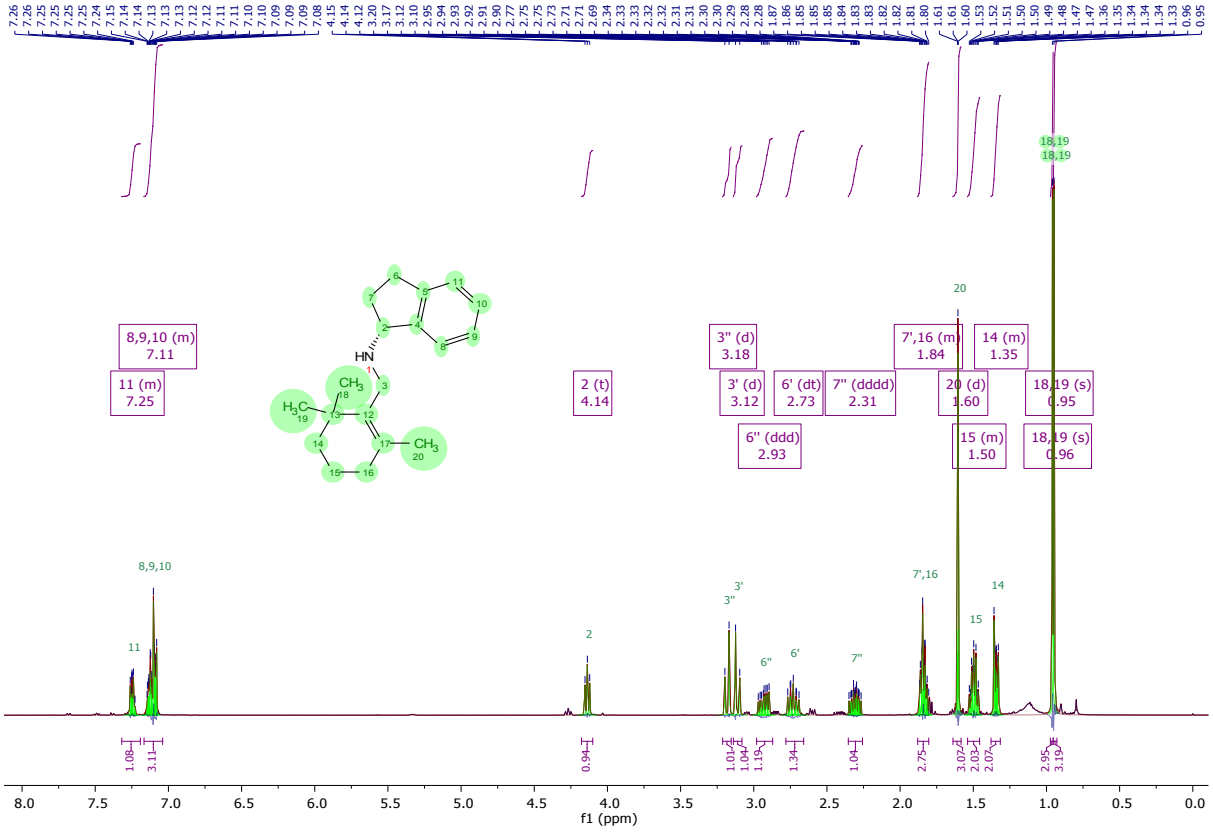
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.19 (m, 1H), 7.17 – 7.04 (m, 3H), 4.14 (t, *J* = 6.4 Hz, 1H), 3.18 (d, *J* = 11.4 Hz, 1H), 3.12 (d, *J* = 11.4 Hz, 1H), 2.93 (ddd, *J* = 15.9, 8.5, 5.1 Hz, 1H), 2.73 (dt, *J* = 15.9, 8.5, 6.8 Hz, 1H), 2.31 (dddd, *J* = 12.3, 8.5, 6.8, 5.1 Hz, 1H), 1.88 – 1.80 (m, 3H), 1.60 (d, *J* = 0.9 Hz, 3H), 1.54 – 1.46 (m, 2H), 1.38 – 1.32 (m, 2H), 0.96 (s, 3H), 0.95 (s, 3H).

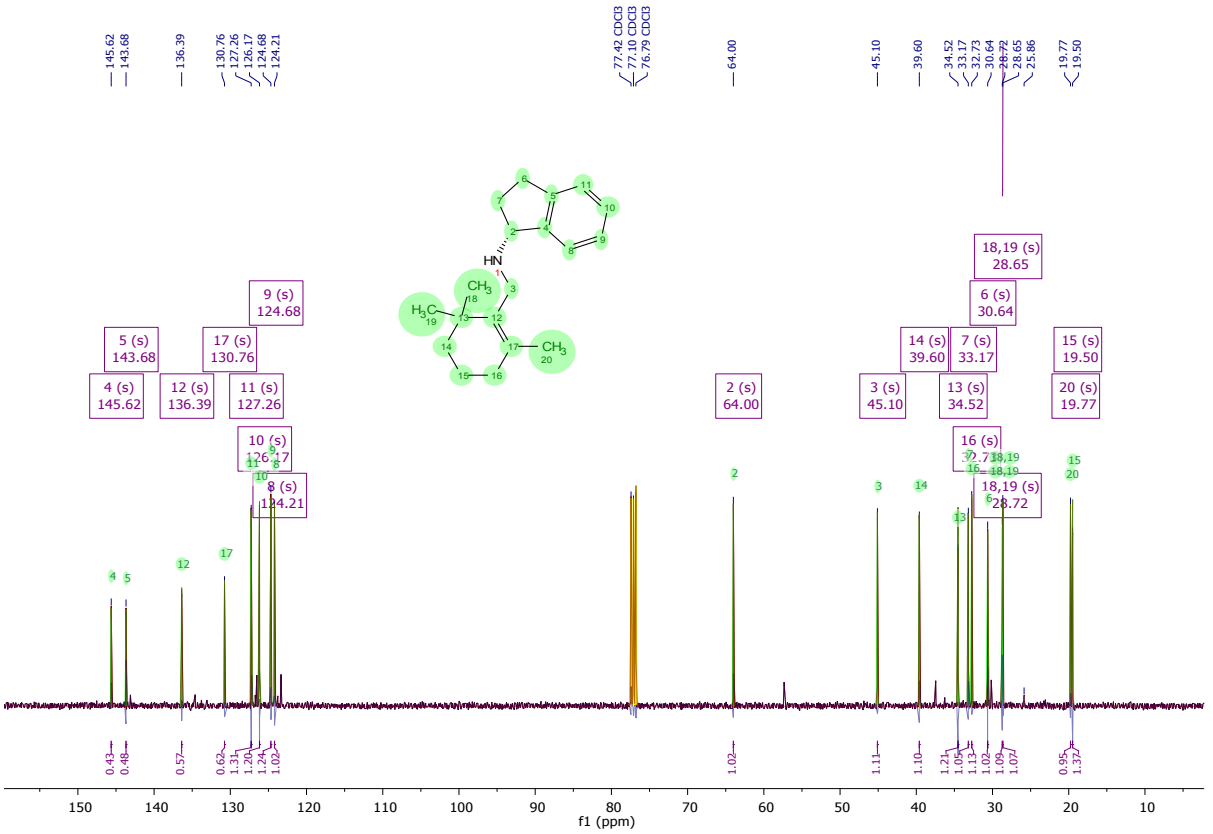
^{13}C NMR (101 MHz, Chloroform-*d*) δ 145.6, 143.7, 136.4, 130.8, 127.3, 126.2, 124.7, 124.2, 64.0, 45.1, 39.6, 34.5, 33.2, 32.7, 30.6, 28.7, 28.6, 19.8, 19.5.

IR υ_{max} (film): 3021, 2926, 2846, 1477, 1457, 1358.

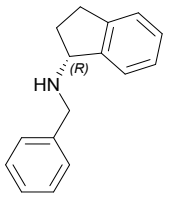
HRMS (EI^+) *m/z* calcd for $C_{19}H_{28}N$ $[M+H]^+$: 270.2216, found 270.2214.

$[\alpha]^{25}_{589}$= -1.4 (*c* 1.0, $CHCl_3$) for 99% ee.


8,9,10 (m)
7.11
11 (m)
7.25
2 (t)
4.14
3" (d)
3.18
3' (d)
3.12
6' (dt)
2.73
7" (dddd)
2.31
6'' (ddd)
2.93
7',16 (m)
1.84
20 (d)
1.60
14 (m)
1.35
15 (m)
1.50
18,19 (s)
0.95
18,19 (s)
0.96
f1 (ppm)


9 (s)
124.68
5 (s)
143.68
17 (s)
130.76
4 (s)
145.62
12 (s)
136.39
11 (s)
127.26
10 (s)
8 (s)
2 (s)
64.00
3 (s)
45.10
14 (s)
39.60
7 (s)
33.17
13 (s)
34.52
16 (s)
18,19 (s)
28.65
6 (s)
30.64
18,19 (s)
28.72
15 (s)
19.50
20 (s)
19.77
f1 (ppm)

(R)-N-benzyl-2,3-dihydro-1H-inden-1-amine



General Procedure D: benzaldehyde (0.40 mL, 3.897 mmol, 1.0 eq), (R)-2,3-dihydro-1H-inden-1-amine (0.5 mL, 3.897 mmol, 1.0 eq), THF (20 mL), $NaB(OAc)_3H$ (991 mg, 4.676 mmol, 1.2 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (CH_2Cl_2:Hexane, 70:30, SiO_2) to afford (R)-N-benzyl-2,3-dihydro-1H-inden-1-amine (740 mg, 3.3124 mmol, 85%) as a pale yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 – 7.33 (m, 4H), 7.32 – 7.17 (m, 2H), 4.33 (t, *J* = 6.7 Hz, 1H), 4.04 – 3.87 (m, 2H), 3.05 (ddd, *J* = 15.9, 8.5, 4.6 Hz, 1H), 2.85 (dt, *J* = 15.8, 7.8 Hz, 1H), 2.47 (dddd, *J* = 12.7, 8.2, 7.0, 4.6 Hz, 1H), 1.91 (dddd, *J* = 12.5, 8.4, 7.3, 6.2 Hz, 1H).

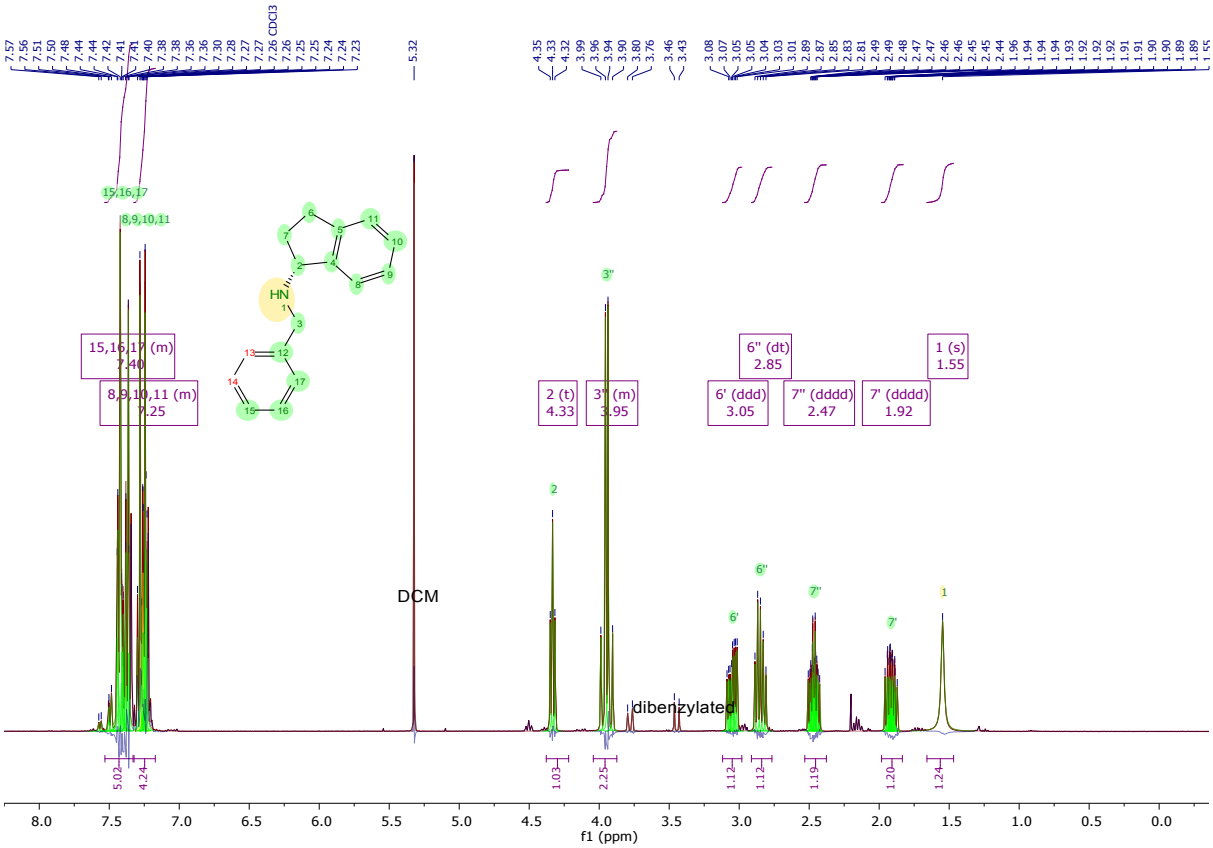
^{13}C NMR (101 MHz, Chloroform-*d*) δ 145.4, 143.7, 140.8, 128.4 (2 C), 128.1 (2 C), 127.4, 126.9, 126.2, 124.8, 124.1, 62.8, 51.4, 33.7, 30.4.

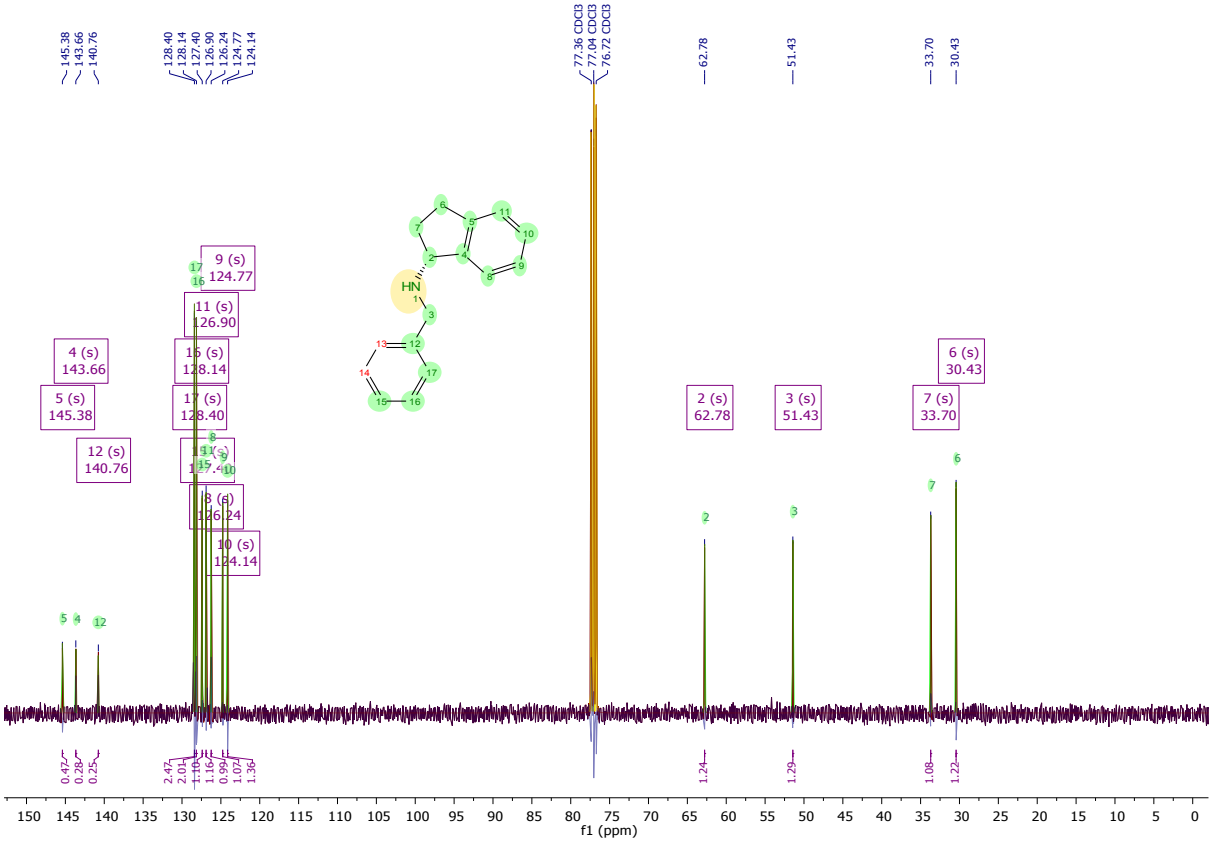
IR υ_{max} (film): 3024, 2938, 2846, 1453.

HRMS (EI^+) *m/z* calcd for $C_{16}H_{18}N$ $[M+H]^+$: 224.1439, found 224.1433.

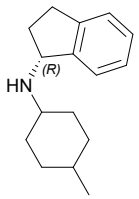
$[\alpha]^{25}_{589}$= -1.7 (*c* 1.7, $CHCl_3$) for 99% ee.

Analytical data are in agreement with the literature.[11]


15,16,17 (m)
7.40
8,9,10,11 (m)
7.25
2 (t)
4.33
3" (m)
3.95
6" (dt)
2.85
6' (ddd)
3.05
7" (dddd)
2.47
7' (dddd)
1.92
1 (s)
1.55
DCM
dibenzylated
f1 (ppm)


9 (s)
124.77
11 (s)
126.90
16 (s)
128.14
17 (s)
128.40
4 (s)
143.66
5 (s)
145.38
12 (s)
140.76
10 (s)
124.14
2 (s)
62.78
3 (s)
51.43
7 (s)
33.70
6 (s)
30.43
f1 (ppm)

(R)-N-(4-methylcyclohexyl)-2,3-dihydro-1H-inden-1-amine



General Procedure D: 4-methylcyclohexan-1-one (0.48 mL, 3.897 mmol, 1.0 eq), (R)-2,3-dihydro-1H-inden-1-amine (0.5 mL, 3.897 mmol, 1.0 eq), dry THF (15 mL), $NaB(OAc)_3H$ (908 mg, 4.286 mmol, 1.1 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (CH_2Cl_2:Hexane, 70:30, SiO_2) to afford (R)-N-(4-methylcyclohexyl)-2,3-dihydro-1H-inden-1-amine (104 mg, 0.4676 mmol, 12%) as a pale yellow oil.

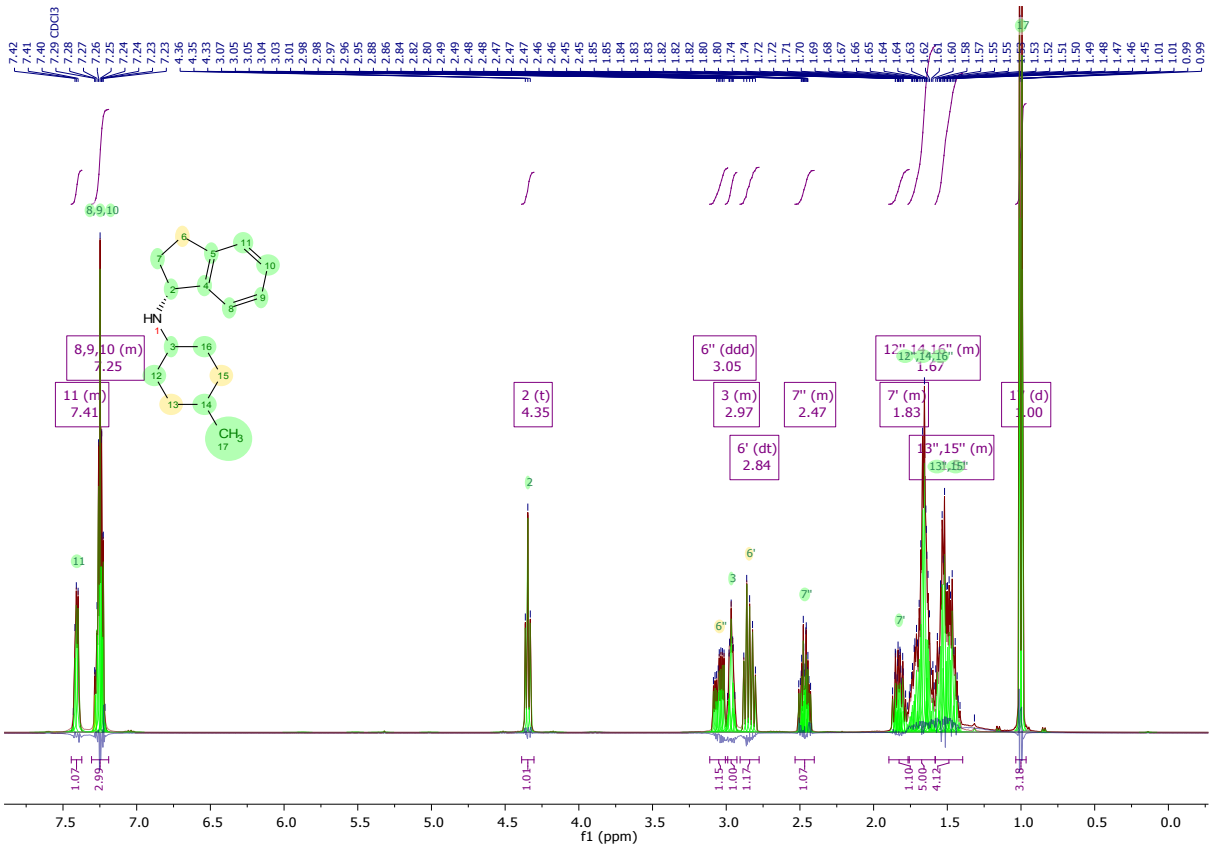
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.37 (m, 1H), 7.31 – 7.19 (m, 3H), 4.35 (t, *J* = 6.7 Hz, 1H), 3.05 (ddd, *J* = 15.8, 8.6, 4.4 Hz, 1H), 3.01 – 2.93 (m, 1H), 2.84 (dt, *J* = 15.8, 7.9 Hz, 1H), 2.53 – 2.40 (m, 1H), 1.90 – 1.76 (m, 1H), 1.77 – 1.58 (m, 5H), 1.58 – 1.40 (m, 4H), 1.00 (d, *J* = 6.7 Hz, 3H).

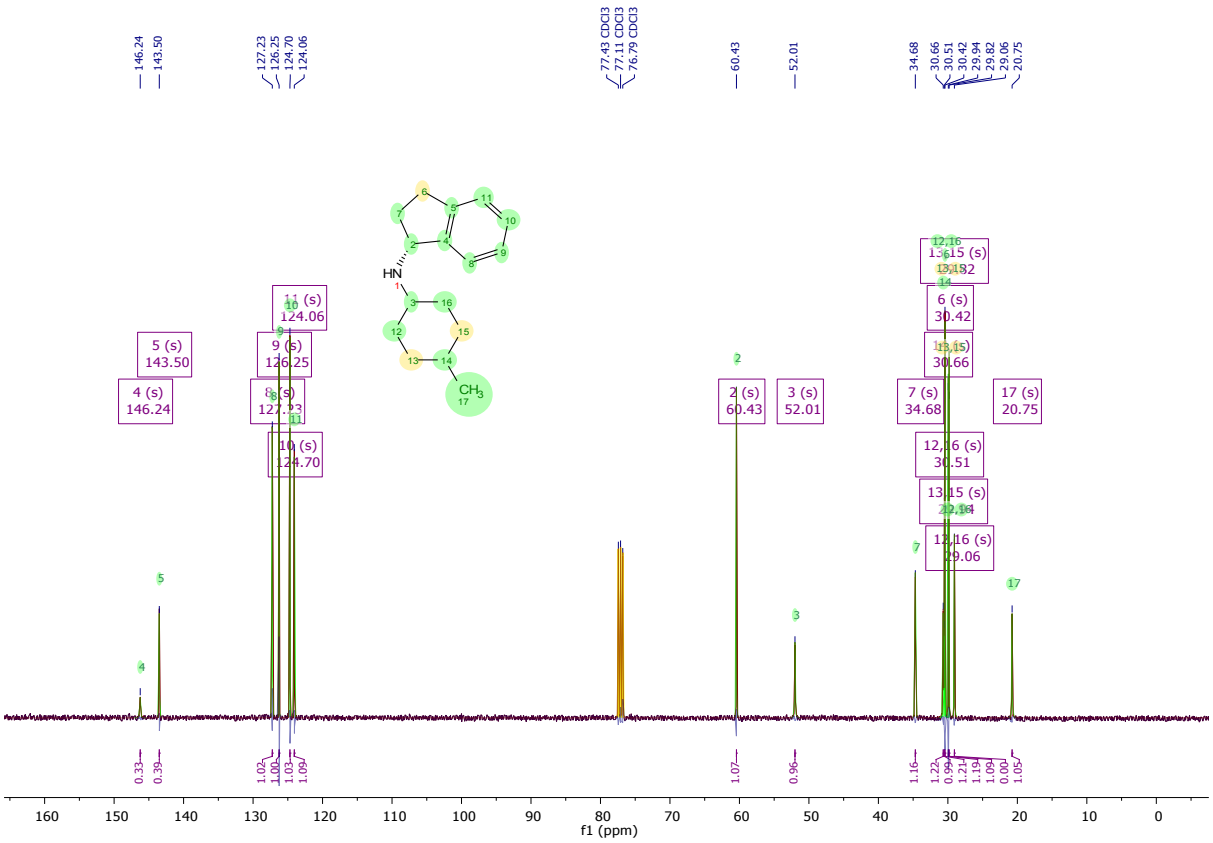
^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.2, 143.5, 127.2, 126.2, 124.7, 124.1, 60.4, 52.0, 34.7, 30.7, 30.5, 30.4, 29.9, 29.8, 29.1, 20.7.

IR υ_{max} (film): 2948, 2847, 2360, 2326, 1455.

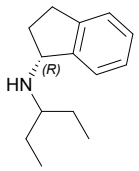
HRMS (EI^+) *m/z* calcd for $C_{16}H_{24}N$ $[M+H]^+$: 230.1903, found 230.1902.

$[\alpha]^{25}_{589}$ = -10.2 (*c* 1.5, $CHCl_3$) for 99% ee.


8,9,10 (m)
7.25
11 (m)
7.41
2 (t)
4.35
6'' (ddd)
3.05
3 (m)
2.97
6' (dt)
2.84
7'' (m)
2.47
7' (m)
1.83
13'',15'' (m)
1.67
17 (d)
1.00
f1 (ppm)


4 (s)
146.24
5 (s)
143.50
9 (s)
126.25
10 (s)
124.70
11 (s)
124.06
2 (s)
60.43
3 (s)
52.01
6 (s)
30.42
7 (s)
34.68
17 (s)
20.75
f1 (ppm)

(R)-N-(pentan-3-yl)-2,3-dihydro-1H-inden-1-amine



General Procedure D: pentan-3-one (0.62 mL, 5.845 mmol, 1.5 eq), (R)-2,3-dihydro-1H-inden-1-amine (0.5 mL, 3.897 mmol, 1.0 eq), THF (15 mL), $NaB(OAc)_3H$ (991 mg, 4.676 mmol, 1.2 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (CH_2Cl_2:Hexane, 70:30, SiO_2) to afford (R)-N-(pentan-3-yl)-2,3-dihydro-1H-inden-1-amine (639 mg, 3.156 mmol, 81%) as a pale yellow oil.

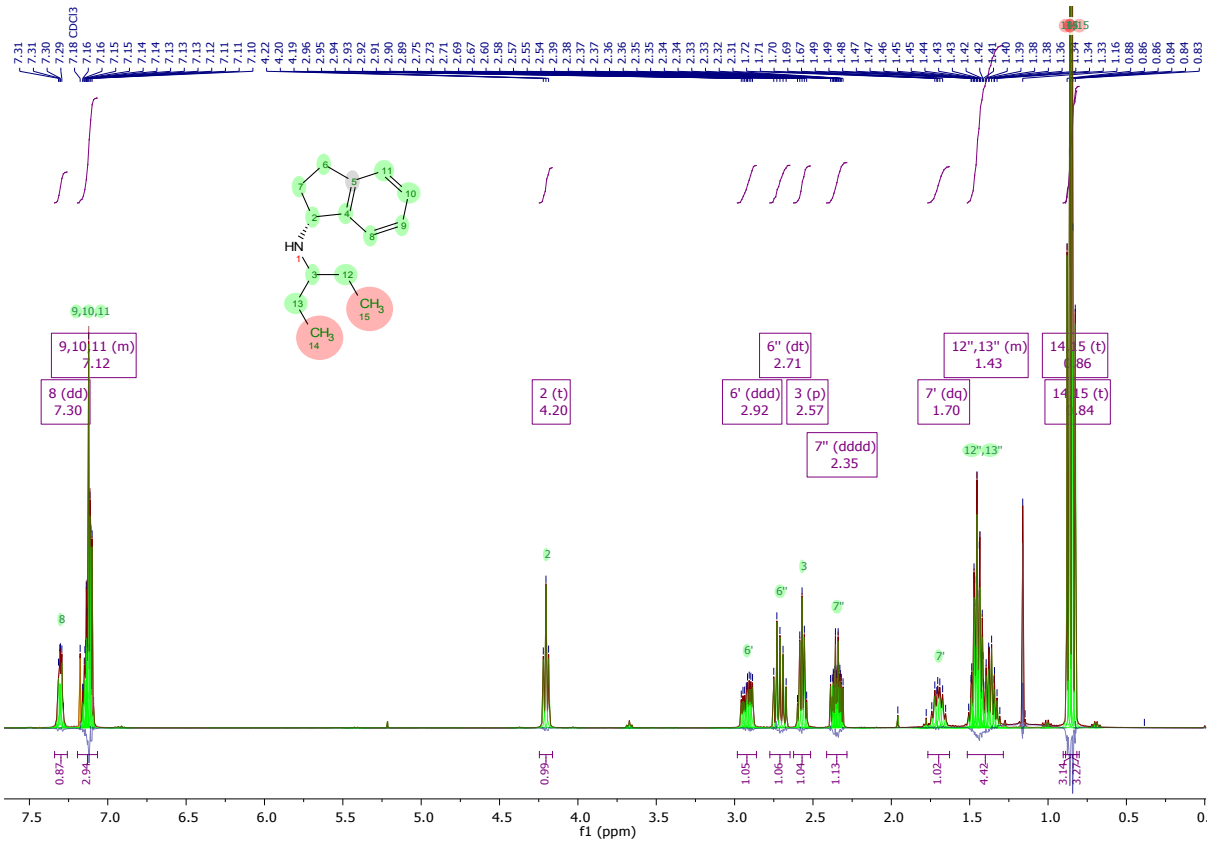
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (dd, *J* = 5.0, 3.5 Hz, 1H), 7.19 – 7.07 (m, 3H), 4.20 (t, *J* = 6.9 Hz, 1H), 2.92 (ddd, *J* = 15.8, 8.5, 4.4 Hz, 1H), 2.71 (dt, *J* = 15.8, 7.7 Hz, 1H), 2.57 (p, *J* = 5.8 Hz, 1H), 2.35 (dddd, *J* = 12.4, 8.5, 6.9, 4.4 Hz, 1H), 1.70 (dq, *J* = 12.4, 7.7 Hz, 1H), 1.52 – 1.29 (m, 4H), 0.86 (t, *J* = 7.5 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H).

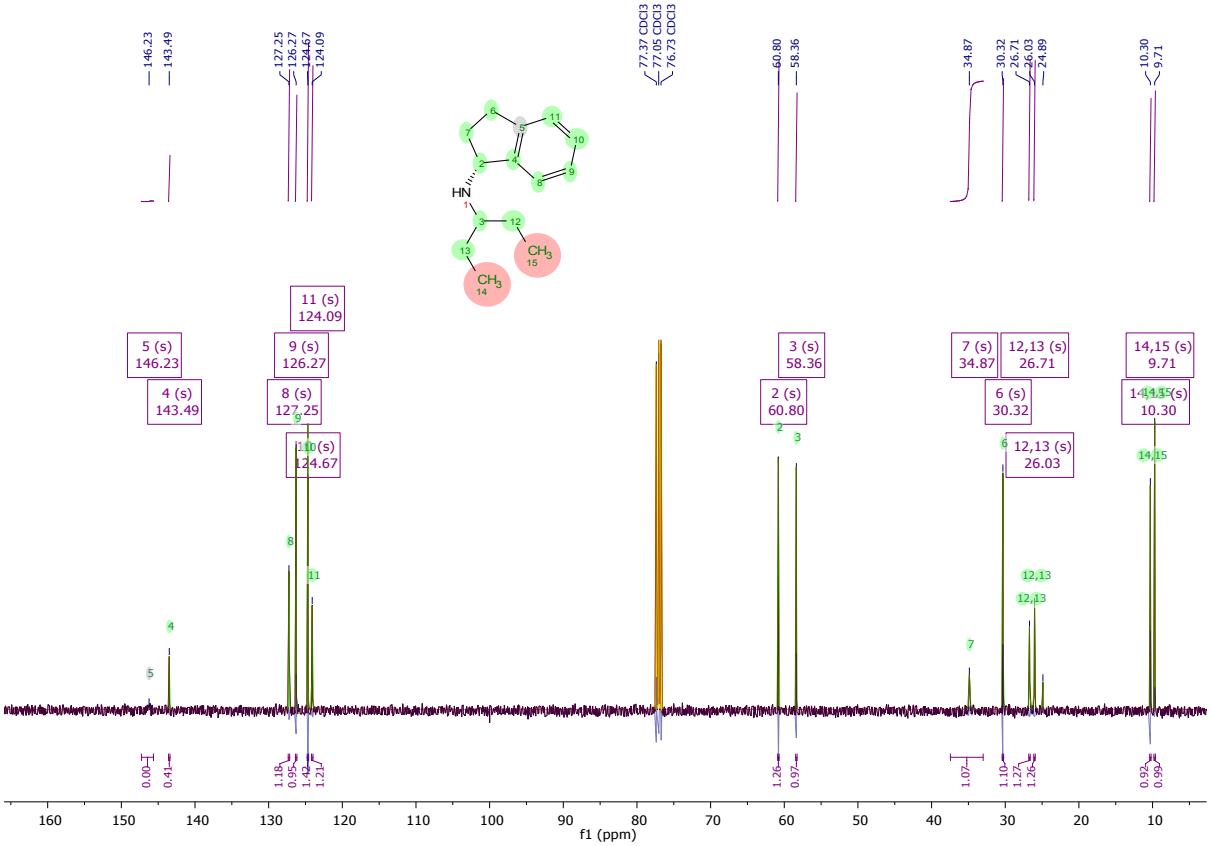
^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.2, 143.5, 127.2, 126.3, 124.7, 124.1, 60.8, 58.4, 34.9, 30.3, 26.7, 26.0, 10.3, 9.7.

IR υ_{max} (film): 2960, 2934, 2360, 2340, 1459.

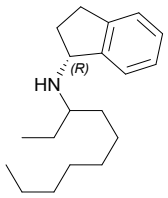
HRMS (EI^+) *m/z* calcd for C_{14} H_{22} N $[M+H]^+$: 204.1747, found 204.1748.

$[\alpha]^{25}_{589}$ = -35.4 (*c* 1.0, $CHCl_3$) for 99% ee.


9,10,11 (m)
7.12
8 (dd)
7.30
2 (t)
4.20
6'' (dt)
2.71
6' (ddd)
2.92
3 (p)
2.57
7'' (dddd)
2.35
12'',13'' (m)
1.43
7' (dq)
1.70
14,15 (t)
0.86
14,15 (t)
0.84
f1 (ppm)


5 (s)
146.23
4 (s)
143.49
11 (s)
124.09
9 (s)
126.27
8 (s)
127.25
10 (s)
124.67
3 (s)
58.36
2 (s)
60.80
7 (s)
34.87
12,13 (s)
26.71
6 (s)
30.32
12,13 (s)
26.03
14,15 (s)
9.71
14,15 (s)
10.30
f1 (ppm)

(1R)-N-(decan-3-yl)-2,3-dihydro-1H-inden-1-amine



General Procedure D: (R)-2,3-dihydro-1H-inden-1-aminium chloride (300 mg, 1.768 mmol, 1.0 eq), Decan-3-one (0.40 mL, 2.122 mmol, 1.2 eq), dry THF (15 mL), $NaB(OAc)_3H$ (599 mg, 2.829 mmol, 1.6 eq)

The crude mixture was treated as described above and was purified by flash column chromatography (CH_2Cl_2:Hexane, 70:30, SiO_2) to afford the mixture of diastereoisomers (1R)-N-(decan-3-yl)-2,3-dihydro-1H-inden-1-amine (350 mg, 1.273 mmol, 72%) as a pale yellow oil.

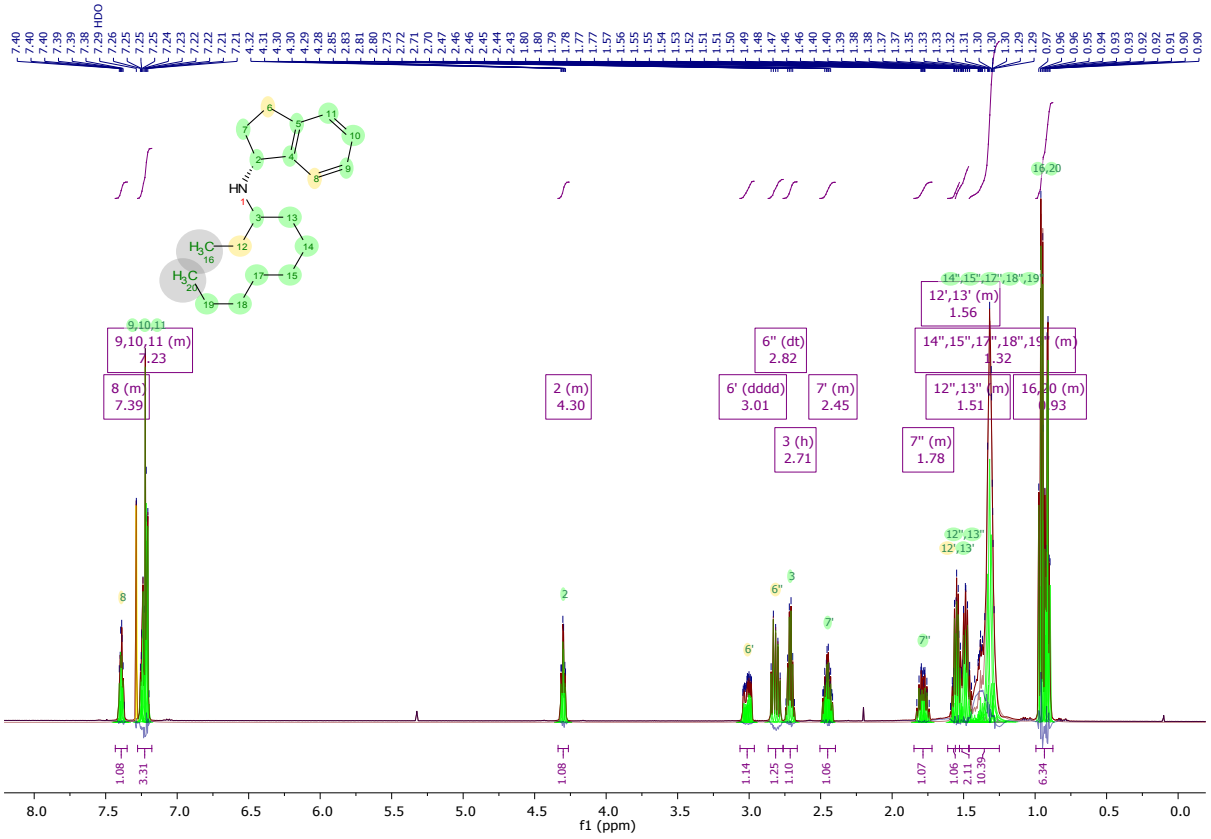
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 – 7.35 (m, 1H), 7.28 – 7.18 (m, 3H), 4.34 – 4.26 (m, 1H), 3.01 (dddd, *J* = 15.7, 8.6, 4.3, 1.4 Hz, 1H), 2.82 (dt, *J* = 15.8, 7.9 Hz, 1H), 2.71 (h, *J* = 5.8 Hz, 1H), 2.50 – 2.40 (m, 1H), 1.85 – 1.72 (m, 1H), 1.61 – 1.53 (m, 1H), 1.56 – 1.46 (m, 2H), 1.46 – 1.25 (m, 10H), 0.99 – 0.88 (m, 6H).

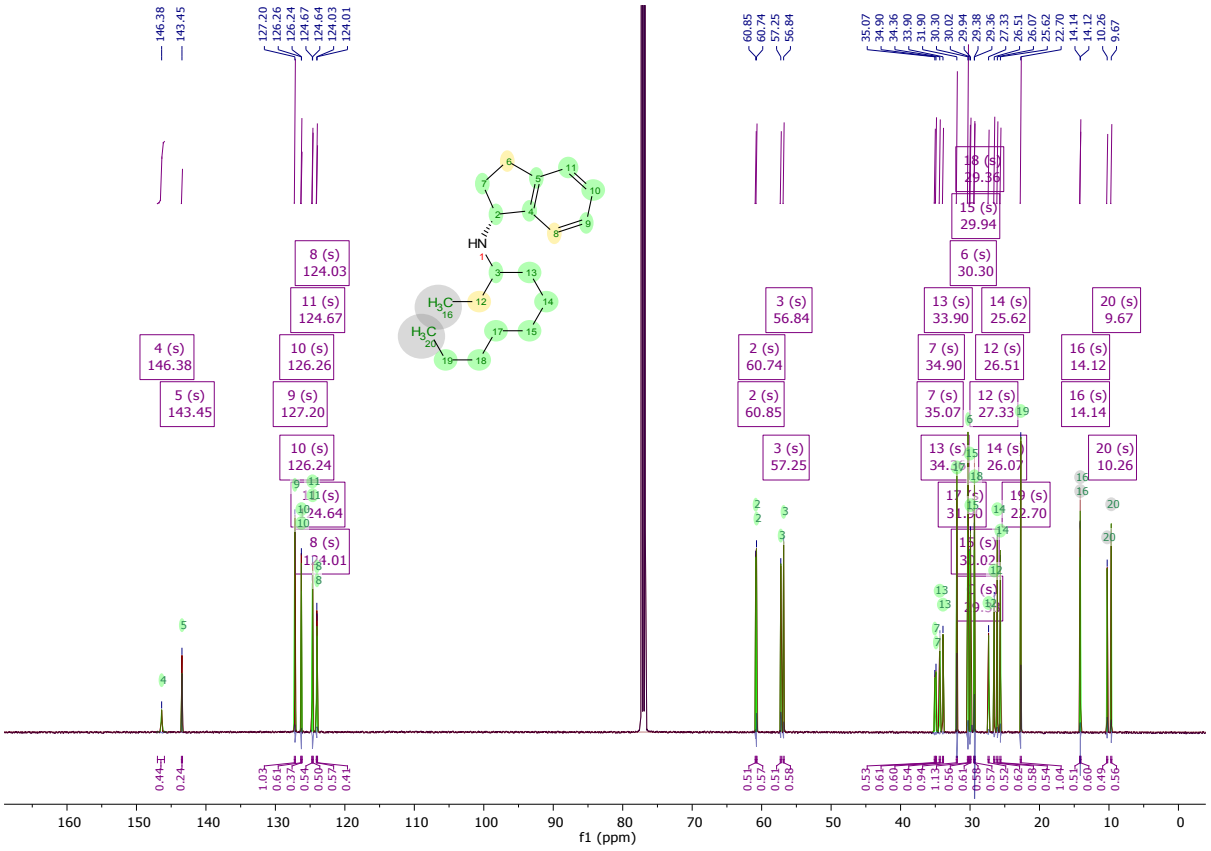
^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.4 (2 C), 143.4 (2 C), 127.2 (2 C), 126.3, 126.2, 124.7, 124.6, 124.0, 124.0, 60.8, 60.7, 57.2, 56.8, 35.1, 34.9, 34.4, 33.9, 31.9 (2 C), 30.3 (2 C), 30.0, 29.9, 29.4, 29.4, 27.3, 26.5, 26.1, 25.6, 22.7 (2 C), 14.1, 14.1, 10.3, 9.7.

IR υ_{max} (film): 2924, 2359, 1434, 1320, 1020.

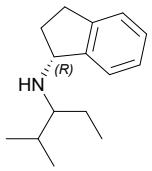
HRMS (EI^+) *m/z* calcd for $C_{19}H_{32}N$ $[M+H]^+$: 274.2529, found 274.2528.

$[\alpha]^{25}_{589}$ = -15.4 (*c* 1.6, $CHCl_3$) for 99% ee.


9,10,11 (m)
7.23
8 (m)
7.39
2 (m)
4.30
6" (dt)
2.82
6' (dddd)
3.01
7' (m)
2.45
3 (h)
2.71
12',13' (m)
1.56
14",15",17",18",19" (m)
1.32
12",13" (m)
1.51
16,20 (m)
0.93
7" (m)
1.78
f1 (ppm)


8 (s)
124.03
11 (s)
124.67
4 (s)
146.38
10 (s)
126.26
5 (s)
143.45
9 (s)
127.20
10 (s)
126.24
3 (s)
56.84
2 (s)
60.74
2 (s)
60.85
3 (s)
57.25
13 (s)
33.90
14 (s)
25.62
7 (s)
34.90
12 (s)
26.51
7 (s)
35.07
12 (s)
27.33
20 (s)
9.67
16 (s)
14.12
16 (s)
14.14
14 (s)
26.07
19 (s)
22.70
6 (s)
30.30
15 (s)
29.94
f1 (ppm)

(1R)-N-(2-methylpentan-3-yl)-2,3-dihydro-1H-inden-1-amine



General Procedure D: (R)-2,3-dihydro-1H-inden-1-aminium chloride (300 mg, 1.768 mmol, 1.0 eq), 2-methylpentan-3-one (0.26 mL, 2.122 mmol, 1.2 eq), dry THF (15 mL), $NaB(OAc)_3H$ (599 mg, 2.829 mmol, 1.6 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (CH_2Cl_2:Hexane, 70:30, SiO_2) to afford the mixture of diastereoisomers (1R)-N-(2-methylpentan-3-yl)-2,3-dihydro-1H-inden-1-amine (234 mg, 1.078 mmol, 61%) as a pale yellow oil.

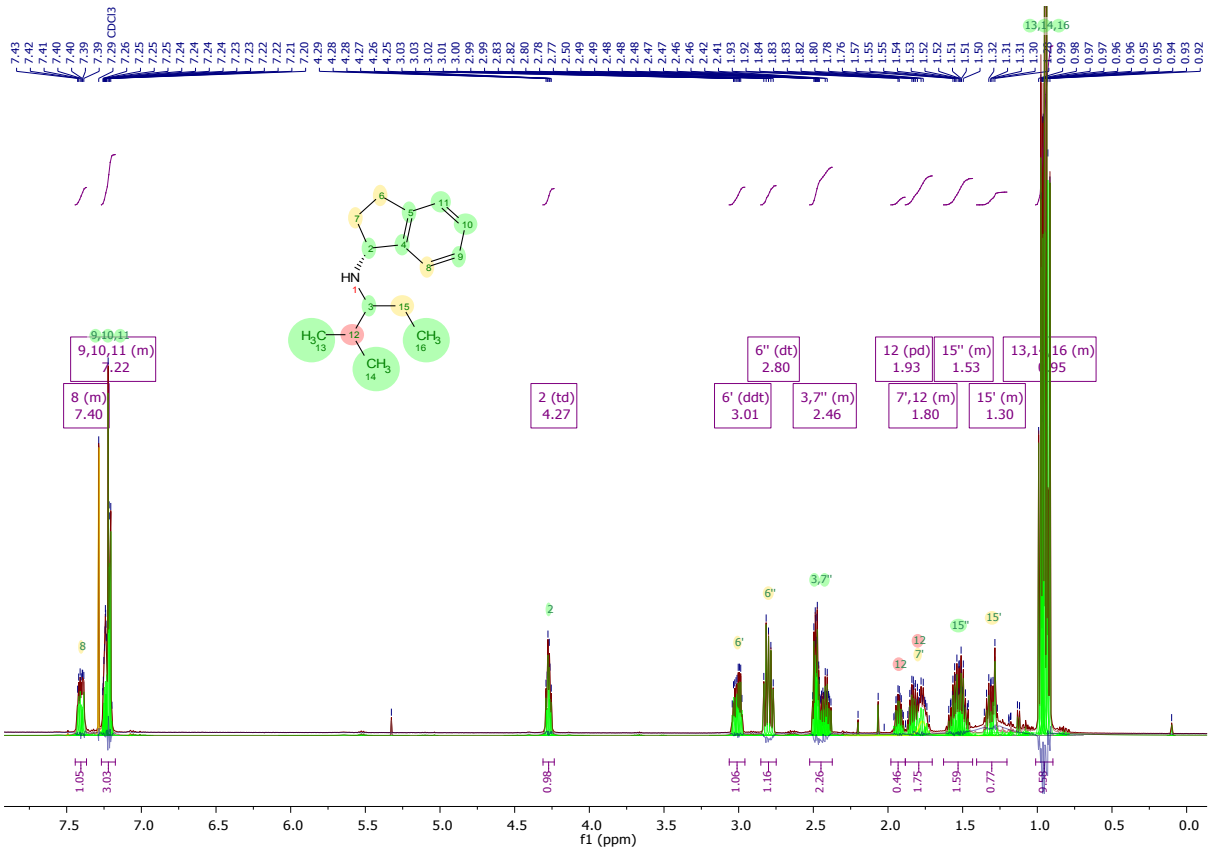
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.37 (m, 1H), 7.27 – 7.17 (m, 3H), 4.27 (td, *J* = 6.6, 4.2 Hz, 1H), 3.01 (ddt, *J* = 16.4, 8.3, 4.1 Hz, 1H), 2.80 (dt, *J* = 15.8, 7.9 Hz, 1H), 2.52 – 2.37 (m, 2H), 1.93 (pd, *J* = 6.9, 4.2 Hz, 1H), 1.88 – 1.70 (m, 2H), 1.63 – 1.43 (m, 1H), 1.41 – 1.20 (m, 1H), 1.01 – 0.90 (m, 9H).

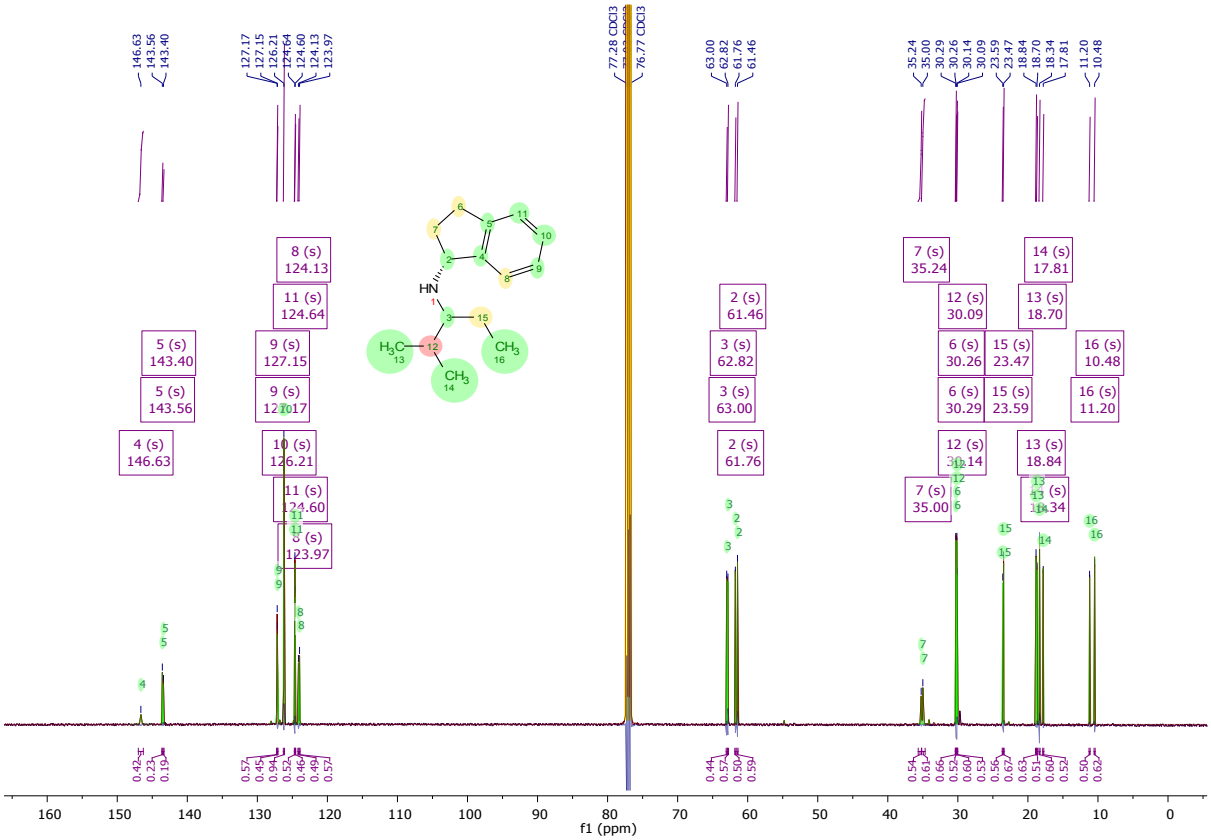
^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.6 (2 C), 143.6, 143.4, 127.2, 127.1, 126.2 (2 C), 124.6, 124.6, 124.1, 124.0, 63.0, 62.8, 61.8, 61.5, 35.2, 35.0, 30.3, 30.3, 30.1, 30.1, 23.6, 23.5, 18.8, 18.7, 18.3, 17.8, 11.2, 10.5.

IR υ_{max} (film): 2924, 2359, 1476, 1301, 1020.

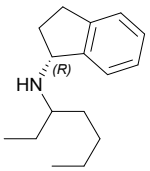
HRMS (EI^+) *m/z* calcd for $C_{15}H_{24}N$ $[M+H]^+$: 218.1903, found 218.1904.

$[\alpha]^{25}_{589}$ = -18.3 (*c* 1.4, $CHCl_3$) for 99% ee.


9,10,11 (m)
7.22
8 (m)
7.40
2 (td)
4.27
6'' (dt)
2.80
6' (ddt)
3.01
3,7'' (m)
2.46
12 (pd)
1.93
15'' (m)
1.53
7',12 (m)
1.80
15' (m)
1.30
f1 (ppm)


8 (s)
124.13
11 (s)
124.64
5 (s)
143.40
9 (s)
127.15
5 (s)
143.56
4 (s)
146.63
10 (s)
126.21
11 (s)
124.60
2 (s)
61.46
3 (s)
62.82
3 (s)
63.00
2 (s)
61.76
7 (s)
35.24
12 (s)
30.09
6 (s)
30.26
15 (s)
23.47
14 (s)
17.81
13 (s)
18.70
16 (s)
10.48
f1 (ppm)

(1R)-N-(heptan-3-yl)-2,3-dihydro-1H-inden-1-amine



General Procedure D: (R)-2,3-dihydro-1H-inden-1-aminium chloride (400 mg, 2.358 mmol, 1.0 eq), Heptan-3-one (0.39 mL, 2.829 mmol, 1.2 eq), dry THF (15 mL), $NaB(OAc)_3H$ (799 mg, 3.772 mmol, 1.6 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (CH_2Cl_2:Hexane, 70:30, SiO_2) to afford the mixture of diastereoisomers (1R)-N-(heptan-3-yl)-2,3-dihydro-1H-inden-1-amine (470 mg, 2.0279 mmol, 86%) as a pale yellow oil.

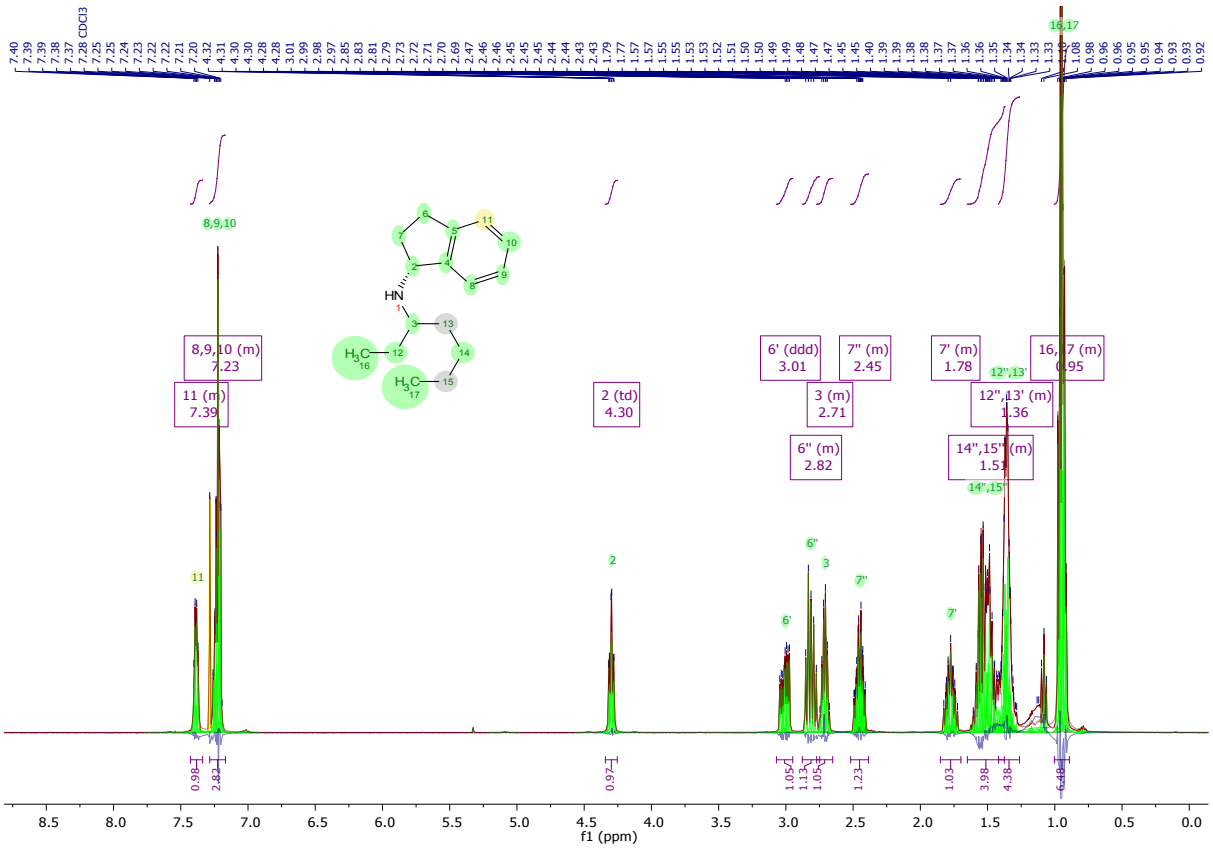
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.34 (m, 1H), 7.28 – 7.17 (m, 3H), 4.30 (td, *J* = 6.8, 1.9 Hz, 1H), 3.01 (ddd, *J* = 15.8, 8.5, 4.3 Hz, 1H), 2.88 – 2.75 (m, 1H), 2.77 – 2.65 (m, 1H), 2.52 – 2.39 (m, 1H), 1.85 – 1.70 (m, 1H), 1.65 – 1.38 (m, 4H), 1.42 – 1.26 (m, 4H), 1.00 – 0.89 (m, 6H).

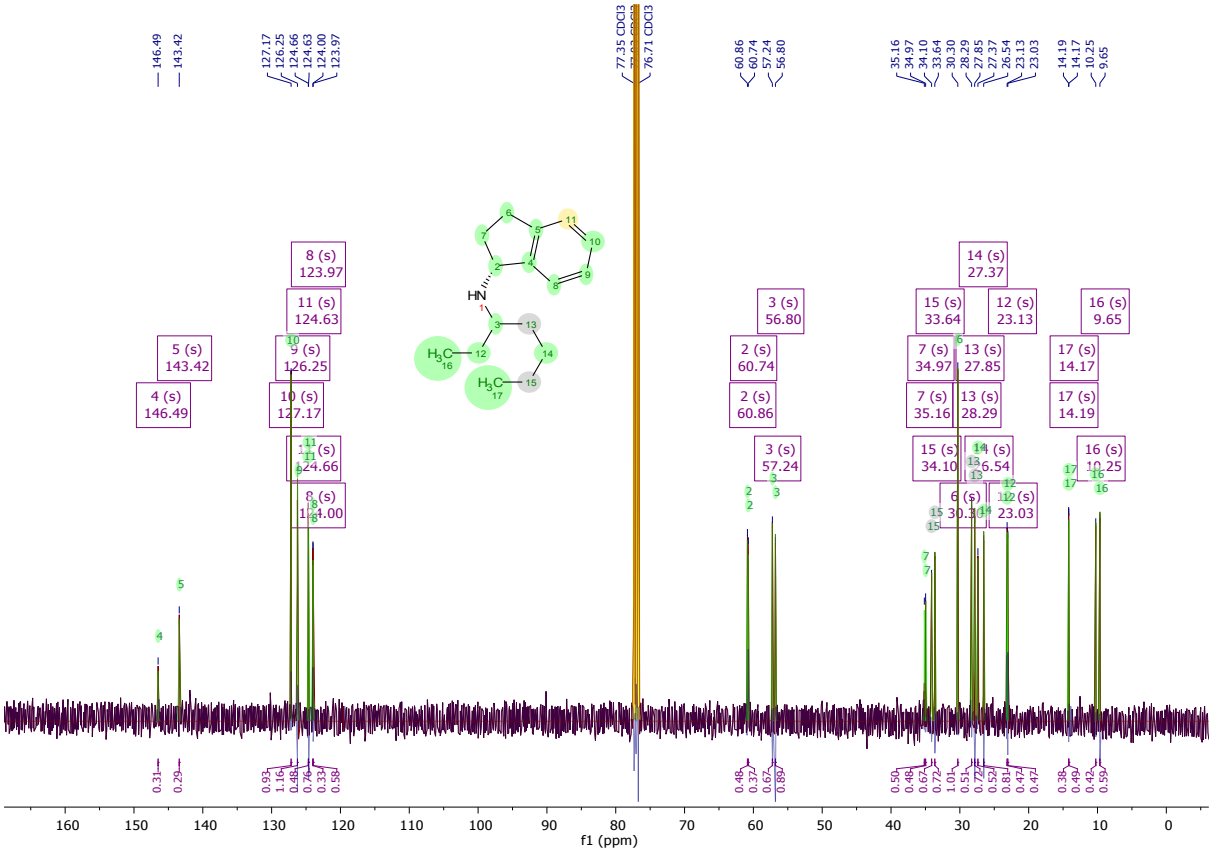
^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.5 (2 C), 143.4 (2 C), 127.2 (2 C), 126.2 (2 C), 124.7, 124.6, 124.0, 124.0, 60.9, 60.7, 57.2, 56.8, 35.2, 35.0, 34.1, 33.6, 30.3 (2 C), 28.3, 27.8, 27.4, 26.5, 23.1, 23.0, 14.2, 14.2, 10.2, 9.6.

IR υ_{max} (film): 2928, 2856, 2360, 1434.

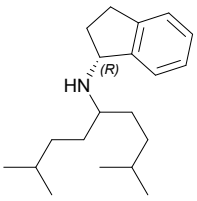
HRMS (EI^+) *m/z* calcd for $C_{16}H_{26}N$ $[M+H]^+$: 232.2060, found 232.2060.

$[\alpha]^{25}_{589}$ = -37.3 (*c* 1.0, $CHCl_3$) for 99% ee.


8,9,10 (m)
7.23
11 (m)
7.39
2 (td)
4.30
6' (ddd)
3.01
7'' (m)
2.45
3 (m)
2.71
6'' (m)
2.82
7' (m)
1.78
12'',13' (m)
1.36
14'',15'' (m)
1.51
16,17 (m)
0.95
f1 (ppm)


8 (s)
123.97
11 (s)
124.63
5 (s)
143.42
9 (s)
126.25
4 (s)
146.49
10 (s)
127.17
3 (s)
56.80
2 (s)
60.74
2 (s)
60.86
3 (s)
57.24
14 (s)
27.37
15 (s)
33.64
12 (s)
23.13
7 (s)
34.97
13 (s)
27.85
7 (s)
35.16
13 (s)
28.29
16 (s)
9.65
17 (s)
14.17
17 (s)
14.19
f1 (ppm)

(R)-N-(2,8-dimethylnonan-5-yl)-2,3-dihydro-1H-inden-1-amine



General Procedure D: (R)-2,3-dihydro-1H-inden-1-aminium chloride (500 mg, 2.947 mmol, 1.0 eq), 2,8-dimethyl-5-oxononan-1-ylium (602 mg, 3.537 mmol, 1.2 eq), dry THF (15 mL), $NaB(OAc)_3H$ (999 mg, 4.716 mmol, 1.6 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (CH_2Cl_2:Hexane, 70:30, SiO_2) to afford (R)-N-(2,8-dimethylnonan-5-yl)-2,3-dihydro-1H-inden-1-amine (557mg, 1.945 mmol, 66%) as a pale yellow oil.

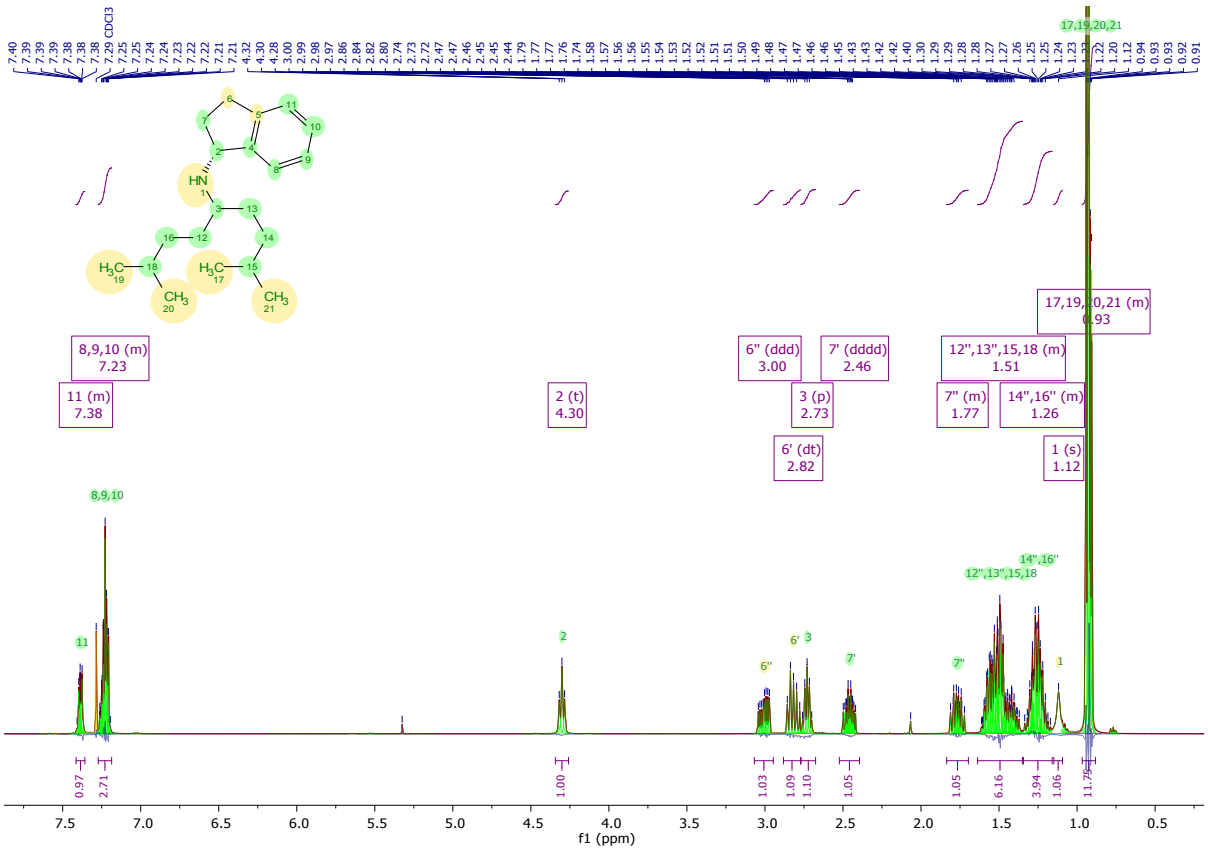
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.36 (m, 1H), 7.27 – 7.19 (m, 3H), 4.30 (t, *J* = 6.8 Hz, 1H), 3.00 (ddd, *J* = 15.8, 8.5, 4.1 Hz, 1H), 2.82 (dt, *J* = 15.9, 8.0 Hz, 1H), 2.73 (p, *J* = 5.8 Hz, 1H), 2.46 (dddd, *J* = 12.3, 8.0, 6.8, 4.1 Hz, 1H), 1.84 – 1.70 (m, 1H), 1.64 – 1.35 (m, 6H), 1.34 – 1.16 (m, 4H), 1.12 (s, 1H), 0.97 – 0.88 (m, 12H).

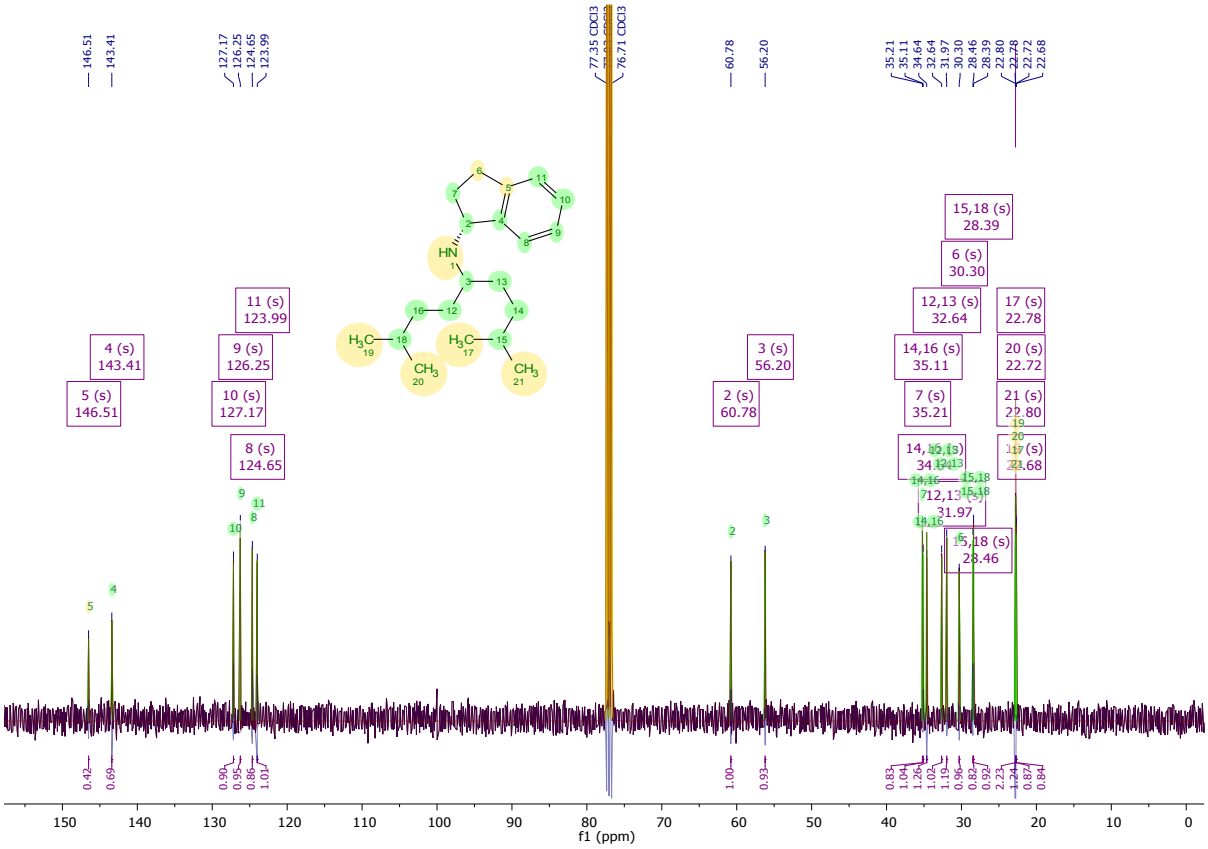
^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.5, 143.4, 127.2, 126.2, 124.6, 124.0, 60.8, 56.2, 35.2, 35.1, 34.6, 32.6, 32.0, 30.3, 28.5, 28.4, 22.8, 22.8, 22.7, 22.7.

IR υ_{max} (film): 2952, 2927, 2868, 1465.

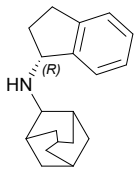
HRMS (EI^+) *m/z* calcd for $C_{20}H_{34}N$ $[M+H]^+$: 288.2686, found 288.2685.

$[\alpha]^{25}_{589}$ = -12.4 (*c* 2.3, $CHCl_3$) for 99% ee.


8,9,10 (m)
7.23
11 (m)
7.38
2 (t)
4.30
6'' (ddd)
3.00
7' (dddd)
2.46
3 (p)
2.73
6' (dt)
2.82
12'',13'',15,18 (m)
1.51
7'' (m)
1.77
14'',16'' (m)
1.26
1 (s)
1.12
f1 (ppm)


11 (s)
123.99
4 (s)
143.41
9 (s)
126.25
5 (s)
146.51
10 (s)
127.17
8 (s)
124.65
3 (s)
56.20
2 (s)
60.78
15,18 (s)
28.39
6 (s)
30.30
12,13 (s)
32.64
17 (s)
22.78
14,16 (s)
35.11
20 (s)
22.72
7 (s)
35.21
21 (s)
22.80
f1 (ppm)

(R)-N-(2,3-dihydro-1H-inden-1-yl)adamantan-2-amine



General Procedure D: (R)-2,3-dihydro-1H-inden-1-aminium chloride (500 mg, 2.947 mmol, 1.0 eq), adamantan-2-one (531 mg, 3.537 mmol, 1.2 eq), dry THF (15 mL), $NaB(OAc)_3H$ (999 mg, 4.716 mmol, 1.6 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (CH_2Cl_2:Hexane, 70:30, SiO_2) then filtered through a strong cation exchange column ISOLUTE® SCX-2 with MeOH to wash off non-basic component followed by ammonia solution in MeOH (2 M), then purified by flash column chromatography (CH_2Cl_2:Hexane, 70:30, SiO_2) to afford (R)-N-(2,3-dihydro-1H-inden-1-yl)adamantan-2-amine (464 mg, 1.739 mmol, 59%) as a pale yellow oil.

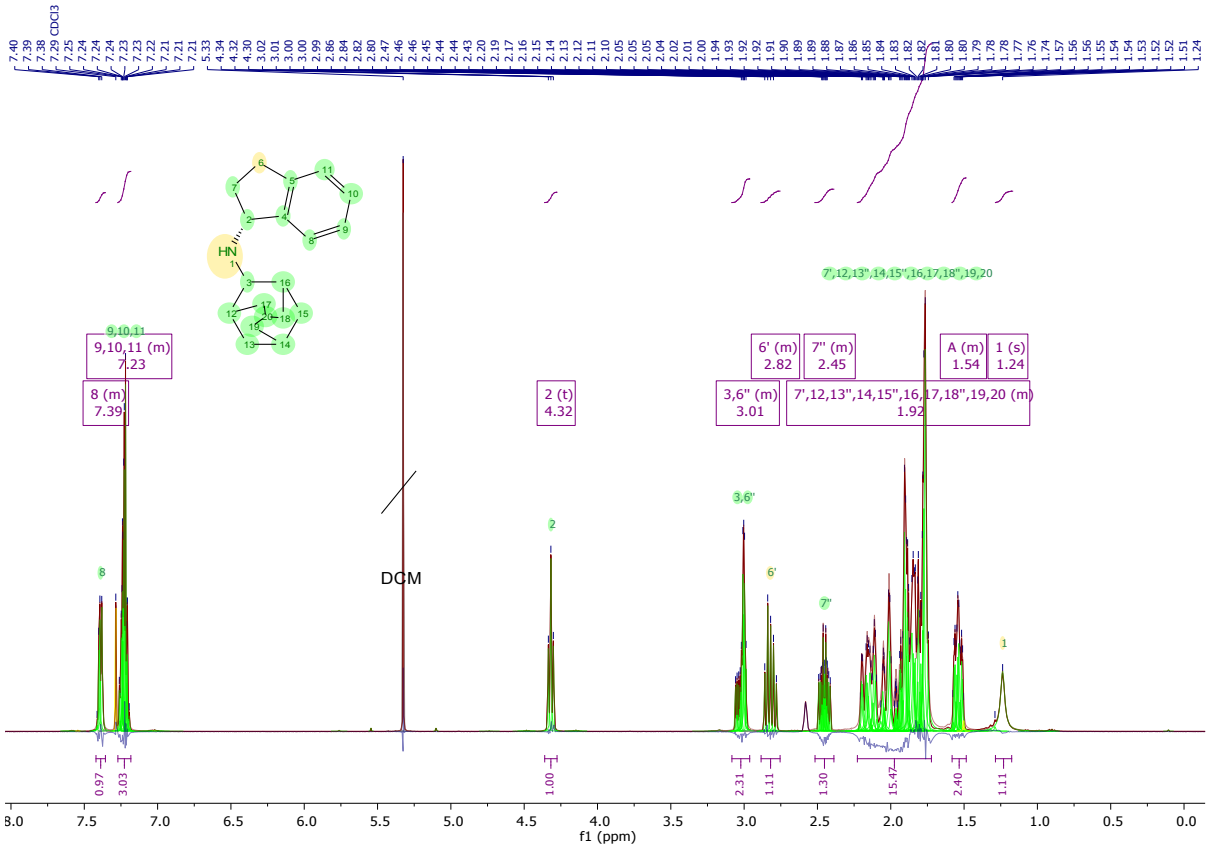
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.36 (m, 1H), 7.27 – 7.18 (m, 3H), 4.32 (t, *J* = 6.8 Hz, 1H), 3.08 – 2.96 (m, 2H), 2.88 – 2.75 (m, 1H), 2.52 – 2.39 (m, 1H), 2.23 – 1.72 (m, 15H), 1.58 – 1.49 (m, 2H), 1.24 (s, 1H).

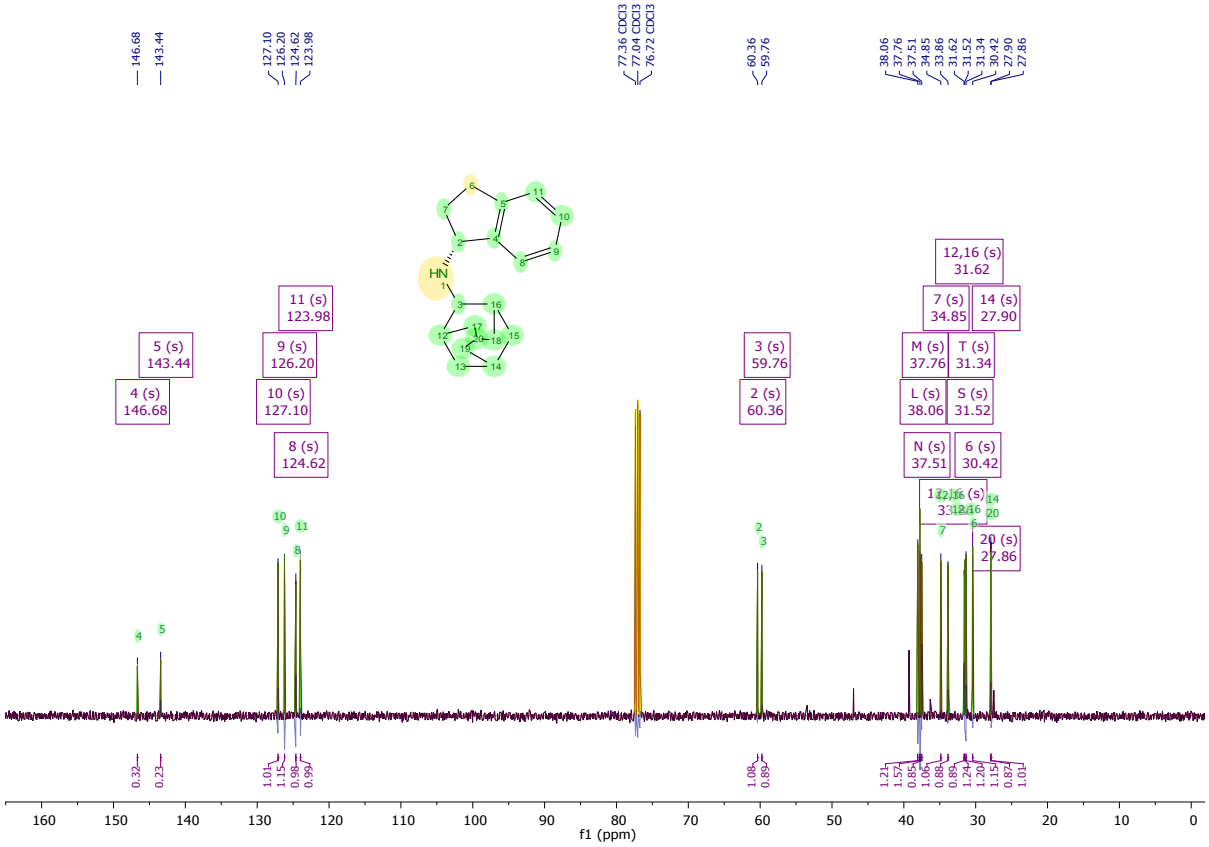
^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.7, 143.4, 127.1, 126.2, 124.6, 124.0, 60.4, 59.8, 38.1, 37.8, 37.5, 34.8, 33.9, 31.6, 31.5, 31.3, 30.4, 27.9, 27.9.

IR υ_{max} (film): 2900, 2847, 1458, 1083.

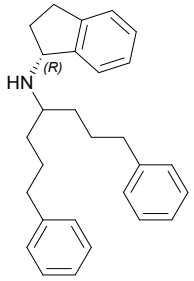
HRMS (EI^+) *m/z* calcd for $C_{19}H_{26}N$ $[M+H]^+$: 268.2060, found 268.2059.

$[\alpha]^{25}_{589}$ = -13.6 (*c* 2.5, $CHCl_3$) for 99% ee.


CDCl3
HN
9,10,11 (m)
7.23
8 (m)
7.39
2 (t)
4.32
6' (m)
2.82
7'' (m)
2.45
3,6'' (m)
3.01
7',12,13'',14,15'',16,17,18'',19,20 (m)
1.92
A (m)
1.54
1 (s)
1.24
DCM
f1 (ppm)


HN
5 (s)
143.44
4 (s)
146.68
11 (s)
123.98
9 (s)
126.20
10 (s)
127.10
8 (s)
124.62
3 (s)
59.76
2 (s)
60.36
12,16 (s)
31.62
7 (s)
34.85
14 (s)
27.90
M (s)
37.76
T (s)
31.34
L (s)
38.06
S (s)
31.52
N (s)
37.51
6 (s)
30.42
20 (s)
27.86
f1 (ppm)

(R)-N-(1,7-diphenylheptan-4-yl)-2,3-dihydro-1H-inden-1-amine



General Procedure D: (R)-2,3-dihydro-1H-inden-1-aminium chloride (650 mg, 3.843 mmol, 1.0 eq), 1,7-diphenylheptan-4-one (1024 mg, 3.843 mmol, 1.0 eq), dry THF (15 mL), $NaB(OAc)_3H$ (1303 mg, 6.148 mmol, 1.6 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane:EtOAc, 90:10, SiO_2) to afford (R)-N-(1,7-diphenylheptan-4-yl)-2,3-dihydro-1H-inden-1-amine (683 mg, 1.768 mmol, 46%) as a pale yellow oil.

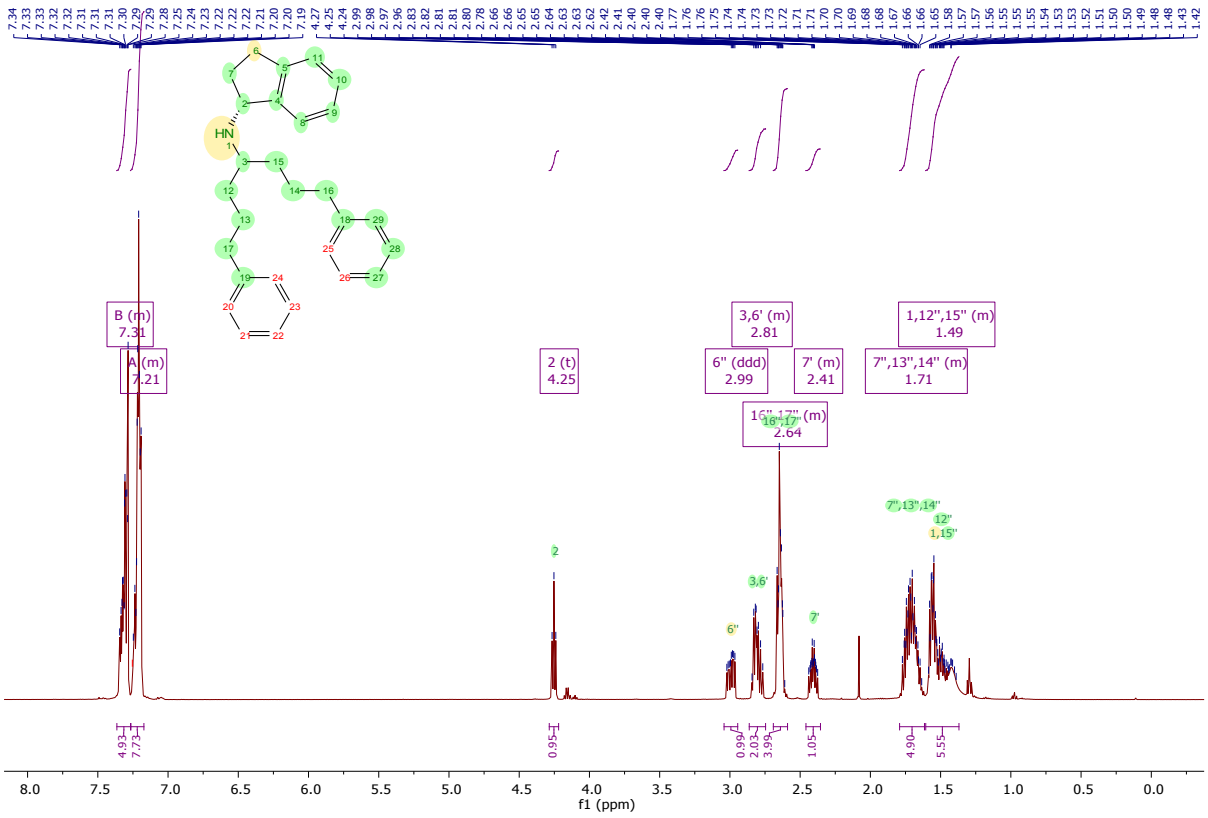
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.26 (m, 5H), 7.27 – 7.17 (m, 9H), 4.25 (t, *J* = 6.7 Hz, 1H), 2.99 (ddd, *J* = 15.8, 8.4, 4.4 Hz, 1H), 2.86 – 2.75 (m, 2H), 2.69 – 2.59 (m, 4H), 2.46 – 2.36 (m, 1H), 1.79 – 1.61 (m, 5H), 1.61 – 1.37 (m, 5H).

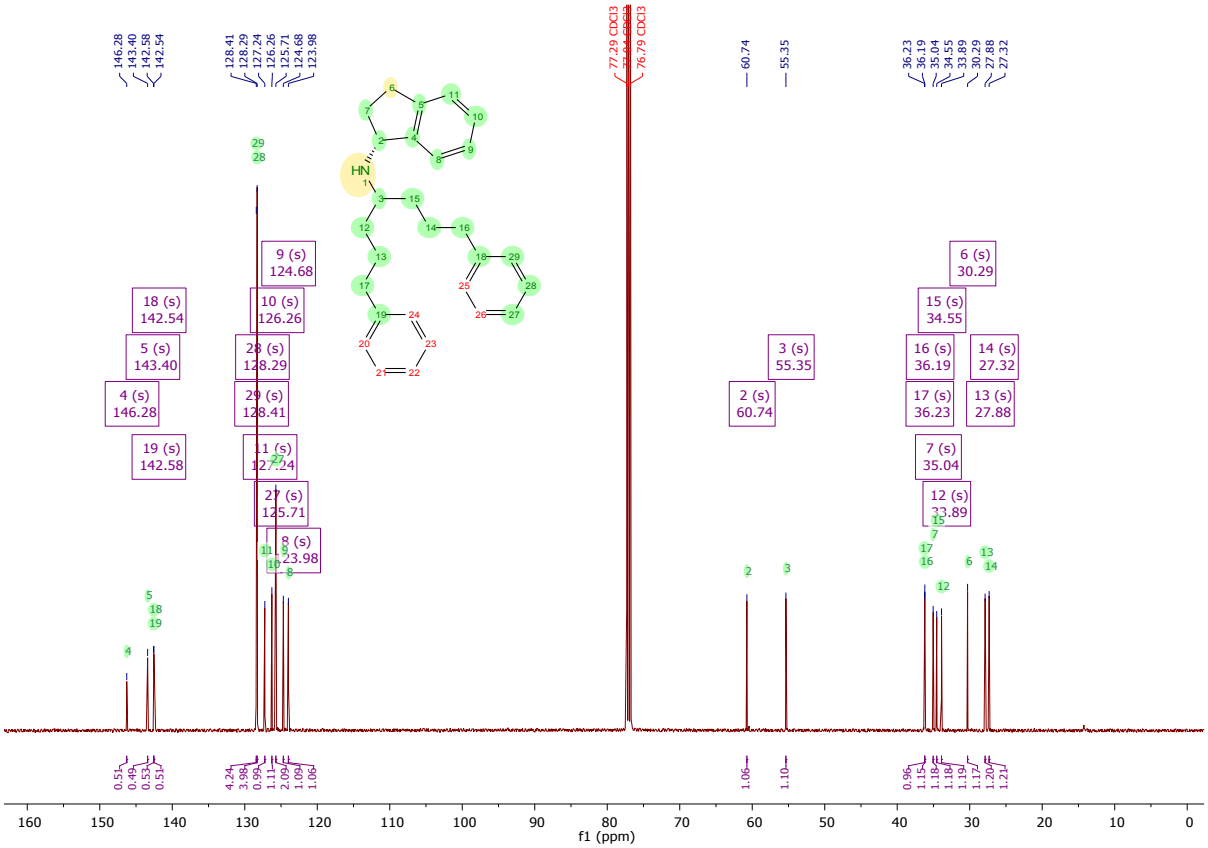
^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.3, 143.4, 142.6, 142.5, 128.4 (4 C), 128.3 (4 C), 127.2, 126.3, 125.7 (2 C), 124.7, 124.0, 60.7, 55.3, 36.2, 36.2, 35.0, 34.5, 33.9, 30.3, 27.9, 27.3.

IR υ_{max} (film): 2932, 2854, 1453.

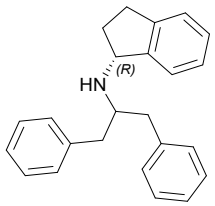
HRMS (EI^+) *m/z* calcd for $C_{28}H_{34}N$ $[M+H]^+$: 384.2686, found 384.2683.

$[\alpha]^{25}_{589}$ = -20.1 (*c* 1.0, $CHCl_3$) for 99% ee.


B (m)
7.31
A (m)
7.21
2 (t)
4.25
3,6' (m)
2.81
6'' (ddd)
2.99
7' (m)
2.41
16'',17'' (m)
2.64
1,12'',15'' (m)
1.49
7'',13'',14'' (m)
1.71
f1 (ppm)


9 (s)
124.68
10 (s)
126.26
18 (s)
142.54
5 (s)
143.40
4 (s)
146.28
19 (s)
142.58
3 (s)
55.35
2 (s)
60.74
6 (s)
30.29
15 (s)
34.55
16 (s)
36.19
14 (s)
27.32
17 (s)
36.23
13 (s)
27.88
7 (s)
35.04
12 (s)
33.89
f1 (ppm)

(R)-N-(1,3-diphenylpropan-2-yl)-2,3-dihydro-1H-inden-1-amine



General Procedure D: (R)-2,3-dihydro-1H-inden-1-aminium chloride (700 mg, 4.138 mmol, 1.0 eq), 1,3-diphenylpropan-2-one (870 mg, 4.138 mmol, 1.0 eq), dry THF (15 mL), $NaB(OAc)_3H$ (1403 mg, 6.621 mmol, 1.6 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (CH_2Cl_2:Hexane, 70:30, SiO_2) then filtered through a strong cation exchange column ISOLUTE® SCX-2 with MeOH to wash off non-basic component followed by ammonia solution in MeOH (2 M) to afford (R)-N-(1,3-diphenylpropan-2-yl)-2,3-dihydro-1H-inden-1-amine (774 mg, 2.359 mmol, 57%) as a pale yellow oil.

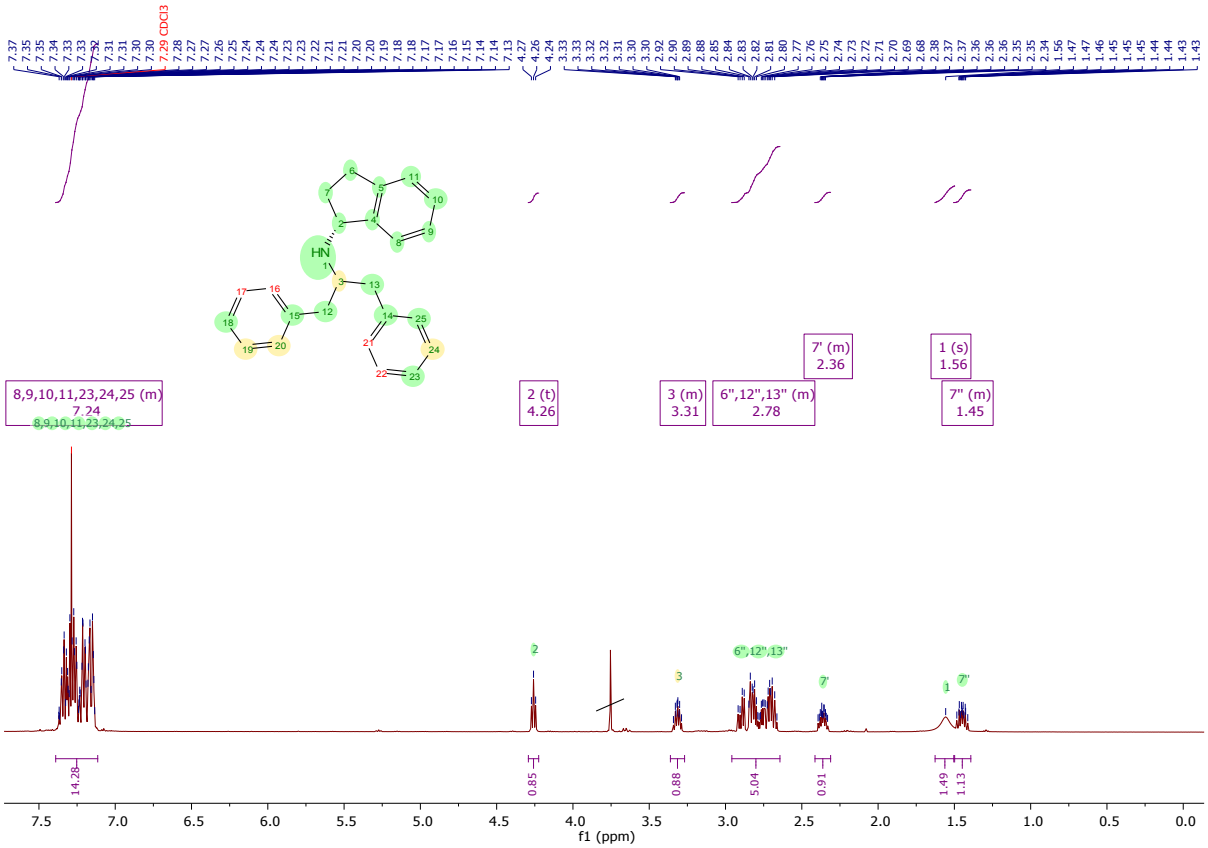
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.11 (m, 14H), 4.26 (t, *J* = 6.9 Hz, 1H), 3.36 – 3.27 (m, 1H), 2.96 – 2.64 (m, 6H), 2.41 – 2.31 (m, 1H), 1.56 (s, 1H), 1.50 – 1.39 (m, 1H).

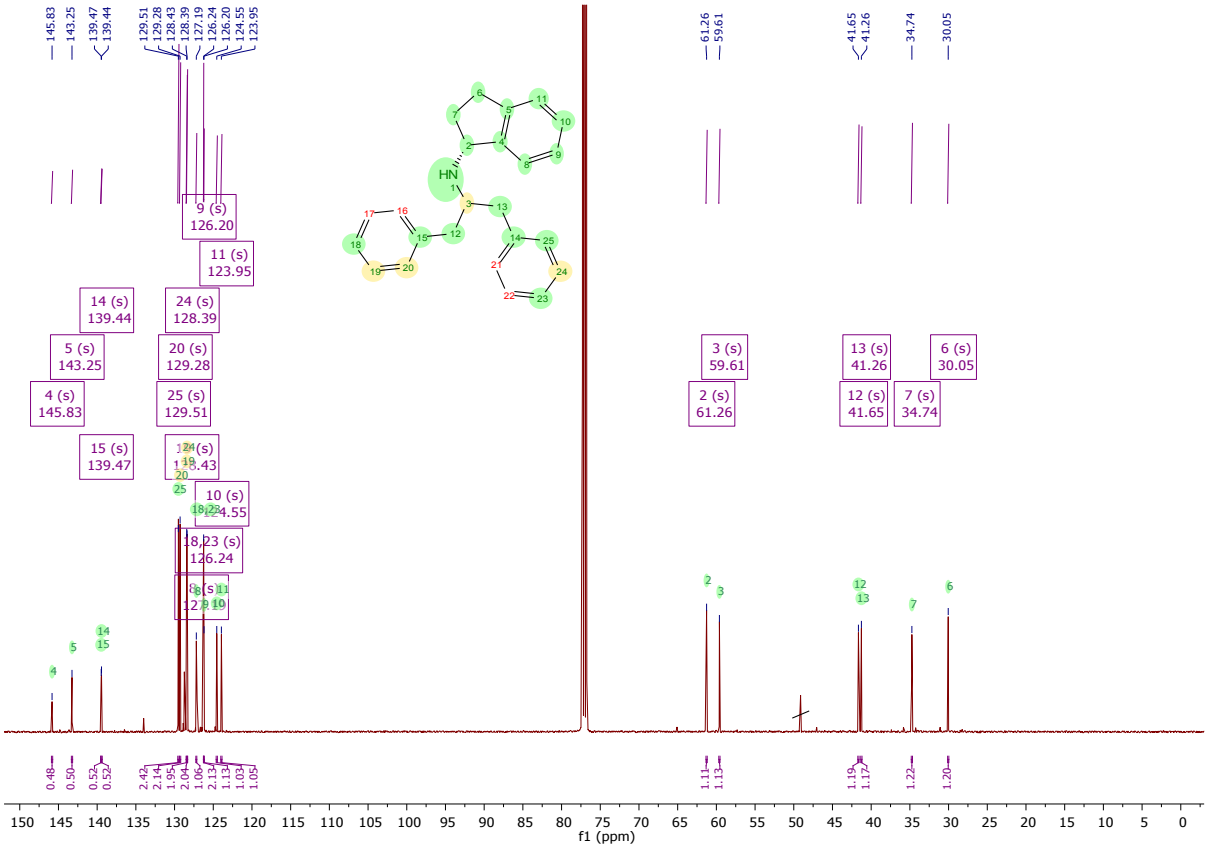
^{13}C NMR (126 MHz, Chloroform-*d*) δ 145.8, 143.2, 139.5, 139.4, 129.5 (2 C), 129.3 (2 C), 128.4 (2 C), 128.4 (2 C), 127.2, 126.2 (2 C), 126.2, 124.5, 123.9, 61.3, 59.6, 41.6, 41.3, 34.7, 30.0.

IR υ_{max} (film): 3025, 2924, 1495, 1453.

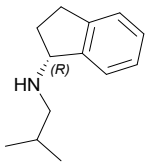
HRMS (EI^+) *m/z* calcd for C_{24} H_{26} N $[M+H]^+$: 328.2060, found 328.2058.

$[\alpha]^{25}_{589}$ = -35.1 (*c* 2.1, $CHCl_3$) for 99% ee.


8,9,10,11,23,24,25 (m)
7.24
2 (t)
4.26
3 (m)
3.31
6",12",13" (m)
2.78
7' (m)
2.36
1 (s)
1.56
7" (m)
1.45
f1 (ppm)


9 (s)
126.20
11 (s)
123.95
14 (s)
139.44
24 (s)
128.39
5 (s)
143.25
20 (s)
129.28
4 (s)
145.83
25 (s)
129.51
15 (s)
139.47
10 (s)
18,23 (s)
126.24
3 (s)
59.61
2 (s)
61.26
13 (s)
41.26
12 (s)
41.65
6 (s)
30.05
7 (s)
34.74
f1 (ppm)

(R)-N-isobutyl-2,3-dihydro-1H-inden-1-amine



General Procedure D: (R)-2,3-dihydro-1H-inden-1-aminium chloride (700 mg, 4.138 mmol, 1.0 eq), isobutyraldehyde (1.06 mL, 4.138 mmol, 1.0 eq), dry THF (15 mL), $NaB(OAc)_3H$ (1403 mg, 6.621 mmol, 1.6 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane:EtOAc, 90:10, SiO_2) to afford (R)-N-isobutyl-2,3-dihydro-1H-inden-1-amine (520 mg, 2.731 mmol, 66%) as a pale yellow oil.

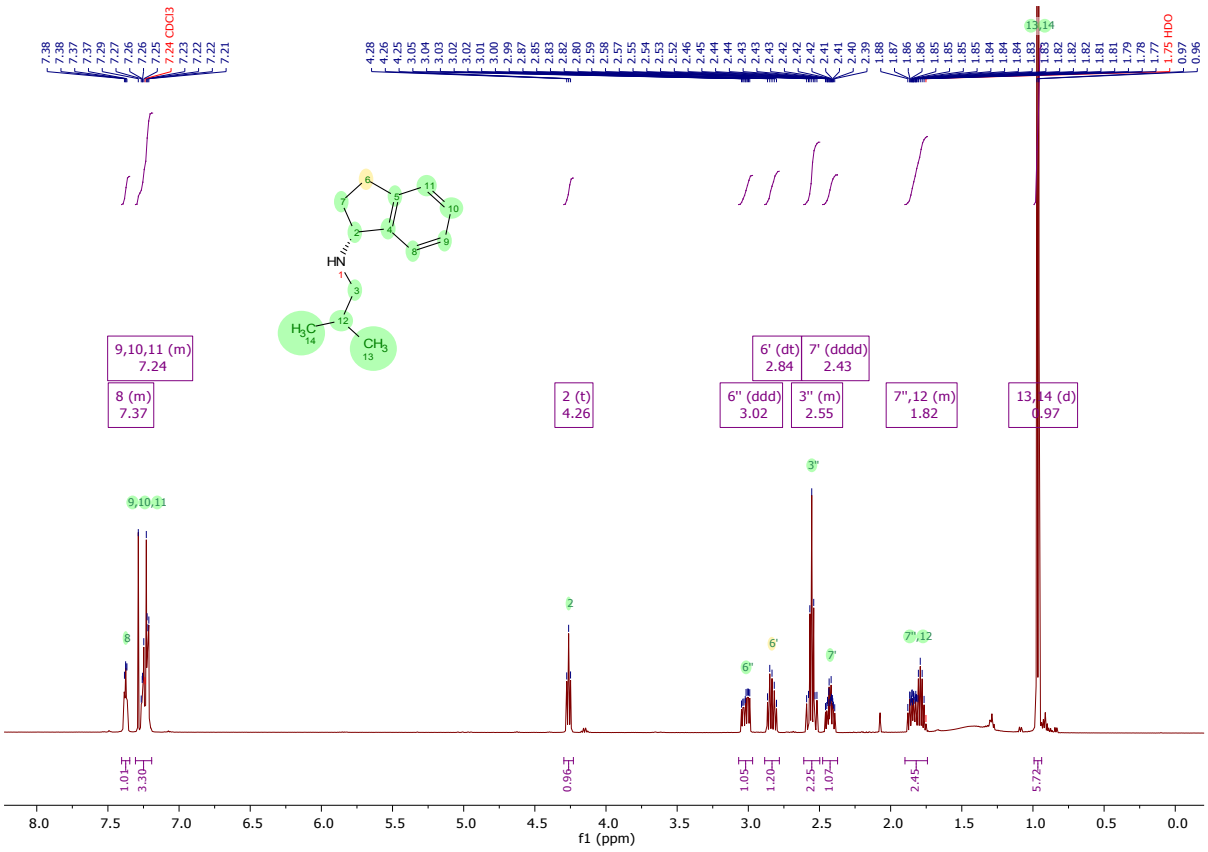
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.35 (m, 1H), 7.31 – 7.19 (m, 3H), 4.26 (t, *J* = 6.7 Hz, 1H), 3.02 (ddd, *J* = 15.8, 8.6, 4.5 Hz, 1H), 2.84 (dt, *J* = 15.8, 7.9 Hz, 1H), 2.61 – 2.50 (m, 2H), 2.43 (dddd, *J* = 12.6, 8.2, 7.0, 4.5 Hz, 1H), 1.90 – 1.74 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 6H).

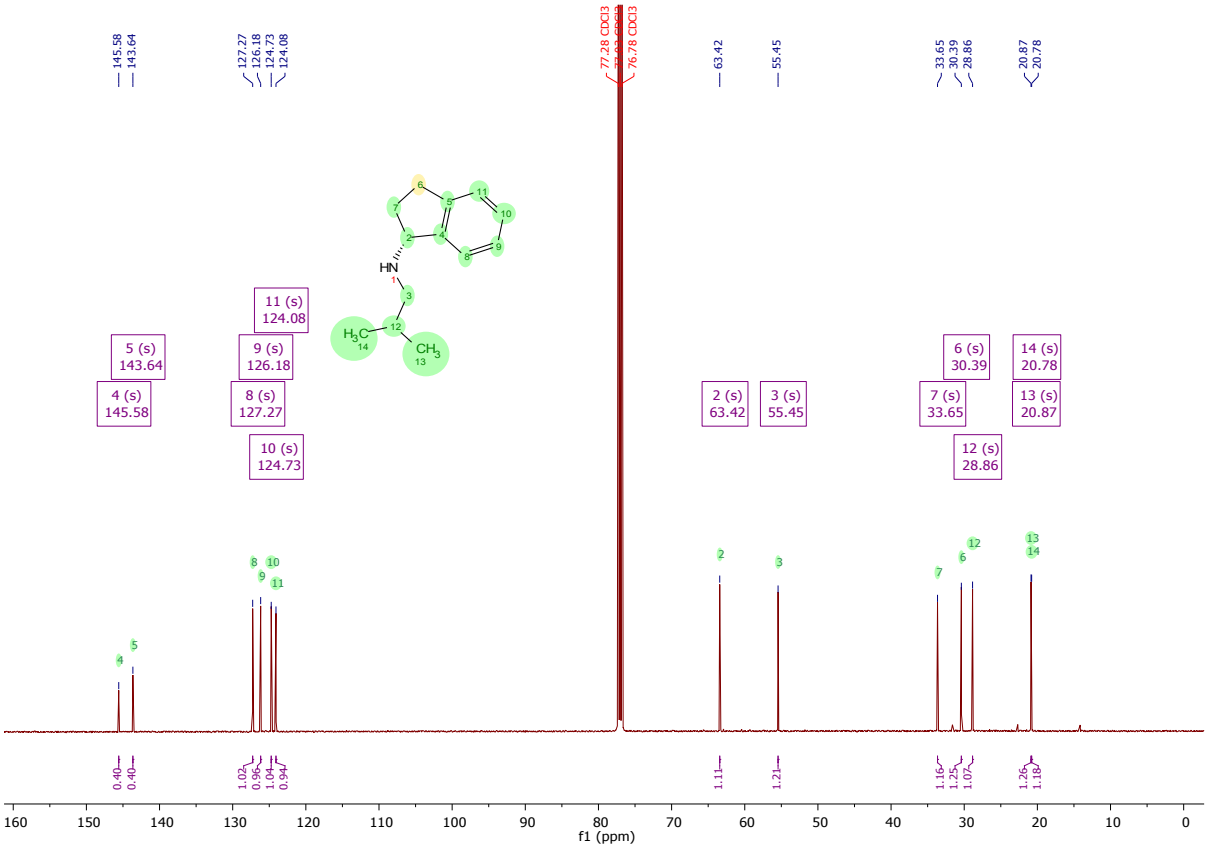
^{13}C NMR (126 MHz, Chloroform-*d*) δ 145.6, 143.6, 127.3, 126.2, 124.7, 124.1, 63.4, 55.4, 33.6, 30.4, 28.9, 20.9, 20.8.

IR υ_{max} (film): 3025, 2924, 1495, 1453.

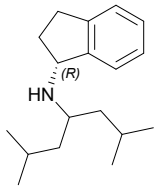
HRMS (EI^+) *m/z* calcd for C_{24} H_{26} N $[M+H]^+$: 328.2060, found 328.2058.

$[\alpha]^{25}_{589}$ = -35.1 (*c* 2.1, $CHCl_3$) for 99% ee.


9,10,11 (m)
7.24
8 (m)
7.37
2 (t)
4.26
6' (dt)
2.84
7' (dddd)
2.43
6'' (ddd)
3.02
3'' (m)
2.55
7'',12 (m)
1.82
13,14 (d)
0.97
f1 (ppm)


11 (s)
124.08
5 (s)
143.64
9 (s)
126.18
4 (s)
145.58
8 (s)
127.27
10 (s)
124.73
2 (s)
63.42
3 (s)
55.45
6 (s)
30.39
14 (s)
20.78
7 (s)
33.65
13 (s)
20.87
12 (s)
28.86
f1 (ppm)

(R)-N-(2,6-dimethylheptan-4-yl)-2,3-dihydro-1H-inden-1-amine



General Procedure D: (R)-2,3-dihydro-1H-inden-1-aminium chloride (200 mg, 1.182 mmol, 1.0 eq), 2,6-dimethylheptan-4-one (0.21 mL, 1.182 mmol, 1.0 eq), $NaB(OAc)_3H$ (401 mg, 1.892 mmol, 1.6 eq).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane:EtOAc, 80:20, SiO_2) to afford (R)-N-(2,6-dimethylheptan-4-yl)-2,3-dihydro-1H-inden-1-amine (85 mg, 0.331 mmol, 28%) as a pale yellow oil.

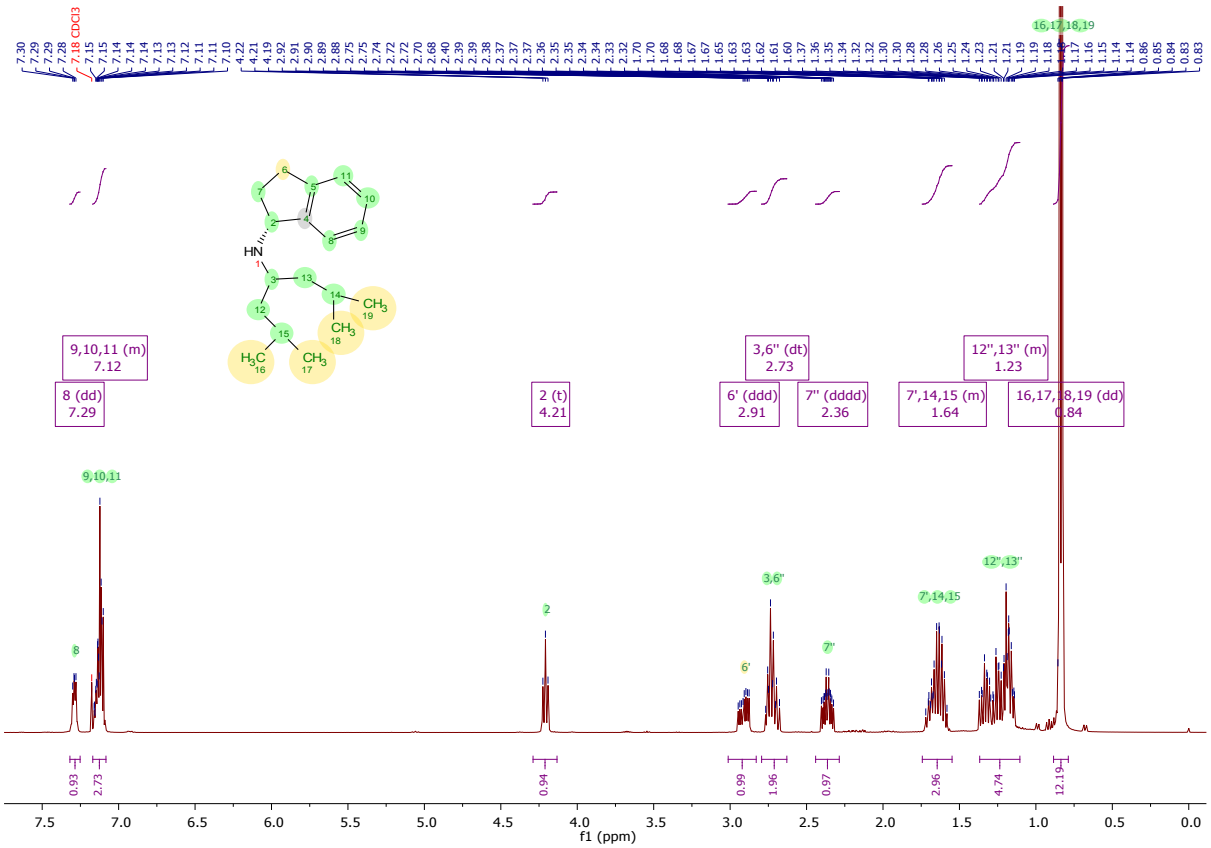
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 (dd, *J* = 5.0, 3.6 Hz, 1H), 7.17 – 7.08 (m, 3H), 4.21 (t, *J* = 6.7 Hz, 1H), 2.91 (ddd, *J* = 15.8, 8.4, 4.3 Hz, 1H), 2.73 (dt, *J* = 16.0, 7.6 Hz, 2H), 2.36 (dddd, *J* = 12.4, 8.0, 6.8, 4.3 Hz, 1H), 1.74 – 1.55 (m, 3H), 1.37 – 1.10 (m, 4H), 0.84 (dd, *J* = 6.6, 2.2 Hz, 12H).

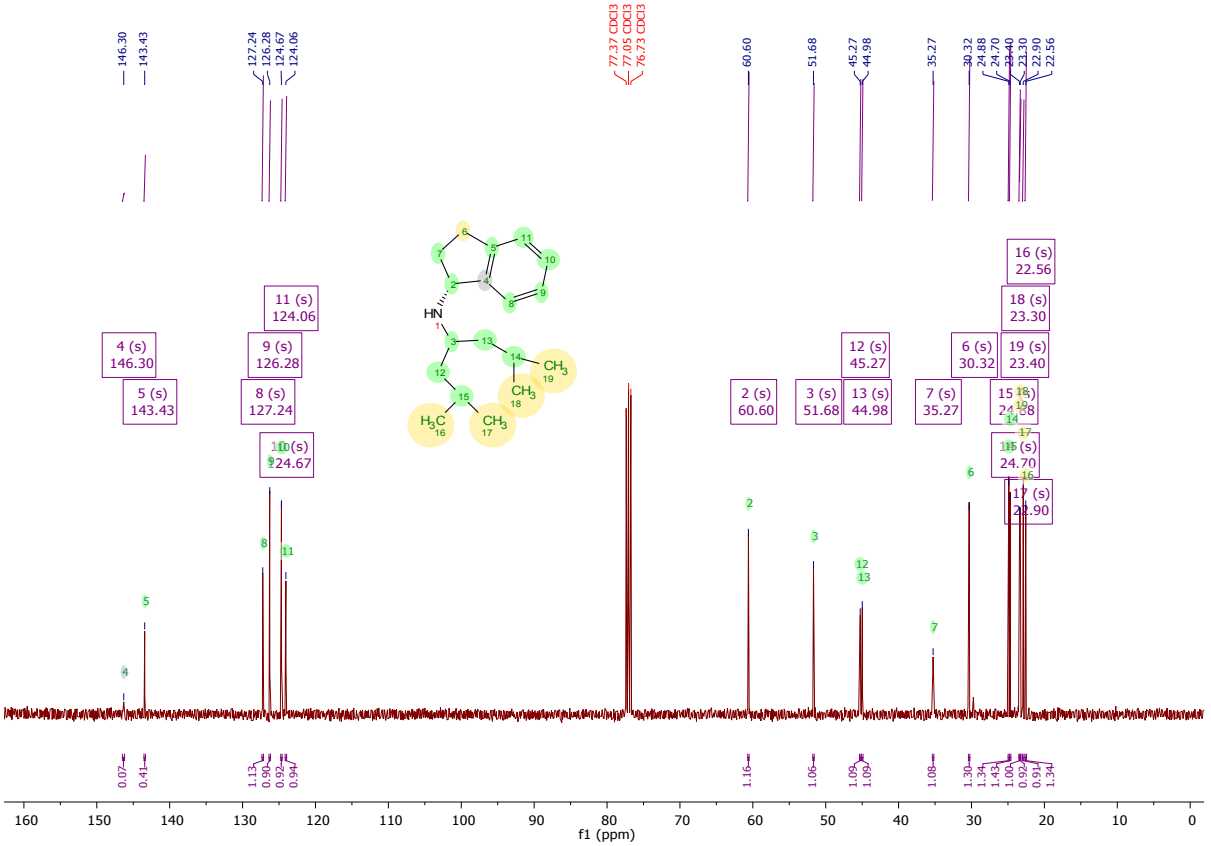
^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.3, 143.4, 127.2, 126.3, 124.7, 124.1, 60.6, 51.7, 45.3, 45.0, 35.3, 30.3, 24.9, 24.7, 23.4, 23.3, 22.9, 22.6.

IR υ_{max} (film): 3659, 2980, 2361, 1462, 1382, 1251, 1154, 1082.

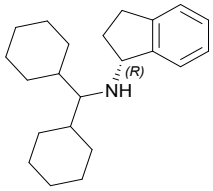
HRMS (EI^+) *m/z* calcd for $C_{18}H_{30}N$ $[M+H]^+$: 260.2373, found 260.2370.

$[\alpha]^{25}_{589}$ = -25.0 (*c* 1.0, $CHCl_3$) for 99% ee.


9,10,11 (m)
7.12
8 (dd)
7.29
2 (t)
4.21
3,6'' (dt)
2.73
6' (ddd)
2.91
7'' (dddd)
2.36
12'',13'' (m)
1.23
7',14,15 (m)
1.64
16,17,18,19 (dd)
0.84
f1 (ppm)


4 (s)
146.30
5 (s)
143.43
11 (s)
124.06
9 (s)
126.28
8 (s)
127.24
10 (s)
124.67
2 (s)
60.60
3 (s)
51.68
12 (s)
45.27
13 (s)
44.98
7 (s)
35.27
6 (s)
30.32
19 (s)
23.40
18 (s)
23.30
16 (s)
22.56
17 (s)
22.90
15 (s)
24.70
f1 (ppm)

(R)-N-(dicyclohexylmethyl)-2,3-dihydro-1H-inden-1-amine



(R)-2,3-dihydro-1H-inden-1-aminium chloride (500 mg, 2.956 mmol, 1.0 eq), was mixed with aq. NaOH (2M, 10mL) and CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. 4-(cyclohexanecarbonyl)cyclohexan-1-ylium (0.58 mL, 2.956 mmol, 1.0 eq) was then added to a stirring solution of the freshly concentrated (R)-2,3-dihydro-1H-inden-1-amine in dry Toluene (15 mL) at rt. After 5min, 25g of activated 4 Å sieves were added. The mixture was then strongly stirred and refluxed for 5 days. When an acceptable ratio of the imine/amine was obtained according to ^{1}H NMR, the mixture was filtered through a pad of celite, rinsed with toluene and concentrated to remove the solvent. After letting it under high vacuum for 30 min, dry ethanol (35 mL) was added followed by $NaBH_4$ (167.7 mg, 4.434 mmol, 1.5 eq) and the suspension was stirred overnight (In practice, the reaction is done after about 2 hours). The solvent is then removed before diluting the mixture with CH_2Cl_2 (20 mL) and NaOH (2 M, *ca* 10 mL). The organic and aqueous layers were partitioned and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane, SiO_2), then filtered through a strong cation exchange column ISOLUTE® SCX-2 with MeOH to wash off non-basic component followed by ammonia solution in MeOH (2 M) to afford (R)-N-(dicyclohexylmethyl)-2,3-dihydro-1H-inden-1-amine (171 mg, 0.709 mmol, 24%) as a brown oil.

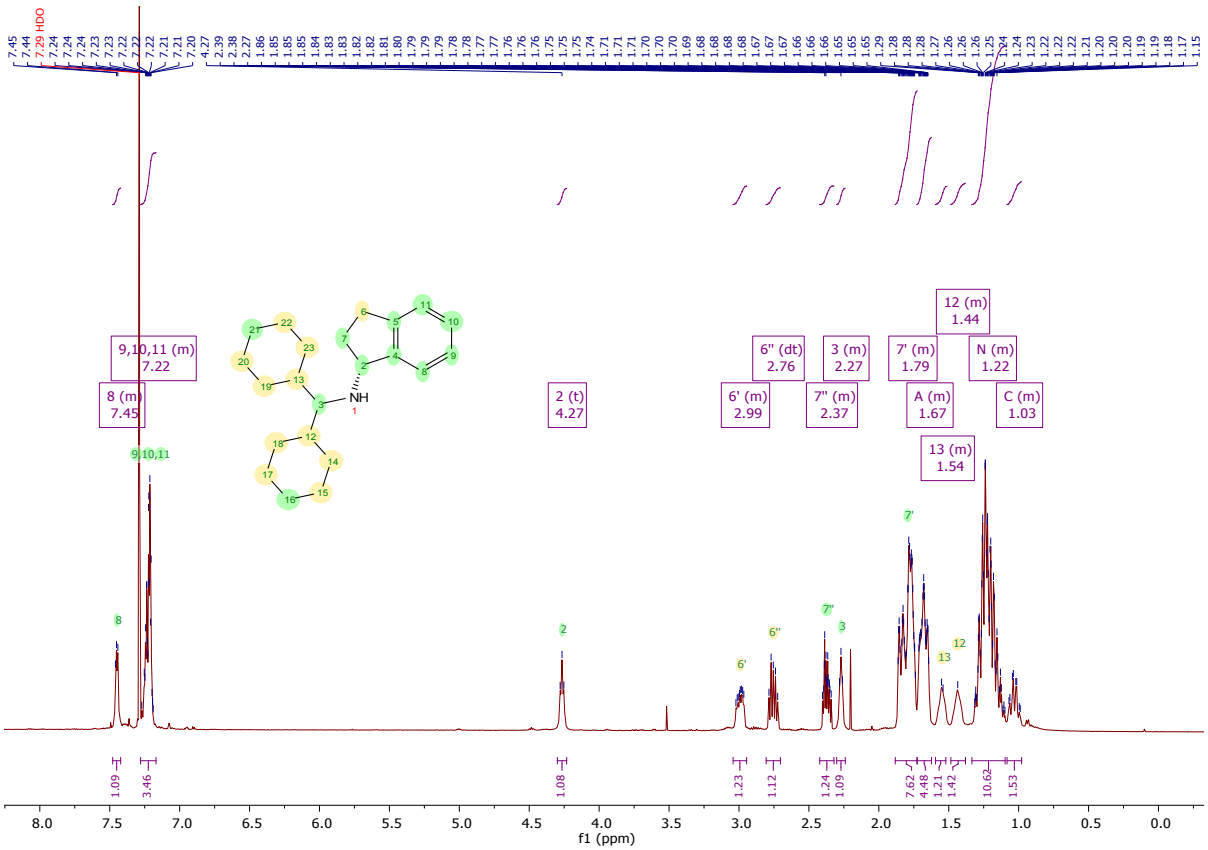
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.48 – 7.42 (m, 1H), 7.28 – 7.17 (m, 3H), 4.27 (t, *J* = 6.6 Hz, 1H), 3.04 – 2.95 (m, 1H), 2.76 (dt, *J* = 15.6, 7.7 Hz, 1H), 2.42 – 2.32 (m, 1H), 2.30 – 2.24 (m, 1H), 1.88 – 1.73 (m, 8H), 1.73 – 1.62 (m, 4H), 1.59 – 1.52 (m, 1H), 1.48 – 1.38 (m, 1H), 1.33 – 1.10 (m, 11H), 1.08 – 0.98 (m, 2H).

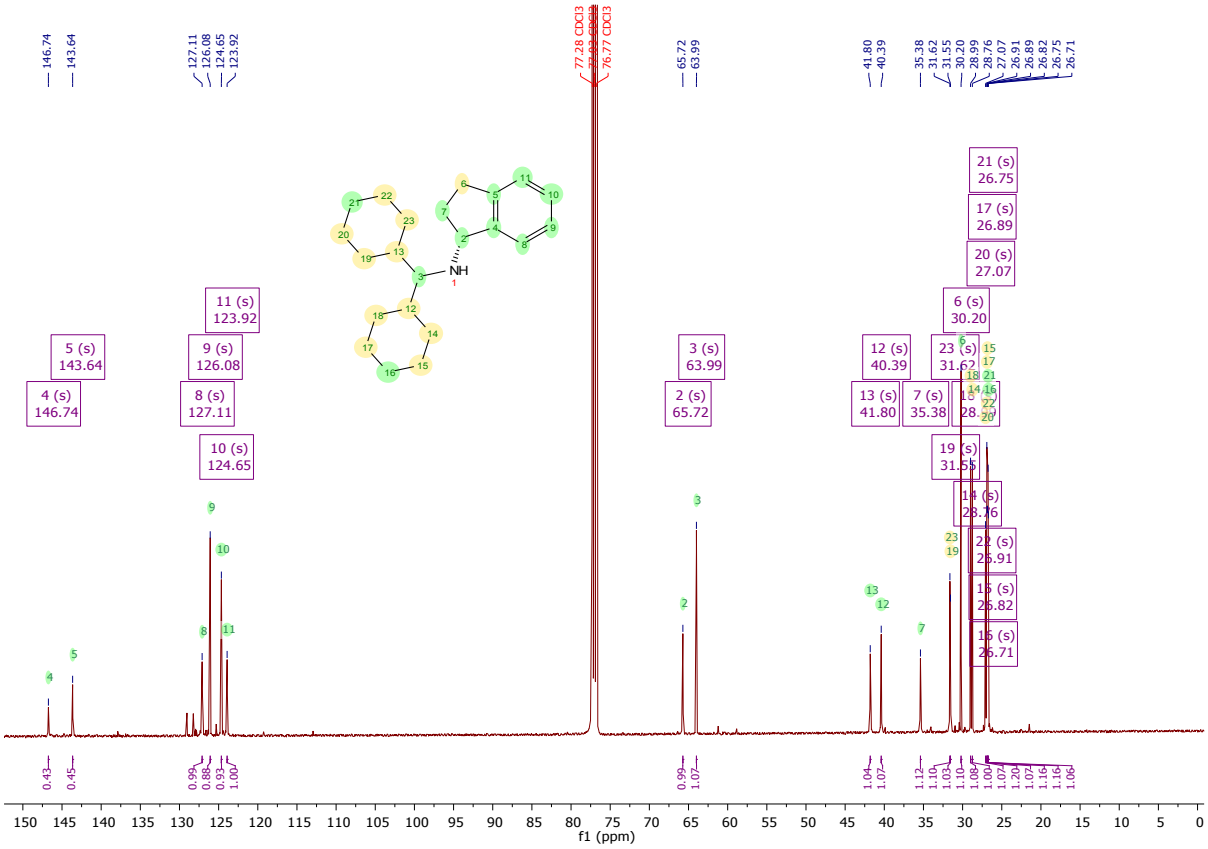
^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.7, 143.6, 127.1, 126.1, 124.6, 123.9, 65.7, 64.0, 41.8, 40.4, 35.4, 31.6, 31.5, 30.2, 29.0, 28.8, 27.1, 26.9, 26.9, 26.8, 26.7, 26.7.

IR υ_{max} (film): 3021, 2849, 1448, 1260, 1126.

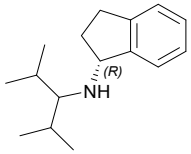
HRMS (EI^+) *m/z* calcd for $C_{22}H_{34}N$ $[M+H]^+$: 312.2686, found 312.2685.

$[\alpha]^{25}_{589}$ = -12.6 (*c* 1.0, $CHCl_3$) for 99% ee.


9,10,11 (m)
7.22
8 (m)
7.45
2 (t)
4.27
6'' (dt)
2.76
6' (m)
2.99
3 (m)
2.27
7'' (m)
2.37
7' (m)
1.79
A (m)
1.67
12 (m)
1.44
N (m)
1.22
C (m)
1.03
13 (m)
1.54
f1 (ppm)


4 (s)
146.74
5 (s)
143.64
8 (s)
127.11
9 (s)
126.08
10 (s)
124.65
11 (s)
123.92
2 (s)
65.72
3 (s)
63.99
13 (s)
41.80
12 (s)
40.39
7 (s)
35.38
23 (s)
31.62
6 (s)
30.20
20 (s)
27.07
17 (s)
26.89
21 (s)
26.75
f1 (ppm)

(R)-N-(2,4-dimethylpentan-3-yl)-2,3-dihydro-1H-inden-1-amine



(R)-2,3-dihydro-1H-inden-1-aminium chloride (500 mg, 2.956 mmol, 1.0 eq) was mixed with aq. NaOH (2M, 10mL) and CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. 2,4-dimethylpentan-3-one (0.42 mL, 2.956 mmol, 1.0 eq) was then added to a stirring solution of the freshly concentrated (R)-2,3-dihydro-1H-inden-1-amine in dry Toluene (15 mL) at rt. After 5min, 25g of sieves were added. The mixture was then strongly stirred and refluxed for 5 days. When an acceptable ratio of the imine/amine was obtained, the mixture was filtered through a pad of celite, rinsed with toluene and concentrated to remove the solvent. After letting it under high vacuum for 30 min, dry ethanol (35 mL) was added followed by $NaBH_4$ (167.7 mg, 4.434 mmol, 1.5 eq) and the suspension was stirred overnight (In practice, the reaction is done after 2 hours). The solvent is then removed before diluting the mixture with CH_2Cl_2 (20 mL) and NaOH (2 M, *ca* 10 mL). The organic and aqueous layers were partitioned and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane, SiO_2), then filtered through a strong cation exchange column ISOLUTE® SCX-2 with MeOH to wash off non-basic component followed by ammonia solution in MeOH (2 M) to afford (S)-N-(2,4-dimethylpentan-3-yl)-2,3-dihydro-1H-inden-1-amine (211 mg, 0.798 mmol, 27%) as a brown oil.

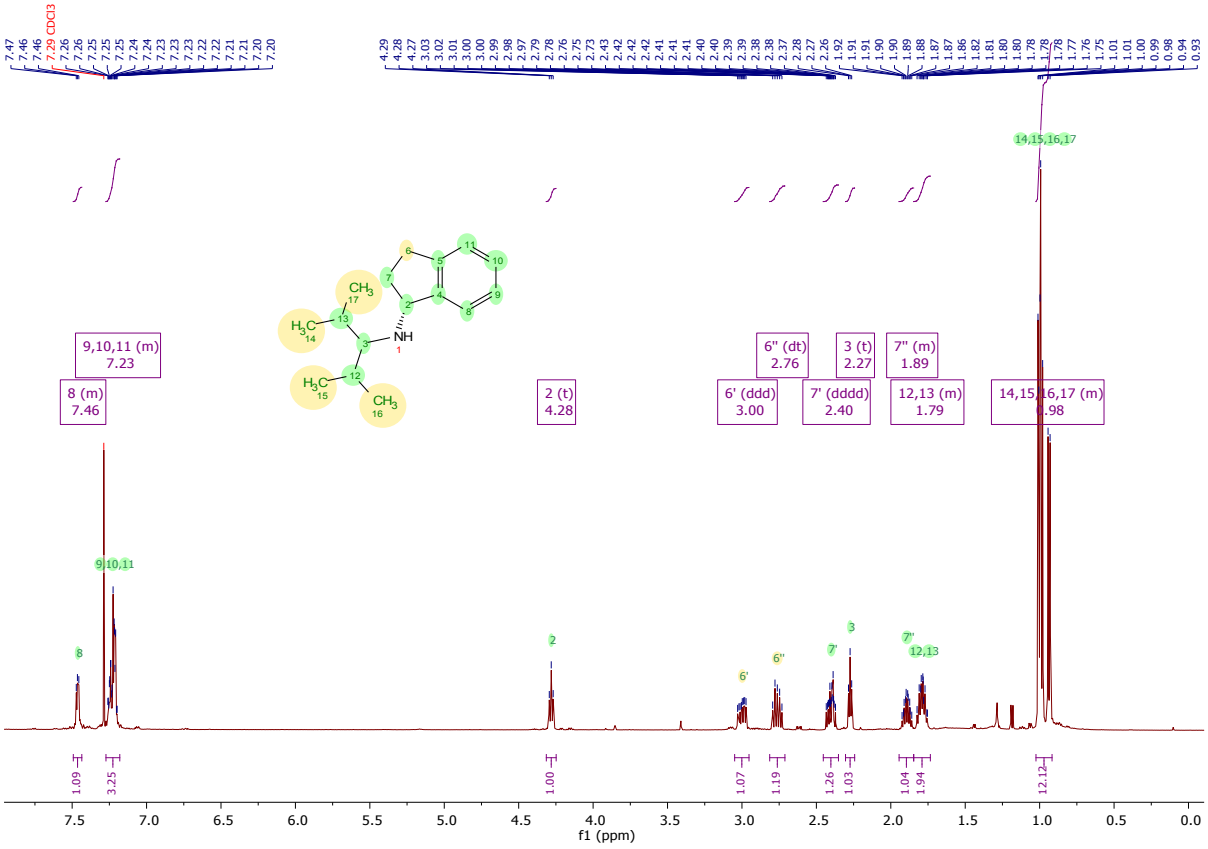
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.49 – 7.44 (m, 1H), 7.27 – 7.18 (m, 3H), 4.28 (t, *J* = 6.5 Hz, 1H), 3.00 (ddd, *J* = 15.6, 8.2, 4.4 Hz, 1H), 2.76 (dt, *J* = 15.6, 7.7 Hz, 1H), 2.40 (dddd, *J* = 12.2, 8.0, 6.5, 4.4 Hz, 1H), 2.27 (t, *J* = 5.4 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.85 – 1.73 (m, 2H), 1.02 – 0.92 (m, 12H).

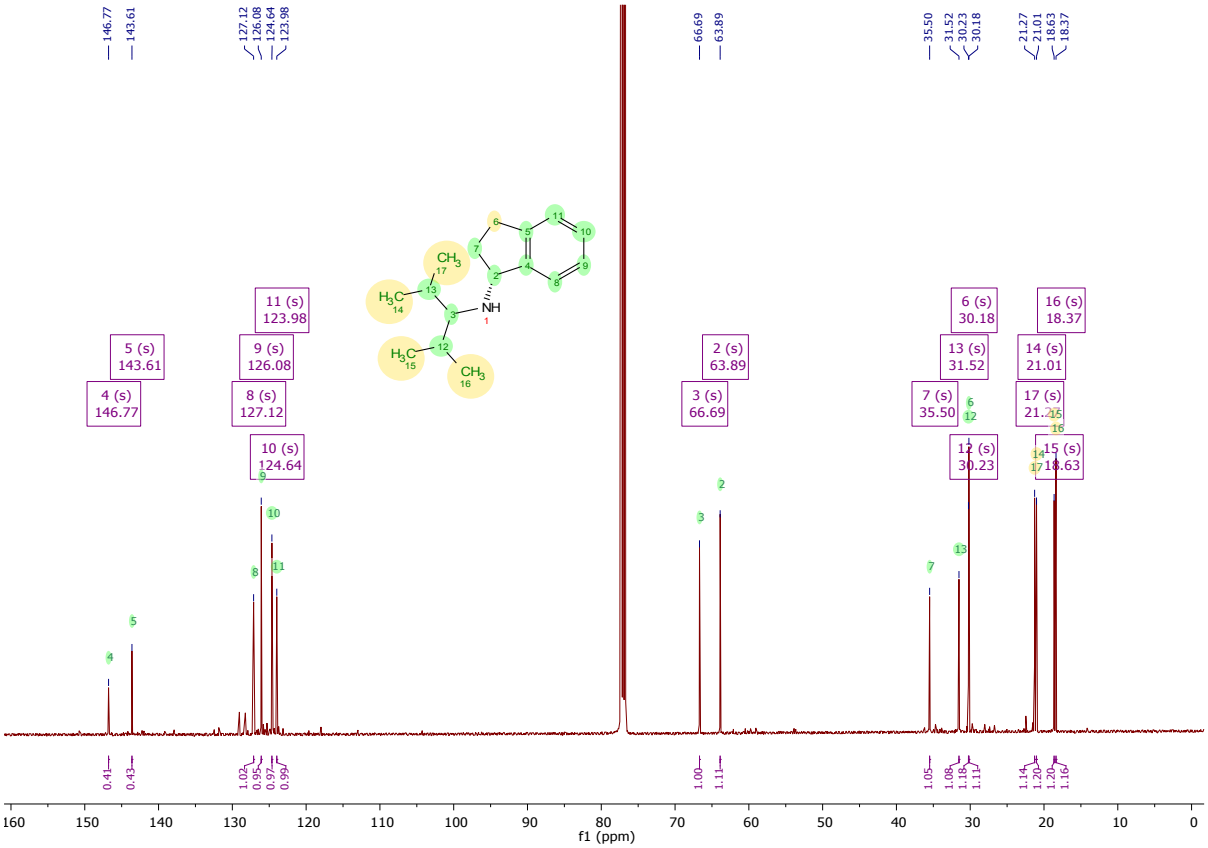
^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.8, 143.6, 127.1, 126.1, 124.6, 124.0, 66.7, 63.9, 35.5, 31.5, 30.2, 30.2, 21.3, 21.0, 18.6, 18.4.

IR υ_{max} (film): 3069, 2956, 2870, 2360, 1472, 1381, 1081.

HRMS (EI^+) *m/z* calcd for C_{16} H_{26} N $[M+H]^+$: 232.2060, found 232.2061.

$[\alpha]^{25}_{589}$ = -18.4 (*c* 1.0, $CHCl_3$) for 99% ee.

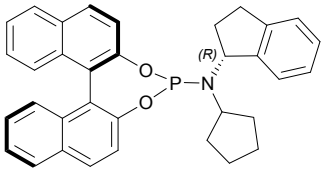

9,10,11 (m)
7.23
8 (m)
7.46
2 (t)
4.28
6'' (dt)
2.76
3 (t)
2.27
7'' (m)
1.89
6' (ddd)
3.00
7' (dddd)
2.40
12,13 (m)
1.79
14,15,16,17 (m)
0.98
f1 (ppm)


4 (s)
146.77
5 (s)
143.61
8 (s)
127.12
9 (s)
126.08
10 (s)
124.64
11 (s)
123.98
3 (s)
66.69
2 (s)
63.89
7 (s)
35.50
13 (s)
31.52
12 (s)
30.23
6 (s)
30.18
17 (s)
21.27
14 (s)
21.01
15 (s)
18.63
16 (s)
18.37
f1 (ppm)

4. Phosphoramidite ligands

Note: All the phosphoramidite ligands were put under high-vacuum for at least 5 h, even though some ligands retained solvent due to their foamy nature.

N-cyclopentyl-N-((R)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L10



General Procedure E: Triethylamine (1.77 mL, 12.722 mmol, 5.0 eq.), PCl_3 (0.27 mL, 3.053 mmol, 1.2 eq.), CH_2Cl_2 (20 mL), (R)-N-cyclopentyl-2,3-dihydro-1H-inden-1-amine (512 mg, 2.544 mmol, 1.0 eq.), (R)-binaphthol (316 mg, 1.1 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-cyclopentyl-N-((R)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (250 mg, 0.4834 mmol, 19%) as a foamy white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 22.1, 8.5 Hz, 2H), 7.72 (dd, *J* = 16.3, 8.4 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.43 (dd, *J* = 8.8, 3.7 Hz, 2H), 7.36 – 7.04 (m, 10H), 4.60 (q, *J* = 8.9 Hz, 1H), 3.24 (dt, *J* = 13.0, 8.1 Hz, 1H), 2.83 – 2.72 (m, 1H), 2.51 (dt, *J* = 23.4, 8.0 Hz, 1H), 2.34 – 2.22 (m, 1H), 2.03 – 1.75 (m, 4H), 1.59 (qt, *J* = 12.1, 5.9 Hz, 3H), 1.32 – 1.16 (m, 2H).

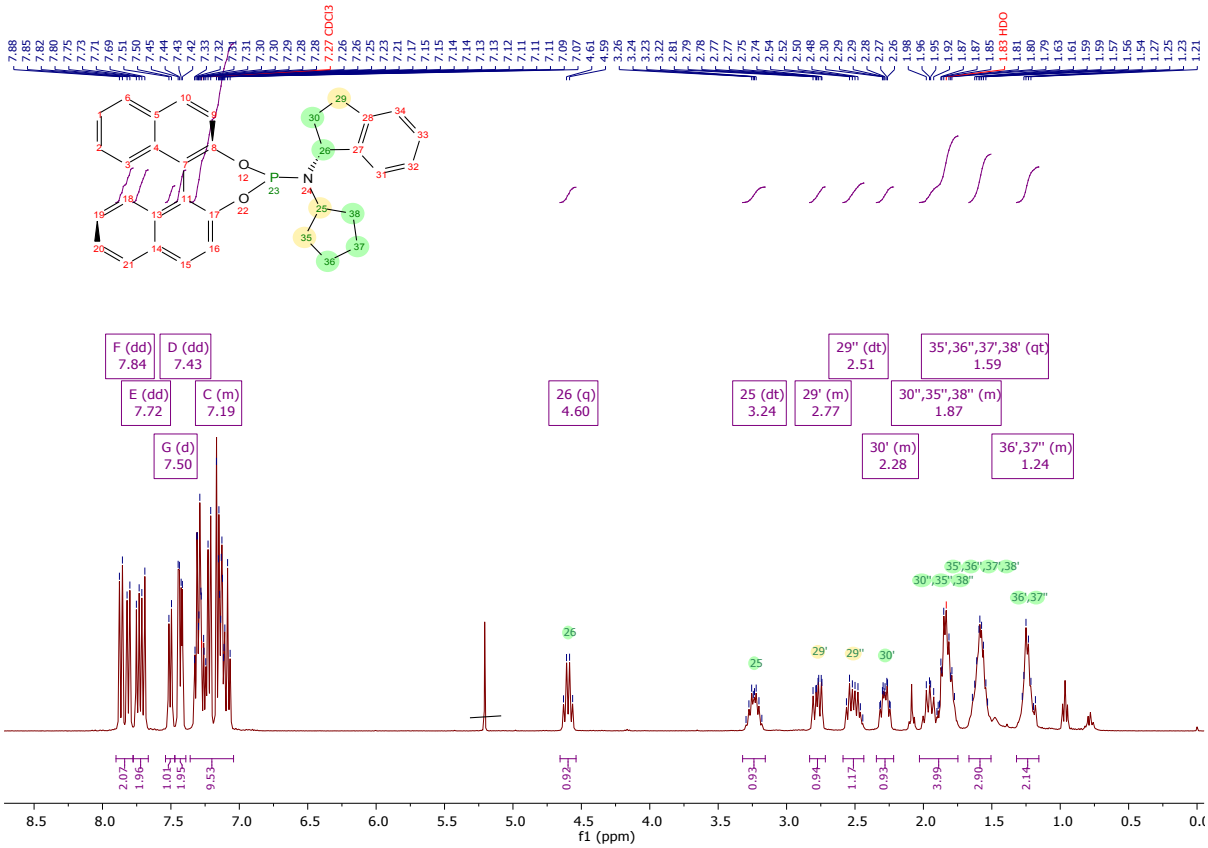
^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.2, 150.1, 150.0, 144.2, 144.2, 143.3, 132.8, 132.7, 131.3, 130.5, 130.2, 129.5, 128.3, 128.2, 127.2, 127.1, 126.3, 125.9, 125.8, 124.8, 124.7, 124.4, 124.3, 124.2, 124.1, 122.4 (2 C), 121.6, 121.6, 60.9, 60.8, 56.5, 56.3, 35.5 – 35.1 (m, 2C), 34.2 – 34.0 (m), 29.9, 24.3, 24.1.

^{31}P NMR (162 MHz, Chloroform-*d*) δ 151.4.

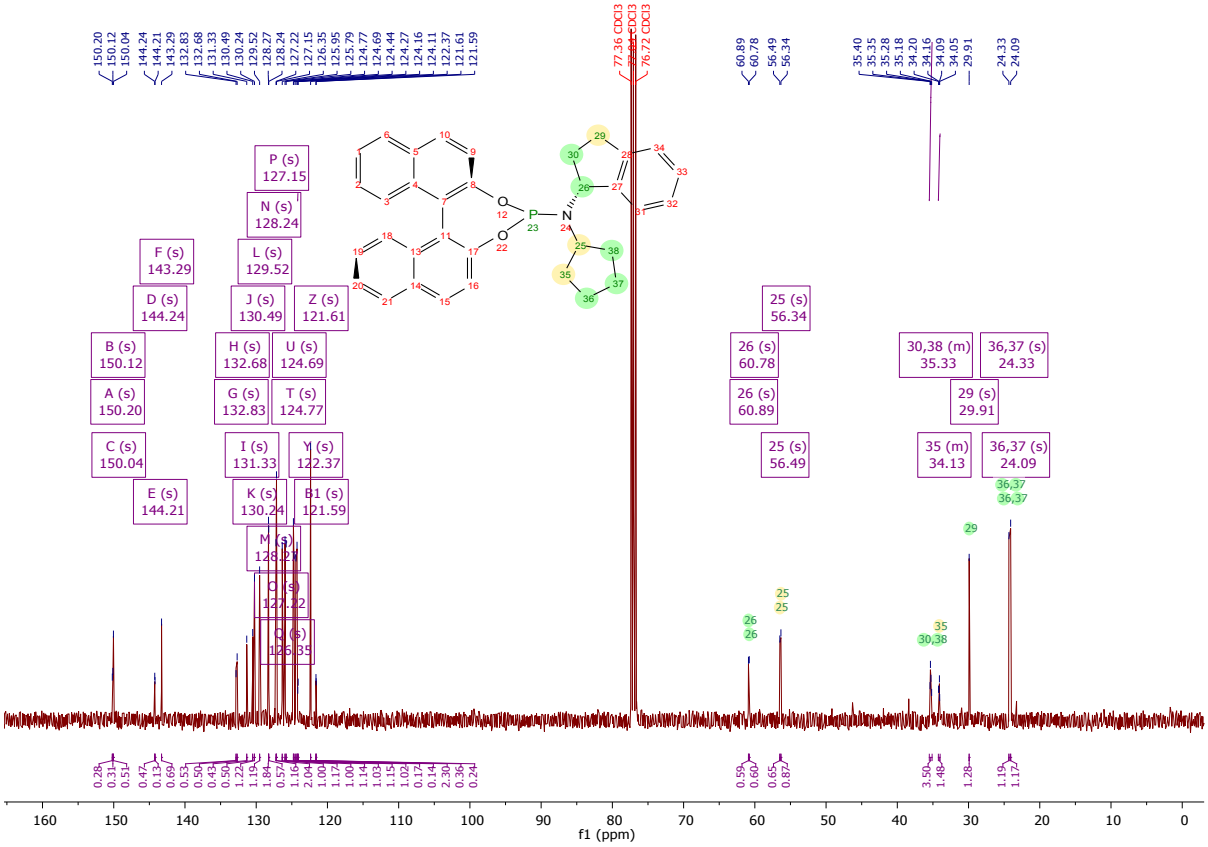
IR υ_{max} (film): 2954, 1589, 1461, 1230, 1125.

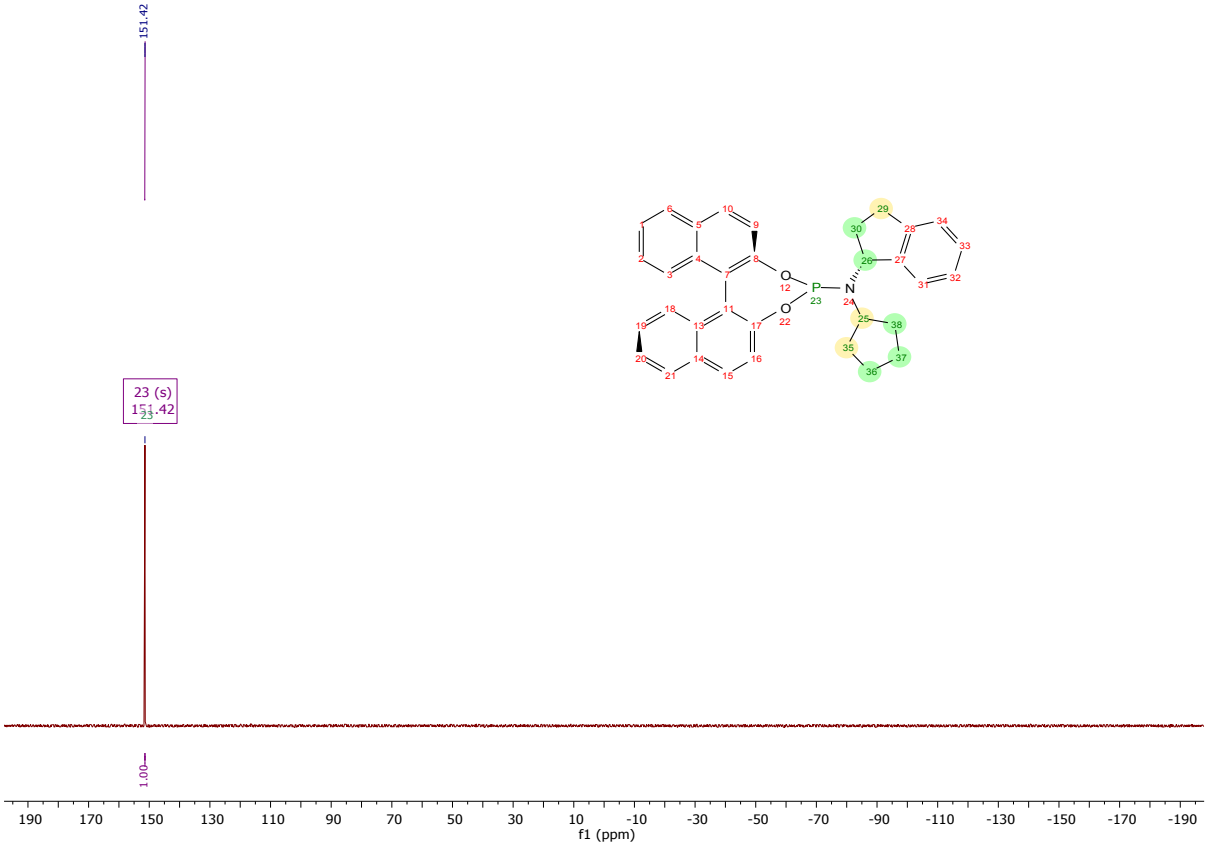
HRMS (EI^+) *m/z* calcd for $C_{34}H_{31}O_2NP$ $[M+H]^+$: 516.2087, found 516.2085.

$[\alpha]^{25}_{589}$= -109.2 (*c* 0.5, $CHCl_3$) for 99% ee.

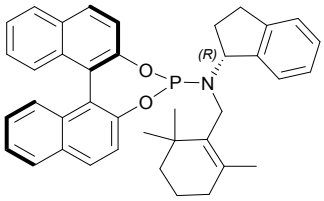


F (dd) 7.84
D (dd) 7.43
E (dd) 7.72
C (m) 7.19
G (d) 7.50
26 (q) 4.60
25 (dt) 3.24
29' (m) 2.77
29'' (dt) 2.51
30'' (m) 1.87
35',36'',37',38' (qt) 1.59
30' (m) 2.28
36',37'' (m) 1.24
f1 (ppm)


P (s) 127.15
N (s) 128.24
F (s) 143.29
L (s) 129.52
D (s) 144.24
J (s) 130.49
Z (s) 121.61
B (s) 150.12
H (s) 132.68
U (s) 124.69
A (s) 150.20
G (s) 132.83
T (s) 124.77
C (s) 150.04
I (s) 131.33
Y (s) 122.37
E (s) 144.21
K (s) 130.24
B1 (s) 121.59
25 (s) 56.34
26 (s) 60.78
26 (s) 60.89
25 (s) 56.49
30,38 (m) 35.33
36,37 (s) 24.33
29 (s) 29.91
35 (m) 34.13
36,37 (s) 24.09
f1 (ppm)


151.42
23 (s)
151.42
1.00
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
f1 (ppm)

N-((R)-2,3-dihydro-1H-inden-1-yl)-N-((2,6,6-trimethylcyclohex-1-en-1-yl)methyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L15



General Procedure E: Triethylamine (2.95mL, 21.193 mmol, 5.0 eq.), PCl_3 (0.37 mL, 4.239 mmol, 1.0 eq.), CH_2Cl_2 (40 mL), (R)-N-((2,6,6-trimethylcyclohex-1-en-1-yl)methyl)-2,3-dihydro-1H-inden-1-amine (1142 mg, 4.239 mmol, 1.0 eq.), (R)-binaphthol (1213 mg, 4.239 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-((R)-2,3-dihydro-1H-inden-1-yl)-N-((2,6,6-trimethylcyclohex-1-en-1-yl)methyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (216 mg, 0.3815 mmol, 9%) as a foamy white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 8.7 Hz, 1H), 7.82 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.74 – 7.63 (m, 2H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.39 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.35 – 7.04 (m, 11H), 4.77 (td, *J* = 7.9, 2.5 Hz, 1H), 3.26 (qd, *J* = 11.5, 6.7 Hz, 2H), 2.78 (dt, *J* = 16.0, 6.6 Hz, 1H), 2.51 (dt, *J* = 16.4, 8.4 Hz, 1H), 2.07 (td, *J* = 8.1, 6.5 Hz, 2H), 1.86 (t, *J* = 6.3 Hz, 2H), 1.74 (s, 3H), 1.54 – 1.44 (m, 3H), 1.43 – 1.34 (m, 2H), 1.03 (s, 6H).

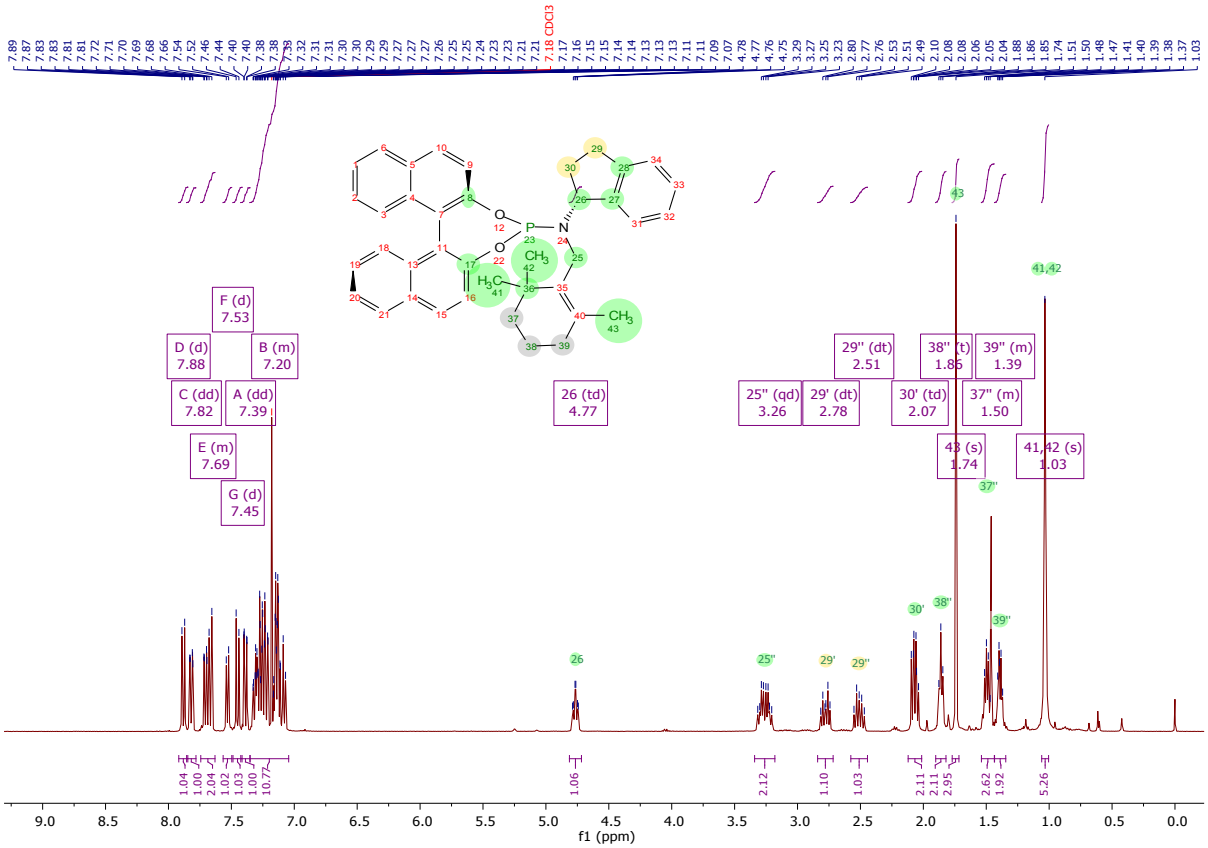
^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.7, 150.6, 150.2, 143.9, 141.8, 135.2, 135.2, 132.9, 132.9, 132.7, 131.3, 131.3, 131.2, 130.3, 130.2, 129.6, 128.2, 128.2, 127.3, 127.2, 127.1, 126.0, 125.9, 125.7, 125.0, 124.9, 124.6, 124.3, 124.3, 124.1, 122.5, 122.4, 122.4, 121.4, 121.3, 61.1, 61.0, 41.6, 41.3, 39.3, 34.8, 32.6, 30.5, 30.2, 28.9, 28.9, 28.3, 28.3, 20.7, 20.6, 19.2.

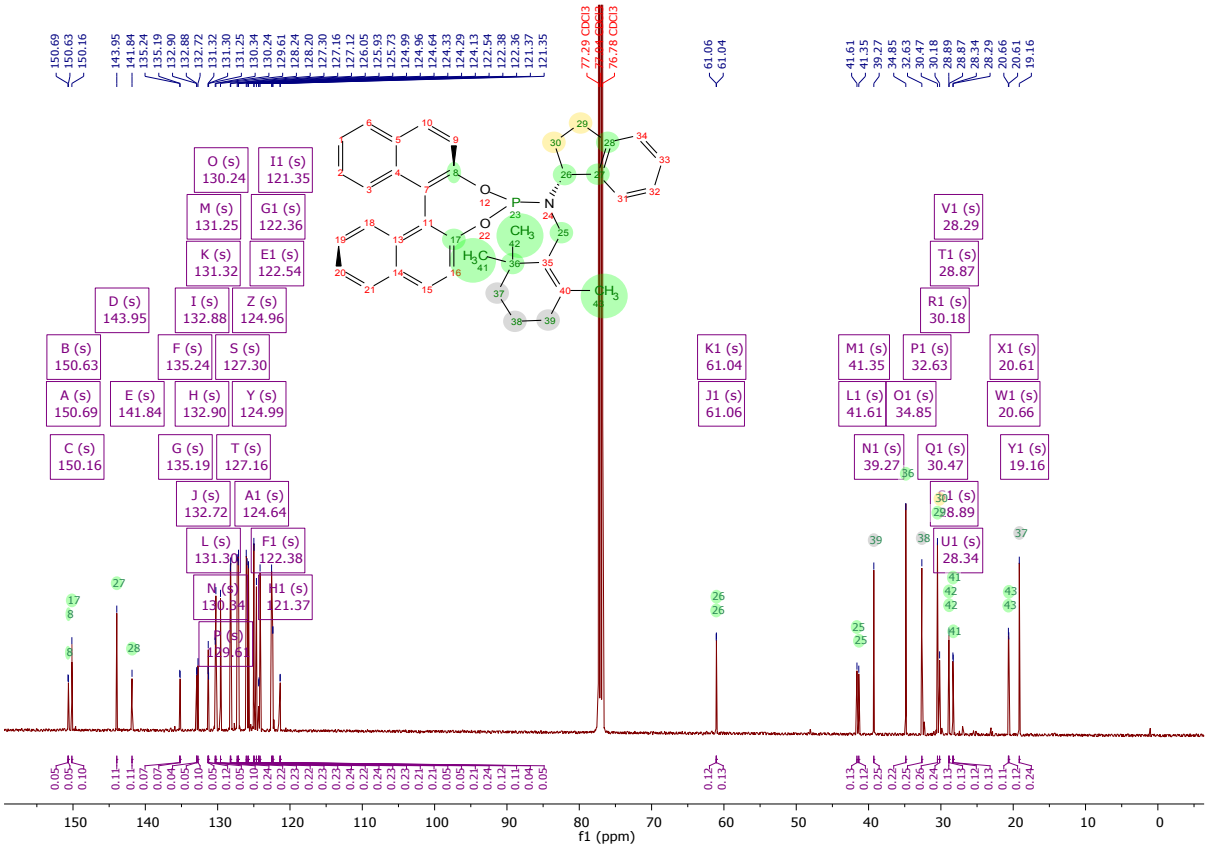
^{31}P NMR (162 MHz, Chloroform-*d*) δ 147.1.

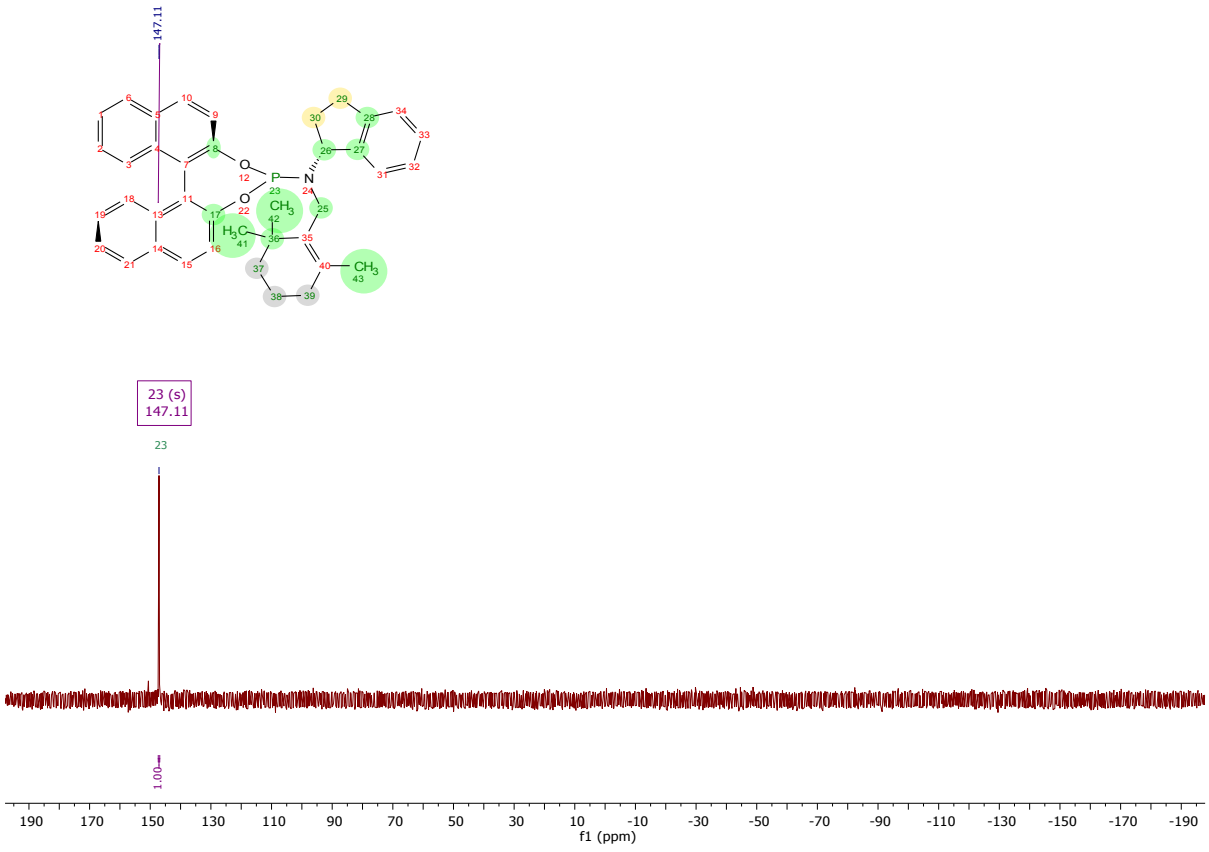
IR υ_{max} (film): 2360, 2340, 1230, 1069.

HRMS (EI$^+$) *m/z* calcd for C_{39} H_{39} O_2 N P $[M+H]^+$: 584.2713, found 584.2708.

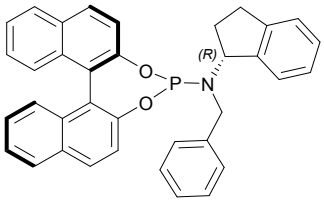
$[\alpha]^{25}_{589}$= -15.0 (*c* 0.5, $CHCl_3$) for 99% ee.


F (d) 7.53
D (d) 7.88
B (m) 7.20
C (dd) 7.82
A (dd) 7.39
E (m) 7.69
G (d) 7.45
26 (td) 4.77
29'' (dt) 2.51
38'' (t) 1.85
39'' (m) 1.39
25'' (qd) 3.26
29' (dt) 2.78
30' (td) 2.07
37'' (m) 1.50
43 (s) 1.74
41,42 (s) 1.03
f1 (ppm)


O (s) 130.24
I1 (s) 121.35
M (s) 131.25
G1 (s) 122.36
K (s) 131.32
E1 (s) 122.54
D (s) 143.95
I (s) 132.88
Z (s) 124.96
B (s) 150.63
F (s) 135.24
S (s) 127.30
A (s) 150.69
E (s) 141.84
H (s) 132.90
Y (s) 124.99
C (s) 150.16
G (s) 135.19
T (s) 127.16
J (s) 132.72
A1 (s) 124.64
L (s) 131.30
F1 (s) 122.38
N (s) 130.84
H1 (s) 121.37
R (s) 129.61
K1 (s) 61.04
J1 (s) 61.06
V1 (s) 28.29
T1 (s) 28.87
R1 (s) 30.18
M1 (s) 41.35
P1 (s) 32.63
X1 (s) 20.61
L1 (s) 41.61
O1 (s) 34.85
W1 (s) 20.66
N1 (s) 39.27
Q1 (s) 30.47
Y1 (s) 19.16
f1 (ppm)


147.11
23 (s)
147.11
23
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

N-benzyl-N-((R)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L9



General Procedure E: Triethylamine (1.56 mL, 11.195 mmol, 5.0 eq.), PCl_3 (0.20 mL, 2.239 mmol, 1.0 eq.), CH_2Cl_2 (20 mL), (R)-N-benzyl-2,3-dihydro-1H-inden-1-amine (500 mg, 2.239 mmol, 1.0 eq.), (R)-binaphthol (641 mg, 2.239 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-benzyl-N-((R)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (396 mg, 0.739 mmol, 33%) as a foamy white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 8.8 Hz, 1H), 7.87 – 7.79 (m, 1H), 7.78 – 7.66 (m, 2H), 7.52 (dd, *J* = 8.7, 0.9 Hz, 1H), 7.41 – 7.19 (m, 6H), 7.19 – 7.02 (m, 11H), 4.80 (dt, *J* = 11.7, 7.4 Hz, 1H), 3.98 (dd, *J* = 15.8, 8.6 Hz, 1H), 3.87 (dd, *J* = 15.8, 7.2 Hz, 1H), 2.79 – 2.66 (m, 1H), 2.62 – 2.49 (m, 1H), 2.17 – 2.02 (m, 1H), 2.00 – 1.86 (m, 1H).

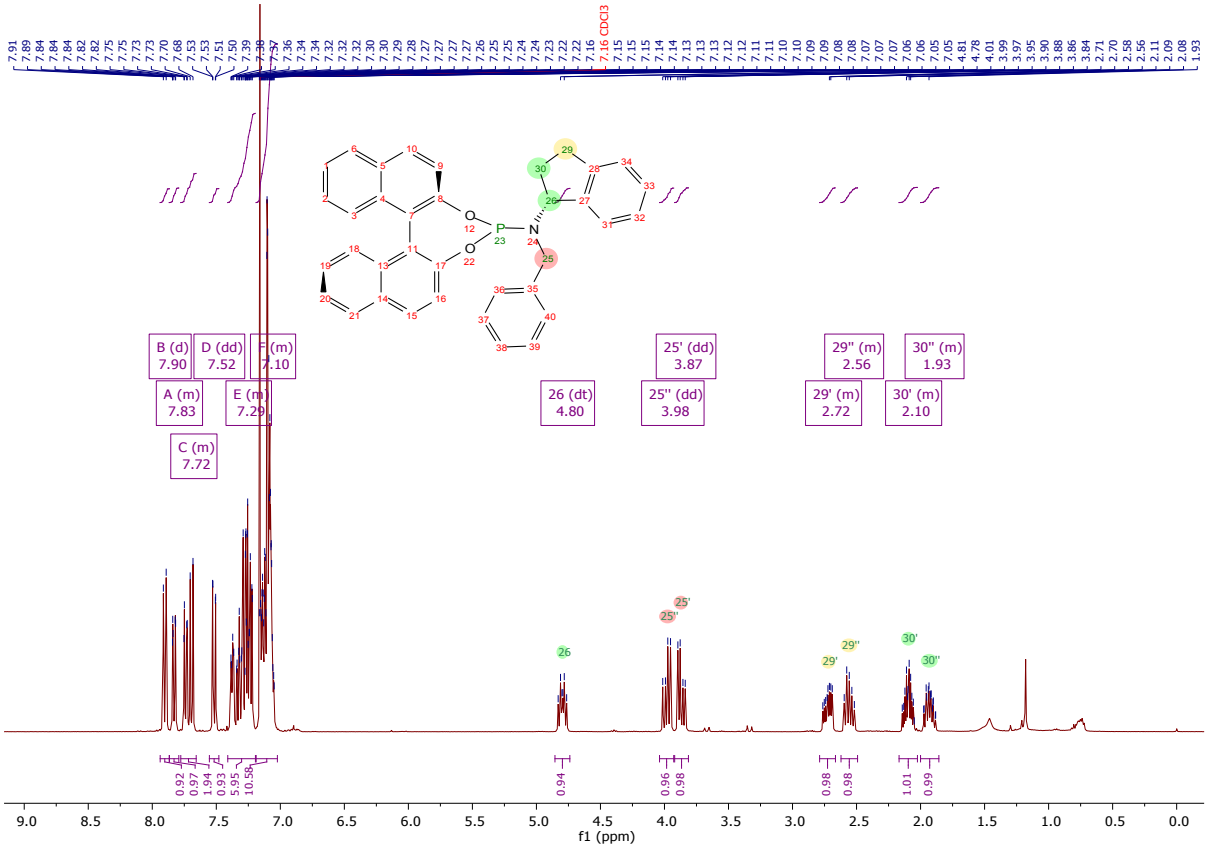
^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.0, 149.9, 149.5, 143.7, 142.7, 142.6, 140.2, 140.2, 132.9, 132.6, 131.4, 130.6, 130.3, 129.8, 128.3, 128.2, 128.0, 127.9, 127.6, 127.1, 127.0, 126.7, 126.1, 126.1, 125.9, 125.1, 124.8, 124.8, 124.5, 124.2, 124.1, 122.2, 122.0, 121.9, 121.9, 62.7, 62.5, 48.2, 48.1, 33.11, 33.1, 30.5.

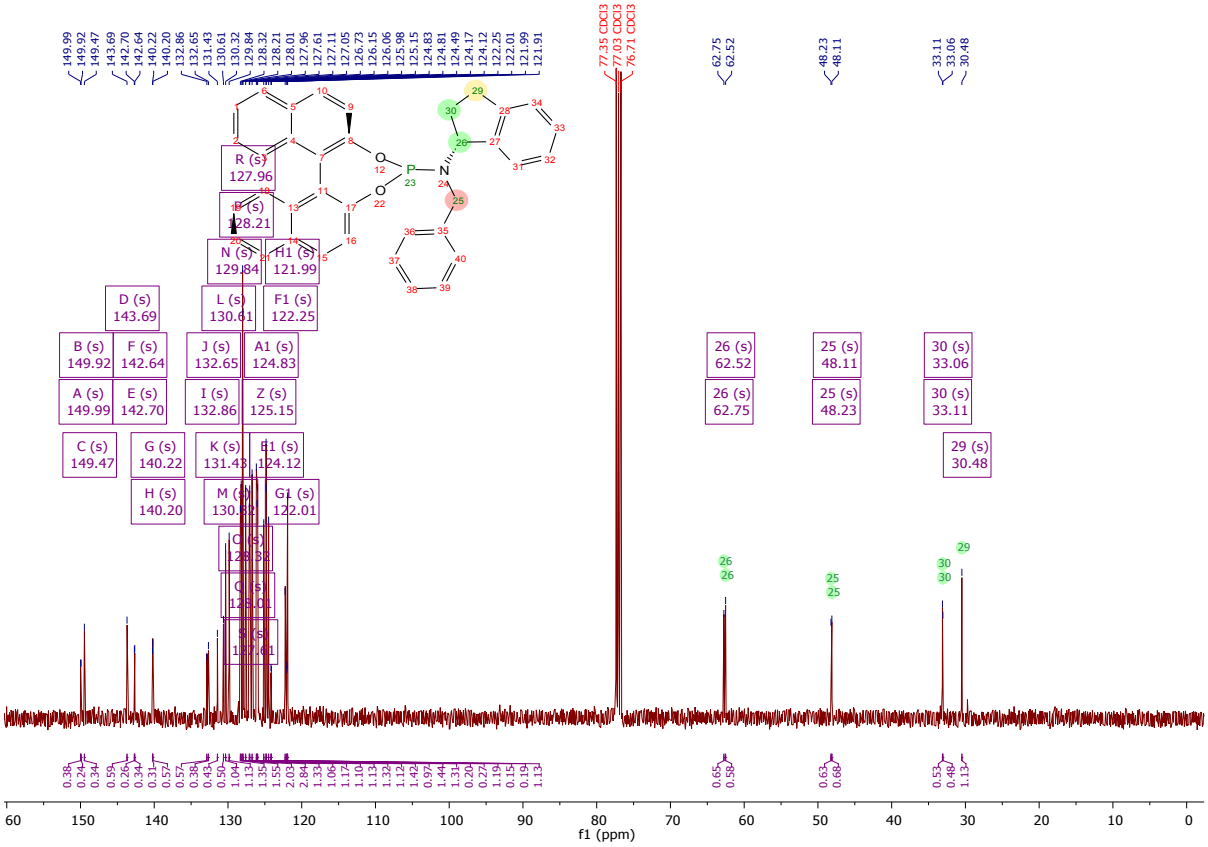
^{31}P NMR (162 MHz, Chloroform-*d*) δ 147.5.

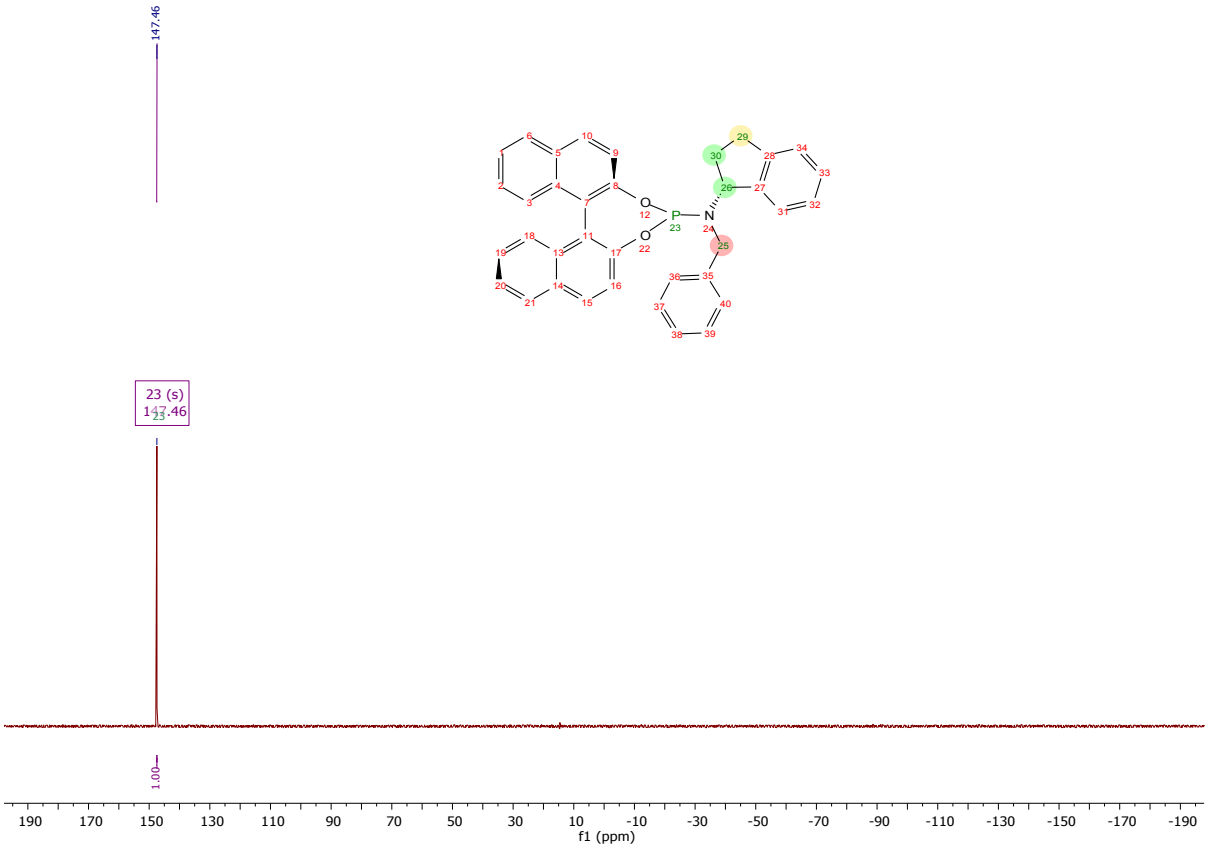
IR υ_{max} (film): 2360, 2340, 1230.

HRMS (EI$^+$) *m/z* calcd for $C_{36}H_{29}O_2NP$ $[M+H]^+$: 538.1930, found 538.1931.

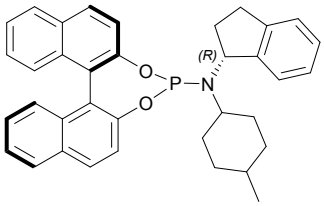
$[\alpha]^{25}_{589}$= -111.5 (*c* 0.5, $CHCl_3$) for 99% ee.


B (d) 7.90
D (dd) 7.52
F (m) 7.10
A (m) 7.83
E (m) 7.29
C (m) 7.72
26 (dt) 4.80
25' (dd) 3.87
25'' (dd) 3.98
29'' (m) 2.56
30'' (m) 1.93
29' (m) 2.72
30' (m) 2.10
f1 (ppm)


R (s) 127.96
D (s) 143.69
L (s) 130.61
F1 (s) 122.25
B (s) 149.92
F (s) 142.64
J (s) 132.65
A1 (s) 124.83
A (s) 149.99
E (s) 142.70
I (s) 132.86
Z (s) 125.15
C (s) 149.47
G (s) 140.22
K (s) 131.43
B1 (s) 124.12
H (s) 140.20
G1 (s) 122.01
26 (s) 62.52
26 (s) 62.75
25 (s) 48.11
25 (s) 48.23
30 (s) 33.06
30 (s) 33.11
29 (s) 30.48
f1 (ppm)


147.46
23 (s)
147.46
1.00
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
f1 (ppm)

N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(4-methylcyclohexyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L7



General Procedure E: Triethylamine (1.10 mL, 7.869 mmol, 5.0 eq.), PCl_3 (0.14 mL, 1.574 mmol, 1.0 eq.), CH_2Cl_2 (20 mL), (R)-N-(4-methylcyclohexyl)-2,3-dihydro-1H-inden-1-amine (361 mg, 1.574 mmol, 1.0 eq.), (R)-binaphthol (451 mg, 1.574 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(4-methylcyclohexyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (97.3 mg, 0.173 mmol, 11%) as a foamy white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 – 7.67 (m, 4H), 7.55 – 7.47 (m, 1H), 7.49 – 7.37 (m, 2H), 7.34 – 7.05 (m, 10H), 4.66 (dt, *J* = 12.2, 8.0 Hz, 1H), 2.80 (ddt, *J* = 14.2, 7.4, 3.5 Hz, 1H), 2.65 – 2.47 (m, 2H), 2.36 – 2.21 (m, 1H), 2.04 – 1.26 (m, 8H), 1.20 – 0.95 (m, 2H), 0.83 (d, *J* = 7.1 Hz, 2H), 0.64 (d, *J* = 6.5 Hz, 1H), 0.61 – 0.40 (m, 1H).

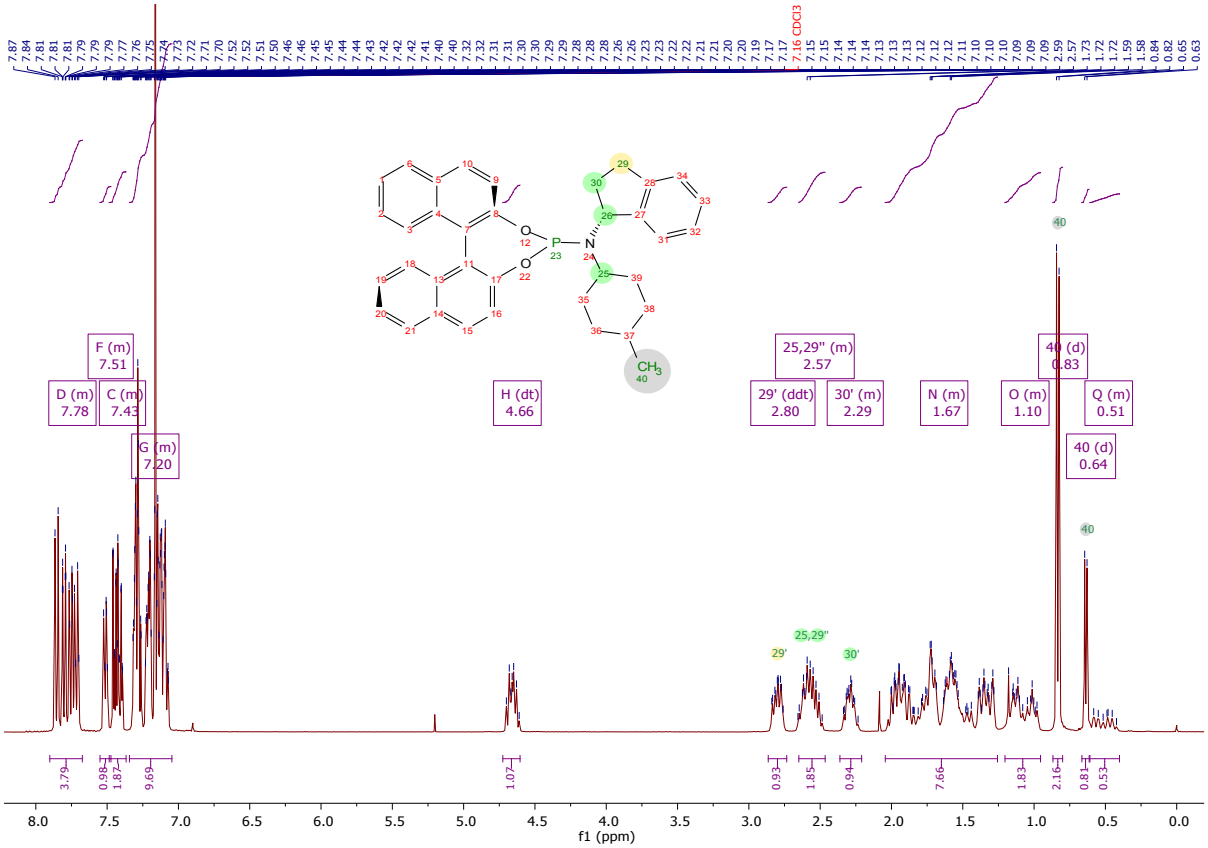
^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.4, 150.3, 150.0, 144.6 – 144.0 (m), 143.2, 132.8, 132.7, 131.3, 130.5, 130.2, 129.5, 128.3, 128.2, 127.2, 127.1, 126.4, 126.3, 125.9, 125.8, 124.8, 124.6, 124.5, 124.3, 124.1, 124.1, 122.4, 122.4, 122.2, 121.6, 121.6, 60.6, 60.5, 55.0, 54.9, 54.5, 54.4, 36.4 – 35.7 (m), 34.9, 31.8, 31.6, 31.6, 30.5 – 30.2 (m), 29.9, 29.2 – 28.6 (m), 25.9, 22.1, 17.3.

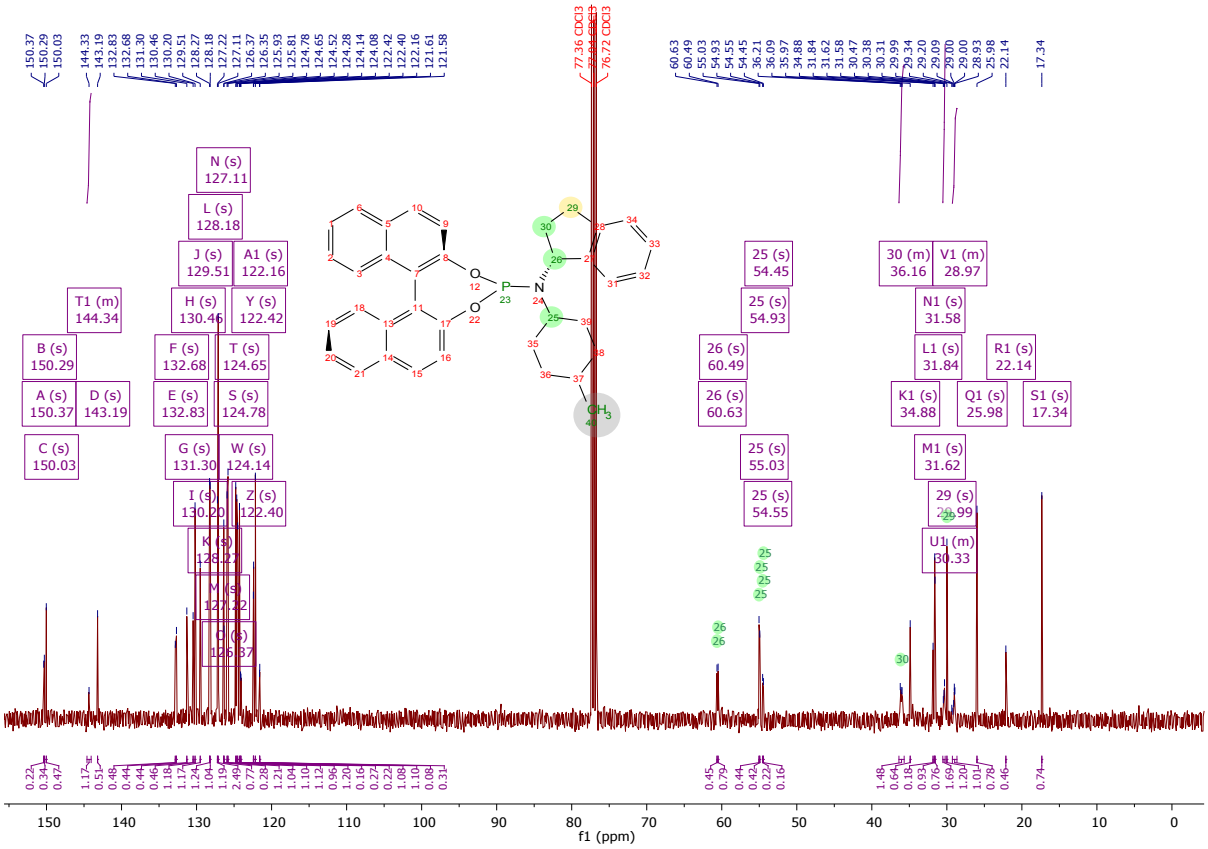
^{31}P NMR (162 MHz, Chloroform-*d*) δ 151.4.

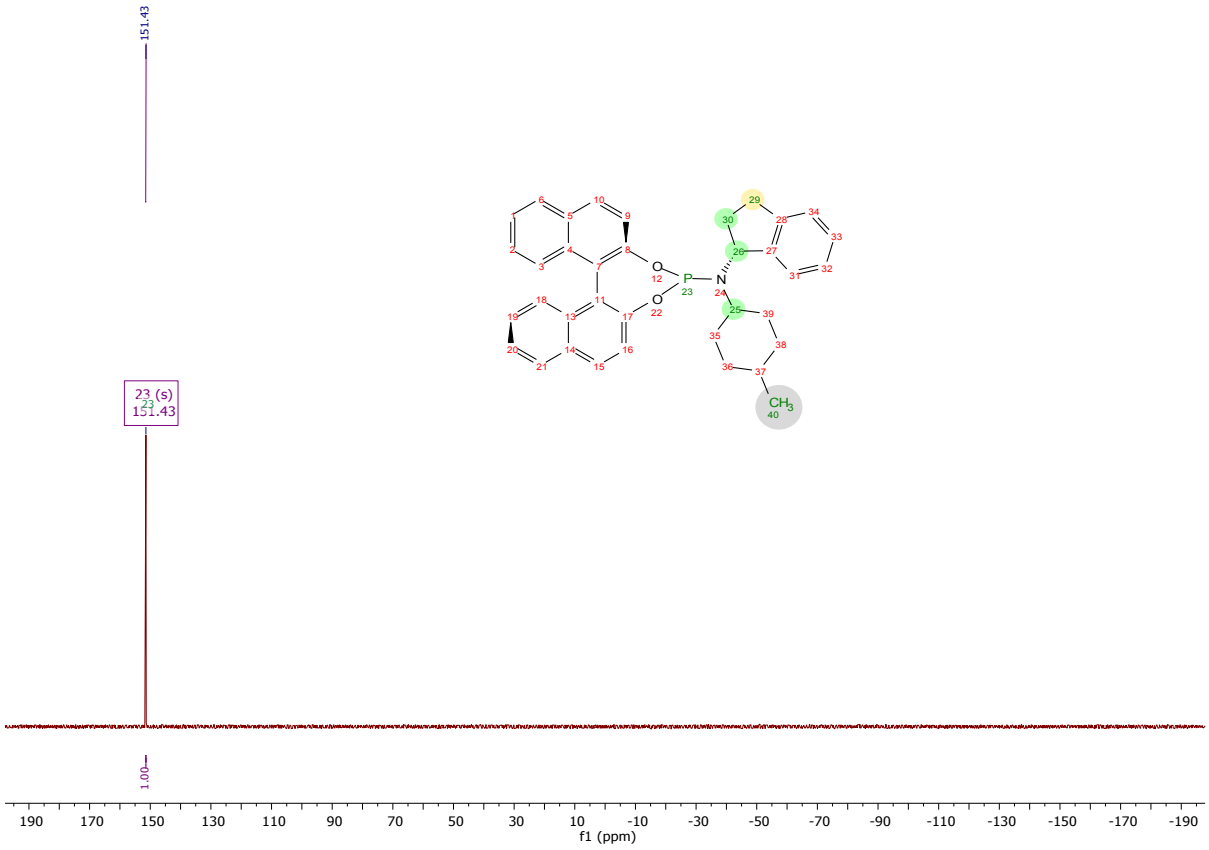
IR υ_{max} (film): 2360, 2341, 1212.

HRMS (EI$^+$) *m/z* calcd for $C_{36}H_{35}O_2NP$ $[M+H]^+$: 544.2400, found 544.2399.

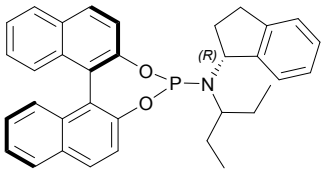
$[\alpha]^{25}_{589}$= -95.8 (*c* 1.3, $CHCl_3$) for 99% ee.


F (m) 7.51
D (m) 7.78
C (m) 7.43
G (m) 7.20
H (dt) 4.66
25,29'' (m) 2.57
29' (ddt) 2.80
30' (m) 2.29
N (m) 1.67
O (m) 1.10
40 (d) 0.83
Q (m) 0.51
40 (d) 0.64
f1 (ppm)


N (s) 127.11
L (s) 128.18
J (s) 129.51
A1 (s) 122.16
T1 (m) 144.34
H (s) 130.46
Y (s) 122.42
B (s) 150.29
F (s) 132.68
T (s) 124.65
A (s) 150.37
D (s) 143.19
E (s) 132.83
S (s) 124.78
C (s) 150.03
G (s) 131.30
W (s) 124.14
I (s) 130.20
Z (s) 122.40
25 (s) 54.45
25 (s) 54.93
26 (s) 60.49
26 (s) 60.63
25 (s) 55.03
25 (s) 54.55
30 (m) 36.16
V1 (m) 28.97
N1 (s) 31.58
L1 (s) 31.84
R1 (s) 22.14
K1 (s) 34.88
Q1 (s) 25.98
S1 (s) 17.34
M1 (s) 31.62
29 (s)
U1 (m) 30.33
f1 (ppm)


151.43
23 (s)
23
151.43
1.00
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
f1 (ppm)
O
P
N
O
CH3
40

N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(pentan-3-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L17



General Procedure E: Triethylamine (2.18 mL, 15.615 mmol, 5.0 eq.), PCl_3 (0.27 mL, 3.123 mmol, 1.0 eq.), CH_2Cl_2 (20 mL), (R)-N-(pentan-3-yl)-2,3-dihydro-1H-inden-1-amine (635 mg, 3.123 mmol, 1.0 eq.), (R)-binaphthol (894 mg, 3.123 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(pentan-3-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (894 mg, 1.718 mmol, 55%) as a foamy white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 8.8 Hz, 1H), 7.93 – 7.86 (m, 3H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.47 – 7.16 (m, 9H), 4.77 (dt, *J* = 14.9, 7.8 Hz, 1H), 3.06 – 2.94 (m, 1H), 2.85 – 2.76 (m, 1H), 2.76 – 2.64 (m, 1H), 2.51 – 2.37 (m, 1H), 2.28 – 2.13 (m, 1H), 1.98 – 1.83 (m, 1H), 1.82 – 1.66 (m, 1H), 1.66 – 1.42 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.76 (t, *J* = 7.4 Hz, 3H).

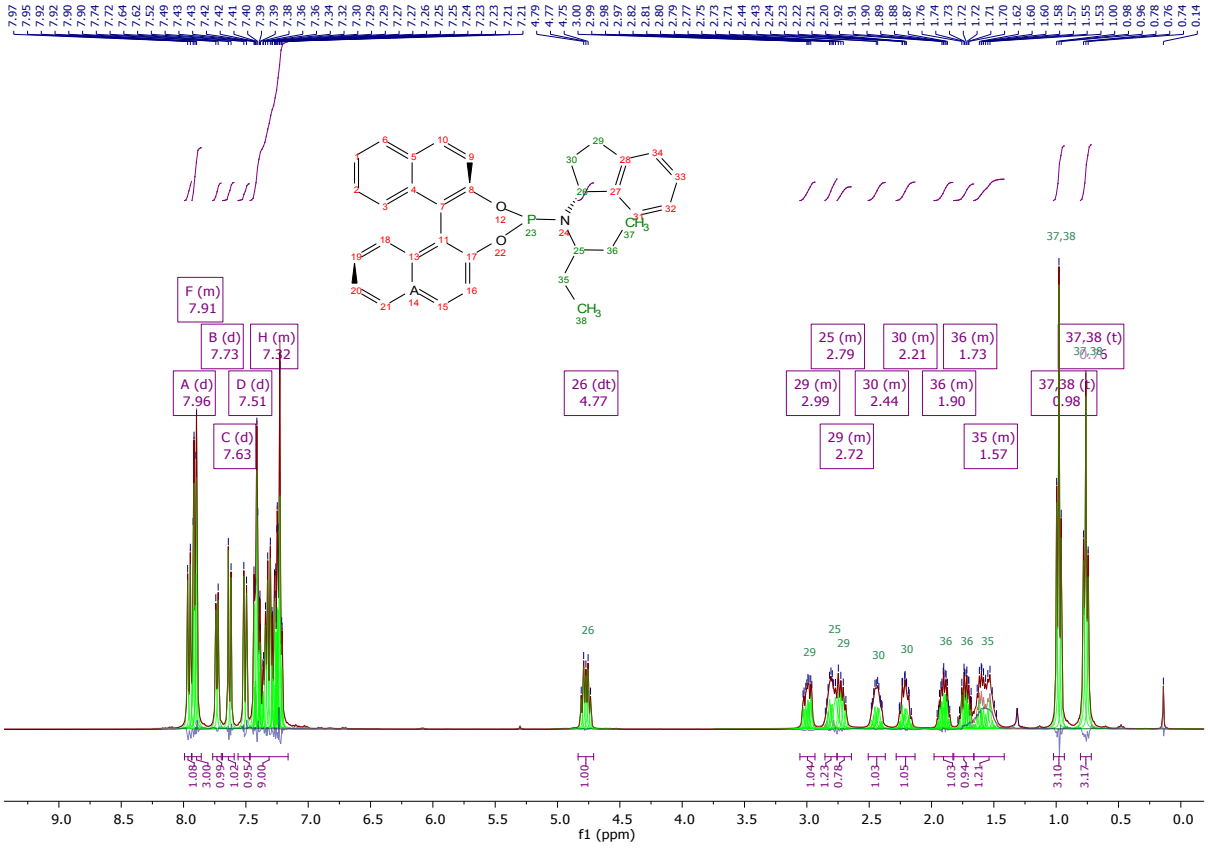
^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.3, 150.3, 149.9, 144.4, 143.4, 132.8, 132.8, 131.3, 130.4, 130.2, 129.6, 128.3, 128.21 127.4, 127.2, 127.1, 126.4, 125.9, 125.9, 125.2, 124.8, 124.7, 124.3, 124.1, 124.0, 122.4, 122.4, 122.3, 59.9, 59.8, 57.9, 57.9, 36.7 – 36.2 (m), 30.4, 29.5, 29.5, 27.3 – 27.1 (m), 11.5, 11.5.

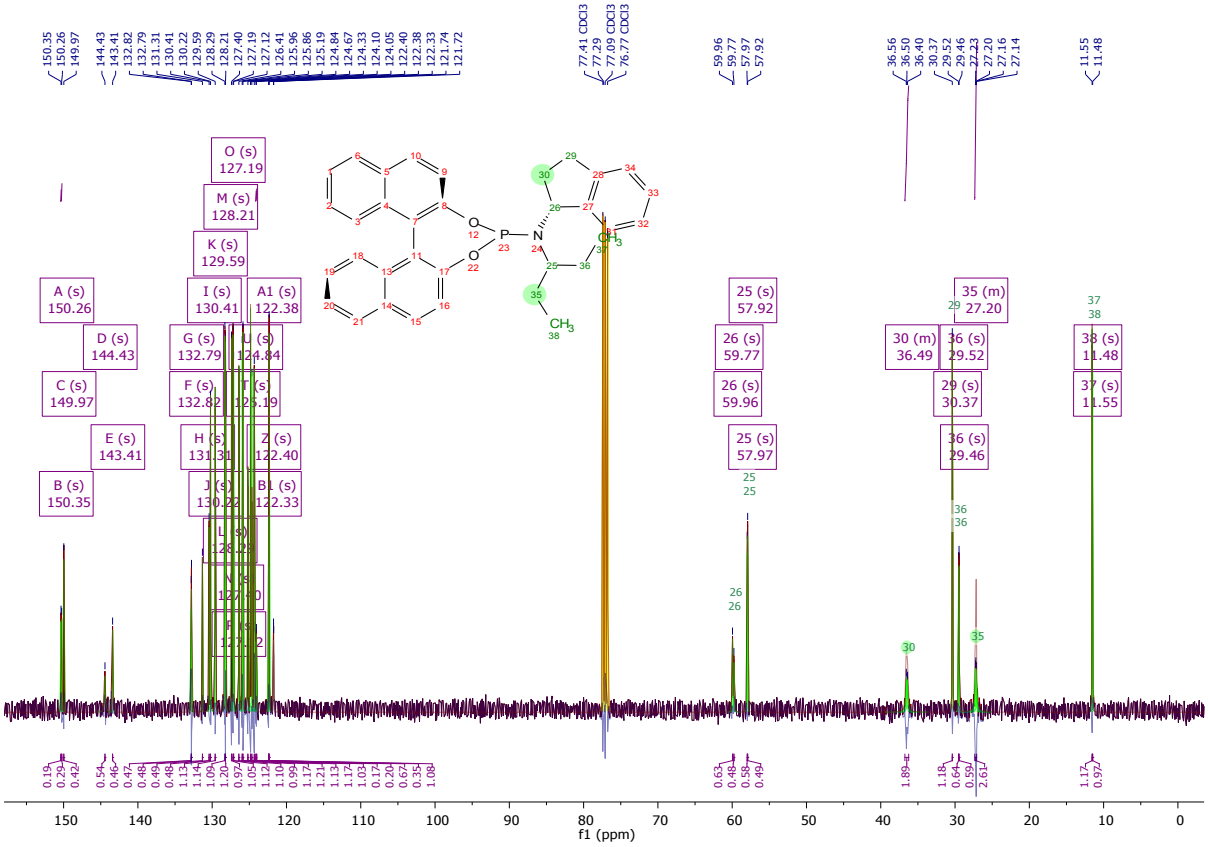
^{31}P NMR (162 MHz, Chloroform-*d*) δ 149.3.

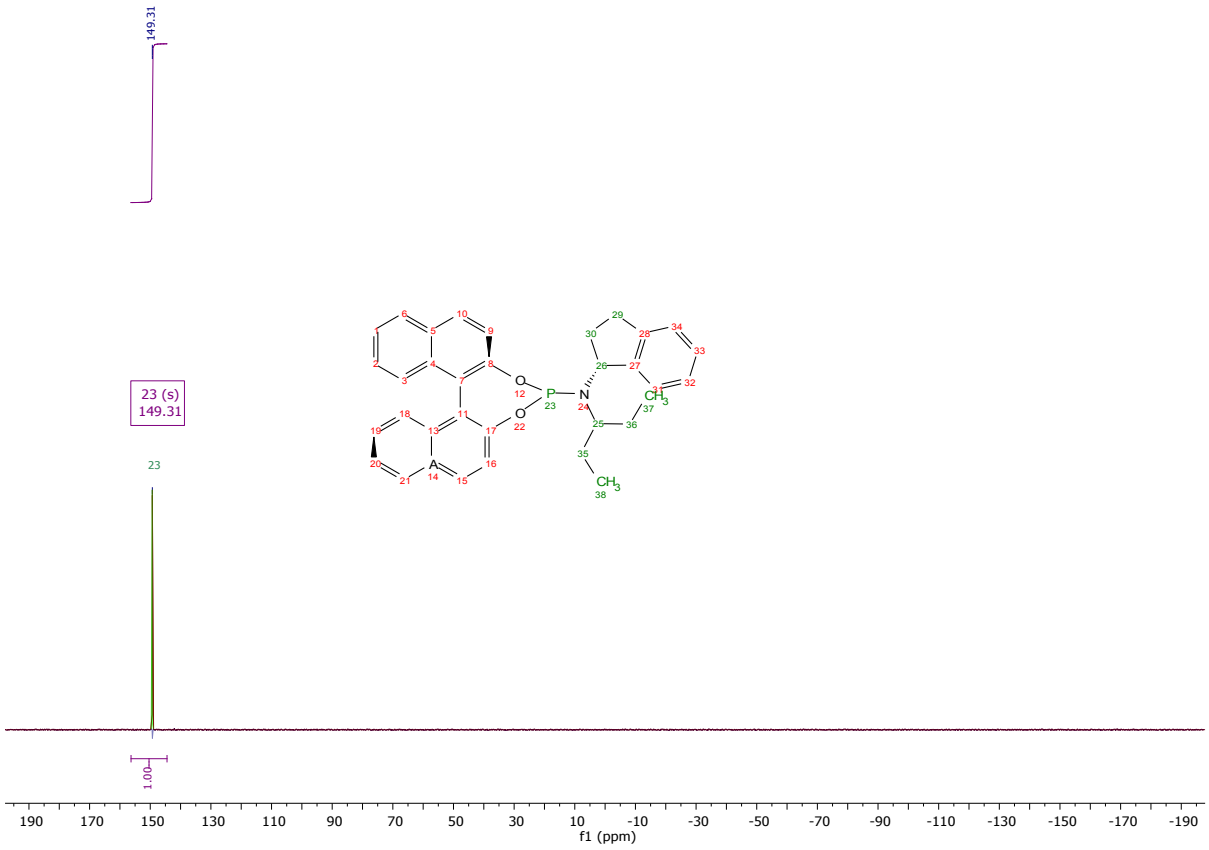
IR υ_{max} (film): 2360, 1212.

HRMS (EI$^+$) *m/z* calcd for $C_{34}H_{33}O_2NP$ $[M+H]^+$: 518.2243, found 518.2244.

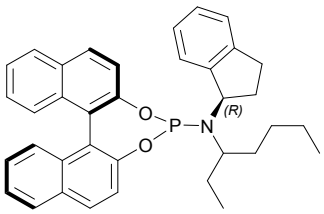
$[\alpha]^{25}_{589}$= -124.8 (*c* 1.2, $CHCl_3$) for 99% ee.


F (m) 7.91
B (d) 7.73
H (m) 7.32
A (d) 7.96
D (d) 7.51
C (d) 7.63
26 (dt) 4.77
25 (m) 2.79
30 (m) 2.21
36 (m) 1.73
37,38 (t)
29 (m) 2.99
30 (m) 2.44
36 (m) 1.90
37,38 (t) 0.98
29 (m) 2.72
35 (m) 1.57
f1 (ppm)


O (s) 127.19
M (s) 128.21
K (s) 129.59
A (s) 150.26
I (s) 130.41
A1 (s) 122.38
D (s) 144.43
G (s) 132.79
U (s) 124.84
C (s) 149.97
F (s) 132.82
T (s) 125.19
E (s) 143.41
H (s) 131.31
Z (s) 122.40
B (s) 150.35
J (s) 130.22
B1 (s) 122.33
25 (s) 57.92
26 (s) 59.77
26 (s) 59.96
25 (s) 57.97
35 (m) 27.20
30 (m) 36.49
36 (s) 29.52
29 (s) 30.37
36 (s) 29.46
38 (s) 11.48
37 (s) 11.55
f1 (ppm)


149.31
23 (s)
149.31
23
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(heptan-3-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L16



General Procedure E: Triethylamine (1.19 mL, 8.566 mmol, 5.0 eq.), PCl_3 (0.15 mL, 1.713 mmol, 1.0 eq.), CH_2Cl_2 (20 mL), (1R)-N-(heptan-3-yl)-2,3-dihydro-1H-inden-1-amine (396 mg, 1.713 mmol, 1.0 eq.), (R)-binaphthol (490 mg, 1.713 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(heptan-3-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (40 mg, 0.068 mmol, 4%) as a foamy white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 – 7.75 (m, 4H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.36 – 7.22 (m, 4H), 7.26 – 7.07 (m, 6H), 4.65 (dt, *J* = 14.7, 7.5 Hz, 1H), 2.95 – 2.83 (m, 1H), 2.81 – 2.70 (m, 1H), 2.69 – 2.56 (m, 1H), 2.40 – 2.25 (m, 1H), 2.09 (p, *J* = 8.8 Hz, 1H), 1.81 – 1.64 (m, 1H), 1.63 – 1.51 (m, 1H), 1.49 – 1.27 (m, 3H), 1.26 – 1.01 (m, 4H), 0.90 – 0.71 (m, 6H), 0.64 (t, *J* = 7.4 Hz, 2H).

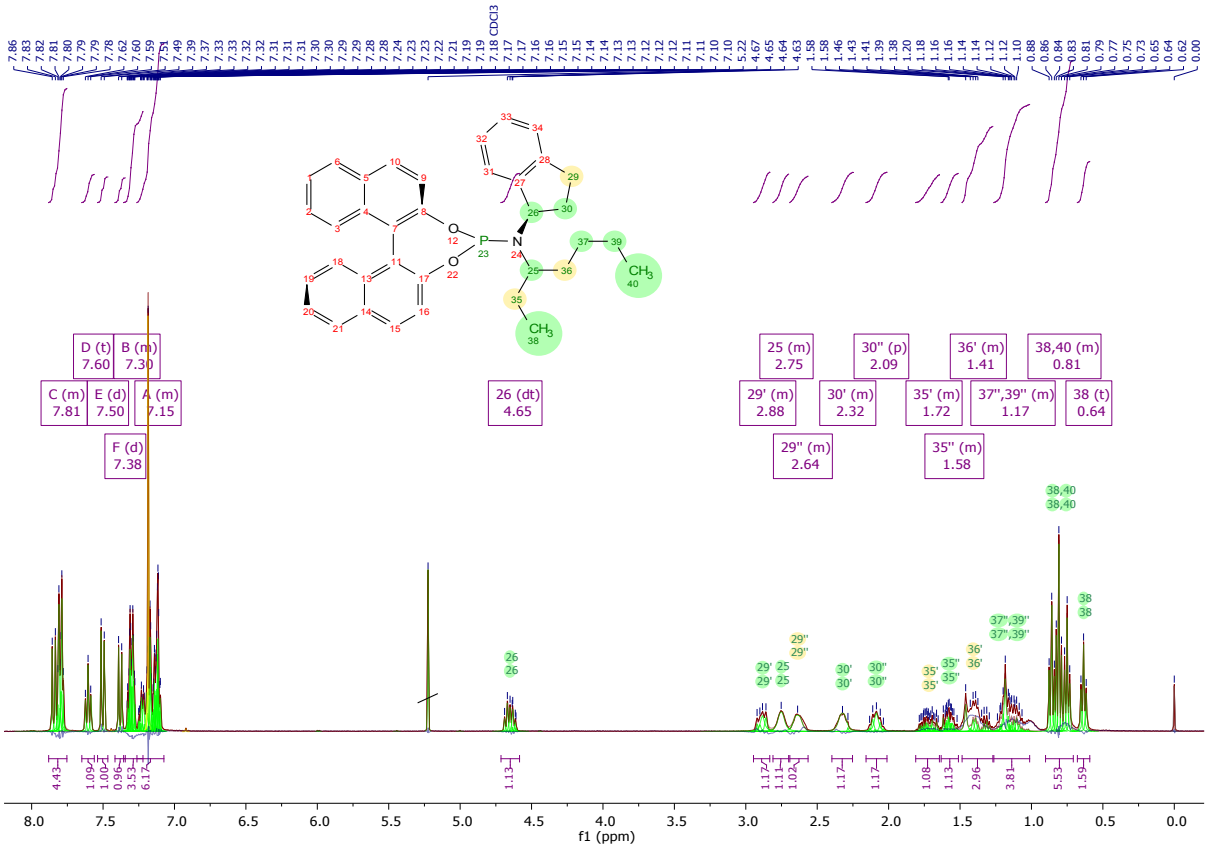
^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.3, 150.3, 150.2, 150.2, 149.9, 149.9, 144.5, 143.4, 143.3, 132.8, 132.7, 131.3, 130.4, 130.4, 130.2, 129.5, 129.5, 128.2, 128.1, 127.4, 127.3, 127.1, 127.1, 127.1, 126.4, 126.4, 125.9, 125.8, 125.2, 125.1, 124.8, 124.6, 124.3, 124.3, 124.0, 123.9, 122.3, 122.3, 122.3, 122.2, 121.8, 121.7, 121.7, 121.7, 59.8, 59.6, 56.7, 56.6, 56.4, 56.3, 36.8, 36.8, 37.0 – 35.9 (m), 34.7 – 33.9 (m), 30.4, 29.5, 29.5, 29.4, 28.7, 28.0 – 27.1 (m), 23.1, 22.8, 14.2, 14.1, 11.5, 11.4.

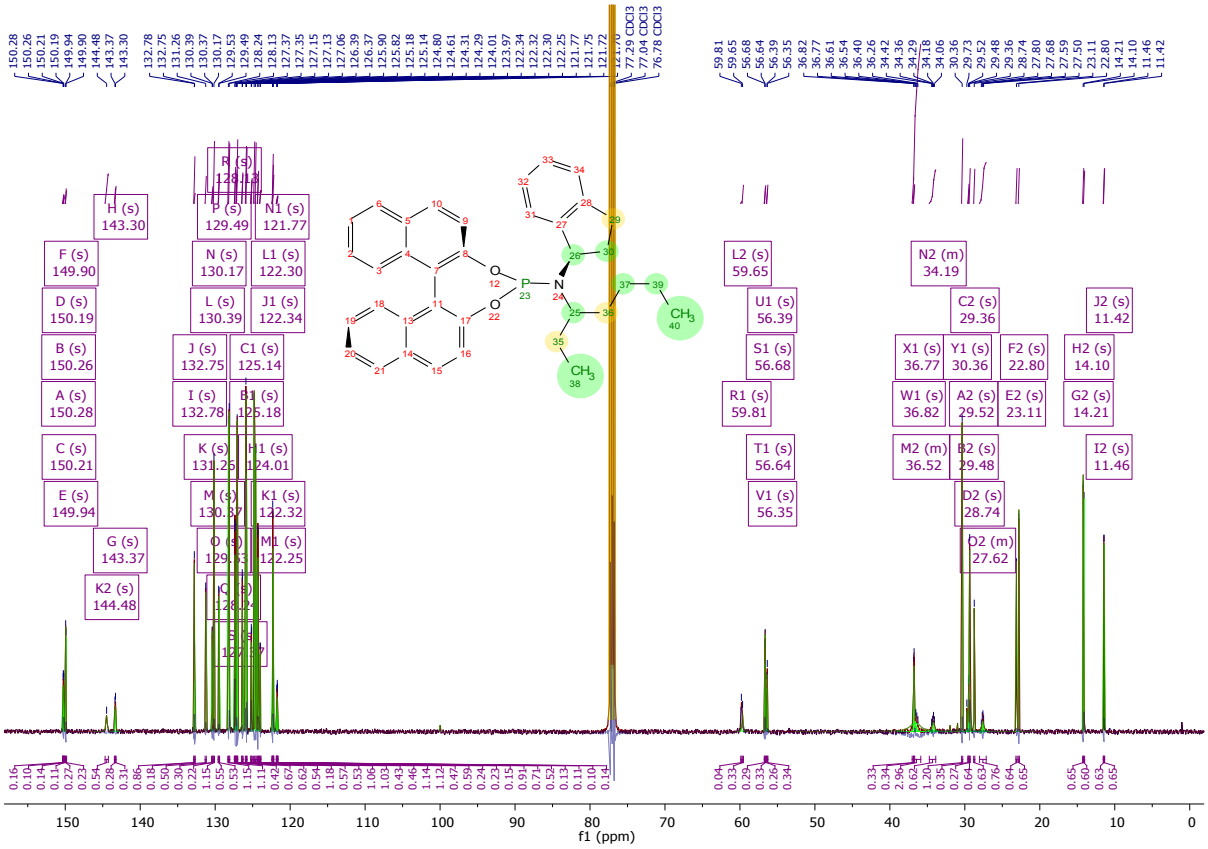
^{31}P NMR (162 MHz, Chloroform-*d*) δ 149.6, 149.5.

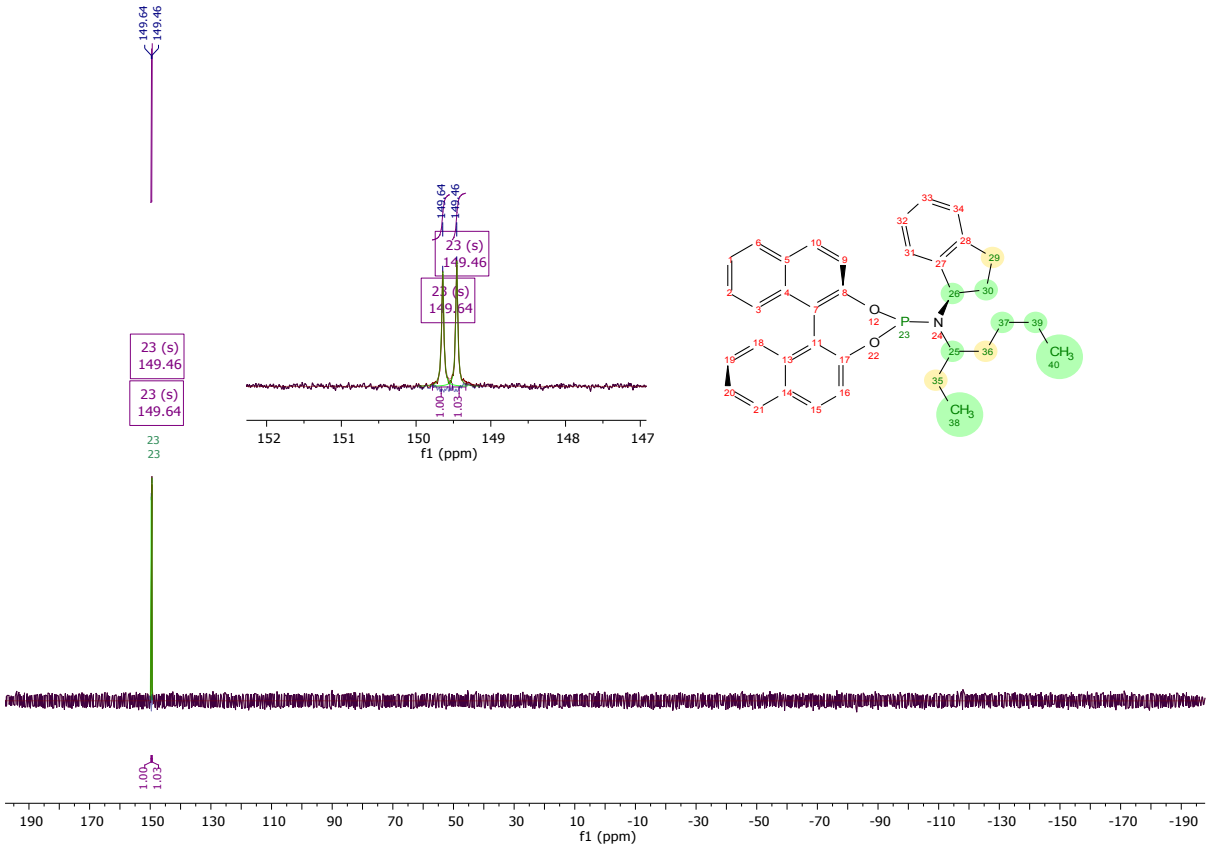
IR υ_{max} (film): 2956, 2932, 2360, 1430, 1212.

HRMS (EI^+) *m/z* calcd for $C_{36}H_{37}O_2NP$ $[M+H]^+$: 546.2556, found 546.2555.

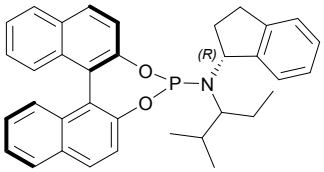
$[\alpha]^{25}_{589}$= -106.9 (*c* 1.5, $CHCl_3$) for a mixture of diastereoisomers at 99% ee.


CDCl3
D (t) 7.60
B (m) 7.30
C (m) 7.81
E (d) 7.50
A (m) 7.15
F (d) 7.38
26 (dt) 4.65
25 (m) 2.75
30" (p) 2.09
36' (m) 1.41
38,40 (m) 0.81
29' (m) 2.88
30' (m) 2.32
35' (m) 1.72
37",39" (m) 1.17
38 (t) 0.64
29" (m) 2.64
35" (m) 1.58
f1 (ppm)


H (s) 143.30
P (s) 129.49
N1 (s) 121.77
F (s) 149.90
N (s) 130.17
L1 (s) 122.30
D (s) 150.19
L (s) 130.39
J1 (s) 122.34
B (s) 150.26
J (s) 132.75
C1 (s) 125.14
A (s) 150.28
I (s) 132.78
B1 (s) 125.18
C (s) 150.21
K (s) 131.25
H1 (s) 124.01
E (s) 149.94
K1 (s) 122.32
G (s) 143.37
M1 (s) 122.25
K2 (s) 144.48
L2 (s) 59.65
U1 (s) 56.39
S1 (s) 56.68
R1 (s) 59.81
T1 (s) 56.64
V1 (s) 56.35
N2 (m) 34.19
C2 (s) 29.36
J2 (s) 11.42
X1 (s) 36.77
Y1 (s) 30.36
F2 (s) 22.80
H2 (s) 14.10
W1 (s) 36.82
A2 (s) 29.52
E2 (s) 23.11
G2 (s) 14.21
M2 (m) 36.52
B2 (s) 29.48
I2 (s) 11.46
D2 (s) 28.74
O2 (m) 27.62
f1 (ppm)


149.64
149.46
23 (s)
149.46
23 (s)
149.64
23
23
1.00
1.03
152
151
150
149
148
147
f1 (ppm)
O
P
N
O
CH3
CH3
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
f1 (ppm)

N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(2-methylpentan-3-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L18



General Procedure E: Triethylamine (1.84 mL, 13.227 mmol, 5.0 eq.), PCl_3 (0.23 mL, 2.645 mmol, 1.0 eq.), CH_2Cl_2 (20 mL), (1R)-N-(2-methylpentan-3-yl)-2,3-dihydro-1H-inden-1-amine (575 mg, 2.645 mmol, 1.0 eq.), (R)-binaphthol (757 mg, 2.645 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(2-methylpentan-3-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (577 mg, 1.084 mmol, 41%) as a foamy white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.05 – 7.81 (m, 9H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.48 – 7.07 (m, 20H), 4.89 – 4.77 (m, 2H), 3.00 – 2.86 (m, 2H), 2.70 – 2.54 (m, 4H), 2.31 – 2.16 (m, 2H), 2.19 – 2.02 (m, 4H), 1.93 – 1.78 (m, 2H), 1.72 – 1.62 (m, 1H), 1.60 – 1.50 (m, 1H), 1.16 – 1.08 (m, 3H), 1.06 – 0.93 (m, 11H), 0.71 (d, *J* = 7.0 Hz, 2H).

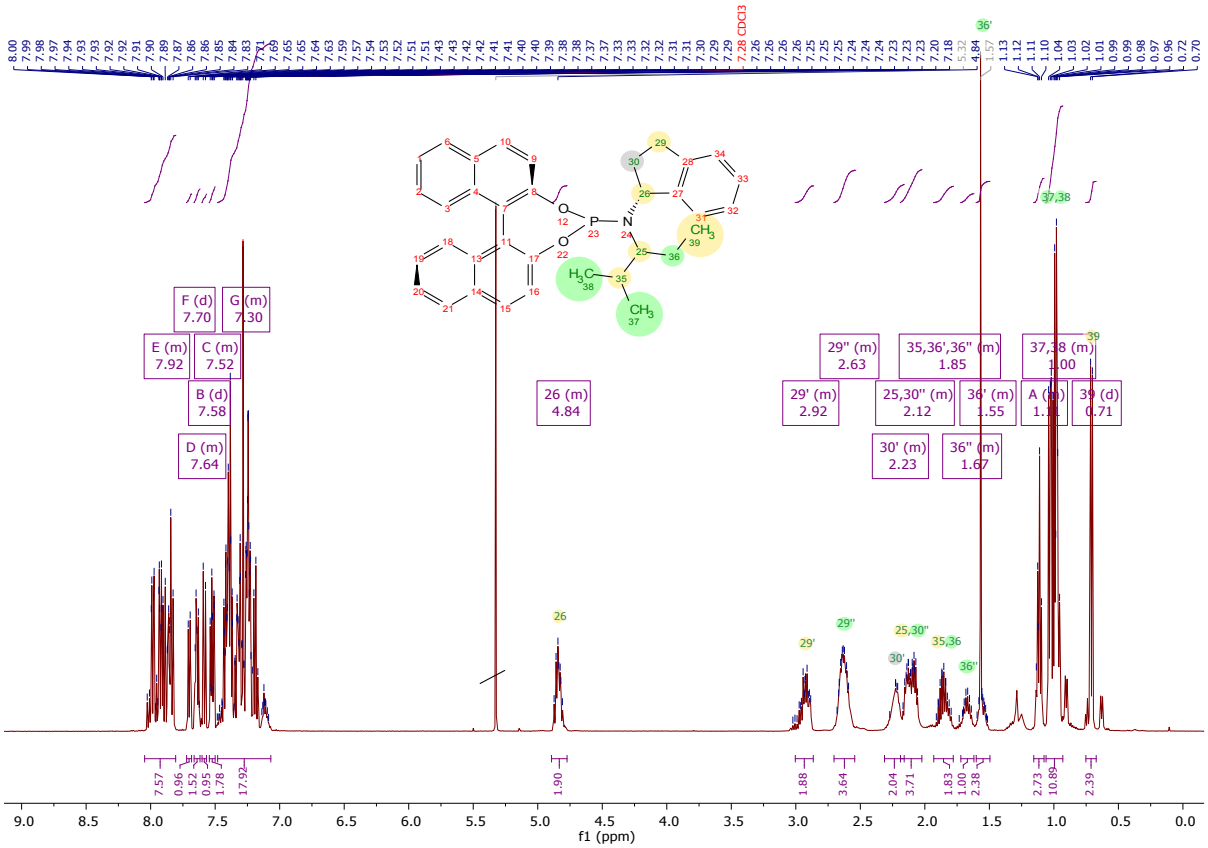
^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.7, 150.6, 150.3, 150.3, 150.0, 149.9, 144.5, 144.2, 143.2, 142.8, 132.8, 132.8, 131.3, 130.4, 130.3, 130.3, 130.2, 129.6, 128.3, 128.2, 128.1, 127.5, 127.5, 127.2, 127.1, 126.1, 126.1, 125.9, 125.9, 125.8, 125.8, 124.7, 124.7, 124.3, 124.2, 122.7, 122.4, 122.3, 122.3, 121.5, 121.5, 121.2, 121.2, 62.3, 62.1, 60.9, 60.8, 34.7 – 33.8 (m), 33.7, 33.6, 32.6, 32.5, 30.6, 30.3, 24.8 – 24.4 (m), 22.7, 22.5, 21.5, 20.9, 18.6, 18.6, 17.7, 17.7, 11.3.

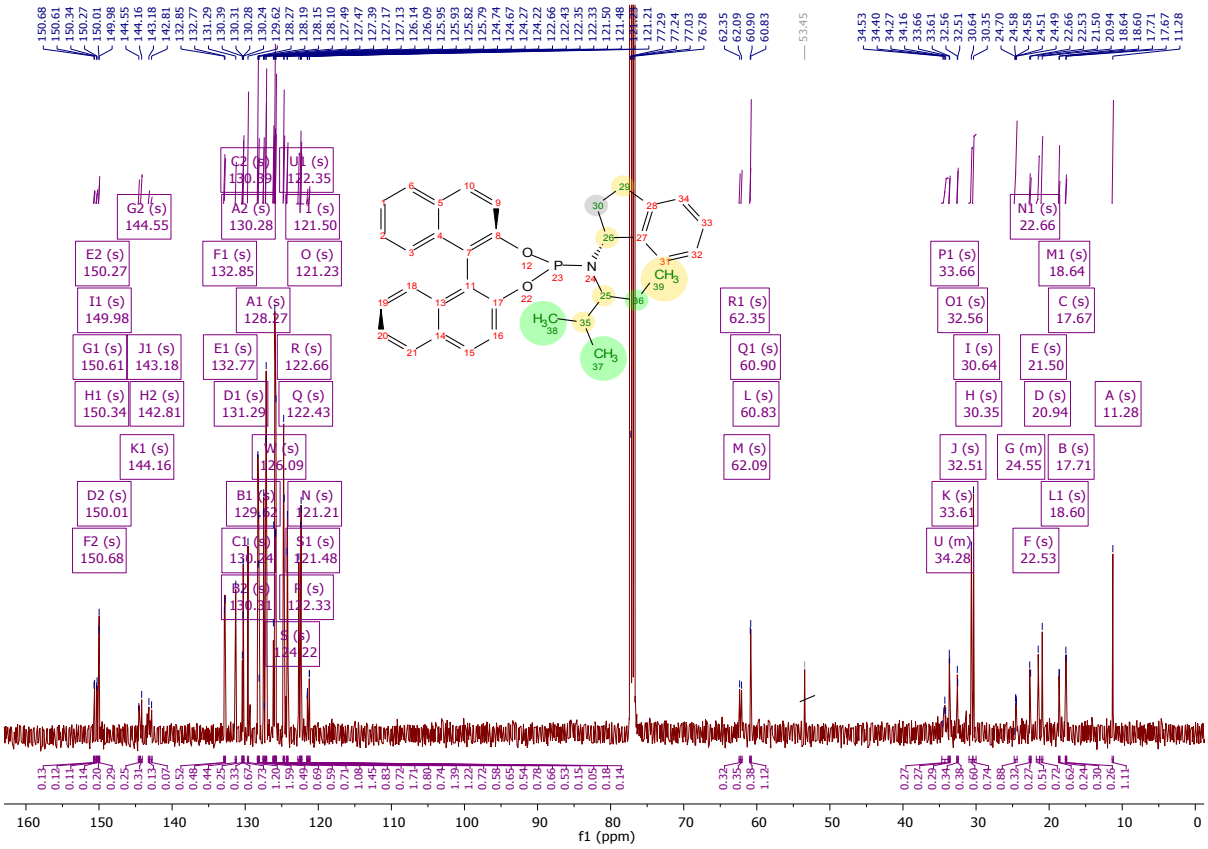
^{31}P NMR (202 MHz, Chloroform-*d*) δ 148.6, 147.9.

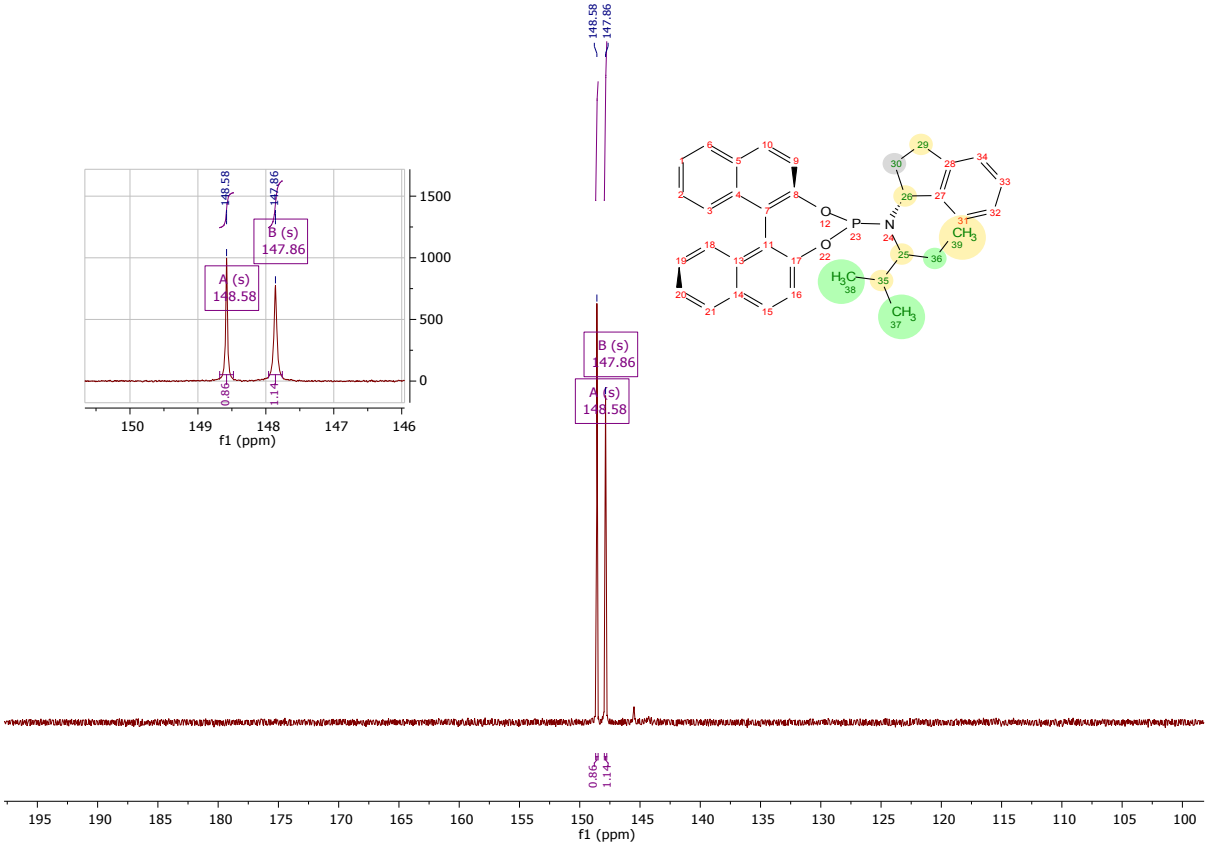
IR υ_{max} (film): 2958, 2870, 1431, 1231.

HRMS (EI^+) *m/z* calcd for $C_{35}H_{35}O_2NP$ $[M+H]^+$: 532.2400, found 532.2408.

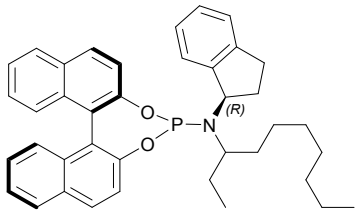
$[\alpha]^{25}_{589}$= -129.0 (*c* 1.0, $CHCl_3$) for a mixture of diastereoisomers at 99% ee.


F (d) 7.70
G (m) 7.30
E (m) 7.92
C (m) 7.52
B (d) 7.58
D (m) 7.64
26 (m) 4.84
29" (m) 2.63
29' (m) 2.92
35,36',36" (m) 1.85
25,30" (m) 2.12
36' (m) 1.55
37,38 (m) 1.00
39 (d) 0.71
30' (m) 2.23
36" (m) 1.67
f1 (ppm)


C2 (s) 130.39
U1 (s) 122.35
G2 (s) 144.55
A2 (s) 130.28
T1 (s) 121.50
E2 (s) 150.27
F1 (s) 132.85
O (s) 121.23
I1 (s) 149.98
A1 (s) 128.27
G1 (s) 150.61
J1 (s) 143.18
E1 (s) 132.77
R (s) 122.66
H1 (s) 150.34
H2 (s) 142.81
D1 (s) 131.29
Q (s) 122.43
K1 (s) 144.16
W (s) 126.09
D2 (s) 150.01
B1 (s) 129.62
N (s) 121.21
F2 (s) 150.68
C1 (s) 130.24
S1 (s) 121.48
B2 (s) 130.31
P (s) 122.33
S2 (s) 124.22
R1 (s) 62.35
Q1 (s) 60.90
L (s) 60.83
M (s) 62.09
N1 (s) 22.66
P1 (s) 33.66
M1 (s) 18.64
O1 (s) 32.56
C (s) 17.67
I (s) 30.64
E (s) 21.50
H (s) 30.35
D (s) 20.94
A (s) 11.28
J (s) 32.51
G (m) 24.55
B (s) 17.71
K (s) 33.61
L1 (s) 18.60
U (m) 34.28
F (s) 22.53
f1 (ppm)


148.58
147.86
B (s)
147.86
A (s)
148.58
0.86
1.14
f1 (ppm)
O
P
N
CH3
H3C

N-(decan-3-yl)-N-((R)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L22



General Procedure E: Triethylamine (0.88 mL, 6.281 mmol, 5.0 eq.), PCl_3 (0.11 mL, 1.256 mmol, 1.0 eq.), CH_2Cl_2 (20 mL), (1R)-N-(decan-3-yl)-2,3-dihydro-1H-inden-1-amine (343 mg, 1.256 mmol, 1.0 eq.), (R)-binaphthol (360 mg, 1.256 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-(decan-3-yl)-N-((R)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (21 mg, 0.038 mmol, 3%) as a foamy white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.98 – 7.87 (m, 4H), 7.71 (dd, *J* = 9.7, 7.7 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.48 (dd, *J* = 8.8, 3.1 Hz, 1H), 7.44 – 7.37 (m, 3H), 7.36 – 7.19 (m, 6H), 4.76 (dtd, *J* = 15.6, 7.8, 2.7 Hz, 1H), 3.05 – 2.95 (m, 1H), 2.92 – 2.81 (m, 1H), 2.80 – 2.68 (m, 1H), 2.50 – 2.37 (m, 1H), 2.23 – 2.15 (m, 1H), 1.82 (dtdd, *J* = 32.9, 16.6, 8.2, 4.4 Hz, 1H), 1.74 – 1.61 (m, 1H), 1.60 – 1.41 (m, 3H), 1.40 – 1.05 (m, 6H), 1.00 – 0.83 (m, 7H), 0.74 (t, *J* = 7.4 Hz, 2H).

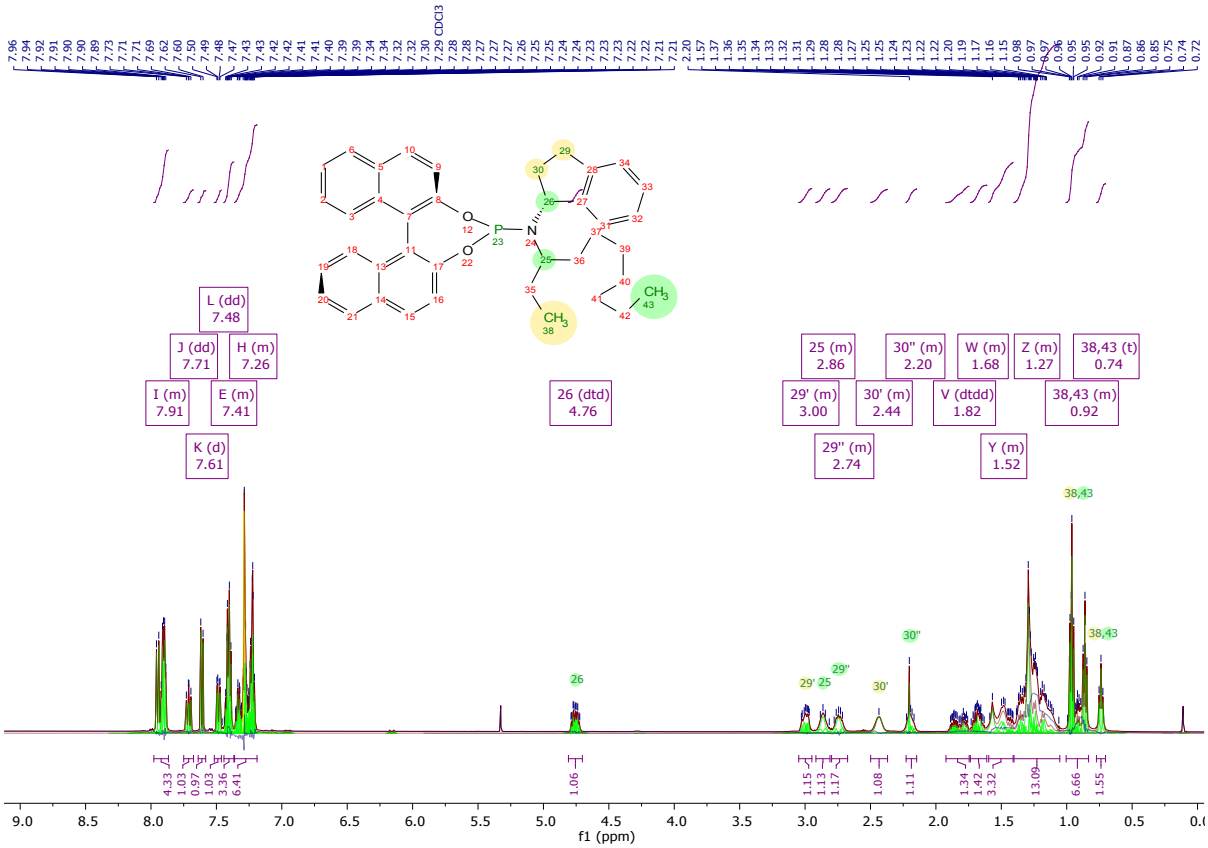
^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.3, 150.2, 150.20 150.2, 149.9, 149.9, 144.5, 143.3, 143.3, 132.8, 132.8, 131.3, 130.4, 130.2, 129.5, 129.5, 128.2, 128.1, 127.4, 127.3, 127.1, 127.1, 127.1, 126.4, 126.4, 125.9, 125.8, 125.2, 125.1, 124.8, 124.6, 124.3, 124.0, 123.9, 122.3, 122.3, 122.3, 122.2, 121.8, 121.8, 121.7, 121.7, 60.3 – 59.4 (m), 56.7, 56.6, 56.3, 56.3, 37.1, 37.1, 36.9 – 36.2 (m), 34.7 – 34.0 (m), 31.9, 31.9, 30.4, 30.0, 29.7, 29.5, 29.4, 29.3, 27.7 – 27.4 (m), 27.2, 26.5, 22.8, 22.6, 14.2, 14.1, 11.5, 11.4.

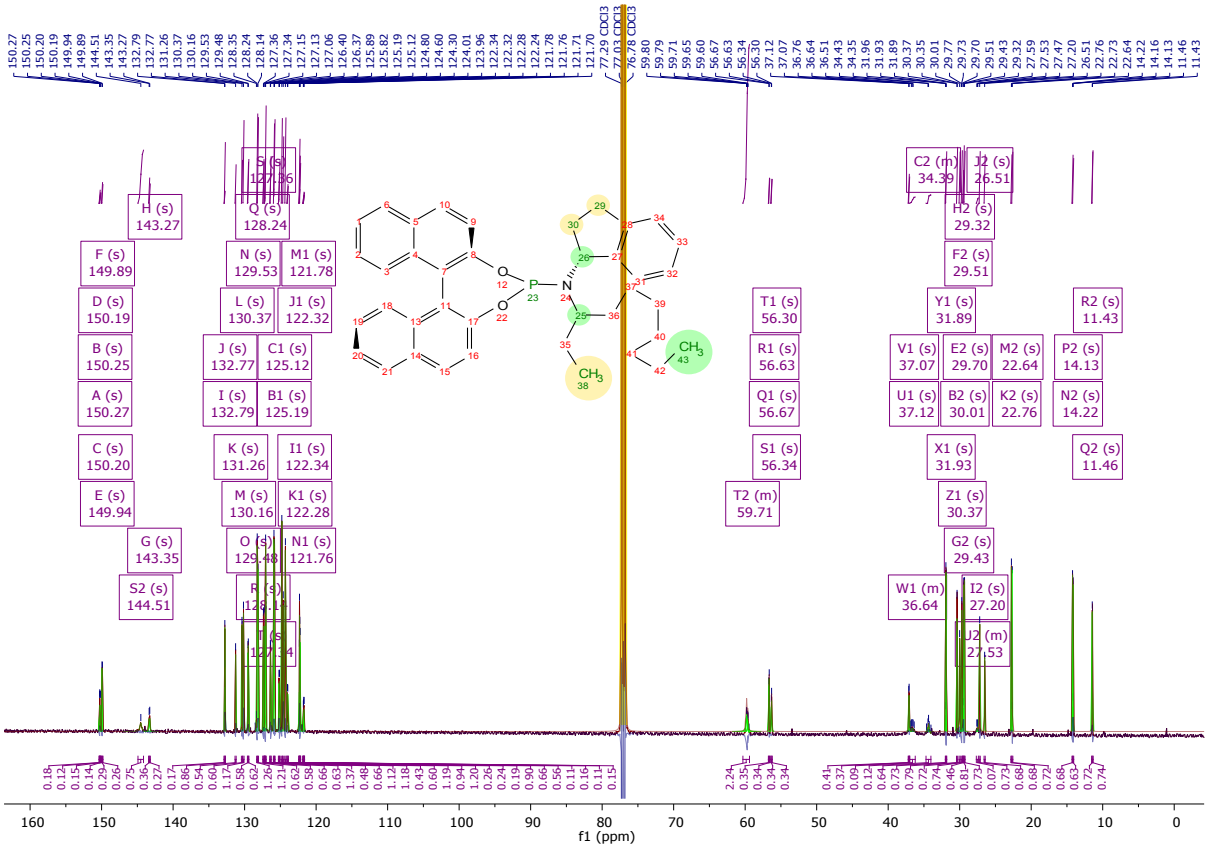
^{31}P NMR (162 MHz, Chloroform-*d*) δ 149.6, 149.4.

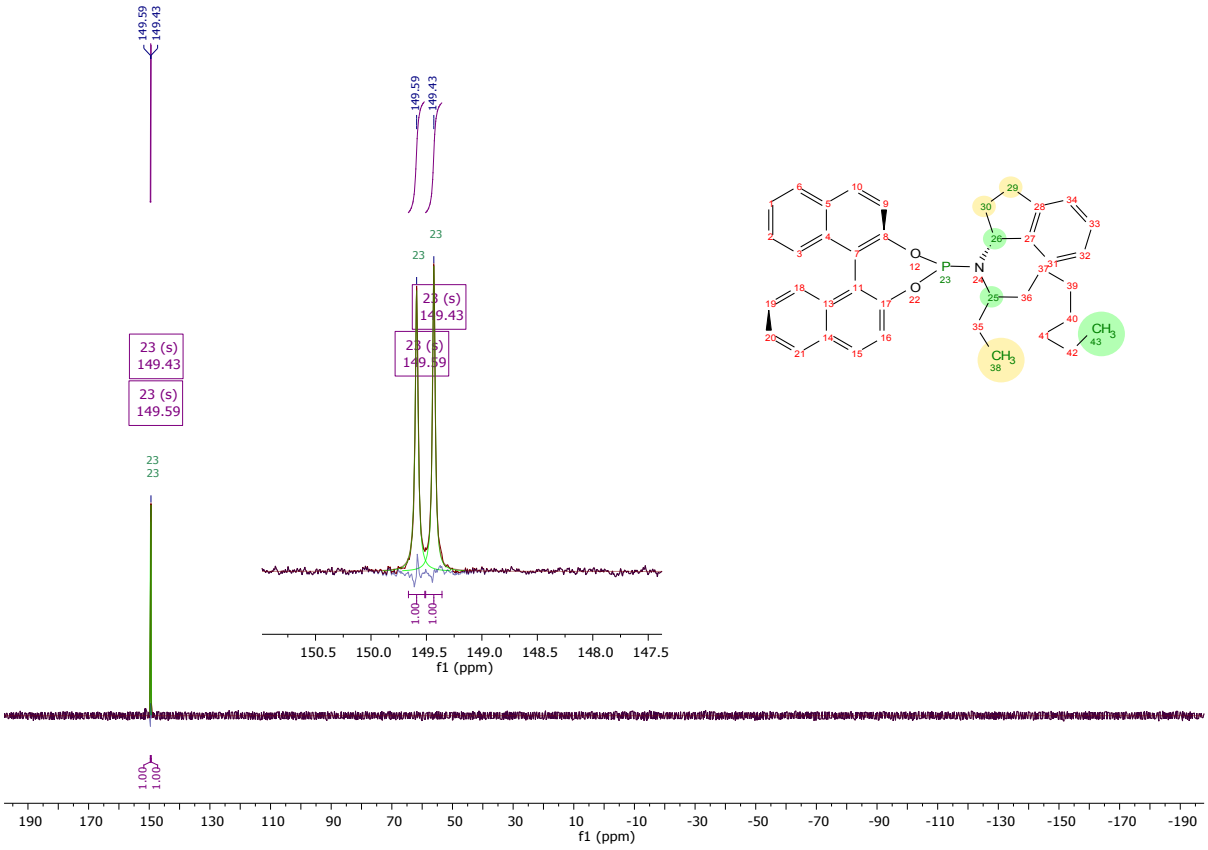
IR υ_{max} (film): 2955, 2854, 1431, 1231.

HRMS (EI$^+$) *m/z* calcd for C_{39} H_{43} O_2 N P $[M+H]^+$: 588.3026, found 588.3024.

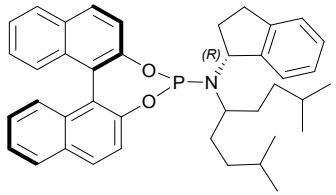
$[\alpha]^{25}_{589}$= -50.8 (*c* 2.5, $CHCl_3$) for a mixture of diastereoisomers at 99% ee.


L (dd) 7.48
J (dd) 7.71
H (m) 7.26
I (m) 7.91
E (m) 7.41
K (d) 7.61
26 (dtd) 4.76
25 (m) 2.86
30'' (m) 2.20
W (m) 1.68
Z (m) 1.27
38,43 (t) 0.74
29' (m) 3.00
30' (m) 2.44
V (dtdd) 1.82
38,43 (m) 0.92
29'' (m) 2.74
Y (m) 1.52
f1 (ppm)


H (s) 143.27
F (s) 149.89
D (s) 150.19
B (s) 150.25
A (s) 150.27
C (s) 150.20
E (s) 149.94
G (s) 143.35
S2 (s) 144.51
Q (s) 128.24
N (s) 129.53
M1 (s) 121.78
L (s) 130.37
J1 (s) 122.32
J (s) 132.77
C1 (s) 125.12
I (s) 132.79
B1 (s) 125.19
K (s) 131.26
I1 (s) 122.34
M (s) 130.16
K1 (s) 122.28
N1 (s) 121.76
T1 (s) 56.30
R1 (s) 56.63
Q1 (s) 56.67
S1 (s) 56.34
T2 (m) 59.71
C2 (m) 34.39
J2 (s) 26.51
F2 (s) 29.32
Y1 (s) 31.89
R2 (s) 11.43
V1 (s) 37.07
E2 (s) 29.70
M2 (s) 22.64
P2 (s) 14.13
U1 (s) 37.12
B2 (s) 30.01
K2 (s) 22.76
N2 (s) 14.22
X1 (s) 31.93
Q2 (s) 11.46
Z1 (s) 30.37
G2 (s) 29.43
W1 (m) 36.64
I2 (s) 27.20
J2 (m) 27.53
f1 (ppm)


149.59
149.43
23 (s)
149.43
23 (s)
149.59
23
23
1.00
1.00
150.5
150.0
149.5
149.0
148.5
148.0
147.5
f1 (ppm)
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
f1 (ppm)
O
P
N
CH3
CH3

N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(2,8-dimethylnonan-5-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L13



General Procedure E: Triethylamine (0.83 mL, 5.927 mmol, 5.0 eq.), PCl_3 (0.10 mL, 1.185 mmol, 1.0 eq.), CH_2Cl_2 (20 mL), (R)-N-(2,8-dimethylnonan-5-yl)-2,3-dihydro-1H-inden-1-amine (341 mg, 1.185 mmol, 1.0 eq.), (R)-binaphthol (339 mg, 1.185 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(2,8-dimethylnonan-5-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (153 mg, 0.261 mmol, 22%) as a foamy white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 – 7.75 (m, 4H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.26 – 7.08 (m, 7H), 4.67 (dt, *J* = 15.1, 7.8 Hz, 1H), 2.89 (ddd, *J* = 16.0, 8.9, 3.3 Hz, 1H), 2.79 – 2.74 (m, 1H), 2.70 – 2.56 (m, 1H), 2.40 – 2.24 (m, 1H), 2.14 – 2.02 (m, 1H), 1.74 – 1.49 (m, 2H), 1.48 – 1.16 (m, 3H), 1.16 – 1.03 (m, 1H), 0.91 – 0.70 (m, 15H).

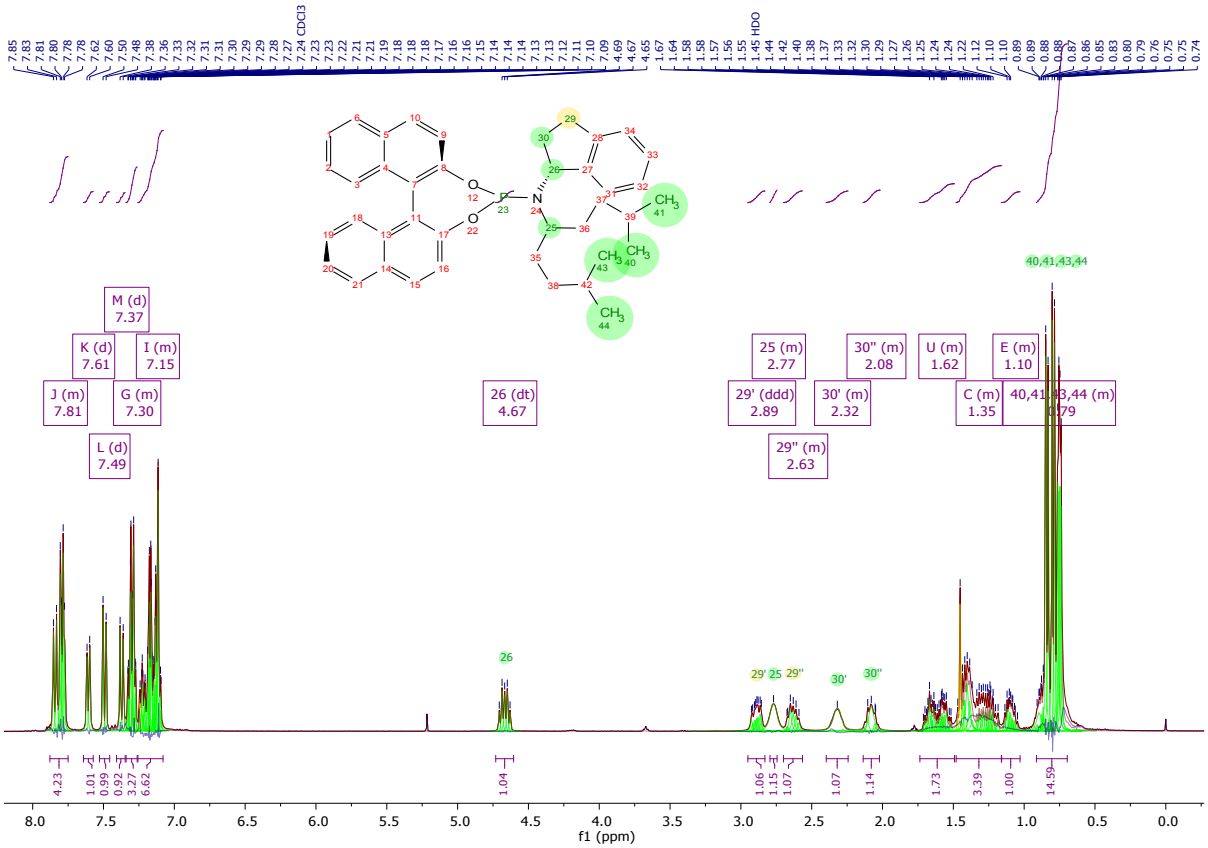
^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.3, 150.2, 149.9, 144.5, 143.3, 132.8, 131.3, 130.3, 130.2, 129.6, 128.2, 128.1, 127.4, 127.1, 127.1, 126.4, 125.9, 125.8, 125.2, 124.8, 124.6, 124.3, 124.0, 123.9, 122.3, 122.3, 121.7, 121.7, 59.8, 59.8 – 59.6 (m), 55.6, 55.6, 37.0 – 36.0 (m), 36.2, 35.7, 35.1, 33.3 – 32.3 (m), 30.4, 28.7, 28.1, 23.0, 22.8, 22.6, 22.5.

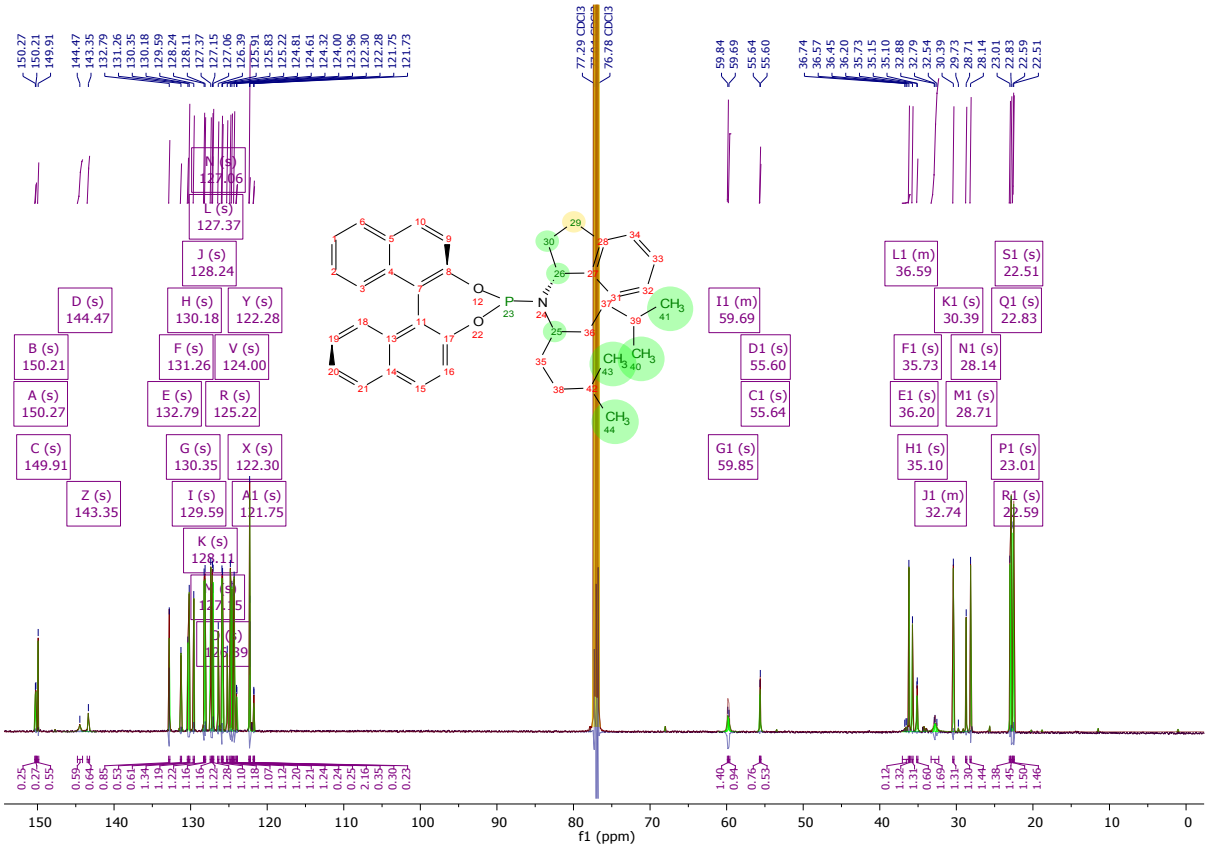
^{31}P NMR (162 MHz, Chloroform-*d*) δ 149.6.

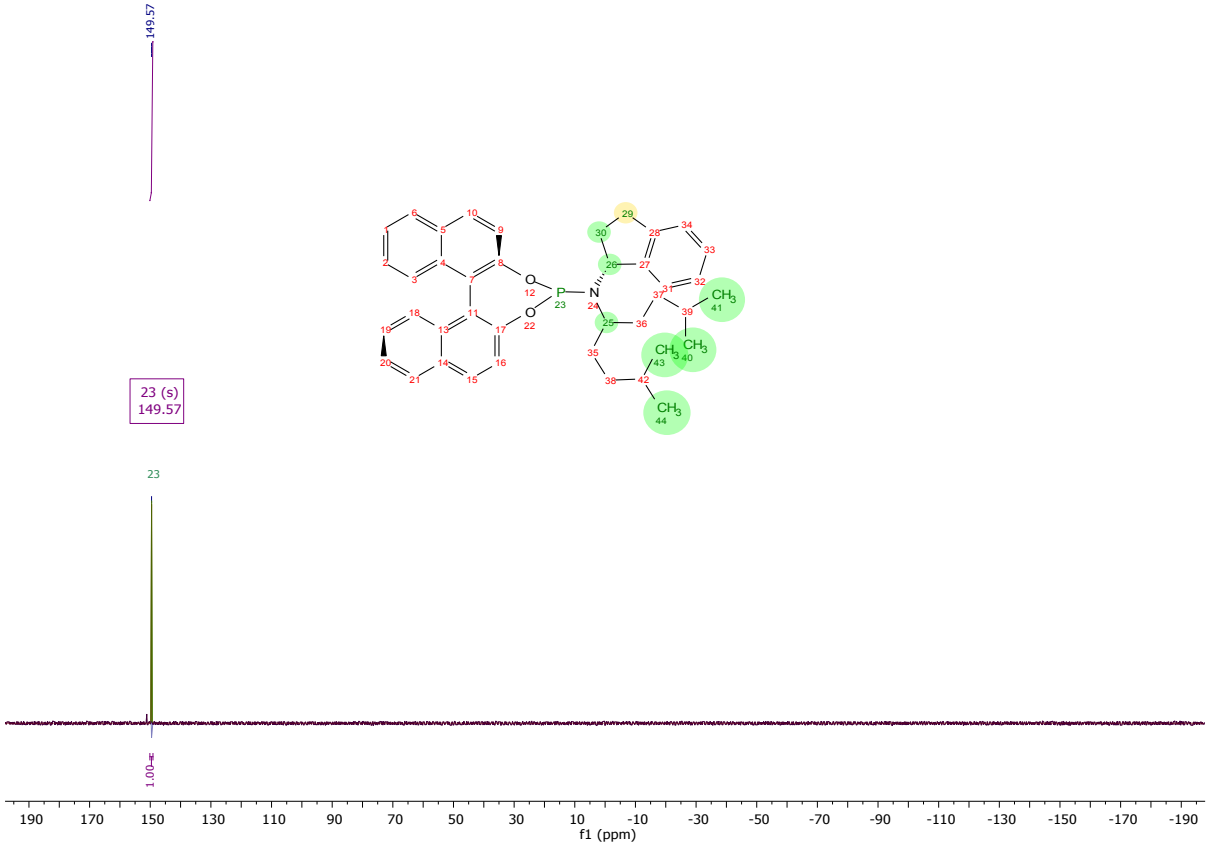
IR υ_{max} (film): 2952, 2360, 1431, 1231, 1067.

HRMS (EI^+) *m/z* calcd for C_{35} H_{35} O_2 N P $[M+H]^+$: 532.2400, found 532.2398.

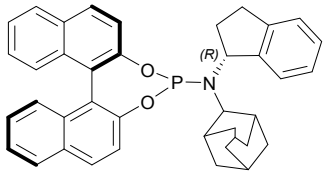
$[\alpha]^{25}_{589}$= -108.8 (*c* 1.1, $CHCl_3$) for 99% ee.


M (d) 7.37
K (d) 7.61
I (m) 7.15
J (m) 7.81
G (m) 7.30
L (d) 7.49
26 (dt) 4.67
25 (m) 2.77
29' (ddd) 2.89
29'' (m) 2.63
30'' (m) 2.08
30' (m) 2.32
U (m) 1.62
E (m) 1.10
C (m) 1.35
40,41,43,44 (m) 1.79
f1 (ppm)


D (s) 144.47
B (s) 150.21
A (s) 150.27
C (s) 149.91
Z (s) 143.35
N (s) 127.06
L (s) 127.37
J (s) 128.24
H (s) 130.18
Y (s) 122.28
F (s) 131.26
V (s) 124.00
E (s) 132.79
R (s) 125.22
G (s) 130.35
X (s) 122.30
I (s) 129.59
A1 (s) 121.75
K (s) 128.11
M (s) 127.15
O (s) 125.39
I1 (m) 59.69
D1 (s) 55.60
C1 (s) 55.64
G1 (s) 59.85
L1 (m) 36.59
S1 (s) 22.51
K1 (s) 30.39
Q1 (s) 22.83
F1 (s) 35.73
N1 (s) 28.14
E1 (s) 36.20
M1 (s) 28.71
H1 (s) 35.10
P1 (s) 23.01
J1 (m) 32.74
R1 (s) 22.59
f1 (ppm)


149.57
23 (s)
149.57
23
1.00
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
f1 (ppm)

N-(adamantan-2-yl)-N-((R)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L19



General Procedure E: Triethylamine (1.13 mL, 8.130 mmol, 5.0 eq.), PCl_3 (0.14 mL, 1.626 mmol, 1.0 eq.), CH_2Cl_2 (20 mL), (R)-N-(2,3-dihydro-1H-inden-1-yl)adamantan-2-amine (435 mg, 1.626 mmol, 1.0 eq.), (R)-binaphthol (465 mg, 1.626 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-(adamantan-2-yl)-N-((R)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (60 mg, 0.098 mmol, 6%) as a foamy white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.8 Hz, 1H), 7.92 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.76 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.46 – 7.16 (m, 9H), 7.13 (d, *J* = 7.4 Hz, 1H), 4.95 (td, *J* = 8.2, 2.9 Hz, 1H), 3.15 (d, *J* = 20.4 Hz, 1H), 2.81 – 2.67 (m, 2H), 2.65 – 2.57 (m, 1H), 2.52 – 2.41 (m, 1H), 2.19 – 2.12 (m, 2H), 1.98 – 1.82 (m, 3H), 1.79 – 1.51 (m, 8H), 1.44 – 1.37 (m, 1H).

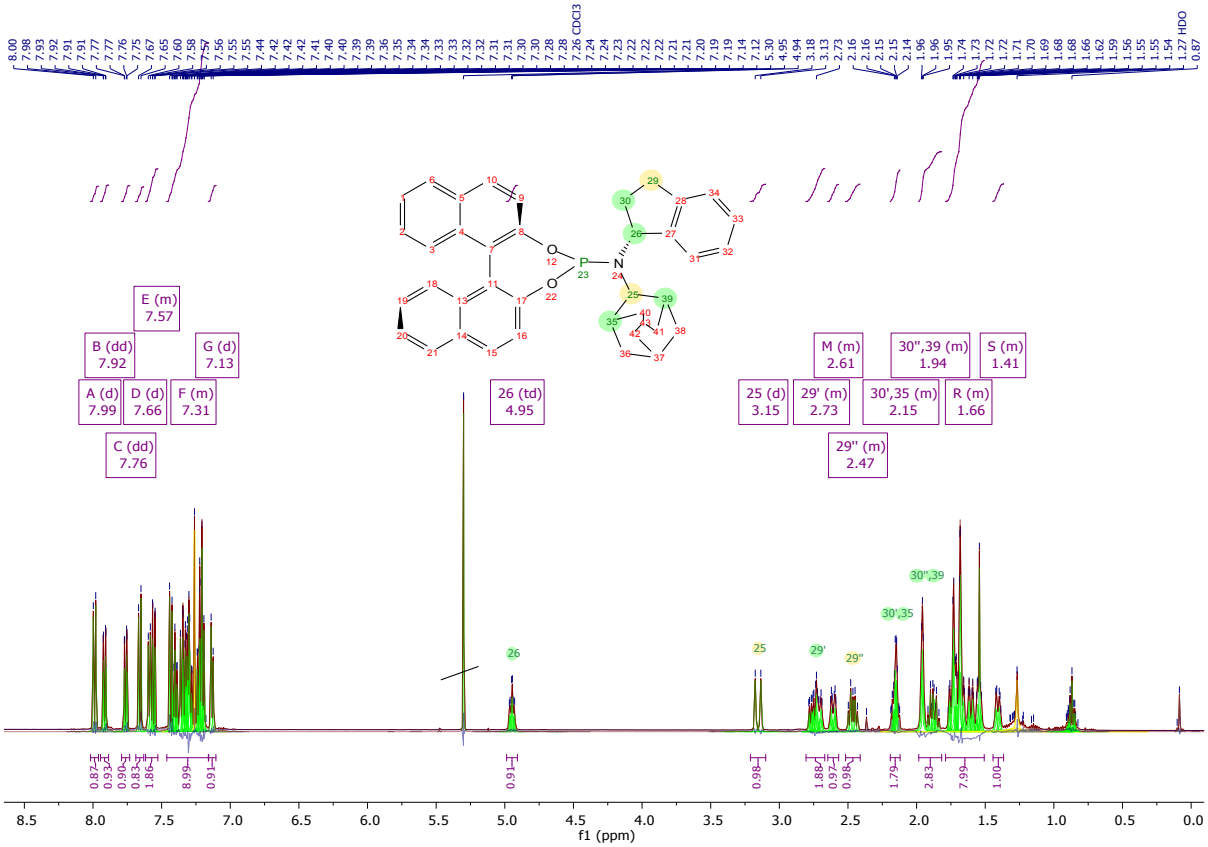
^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.9, 150.9, 149.9, 143.5, 142.9, 132.9, 132.9, 132.7, 131.3, 130.3, 130.3, 129.6, 128.3, 128.1, 127.2, 127.2, 127.1, 125.9, 125.9, 125.7, 124.8, 124.7, 124.5, 124.3, 124.1, 122.6, 122.6, 122.4, 120.8, 120.8, 62.3, 62.3, 61.5, 61.4, 39.7, 39.1, 39.1, 38.5, 38.5, 35.5, 35.5, 35.0, 34.9, 33.0, 32.2, 32.1, 31.6, 31.5, 29.8, 27.6.

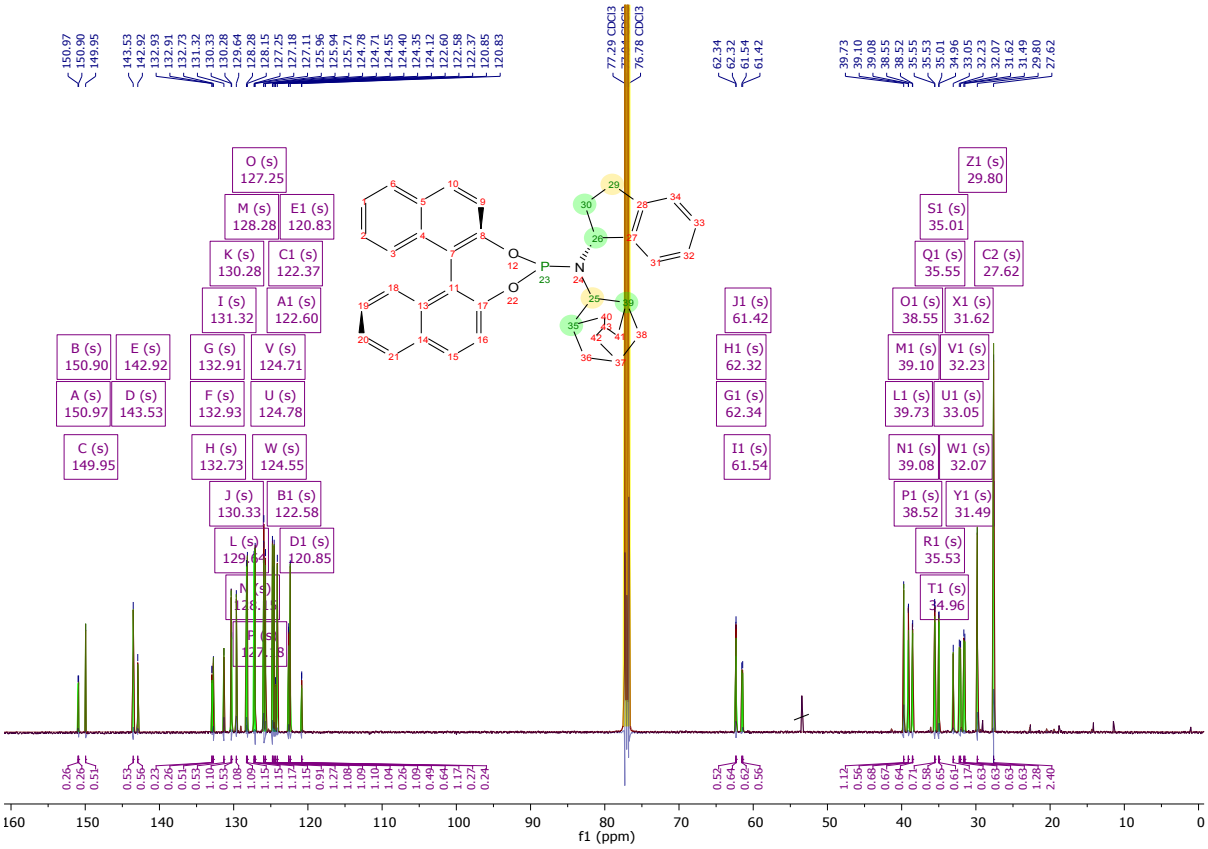
^{31}P NMR (202 MHz, Chloroform-*d*) δ 144.7.

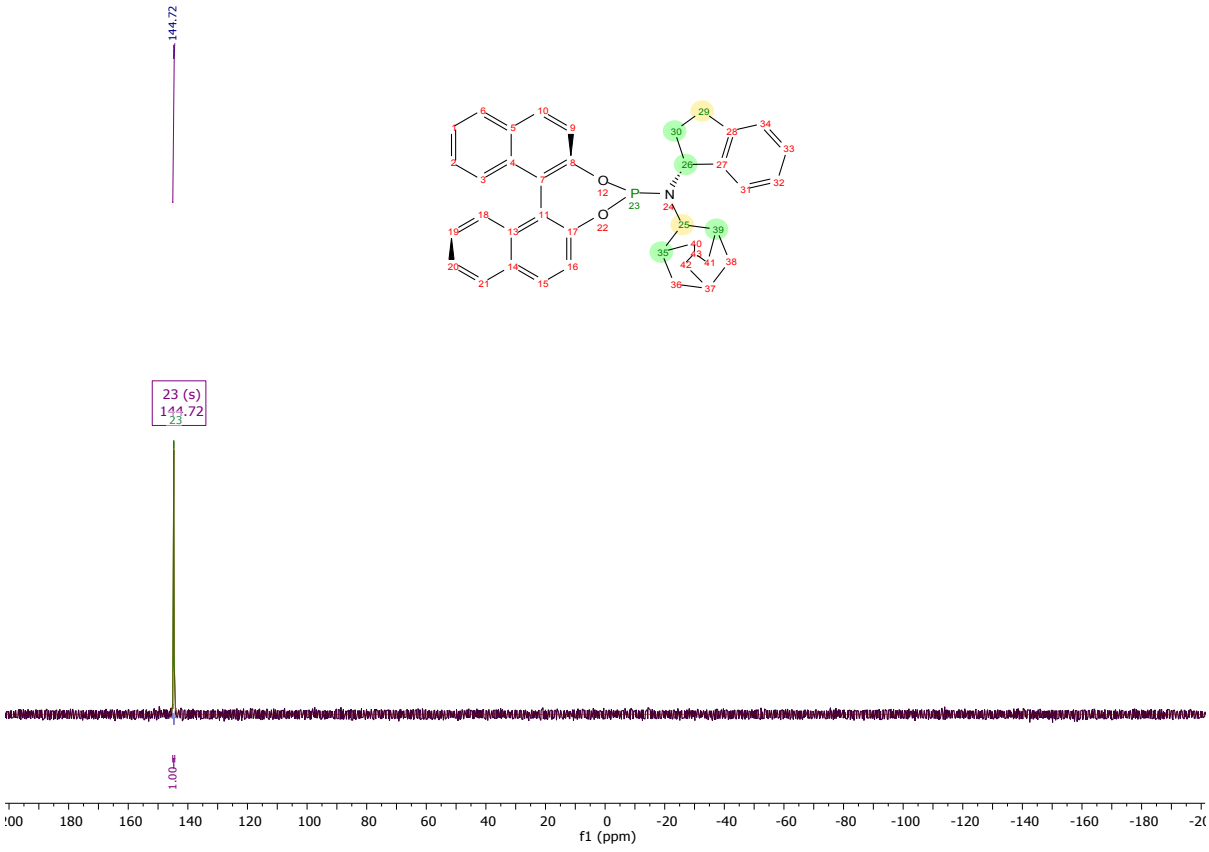
IR υ_{max} (film): 2907, 2850, 2359, 1507, 1214.

HRMS (EI$^+$) *m/z* calcd for $C_{39}H_{37}O_2NP$ $[M+H]^+$: 582.2556, found 582.2556.

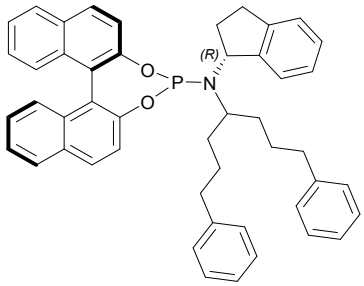
$[\alpha]^{25}_{589}$= -21.0 (*c* 1.5, $CHCl_3$) for 99% ee.


E (m) 7.57
B (dd) 7.92
G (d) 7.13
A (d) 7.99
D (d) 7.66
F (m) 7.31
C (dd) 7.76
26 (td) 4.95
M (m) 2.61
30'',39 (m) 1.94
S (m) 1.41
25 (d) 3.15
29' (m) 2.73
30',35 (m) 2.15
R (m) 1.66
29'' (m) 2.47
f1 (ppm)


O (s) 127.25
M (s) 128.28
E1 (s) 120.83
K (s) 130.28
C1 (s) 122.37
I (s) 131.32
A1 (s) 122.60
B (s) 150.90
E (s) 142.92
G (s) 132.91
V (s) 124.71
A (s) 150.97
D (s) 143.53
F (s) 132.93
U (s) 124.78
C (s) 149.95
H (s) 132.73
W (s) 124.55
J (s) 130.33
B1 (s) 122.58
D1 (s) 120.85
J1 (s) 61.42
H1 (s) 62.32
G1 (s) 62.34
I1 (s) 61.54
Z1 (s) 29.80
S1 (s) 35.01
Q1 (s) 35.55
C2 (s) 27.62
O1 (s) 38.55
X1 (s) 31.62
M1 (s) 39.10
V1 (s) 32.23
L1 (s) 39.73
U1 (s) 33.05
N1 (s) 39.08
W1 (s) 32.07
P1 (s) 38.52
Y1 (s) 31.49
R1 (s) 35.53
T1 (s) 34.96
f1 (ppm)


144.72
23 (s)
144.72
23
1.00
f1 (ppm)

N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(1,7-diphenylheptan-4-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L14



General Procedure E: Triethylamine (1.24 mL, 8.903 mmol, 5.0 eq.), PCl_3 (0.16 mL, 1.781 mmol, 1.0 eq.), CH_2Cl_2 (20 mL), (R)-N-(1,7-diphenylheptan-4-yl)-2,3-dihydro-1H-inden-1-amine (683 mg, 1.781 mmol, 1.0 eq.), (R)-binaphthol (509 mg, 1.781 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(1,7-diphenylheptan-4-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (142 mg, 0.214 mmol, 12%) as a foamy white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 8.8 Hz, 1H), 7.93 – 7.84 (m, 3H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.46 – 7.12 (m, 19H), 7.05 (d, *J* = 7.4 Hz, 2H), 4.71 (dt, *J* = 16.0, 7.8 Hz, 1H), 3.09 – 2.94 (m, 2H), 2.78 – 2.67 (m, 1H), 2.66 – 2.49 (m, 4H), 2.48 – 2.28 (m, 2H), 2.20 – 2.08 (m, 1H), 1.91 – 1.63 (m, 4H), 1.56 – 1.35 (m, 1H), 1.22 – 1.06 (m, 1H).

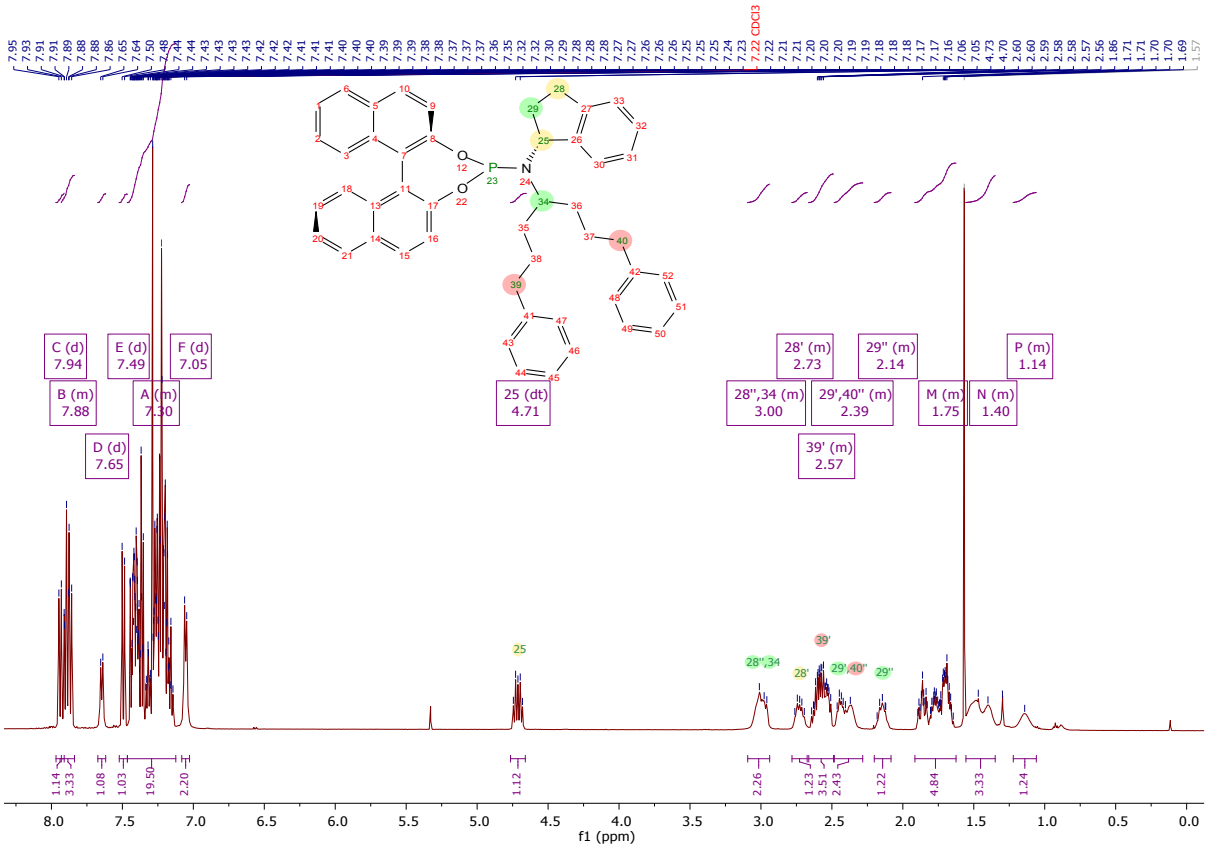
^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.1, 150.0, 149.8, 144.8 – 144.3 (m), 143.4 – 142.9 (m), 142.4, 142.3, 132.8, 132.7, 132.7, 131.3, 130.3, 130.2, 129.5, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 127.4, 127.1, 127.0, 126.5, 125.9, 125.9, 125.8, 125.6, 125.0, 124.9, 124.7, 124.4, 123.9, 123.9, 122.3, 122.3, 122.1, 121.9, 121.8, 59.6, 59.4, 54.5, 37.6 – 36.5 (m), 36.8, 36.2, 35.7, 34.2 – 33.3 (m), 30.4, 28.6, 27.9.

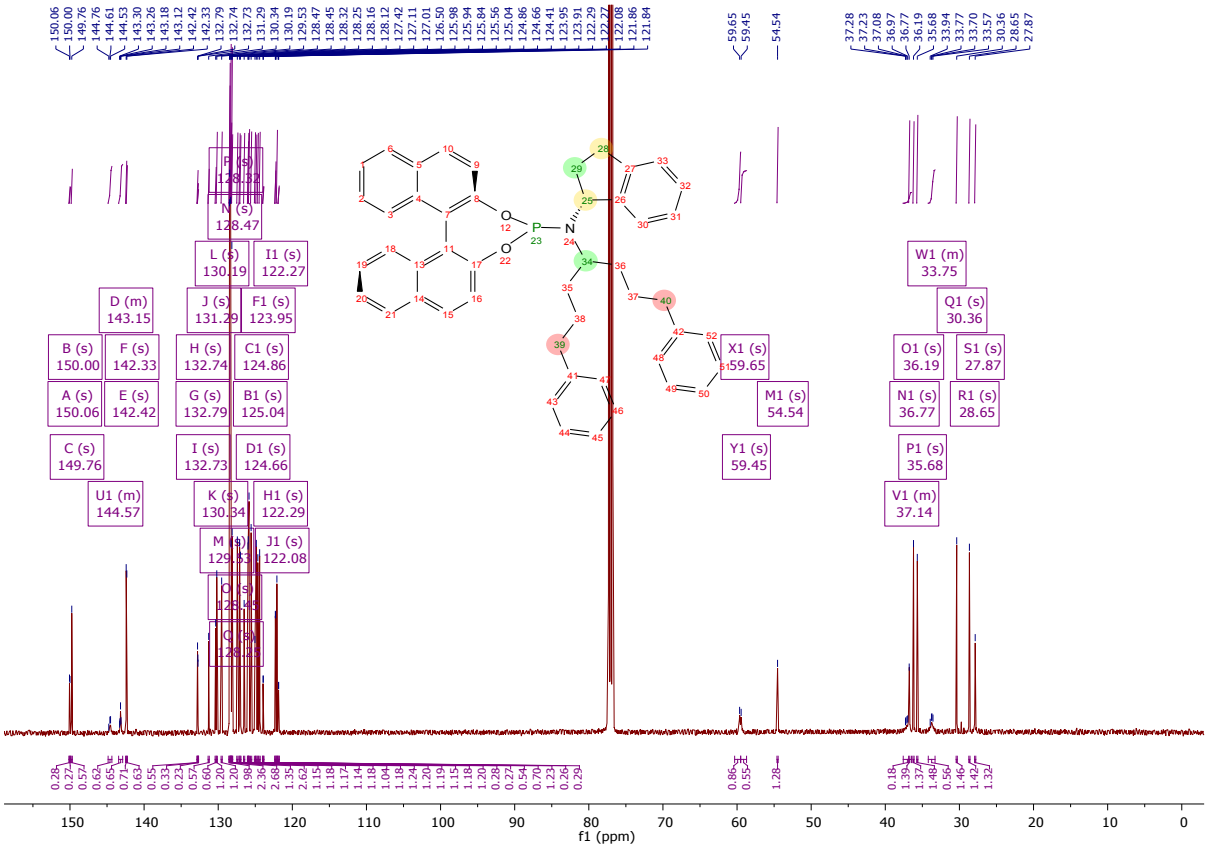
^{31}P NMR (202 MHz, Chloroform-*d*) δ 149.2.

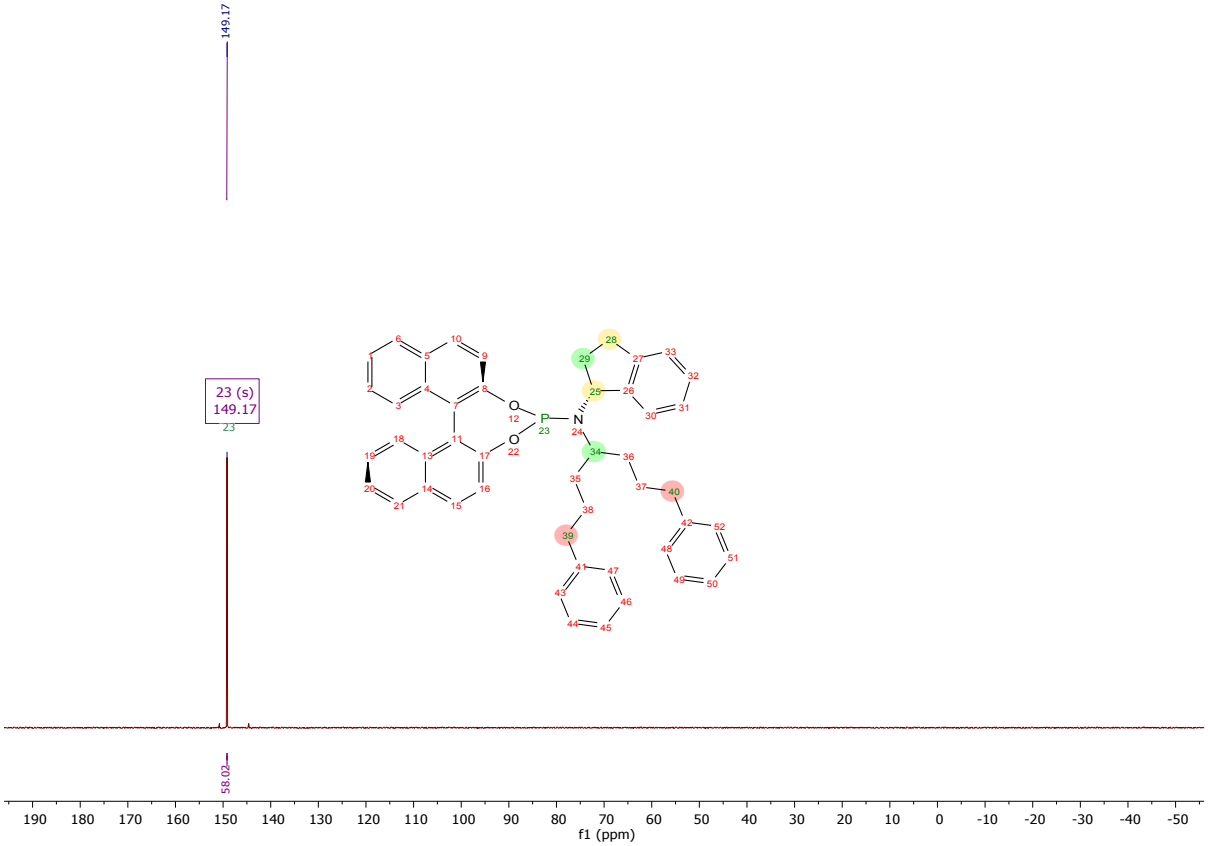
IR υ_{max} (film): 2940, 2855, 1590, 1360, 1154.

HRMS (EI^+) *m/z* calcd for C_{48} H_{45} O_2 N P $[M+H]^+$: 698.3182, found 698.3181.

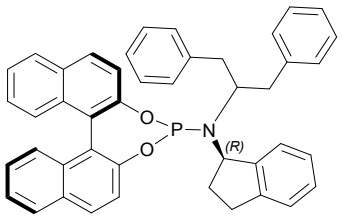
$[\alpha]^{25}_{589}$= -85.5 (*c* 1.0, $CHCl_3$) for 99% ee.


C (d) 7.94
E (d) 7.49
F (d) 7.05
B (m) 7.88
A (m) 7.30
D (d) 7.65
25 (dt) 4.71
28' (m) 2.73
29'' (m) 2.14
P (m) 1.14
28'',34 (m) 3.00
29',40'' (m) 2.39
M (m) 1.75
N (m) 1.40
39' (m) 2.57
f1 (ppm)


F (s) 128.33
N (s) 128.47
L (s) 130.19
I1 (s) 122.27
D (m) 143.15
J (s) 131.29
F1 (s) 123.95
B (s) 150.00
F (s) 142.33
H (s) 132.74
C1 (s) 124.86
A (s) 150.06
E (s) 142.42
G (s) 132.79
B1 (s) 125.04
C (s) 149.76
I (s) 132.73
D1 (s) 124.66
U1 (m) 144.57
K (s) 130.34
H1 (s) 122.29
M (s) 129.53
J1 (s) 122.08
X1 (s) 59.65
M1 (s) 54.54
Y1 (s) 59.45
W1 (m) 33.75
Q1 (s) 30.36
O1 (s) 36.19
S1 (s) 27.87
N1 (s) 36.77
R1 (s) 28.65
P1 (s) 35.68
V1 (m) 37.14
f1 (ppm)


149.17
23 (s)
149.17
23
58.02
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50
f1 (ppm)

N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(1,3-diphenylpropan-2-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L20



General Procedure E: Triethylamine (1.64 mL, 11.757 mmol, 5.0 eq.), PCl_3 (0.21 mL, 2.351 mmol, 1.0 eq.), CH_2Cl_2 (10 mL), (R)-N-(1,3-diphenylpropan-2-yl)-2,3-dihydro-1H-inden-1-amine (770 mg, 2.351 mmol, 1.0 eq.), (R)-binaphthol (673.3 mg, 2.351 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(1,3-diphenylpropan-2-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (110.2 mg, 0.172 mmol, 7%) as a foamy white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 (d, J = 8.8 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.76 – 7.66 (m, 2H), 7.52 – 6.94 (m, 19H), 6.66 – 6.58 (m, 2H), 4.69 – 4.59 (m, 1H), 3.26 – 3.16 (m, 1H), 3.14 – 3.04 (m, 2H), 2.86 – 2.67 (m, 3H), 2.66 – 2.51 (m, 1H), 2.44 – 2.29 (m, 1H), 1.85 – 1.80 (m, 1H).

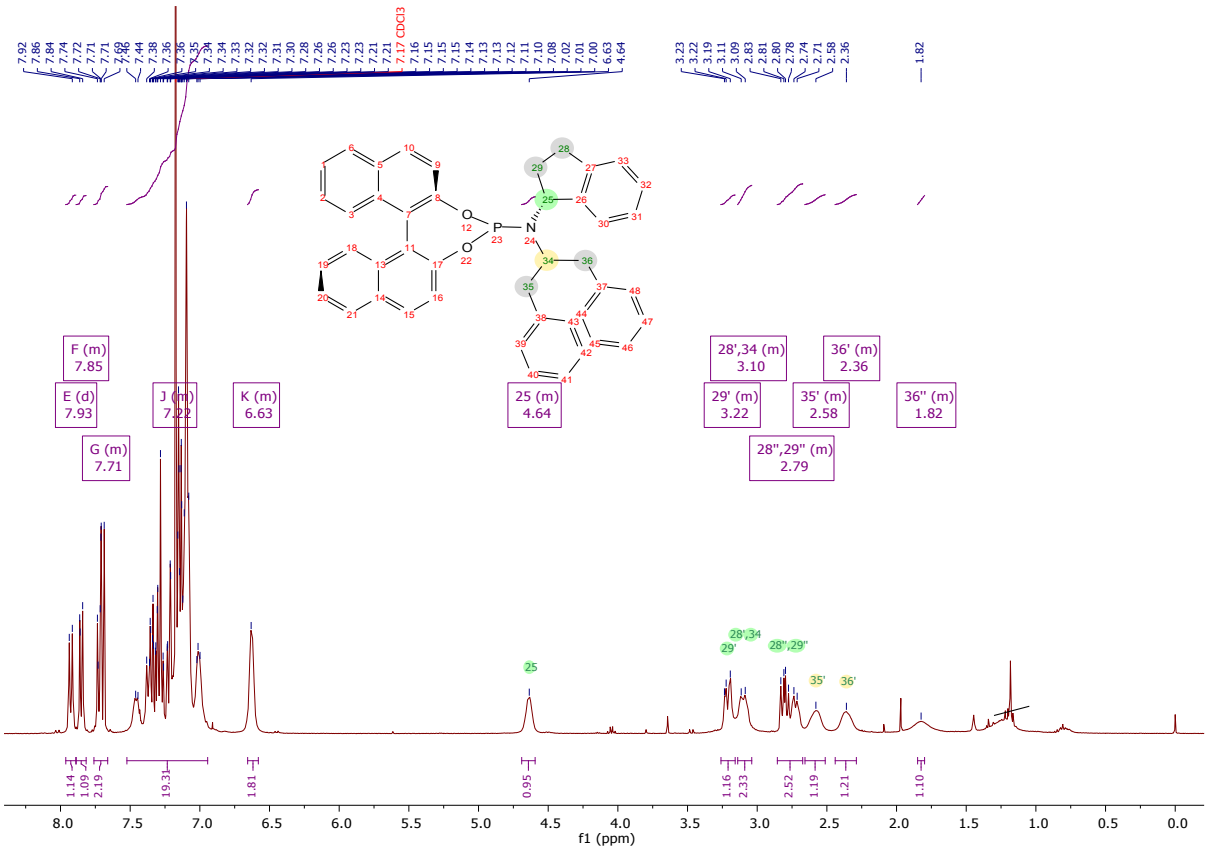
^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.2, 150.1, 149.9, 144.9 – 144.4 (m), 142.4 – 141.9 (m), 139.7, 139.4, 132.8, 132.8, 132.8, 131.4, 130.5, 130.4, 129.8, 129.6, 129.5, 128.3, 128.3, 128.2, 128.1, 127.6, 127.1, 127.1, 126.2, 126.2, 126.1, 125.9, 125.8, 124.8, 124.4, 124.1, 124.0, 122.3, 122.2, 122.1, 121.6, 121.5, 60.9, 60.4 – 59.6 (m), 45.2 – 43.6 (m), 42.4 – 41.6 (m), 34.3 – 32.2 (m), 30.5.

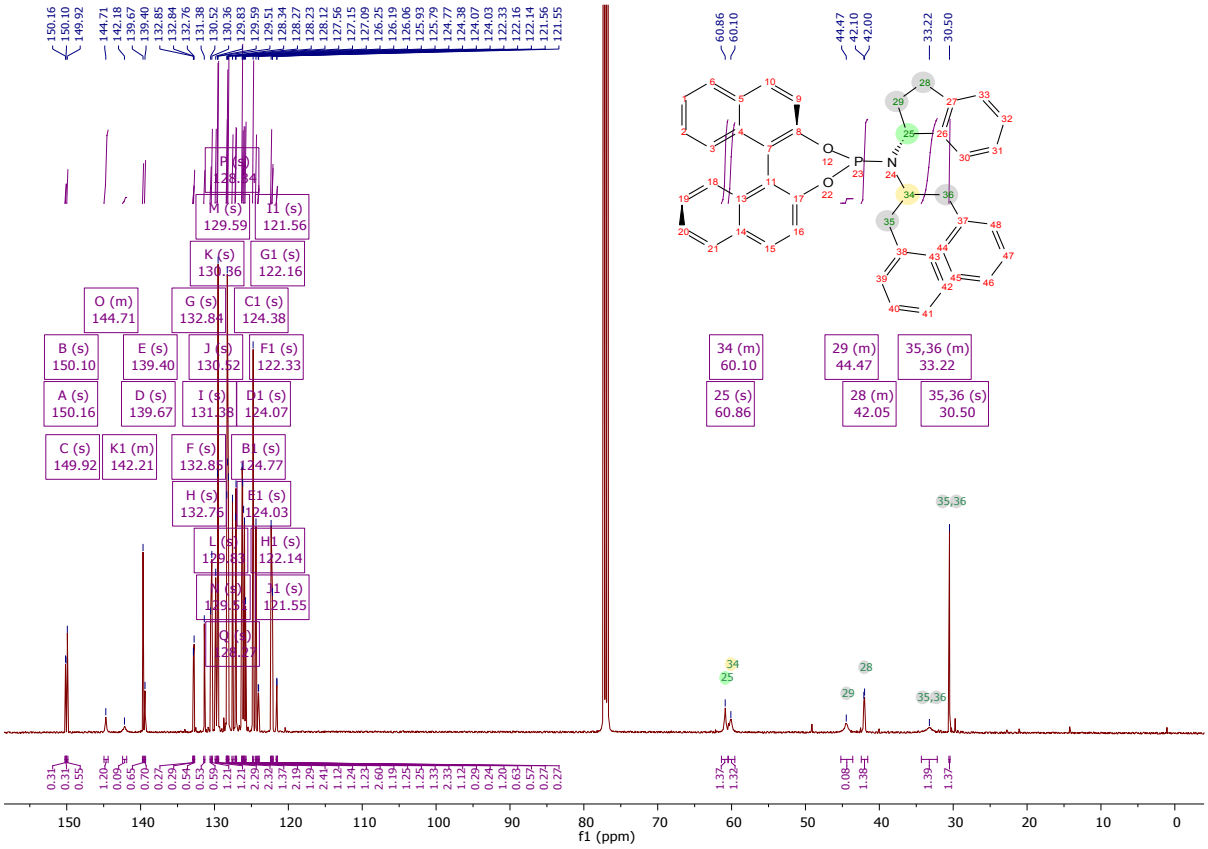
^{31}P NMR (202 MHz, Chloroform-*d*) δ 149.4.

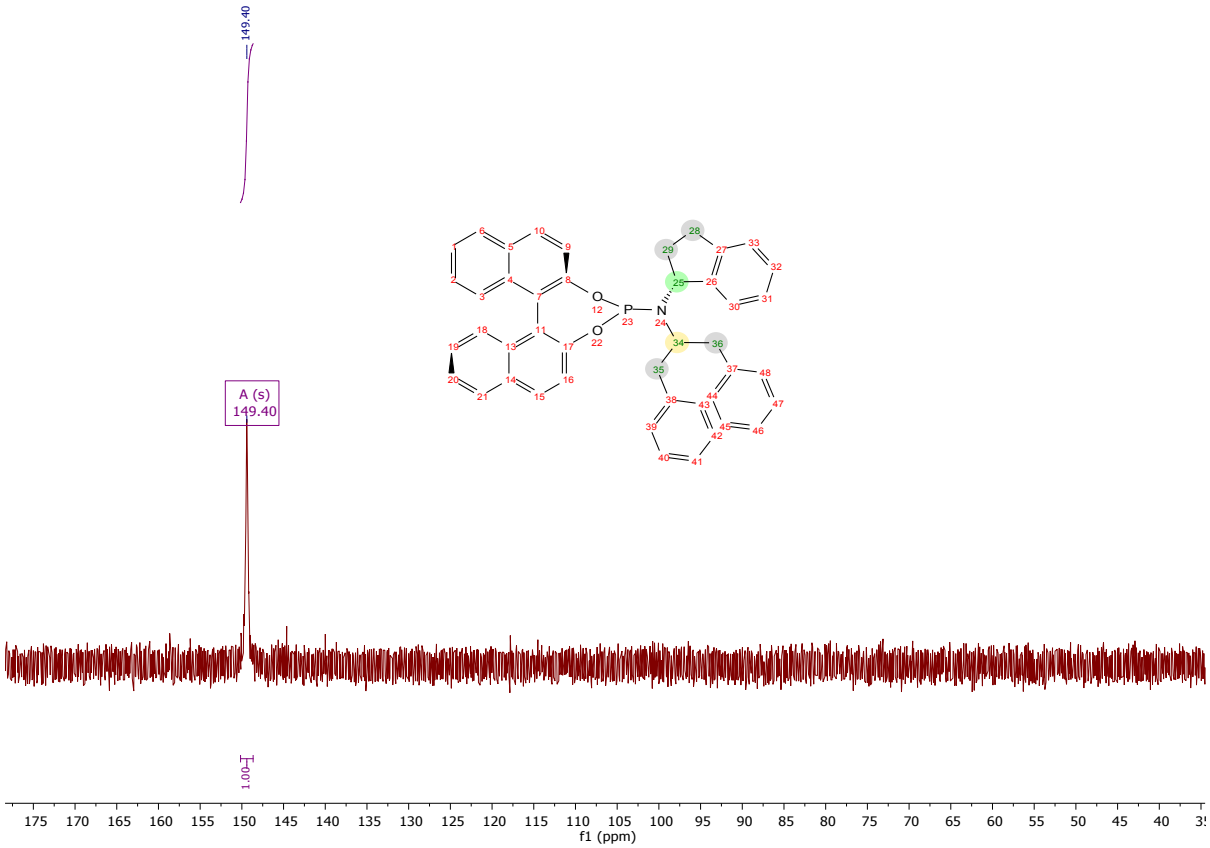
IR υ_{max} (film): 2980, 1462, 1230, 1154, 1030.

HRMS (EI^{+}) *m/z* calcd for $C_{44}H_{37}O_2NP$ $[M+H]^+$: 642.2556, found 642.2554.

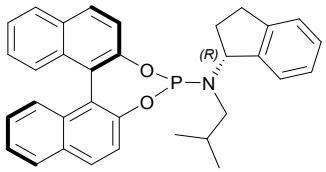
$[\alpha]^{25}_{589}$ = -50.9 (*c* 1.0, $CHCl_3$) for 99% ee.


F (m) 7.85
E (d) 7.93
J (m) 7.22
K (m) 6.63
G (m) 7.71
25 (m) 4.64
28',34 (m) 3.10
29' (m) 3.22
36' (m) 2.36
35' (m) 2.58
36'' (m) 1.82
28'',29'' (m) 2.79
f1 (ppm)


P (s) 128.34
M (s) 129.59
I1 (s) 121.56
K (s) 130.36
G1 (s) 122.16
O (m) 144.71
G (s) 132.84
C1 (s) 124.38
B (s) 150.10
E (s) 139.40
J (s) 130.52
F1 (s) 122.33
A (s) 150.16
D (s) 139.67
I (s) 131.38
D1 (s) 124.07
C (s) 149.92
K1 (m) 142.21
F (s) 132.85
B1 (s) 124.77
H (s) 132.76
E1 (s) 124.03
L (s) 129.63
H1 (s) 122.14
N (s) 129.51
J1 (s) 121.55
Q (s) 28.27
34 (m) 60.10
25 (s) 60.86
29 (m) 44.47
28 (m) 42.05
35,36 (m) 33.22
35,36 (s) 30.50
f1 (ppm)


149.40
A (s)
149.40
1.00
175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40
f1 (ppm)

N-((R)-2,3-dihydro-1H-inden-1-yl)-N-isobutyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L21



General Procedure E: Triethylamine (1.84 mL, 13.207 mmol, 5.0 eq.), PCl_3 (0.23 mL, 2.641 mmol, 1.0 eq.), CH_2Cl_2 (20 mL), (R)-N-isobutyl-2,3-dihydro-1H-inden-1-amine (500 mg, 2.641 mmol, 1.0 eq.), (R)-binaphthol (756.3 mg, 2.641 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-((R)-2,3-dihydro-1H-inden-1-yl)-N-isobutyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (110.2 mg, 0.211 mmol, 8%) as a foamy white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.8 Hz, 1H), 7.98 – 7.92 (m, 1H), 7.90 – 7.81 (m, 2H), 7.61 – 7.54 (m, 2H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.46 – 7.30 (m, 5H), 7.29 – 7.24 (m, 4H), 7.23 – 7.18 (m, 1H), 4.89 (q, *J* = 7.5 Hz, 1H), 2.96 (ddd, *J* = 15.9, 9.2, 4.3 Hz, 1H), 2.82 – 2.65 (m, 3H), 2.32 (dp, *J* = 13.0, 4.3 Hz, 1H), 2.12 (ddt, *J* = 13.7, 9.2, 7.1 Hz, 1H), 1.62 – 1.49 (m, 1H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H).

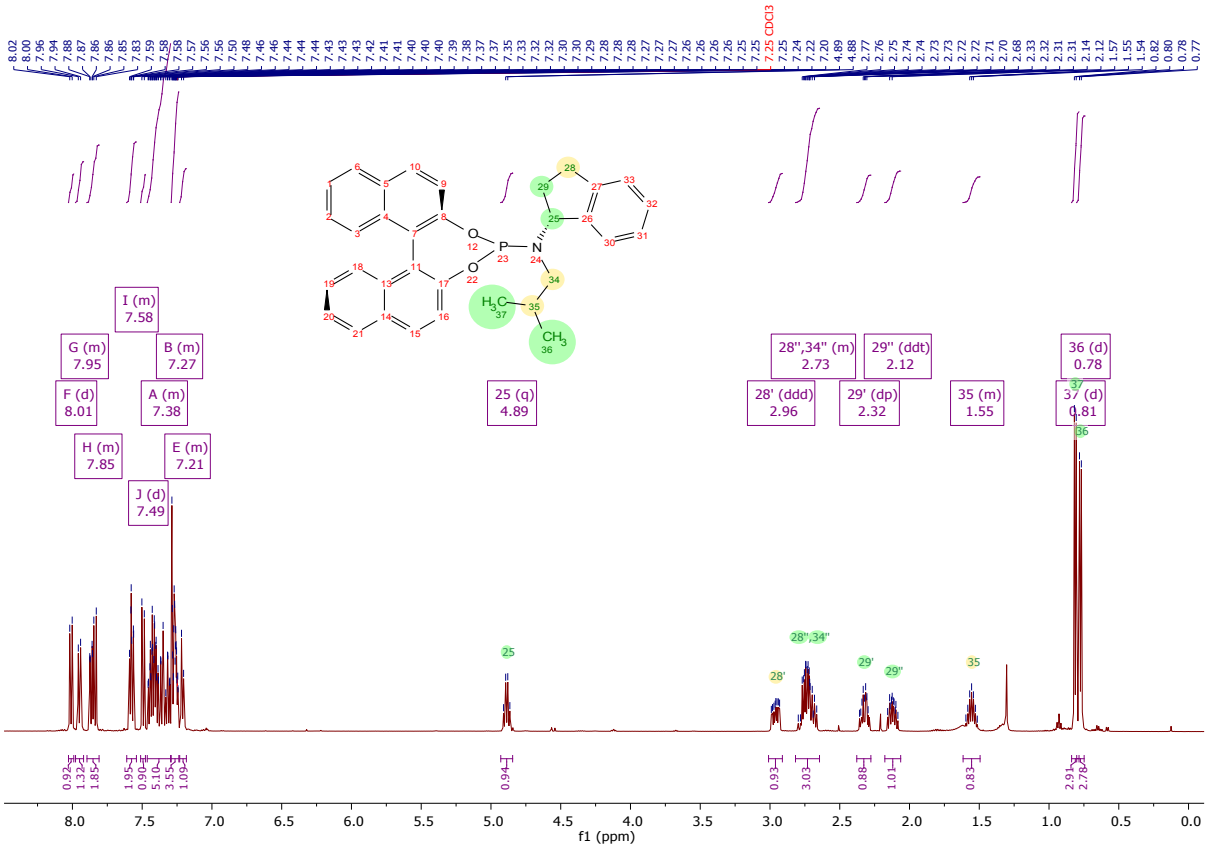
^{13}C NMR (126 MHz, Chloroform-d) δ 150.3, 150.3, 149.6, 143.6, 142.8, 142.8, 132.9, 132.9, 132.7, 131.4, 130.5, 130.3, 129.7, 128.3, 128.2, 127.5, 127.2, 127.1, 126.1, 126.0, 125.9, 125.2, 124.9, 124.7, 124.3, 124.2, 124.1, 122.3, 122.3, 122.2, 121.8, 121.8, 61.8, 61.7, 52.5, 52.4, 32.3, 32.3, 30.5, 28.3, 28.3, 20.4, 20.4, 20.3.

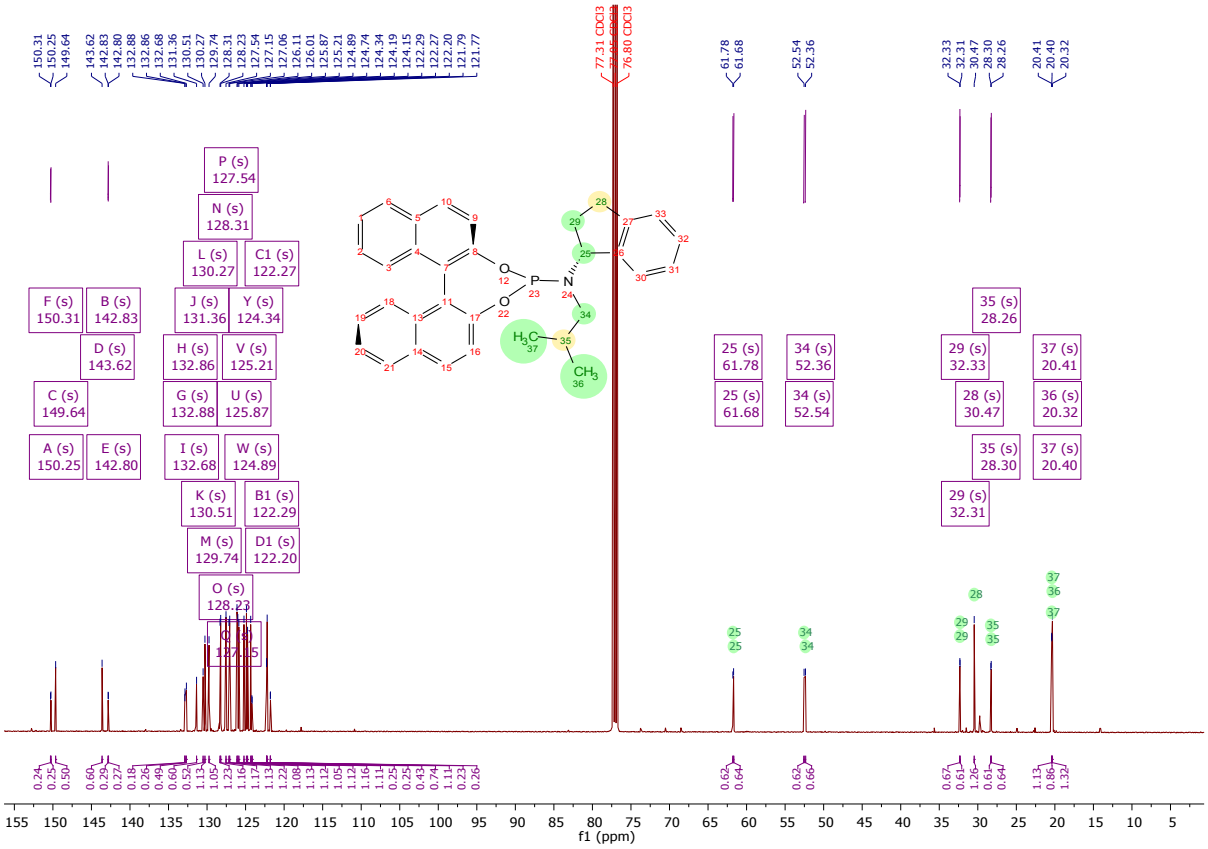
^{31}P NMR (202 MHz, Chloroform-*d*) δ 149.7.

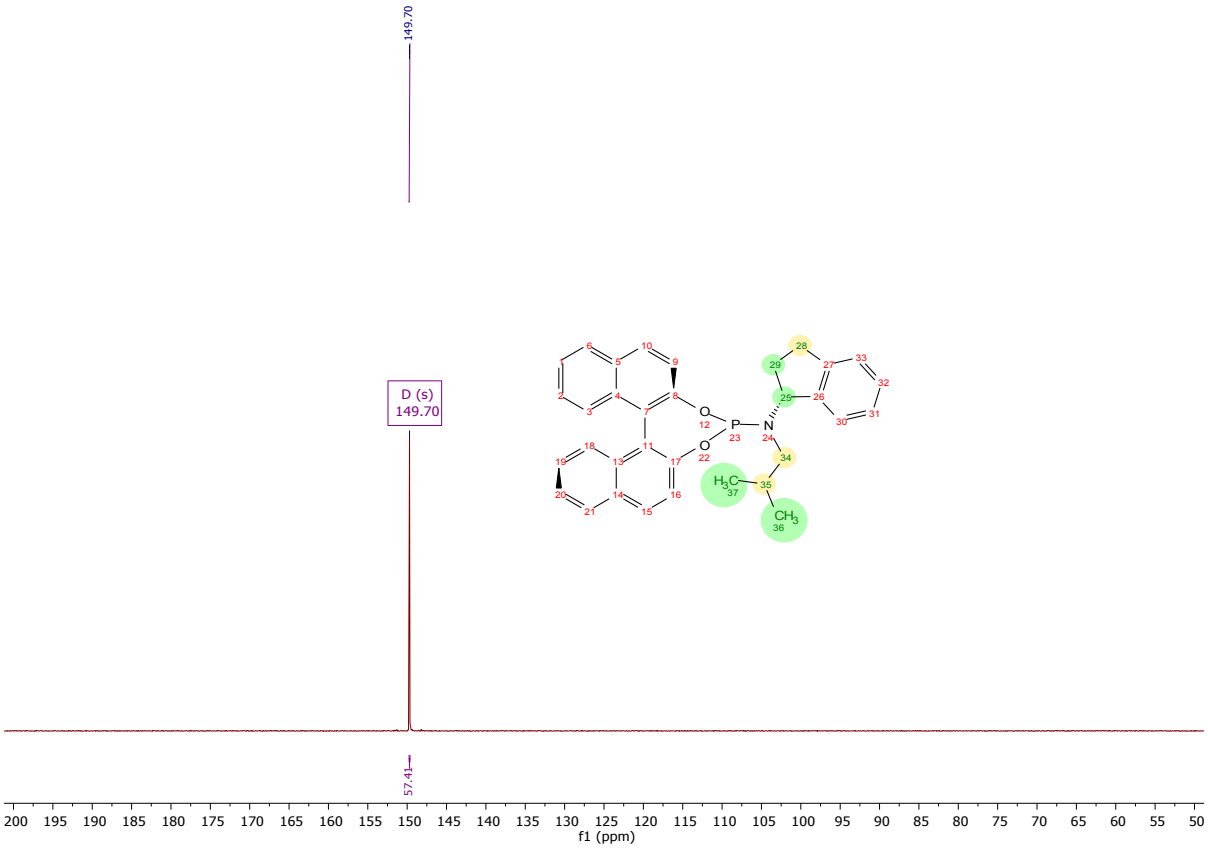
IR υ_{max} (film): 3659, 2980, 1462, 1382, 1231, 1155.

HRMS (EI^+) *m/z* calcd for $C_{33}H_{31}O_2NP$ $[M+H]^+$: 504.2087, found 504.2086.

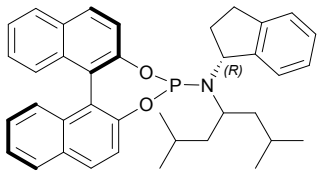
$[\alpha]^{25}_{589}$ = -109.4 (*c* 1.0, $CHCl_3$) for 99% ee.


I (m) 7.58
G (m) 7.95
B (m) 7.27
F (d) 8.01
A (m) 7.38
H (m) 7.85
E (m) 7.21
J (d) 7.49
25 (q) 4.89
28'',34'' (m) 2.73
29'' (ddt) 2.12
28' (ddd) 2.96
29' (dp) 2.32
35 (m) 1.55
36 (d) 0.78
37 (d) 0.81
f1 (ppm)


P (s) 127.54
N (s) 128.31
L (s) 130.27
C1 (s) 122.27
F (s) 150.31
B (s) 142.83
J (s) 131.36
Y (s) 124.34
D (s) 143.62
H (s) 132.86
V (s) 125.21
C (s) 149.64
G (s) 132.88
U (s) 125.87
A (s) 150.25
E (s) 142.80
I (s) 132.68
W (s) 124.89
K (s) 130.51
B1 (s) 122.29
M (s) 129.74
D1 (s) 122.20
O (s) 128.23
25 (s) 61.78
25 (s) 61.68
34 (s) 52.36
34 (s) 52.54
35 (s) 28.26
29 (s) 32.33
37 (s) 20.41
28 (s) 30.47
36 (s) 20.32
35 (s) 28.30
37 (s) 20.40
29 (s) 32.31
f1 (ppm)


149.70
D (s)
149.70
57.41
200 195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50
f1 (ppm)

N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(2,6-dimethylheptan-4-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L12



General Procedure E: Triethylamine (2.36 mL, 16.935 mmol, 5.0 eq.), PCl_3 (0.30 mL, 3.387 mmol, 1.0 eq.), CH_2Cl_2 (25 mL), (R)-N-(2,6-dimethylheptan-4-yl)-2,3-dihydro-1H-inden-1-amine (878 mg, 3.387 mmol, 1.0 eq.), (R)-binaphthol (969.8 mg, 3.387 mmol, 1.0 eq.).

The crude mixture was treated as described above and was purified by flash column chromatography (Hexane: CH_2Cl_2, 80:20, SiO_2) to afford N-((R)-2,3-dihydro-1H-inden-1-yl)-N-(2,6-dimethylheptan-4-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine (406.2 mg, 0.711 mmol, 21%) as a foamy white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.97 – 7.83 (m, 3H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.41 – 7.28 (m, 4H), 7.25 – 7.15 (m, 5H), 4.77 (dt, *J* = 14.2, 7.4 Hz, 1H), 3.20 – 3.16 (m, 1H), 3.05 – 2.95 (m, 1H), 2.77 – 2.67 (m, 1H), 2.35 – 2.31 (m, 1H), 2.21 – 2.13 (m, 1H), 1.91 – 1.79 (m, 1H), 1.61 – 1.49 (m, 4H), 1.40 – 1.23 (m, 1H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H), 0.73 (d, *J* = 5.9 Hz, 3H), 0.43 – 0.24 (m, 3H).

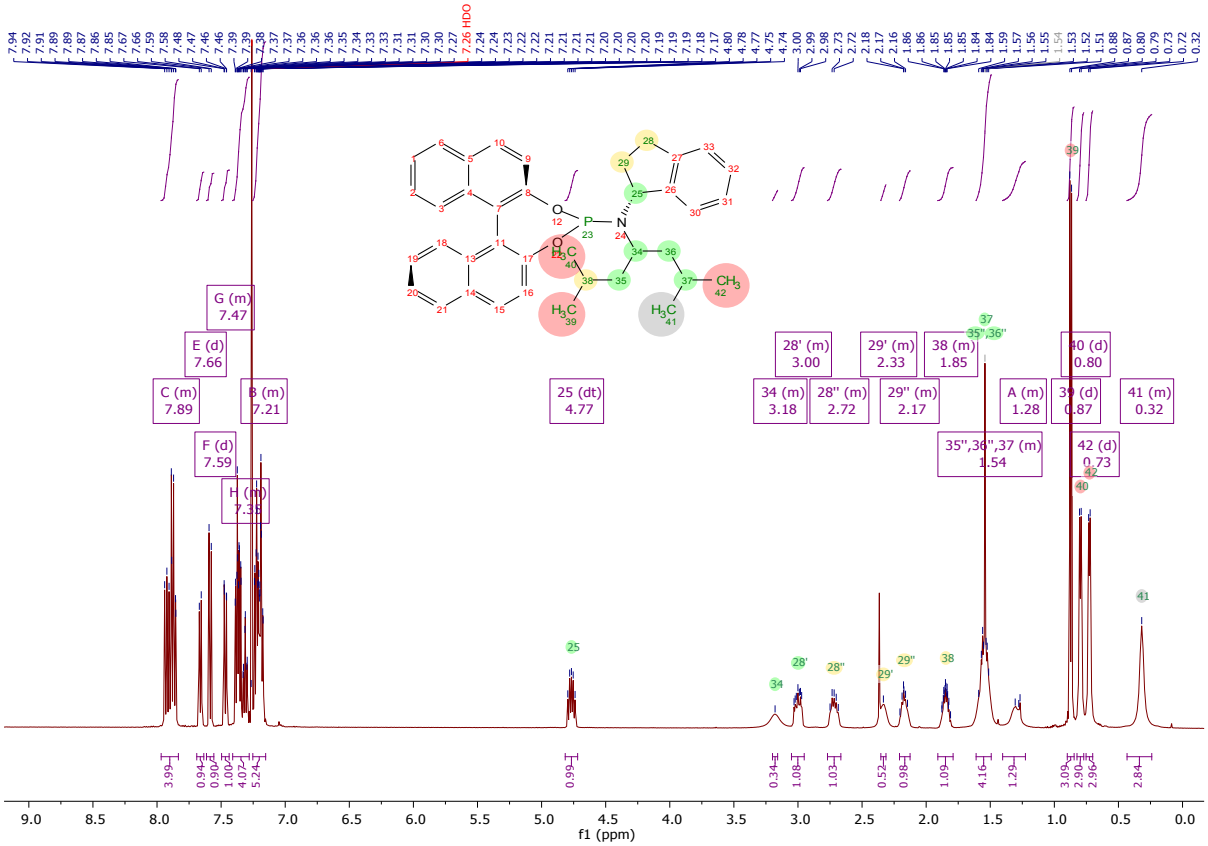
^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.2, 150.1, 149.9, 144.4 – 143.9 (m), 143.7, 132.9, 132.8, 132.8, 131.3, 130.5, 130.2, 129.7, 129.0, 128.2, 128.2, 128.1, 127.5, 127.1, 127.1, 126.3, 125.9, 125.8, 125.7, 125.3, 124.7, 124.6, 124.3, 123.9, 123.9, 122.5, 122.2, 122.2, 121.7, 121.7, 59.7, 51.1, 45.9 – 45.0 (m), 36.4 – 34.3 (m), 30.6, 24.9, 24.5, 23.8, 23.3, 22.6, 20.7.

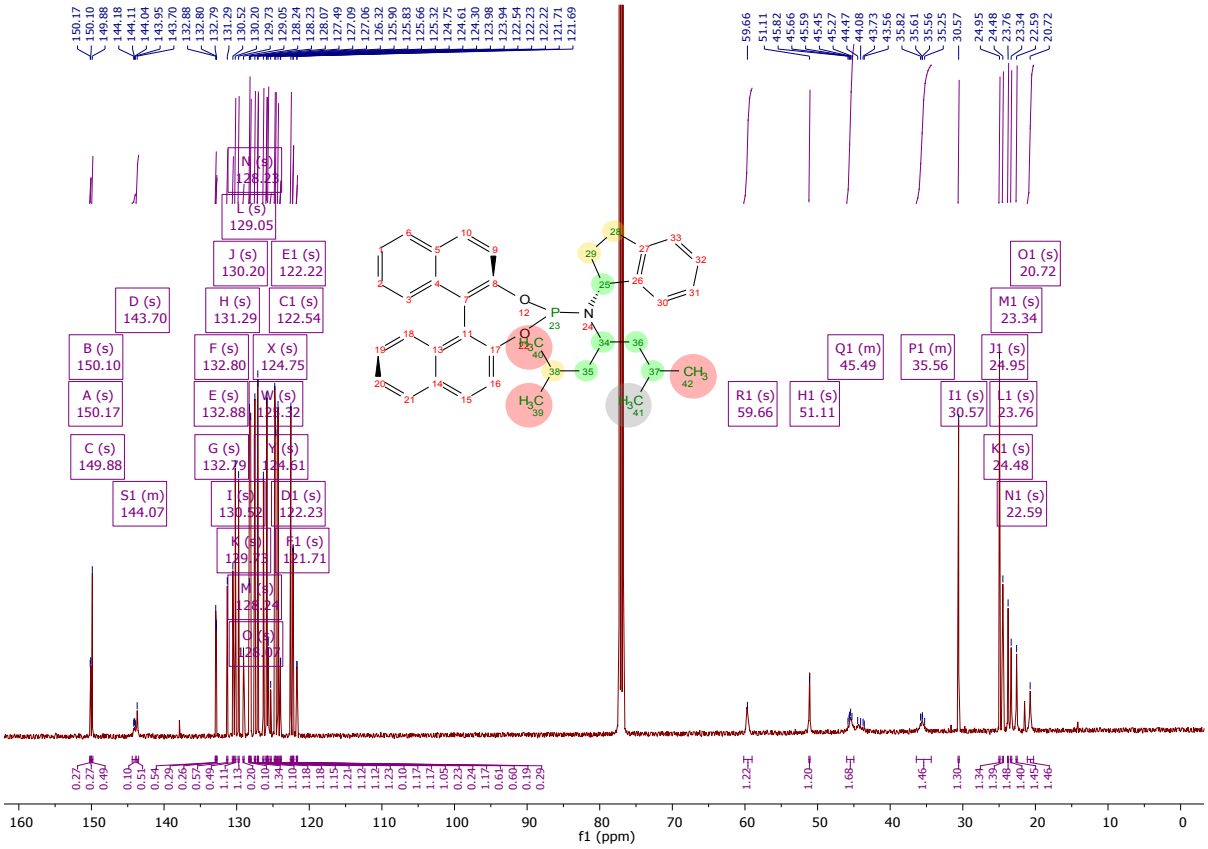
^{31}P NMR (243 MHz, Chloroform-*d*) δ 151.0.

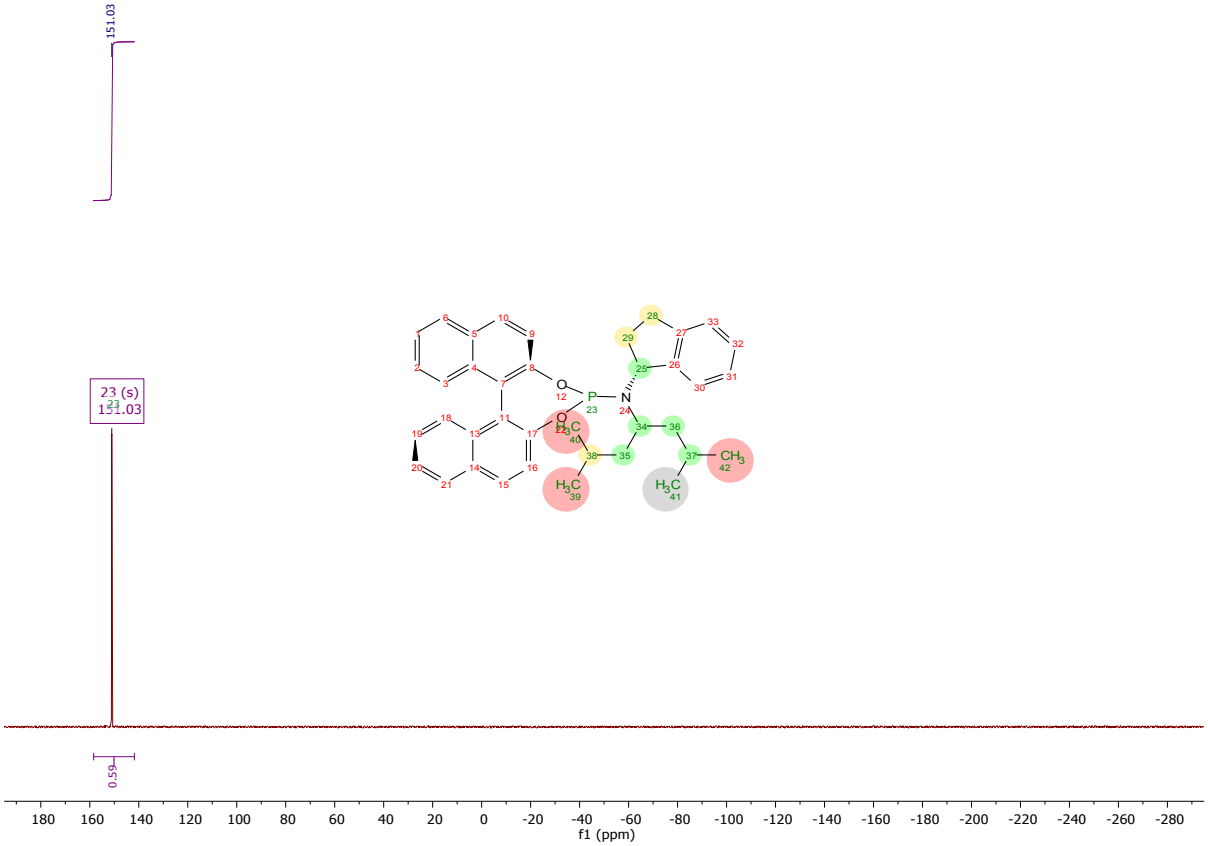
IR υ_{max} (film): 3064, 2954, 2866, 2360, 1590, 1506, 1232, 1064.

HRMS (EI^+) *m/z* calcd for $C_{38}H_{41}O_2NP$ $[M+H]^+$: 574.2869, found 574.2869.

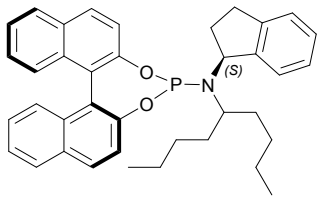
$[\alpha]^{25}_{589}$ = -86.8 (*c* 1.0, $CHCl_3$) for 99% ee.


G (m) 7.47
E (d) 7.66
C (m) 7.89
B (m) 7.21
F (d) 7.59
H (m) 7.35
25 (dt) 4.77
28' (m) 3.00
29' (m) 2.33
38 (m) 1.85
34 (m) 3.18
28'' (m) 2.72
29'' (m) 2.17
35'',36'' 37
35'',36'',37 (m) 1.54
A (m) 1.28
39 (d) 0.87
40 (d) 0.80
41 (m) 0.32
42 (d) 0.73
f1 (ppm)


N (s) 128.23
L (s) 129.05
J (s) 130.20
E1 (s) 122.22
D (s) 143.70
H (s) 131.29
C1 (s) 122.54
B (s) 150.10
F (s) 132.80
X (s) 124.75
A (s) 150.17
E (s) 132.88
W (s) 128.32
C (s) 149.88
G (s) 132.79
Y (s) 124.61
S1 (m) 144.07
I (s) 130.52
D1 (s) 122.23
F1 (s) 121.71
M (s) 128.24
O (s) 128.07
R1 (s) 59.66
H1 (s) 51.11
Q1 (m) 45.49
P1 (m) 35.56
I1 (s) 30.57
L1 (s) 23.76
O1 (s) 20.72
M1 (s) 23.34
J1 (s) 24.95
K1 (s) 24.48
N1 (s) 22.59
f1 (ppm)


151.03
23 (s)
151.03
0.59
180 160 140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240 -260 -280
f1 (ppm)

(11bS)-N-((S)-2,3-dihydro-1H-inden-1-yl)-N-(nonan-5-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L6



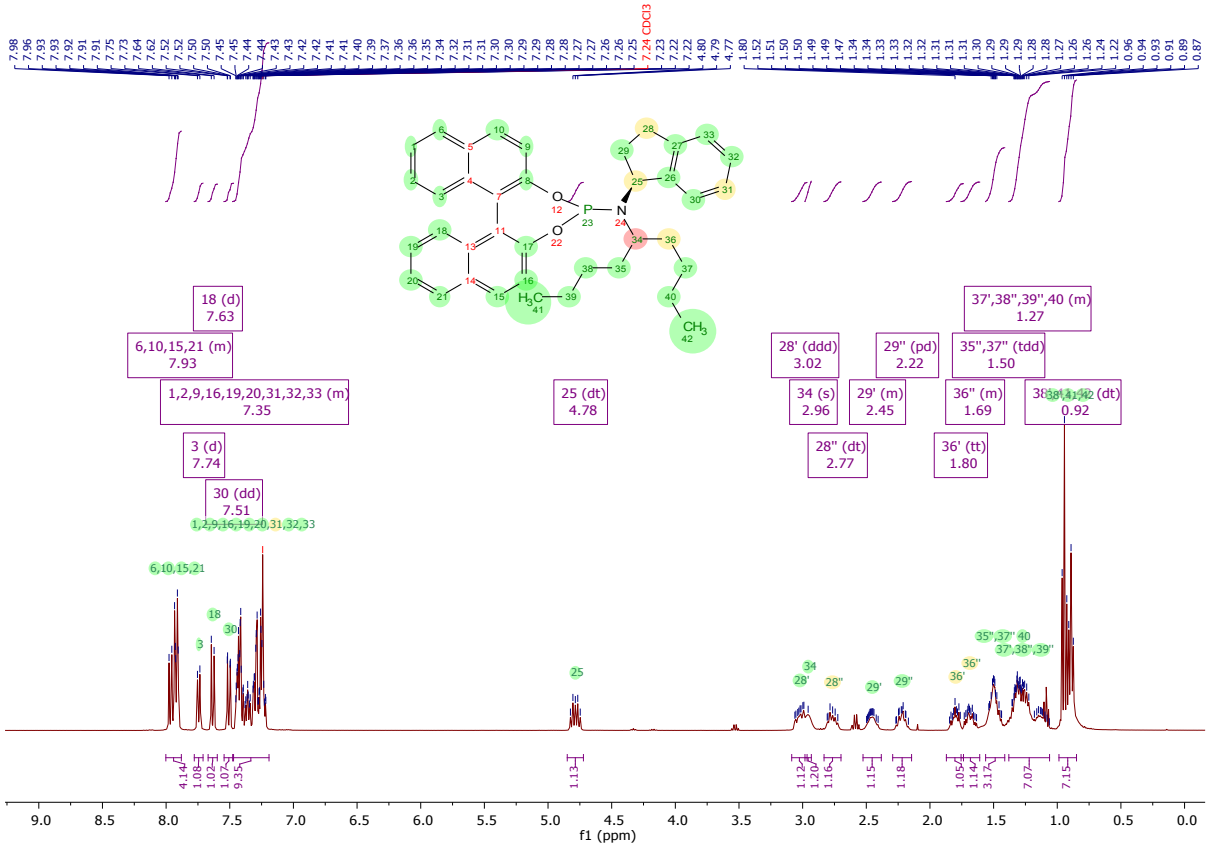
This ligand was part of a shared ligand library and was not synthesised by the author even though it was used in this work. It can be found in previously reported procedures, similar to the General Procedure E.[5]

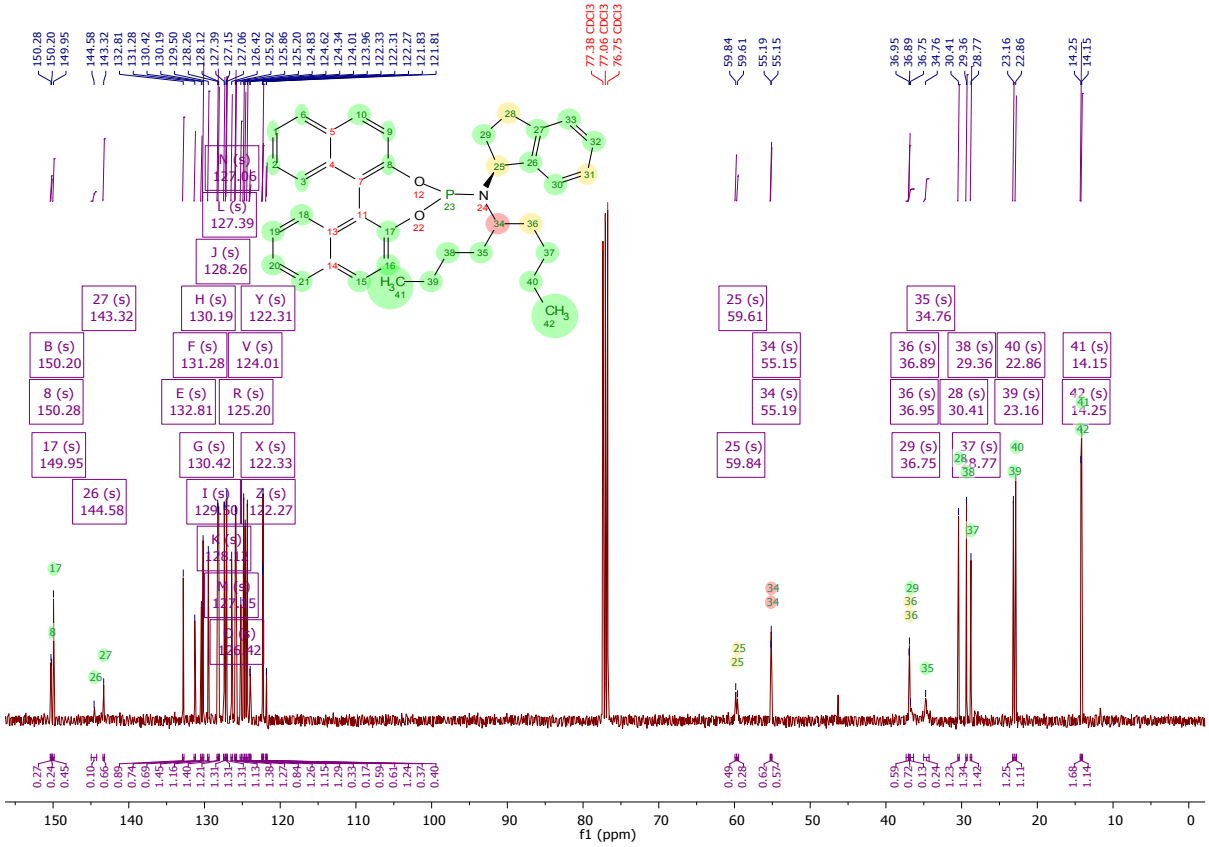
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 – 7.88 (m, 4H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.51 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.48 – 7.19 (m, 9H), 4.78 (dt, *J* = 15.4, 7.8 Hz, 1H), 3.02 (ddd, *J* = 15.9, 9.0, 3.2 Hz, 1H), 2.96 (s, 1H), 2.77 (dt, *J* = 16.3, 8.5 Hz, 1H), 2.53 – 2.38 (m, 1H), 2.22 (pd, *J* = 9.5, 9.0, 4.9 Hz, 1H), 1.80 (tt, *J* = 12.2, 4.4 Hz, 1H), 1.76 – 1.61 (m, 1H), 1.50 (tdd, *J* = 13.1, 9.2, 4.6 Hz, 3H), 1.38 – 1.06 (m, 6H), 0.99 – 0.85 (m, 7H).

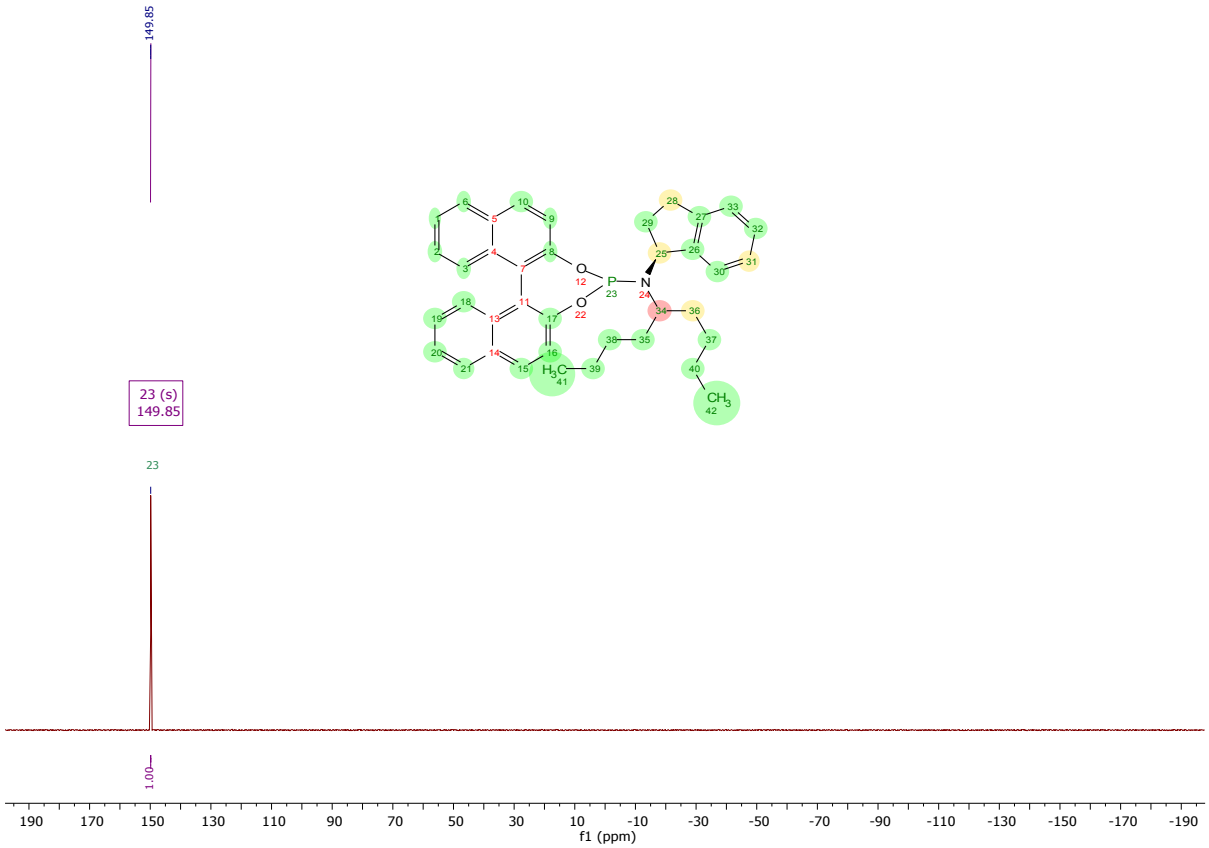
^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.3, 150.2, 149.9, 144.6, 143.3, 132.8, 131.3, 130.4, 130.2, 129.5, 128.3, 128.1, 127.4, 127.1, 127.1, 126.4, 125.9, 125.9, 125.2, 124.8, 124.6, 124.3, 124.0, 123.9, 122.3, 122.3, 122.3, 121.8, 121.8, 59.8, 59.6, 55.2, 55.1, 36.9, 36.9, 36.7 (br m), 34.8 (br m), 30.4, 29.4, 28.8, 23.2, 22.9, 14.2, 14.1.

^{31}P NMR (162 MHz, Chloroform-*d*) δ 149.8.

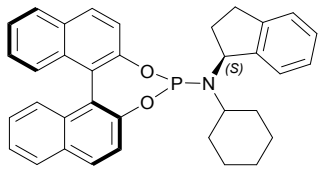
Analytical data are in agreement with the literature.[5]


18 (d)
7.63
6,10,15,21 (m)
7.93
1,2,9,16,19,20,31,32,33 (m)
7.35
3 (d)
7.74
30 (dd)
7.51
25 (dt)
4.78
28' (ddd)
3.02
34 (s)
2.96
28" (dt)
2.77
29" (pd)
2.22
29' (m)
2.45
35",37" (tdd)
1.50
36" (m)
1.69
36' (tt)
1.80
37',38",39",40 (m)
1.27
f1 (ppm)


N (s)
127.06
L (s)
127.39
J (s)
128.26
27 (s)
143.32
H (s)
130.19
Y (s)
122.31
B (s)
150.20
F (s)
131.28
V (s)
124.01
8 (s)
150.28
E (s)
132.81
R (s)
125.20
17 (s)
149.95
G (s)
130.42
X (s)
122.33
26 (s)
144.58
I (s)
129.50
Z (s)
122.27
25 (s)
59.61
34 (s)
55.15
34 (s)
55.19
25 (s)
59.84
35 (s)
34.76
36 (s)
36.89
38 (s)
29.36
40 (s)
22.86
41 (s)
14.15
36 (s)
36.95
28 (s)
30.41
39 (s)
23.16
42 (s)
14.25
29 (s)
36.75
37 (s)
28.77
f1 (ppm)


149.85
23 (s)
149.85
23
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

(11bS)-N-cyclohexyl-N-((S)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L2



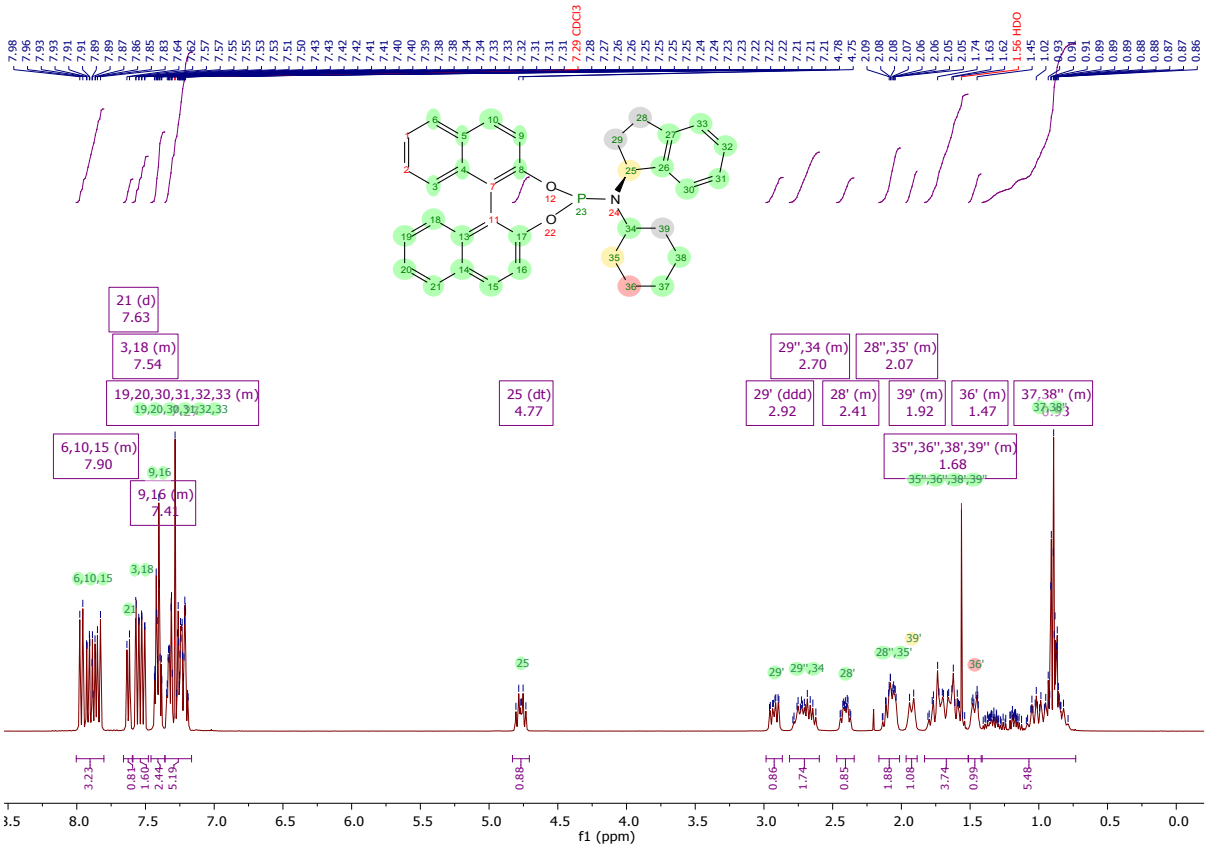
This ligand was part of a shared ligand library and was not synthesised by the author even though it was used in this work. It can be found in previously reported procedures, similar to the General Procedure E.[5]

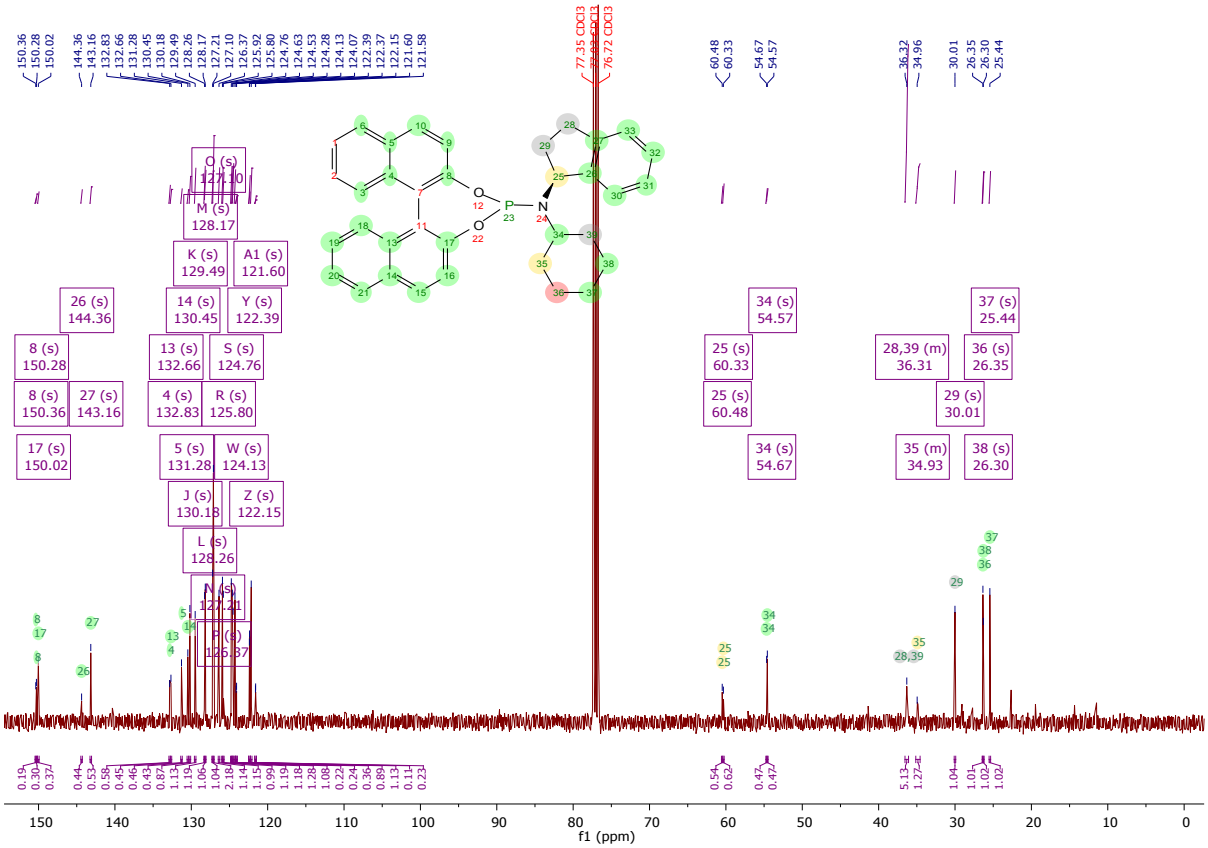
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 – 7.80 (m, 3H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.60 – 7.48 (m, 2H), 7.46 – 7.36 (m, 2H), 7.36 – 7.16 (m, 5H), 4.77 (dt, *J* = 12.6, 8.2 Hz, 1H), 2.92 (ddd, *J* = 15.9, 9.1, 2.4 Hz, 1H), 2.81 – 2.60 (m, 2H), 2.47 – 2.34 (m, 1H), 2.16 – 2.01 (m, 2H), 1.97 – 1.89 (m, 1H), 1.83 – 1.51 (m, 4H), 1.51 – 1.42 (m, 1H), 1.41 – 0.73 (m, 5H).

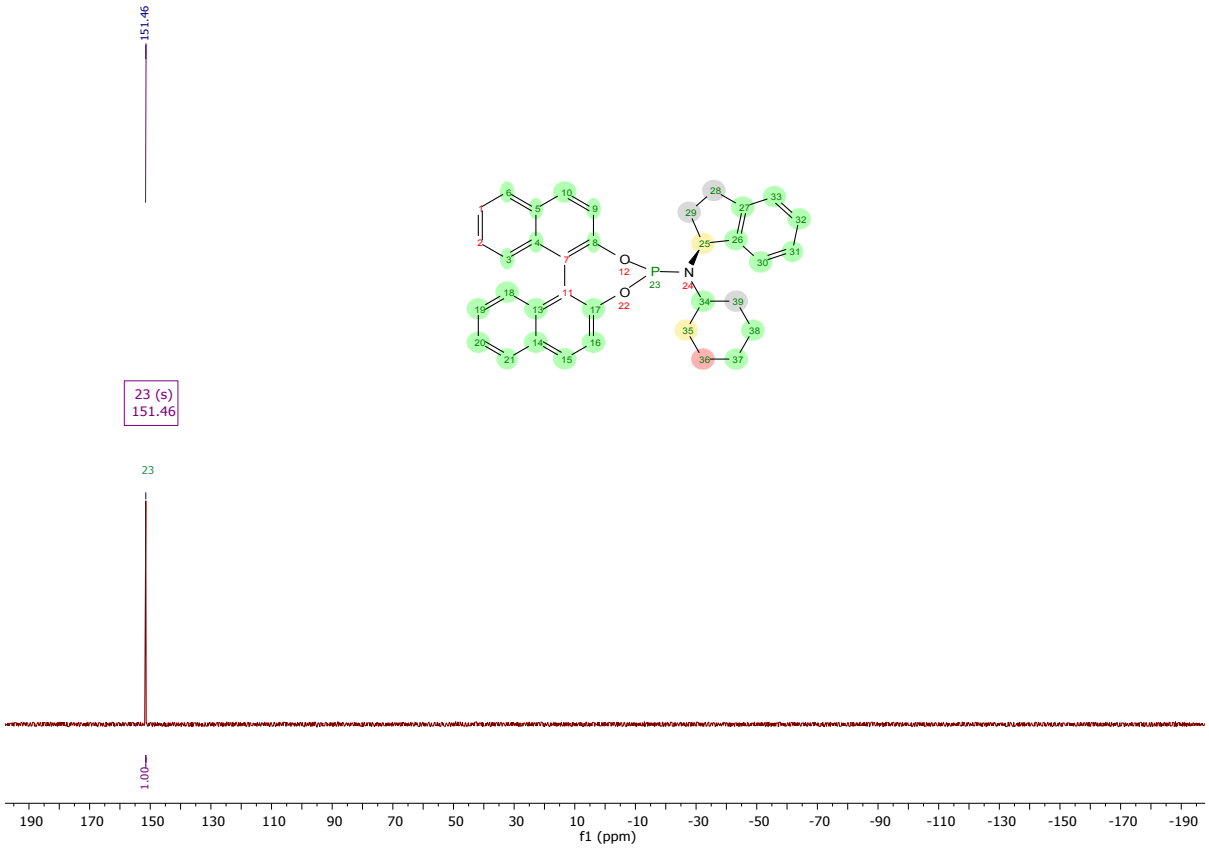
^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.4, 150.3, 150.0, 144.4, 143.2, 132.8, 132.7, 131.3, 130.4, 130.2, 129.5, 128.3, 128.2, 127.2, 127.1 (2 C), 126.4, 125.9, 125.8, 124.8, 124.6, 124.5, 124.3, 124.1, 124.1, 122.4, 122.4, 122.1, 121.6, 121.6, 60.5, 60.3, 54.7, 54.6, 36.5 – 36.1 (br m, 2 C), 34.9 (br m), 30.0, 26.3, 26.3, 25.4.

^{31}P NMR (162 MHz, Chloroform-*d*) δ 151.5.

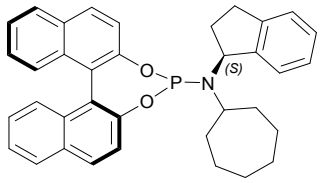
Analytical data are in agreement with the literature.[5]


21 (d)
7.63
3,18 (m)
7.54
19,20,30,31,32,33 (m)
6,10,15 (m)
7.90
9,16 (m)
7.41
25 (dt)
4.77
29'',34 (m)
2.70
28'',35' (m)
2.07
29' (ddd)
2.92
28' (m)
2.41
39' (m)
1.92
36' (m)
1.47
37,38'' (m)
35'',36'',38',39'' (m)
1.68
f1 (ppm)


C (s)
127.10
M (s)
128.17
K (s)
129.49
A1 (s)
121.60
26 (s)
144.36
14 (s)
130.45
Y (s)
122.39
8 (s)
150.28
13 (s)
132.66
S (s)
124.76
8 (s)
150.36
27 (s)
143.16
4 (s)
132.83
R (s)
125.80
17 (s)
150.02
5 (s)
131.28
W (s)
124.13
J (s)
130.18
Z (s)
122.15
L (s)
128.26
N (s)
127.21
F (s)
126.37
34 (s)
54.57
25 (s)
60.33
25 (s)
60.48
34 (s)
54.67
37 (s)
25.44
28,39 (m)
36.31
36 (s)
26.35
29 (s)
30.01
35 (m)
34.93
38 (s)
26.30
f1 (ppm)


151.46
23 (s)
151.46
23
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

(11bS)-N-cycloheptyl-N-((S)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L5



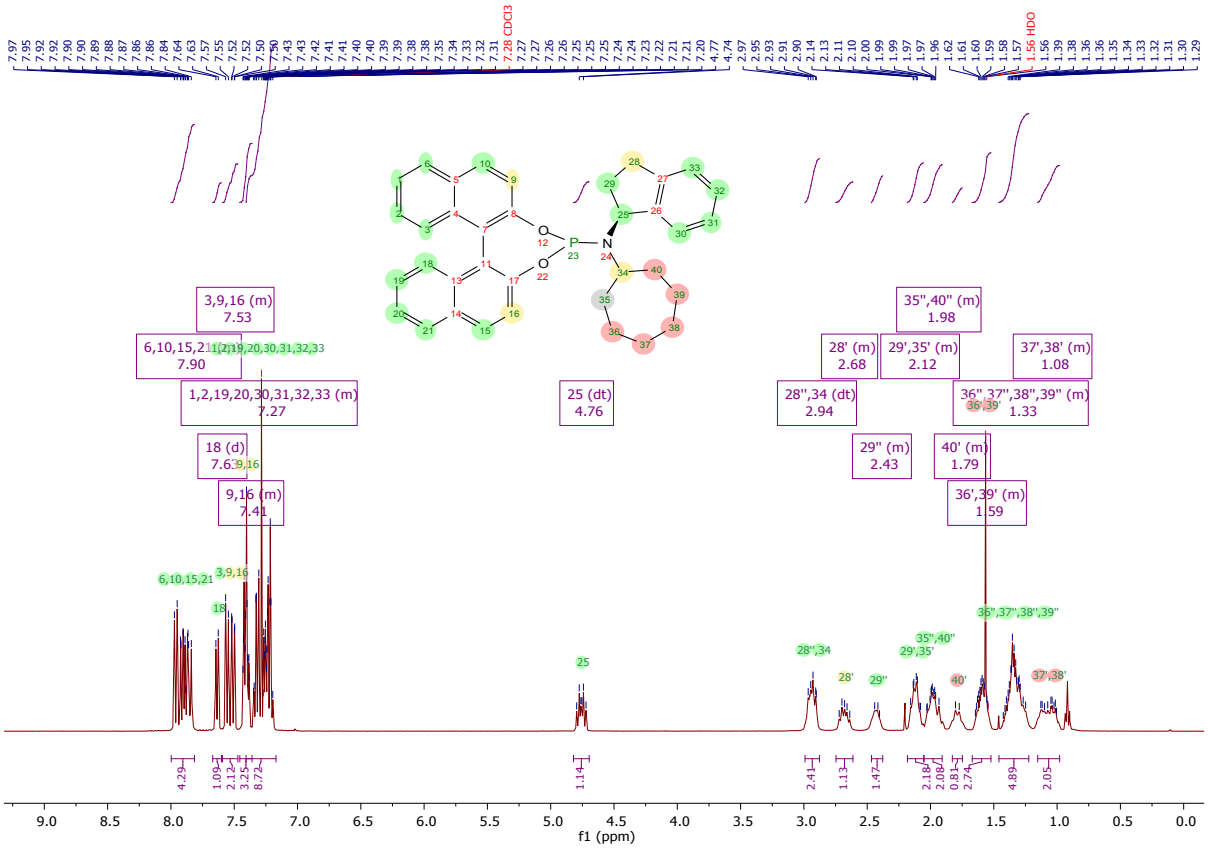
This ligand was part of a shared ligand library and was not synthesised by the author even though it was used in this work. It can be found in previously reported procedures, similar to the General Procedure E.[5]

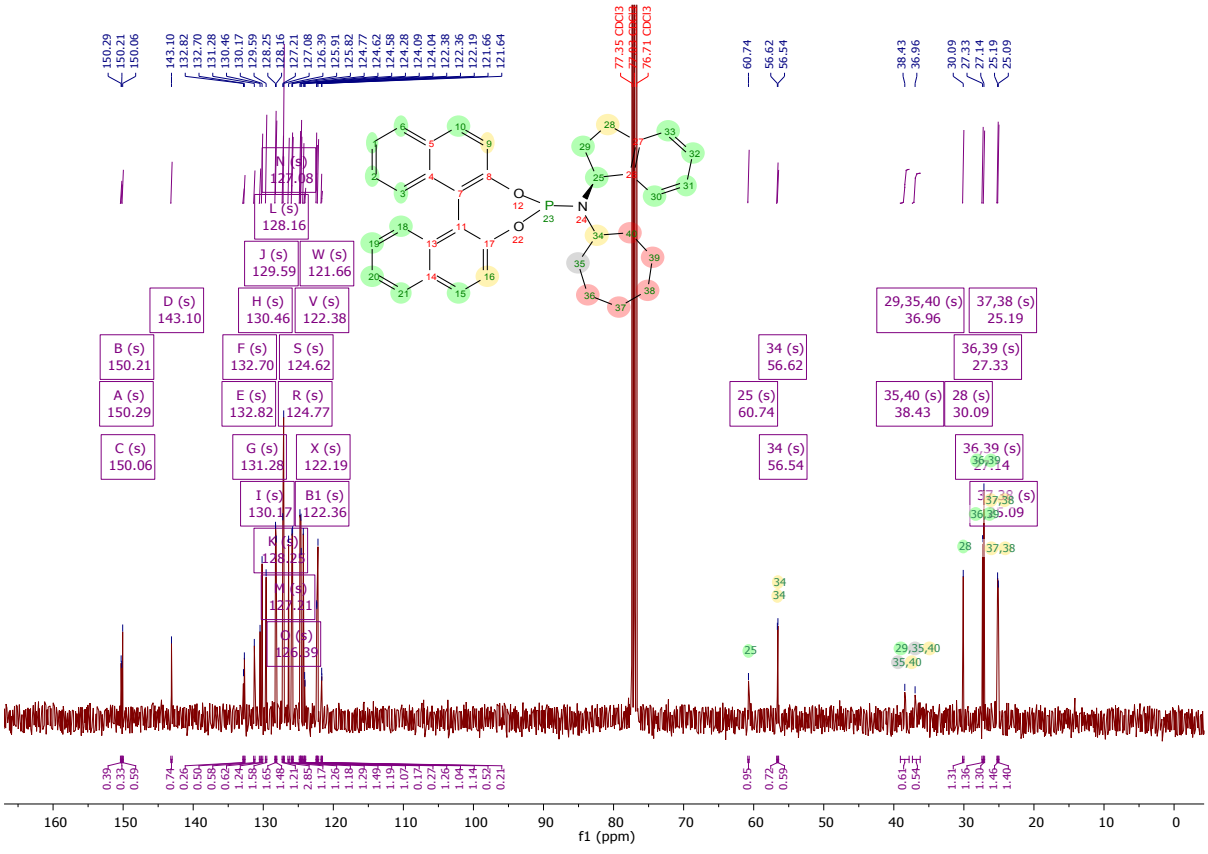
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 – 7.81 (m, 4H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.59 – 7.47 (m, 2H), 7.46 – 7.36 (m, 3H), 7.41 – 7.17 (m, 9H), 4.76 (dt, *J* = 13.2, 8.2 Hz, 1H), 2.94 (dt, *J* = 10.4, 4.9 Hz, 2H), 2.75 – 2.61 (m, 1H), 2.47 – 2.38 (m, 1H), 2.18 – 2.05 (m, 2H), 2.05 – 1.91 (m, 2H), 1.83 – 1.75 (m, 1H), 1.67 – 1.52 (m, 2H), 1.46 – 1.22 (m, 4H), 1.15 – 0.98 (m, 2H).

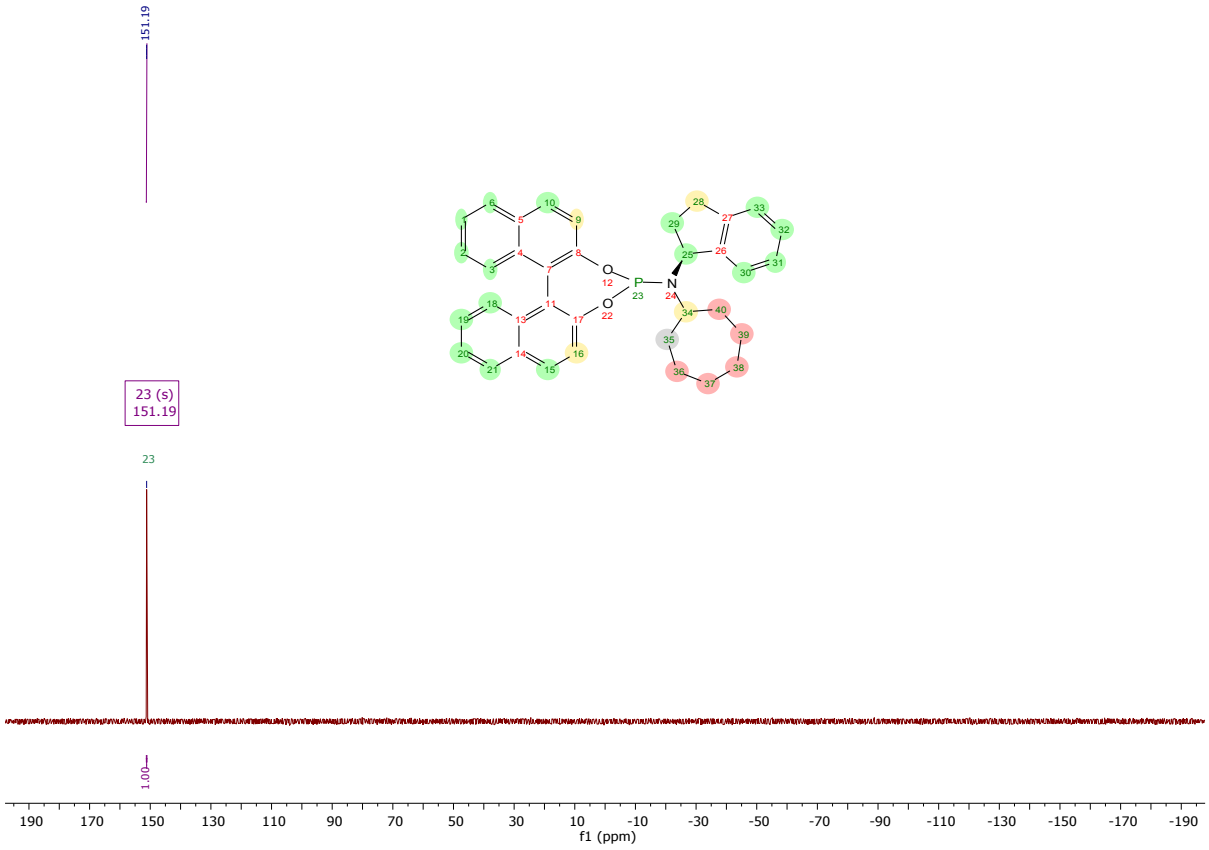
^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.3, 150.2, 150.1, 143.1, 132.8, 132.7, 131.3, 130.5, 130.2, 129.6, 128.2, 128.2, 127.2, 127.1, 126.4, 125.9, 125.8, 124.8, 124.6, 124.6, 124.3, 124.1, 124.0, 122.4, 122.4, 122.2, 121.7, 121.6, 60.7, 56.6, 56.5, 38.4 (m), 36.9 (m), 30.1, 27.3, 27.1, 25.2, 25.1.

^{31}P NMR (162 MHz, Chloroform-*d*) δ 151.2.

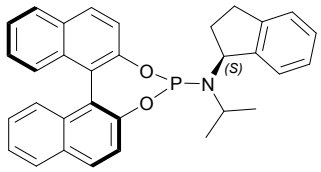
Analytical data are in agreement with the literature.[5]


3,9,16 (m)
7.53
6,10,15,21 (m)
7.90
1,2,19,20,30,31,32,33 (m)
7.27
18 (d)
7.6
9,16 (m)
7.41
25 (dt)
4.76
35",40" (m)
1.98
28' (m)
2.68
29',35' (m)
2.12
37',38' (m)
1.08
28",34 (dt)
2.94
36",37",38",39" (m)
1.33
29" (m)
2.43
40' (m)
1.79
36',39' (m)
1.59
f1 (ppm)


N (s)
127.08
L (s)
128.16
J (s)
129.59
W (s)
121.66
D (s)
143.10
H (s)
130.46
V (s)
122.38
B (s)
150.21
F (s)
132.70
S (s)
124.62
A (s)
150.29
E (s)
132.82
R (s)
124.77
C (s)
150.06
G (s)
131.28
X (s)
122.19
I (s)
130.17
B1 (s)
122.36
29,35,40 (s)
36.96
37,38 (s)
25.19
36,39 (s)
27.33
34 (s)
56.62
25 (s)
60.74
35,40 (s)
38.43
28 (s)
30.09
34 (s)
56.54
36,39 (s)
27.14
37,38 (s)
25.09
f1 (ppm)


151.19
23 (s)
151.19
23
1.00
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
f1 (ppm)

(11bS)-N-((S)-2,3-dihydro-1H-inden-1-yl)-N-isopropyldinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L4



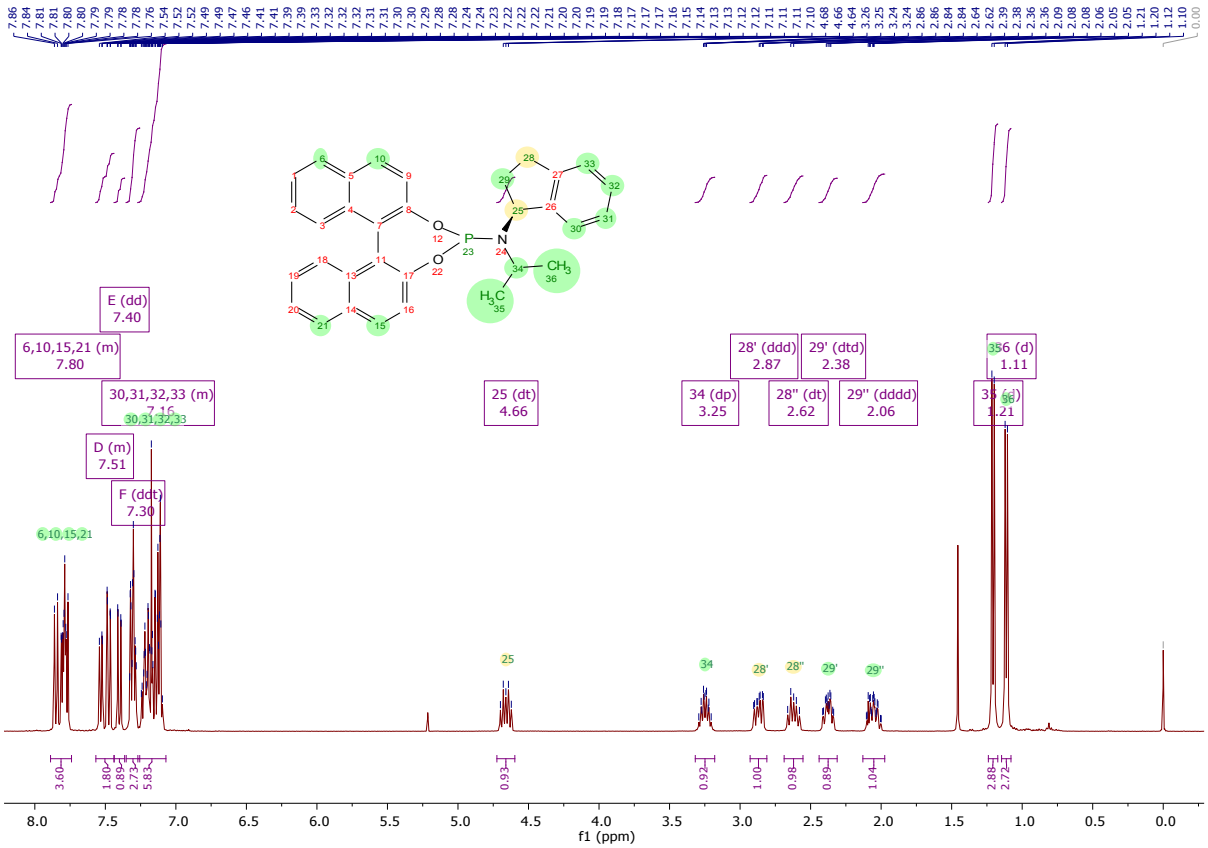
This ligand was part of a shared ligand library and was not synthesised by the author even though it was used in this work. It can be found in previously reported procedures, similar to the General Procedure E.[5]

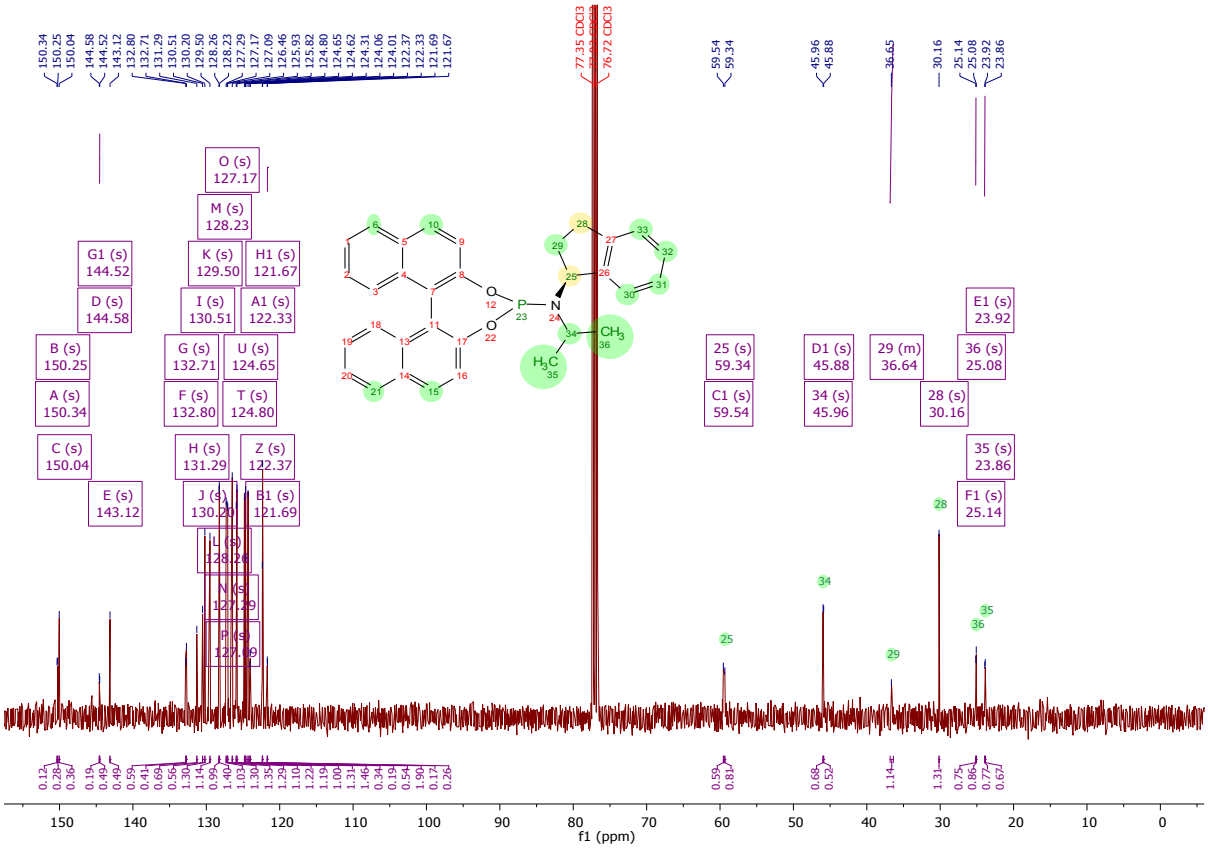
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.74 (m, 4H), 7.57 – 7.44 (m, 2H), 7.40 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.30 (ddt, *J* = 8.2, 6.6, 1.2 Hz, 3H), 7.27 – 7.07 (m, 6H), 4.66 (dt, *J* = 15.4, 8.1 Hz, 1H), 3.25 (dp, *J* = 8.3, 6.6 Hz, 1H), 2.87 (ddd, *J* = 15.9, 9.1, 2.5 Hz, 1H), 2.62 (dt, *J* = 16.4, 8.8 Hz, 1H), 2.38 (dtd, *J* = 12.8, 7.9, 2.6 Hz, 1H), 2.06 (dddd, *J* = 16.0, 12.8, 7.1, 4.5 Hz, 1H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H).

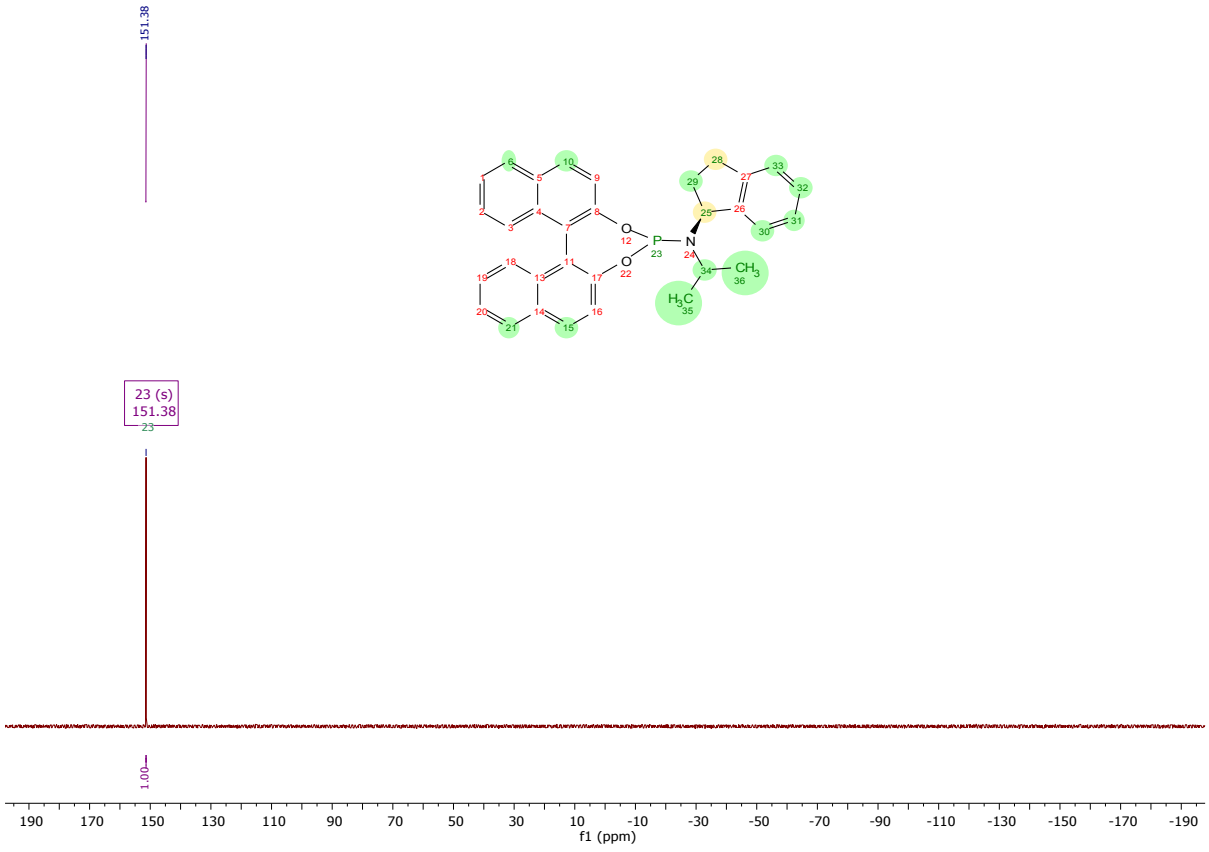
^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.3, 150.2, 150.0, 144.6, 144.5, 143.1, 132.8, 132.7, 131.3, 130.5, 130.2, 129.5, 128.3, 128.2, 127.3, 127.2, 127.1, 126.5, 125.9, 125.8, 124.8, 124.6, 124.6, 124.3, 124.1, 124.0, 122.4, 122.3, 121.7, 121.7, 59.5, 59.3, 45.9, 45.9, 36.8 – 36.4 (m), 30.2, 25.1, 25.1, 23.9, 23.9.

^{31}P NMR (162 MHz, Chloroform-*d*) δ 151.4.

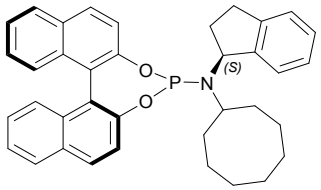
Analytical data are in agreement with the literature.[5]


E (dd)
7.40
6,10,15,21 (m)
7.80
30,31,32,33 (m)
7.16
D (m)
7.51
F (ddt)
7.30
25 (dt)
4.66
34 (dp)
3.25
28' (ddd)
2.87
29' (dtd)
2.38
28'' (dt)
2.62
29'' (dddd)
2.06
36 (d)
1.11
35 (d)
1.21
f1 (ppm)


O (s)
127.17
M (s)
128.23
G1 (s)
144.52
K (s)
129.50
H1 (s)
121.67
D (s)
144.58
I (s)
130.51
A1 (s)
122.33
B (s)
150.25
G (s)
132.71
U (s)
124.65
A (s)
150.34
F (s)
132.80
T (s)
124.80
C (s)
150.04
H (s)
131.29
Z (s)
122.37
E (s)
143.12
J (s)
130.20
B1 (s)
121.69
25 (s)
59.34
C1 (s)
59.54
D1 (s)
45.88
34 (s)
45.96
29 (m)
36.64
28 (s)
30.16
E1 (s)
23.92
36 (s)
25.08
35 (s)
23.86
F1 (s)
25.14
f1 (ppm)


151.38
23 (s)
151.38
23
1.00
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
f1 (ppm)

(11bS)-N-cyclooctyl-N-((S)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L11



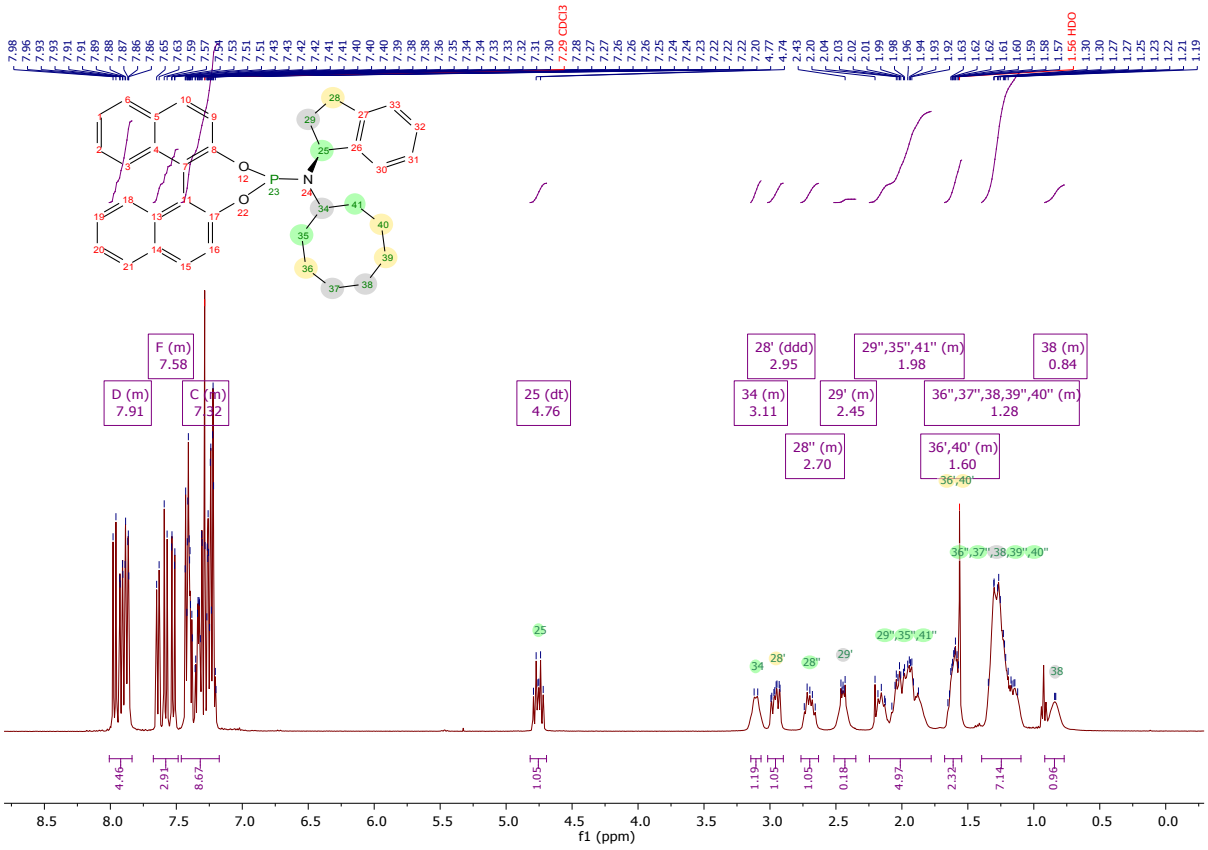
This ligand was part of a shared ligand library and was not synthesised by the author even though it was used in this work. It can be found in previously reported procedures, similar to the General Procedure E.[5]

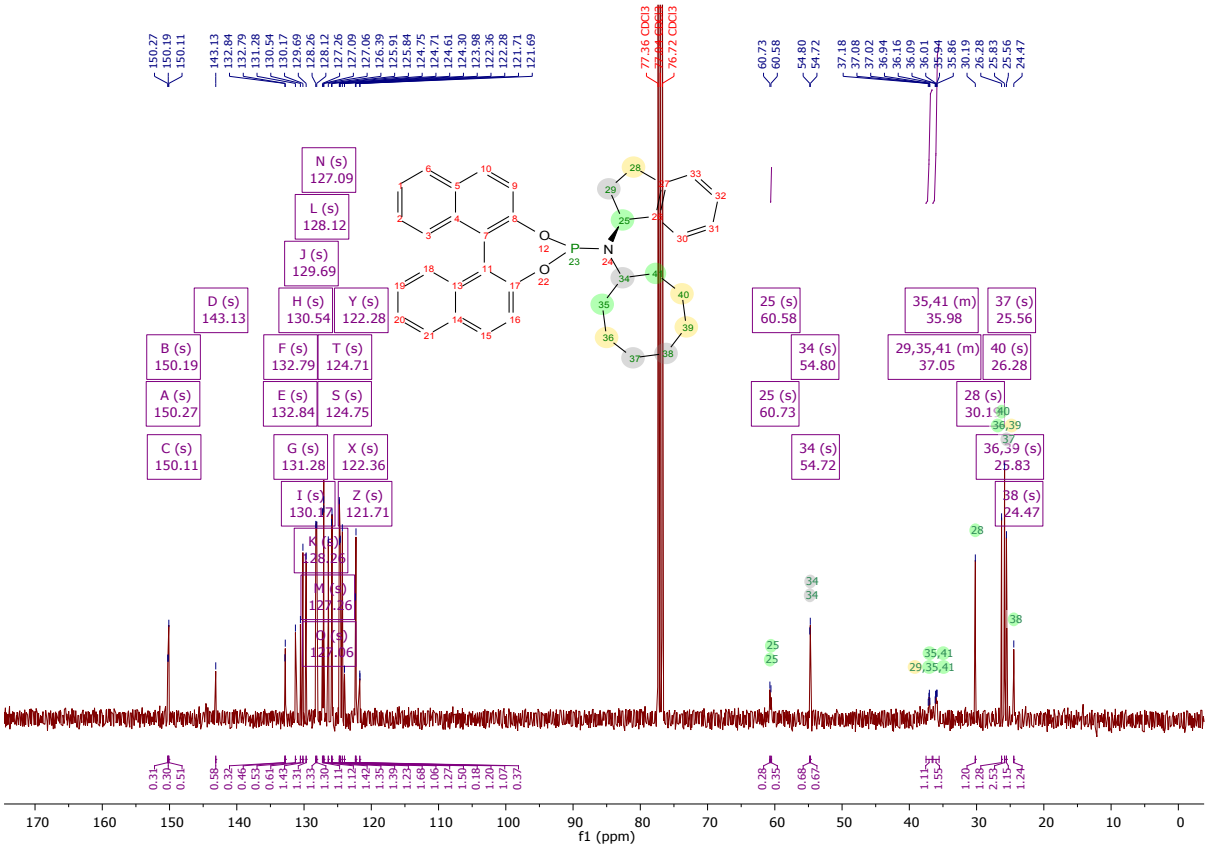
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 – 7.84 (m, 4H), 7.67 – 7.49 (m, 3H), 7.46 – 7.17 (m, 9H), 4.76 (dt, *J* = 13.4, 8.1 Hz, 1H), 3.15 – 3.07 (m, 1H), 2.95 (ddd, *J* = 15.9, 9.2, 2.6 Hz, 1H), 2.76 – 2.63 (m, 1H), 2.51 – 2.35 (m, 0H), 2.25 – 1.78 (m, 5H), 1.68 – 1.55 (m, 2H), 1.40 – 1.10 (m, 7H), 0.92 – 0.77 (m, 1H).

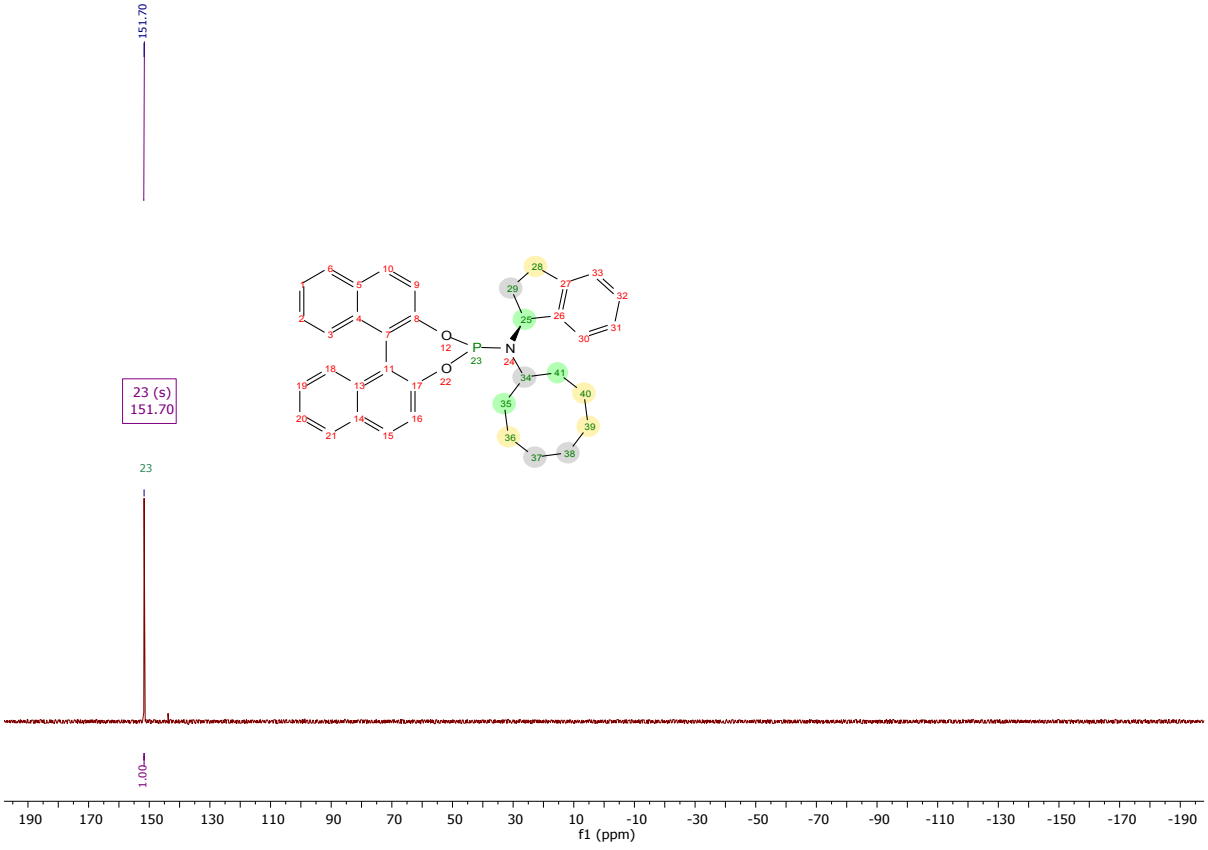
^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.3, 150.2, 150.1, 143.1, 132.8, 132.8, 131.3, 130.5, 130.2, 129.7, 128.3, 128.1, 127.3, 127.1, 127.1, 126.4, 125.9, 125.8, 124.7, 124.7, 124.6, 124.3, 123.9, 122.4, 122.3, 121.7, 60.7, 60.6, 54.8, 54.7, 37.5 – 36.6 (m, 2 C), 36.5 – 35.6 (m), 30.2, 26.3, 25.8, 25.6, 24.5.

^{31}P NMR (162 MHz, Chloroform-*d*) δ 151.7.

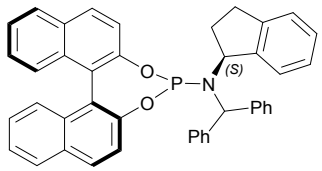
Analytical data are in agreement with the literature.[5]


F (m) 7.58
D (m) 7.91
C (m) 7.32
25 (dt) 4.76
28' (ddd) 2.95
34 (m) 3.11
29'' (m) 2.70
29'' (m) 2.45
29'',35'',41'' (m) 1.98
36'',37'',38,39'',40'' (m) 1.28
36',40' (m) 1.60
38 (m) 0.84
f1 (ppm)


N (s) 127.09
L (s) 128.12
J (s) 129.69
D (s) 143.13
H (s) 130.54
Y (s) 122.28
B (s) 150.19
F (s) 132.79
T (s) 124.71
A (s) 150.27
E (s) 132.84
S (s) 124.75
C (s) 150.11
G (s) 131.28
X (s) 122.36
I (s) 130.17
Z (s) 121.71
25 (s) 60.58
34 (s) 54.80
25 (s) 60.73
34 (s) 54.72
35,41 (m) 35.98
37 (s) 25.56
29,35,41 (m) 37.05
40 (s) 26.28
28 (s) 30.1
36,39 (s) 25.83
38 (s) 24.47
f1 (ppm)


151.70
23 (s)
151.70
23
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

(11bS)-N-benzhydryl-N-((S)-2,3-dihydro-1H-inden-1-yl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine L8



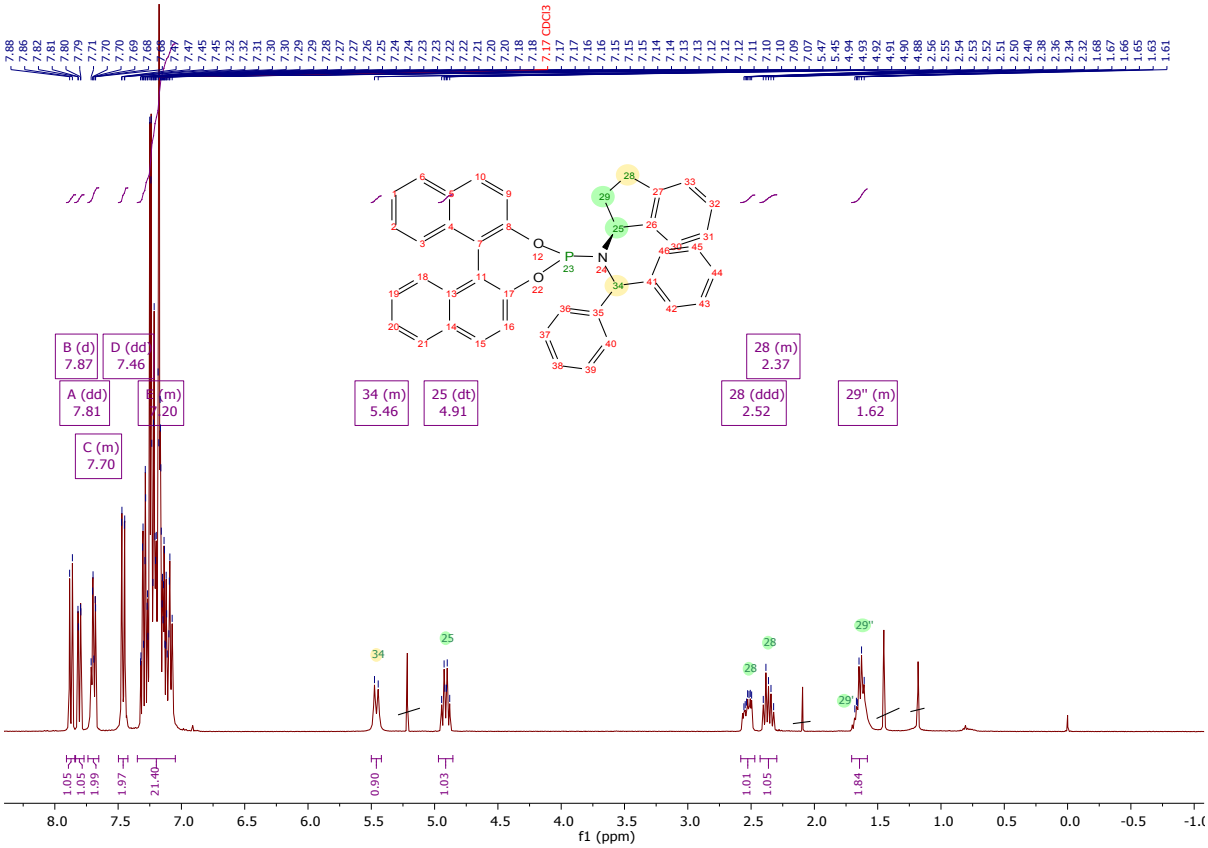
This ligand was part of a shared ligand library and was not synthesised by the author even though it was used in this work. It can be found in previously reported procedures, similar to the General Procedure E.[5]

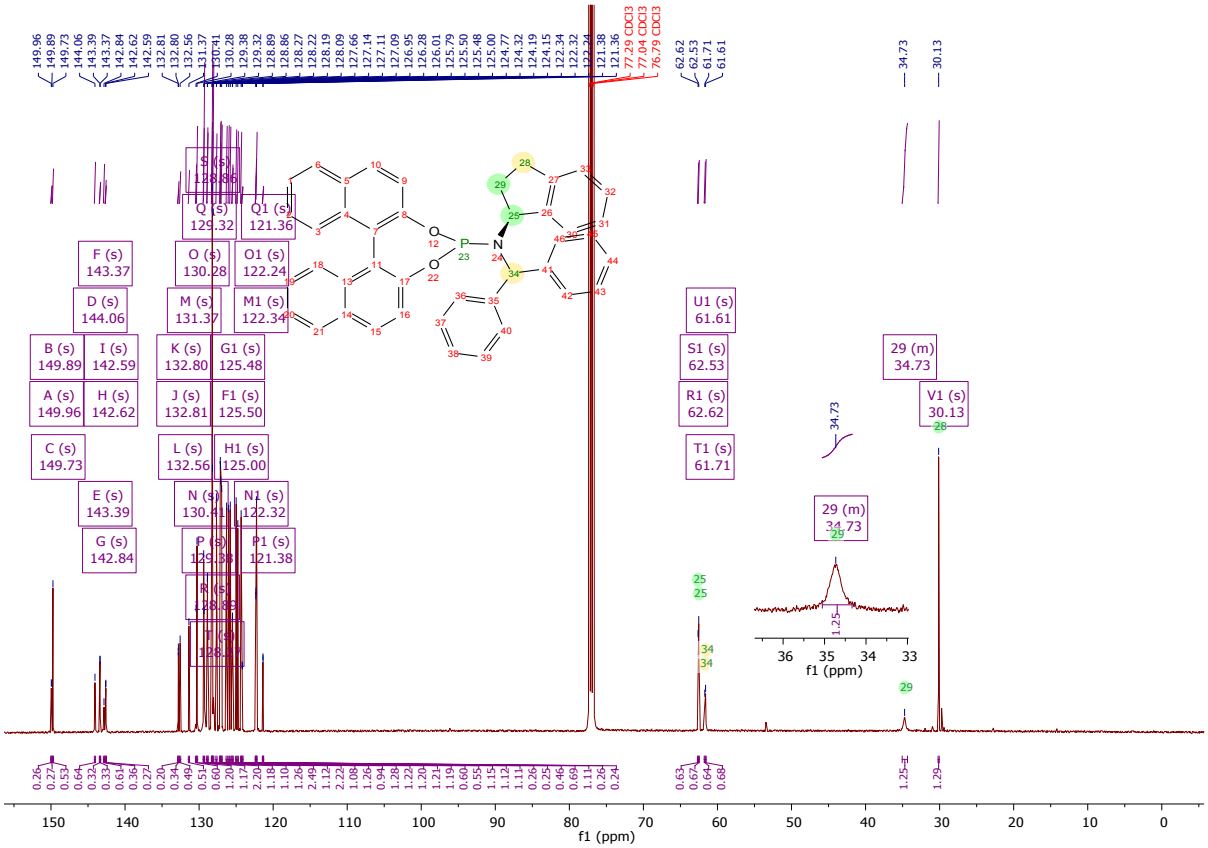
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.8 Hz, 1H), 7.81 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.74 – 7.65 (m, 2H), 7.46 (dd, *J* = 8.8, 1.0 Hz, 2H), 7.35 – 7.05 (m, 22H), 5.50 – 5.42 (m, 1H), 4.91 (dt, *J* = 10.2, 7.8 Hz, 1H), 2.52 (ddd, *J* = 12.7, 8.3, 4.1 Hz, 1H), 2.43 – 2.30 (m, 1H), 1.71 – 1.58 (m, 2H).

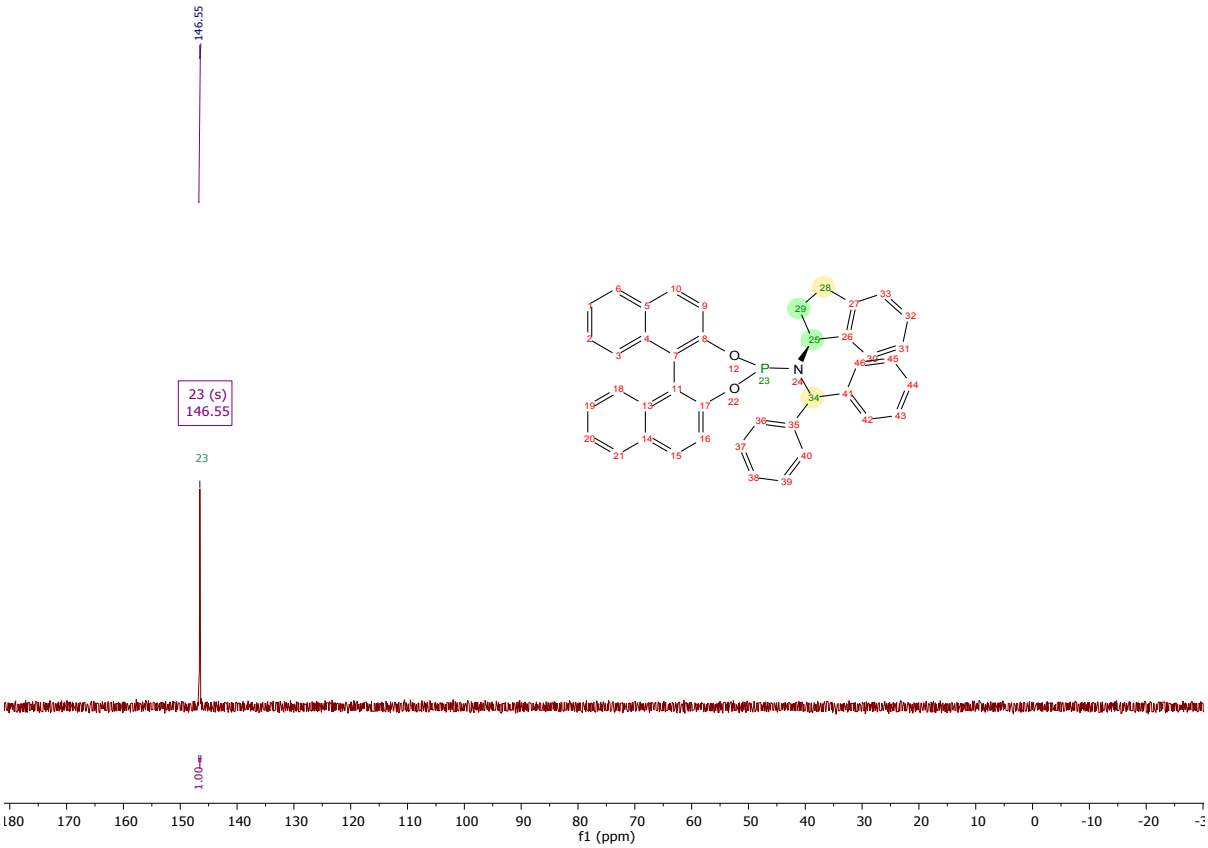
^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.0, 149.9, 149.7, 144.1, 143.4, 143.4, 142.8, 142.6, 142.6, 132.8, 132.8, 132.6, 131.4, 130.4, 130.3, 129.4, 129.3, 128.9, 128.9, 128.3, 128.2, 128.2, 128.1, 127.7, 127.1, 127.1, 127.1, 126.9, 126.3, 126.0, 125.8, 125.5, 125.5, 125.0, 124.8, 124.3, 124.2, 124.1, 122.3, 122.3, 122.2, 121.4, 121.4, 62.6, 62.5, 61.7, 61.6, 35.0 – 34.3 (m), 30.1.

^{31}P NMR (162 MHz, Chloroform-*d*) δ 146.5.

Analytical data are in agreement with the literature.[5]

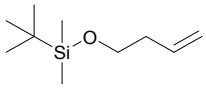

B (d) 7.87
D (dd) 7.46
A (dd) 7.81
C (m) 7.70
34 (m) 5.46
25 (dt) 4.91
28 (m) 2.37
28 (ddd) 2.52
29'' (m) 1.62
f1 (ppm)


F (s) 143.37
D (s) 144.06
B (s) 149.89
I (s) 142.59
A (s) 149.96
H (s) 142.62
C (s) 149.73
E (s) 143.39
G (s) 142.84
Q (s) 129.32
Q1 (s) 121.36
O (s) 130.28
O1 (s) 122.24
M (s) 131.37
M1 (s) 122.34
K (s) 132.80
G1 (s) 125.48
J (s) 132.81
F1 (s) 125.50
L (s) 132.56
H1 (s) 125.00
N (s) 130.41
N1 (s) 122.32
P (s) 129.38
P1 (s) 121.38
U1 (s) 61.61
S1 (s) 62.53
R1 (s) 62.62
T1 (s) 61.71
29 (m) 34.73
V1 (s) 30.13
f1 (ppm)


146.55
23 (s)
146.55
23
1.00
f1 (ppm)

5. Others

(but-3-en-1-yloxy)(tert-butyl)dimethylsilane

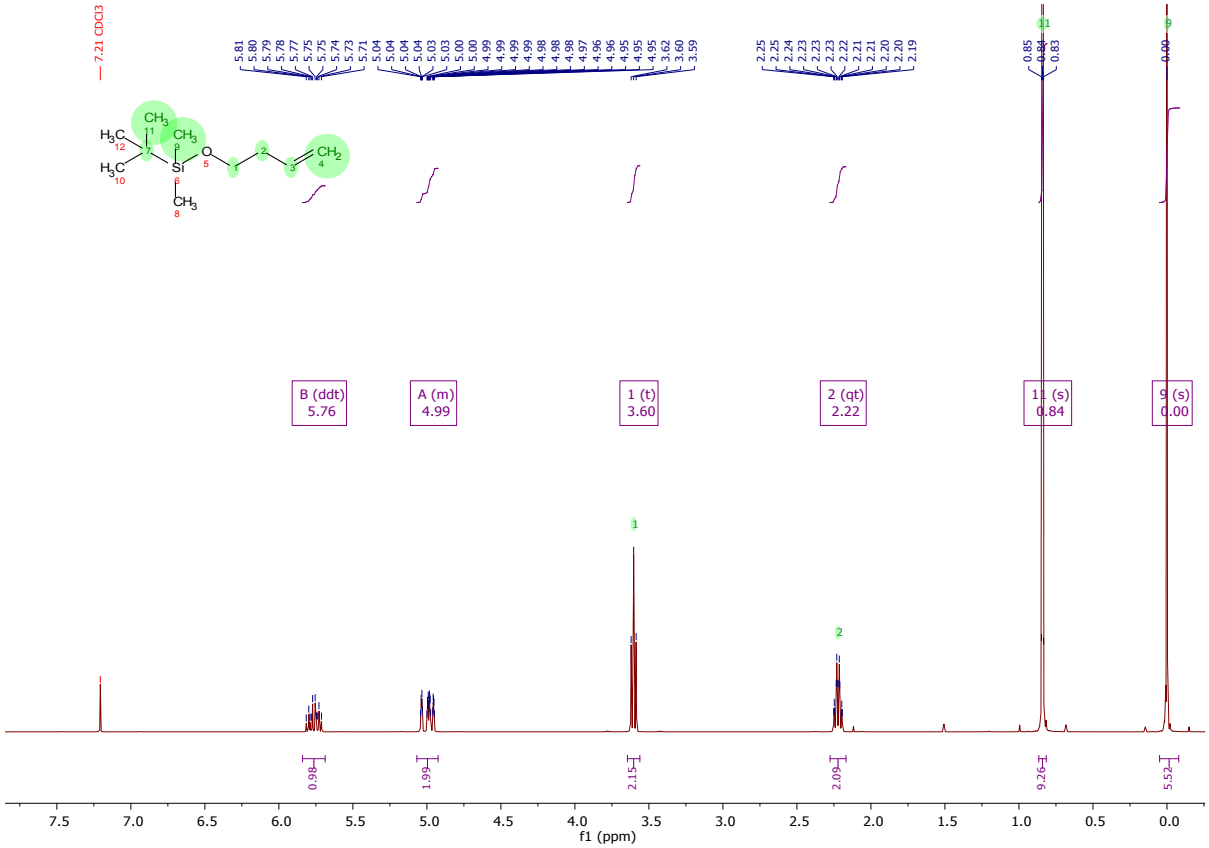


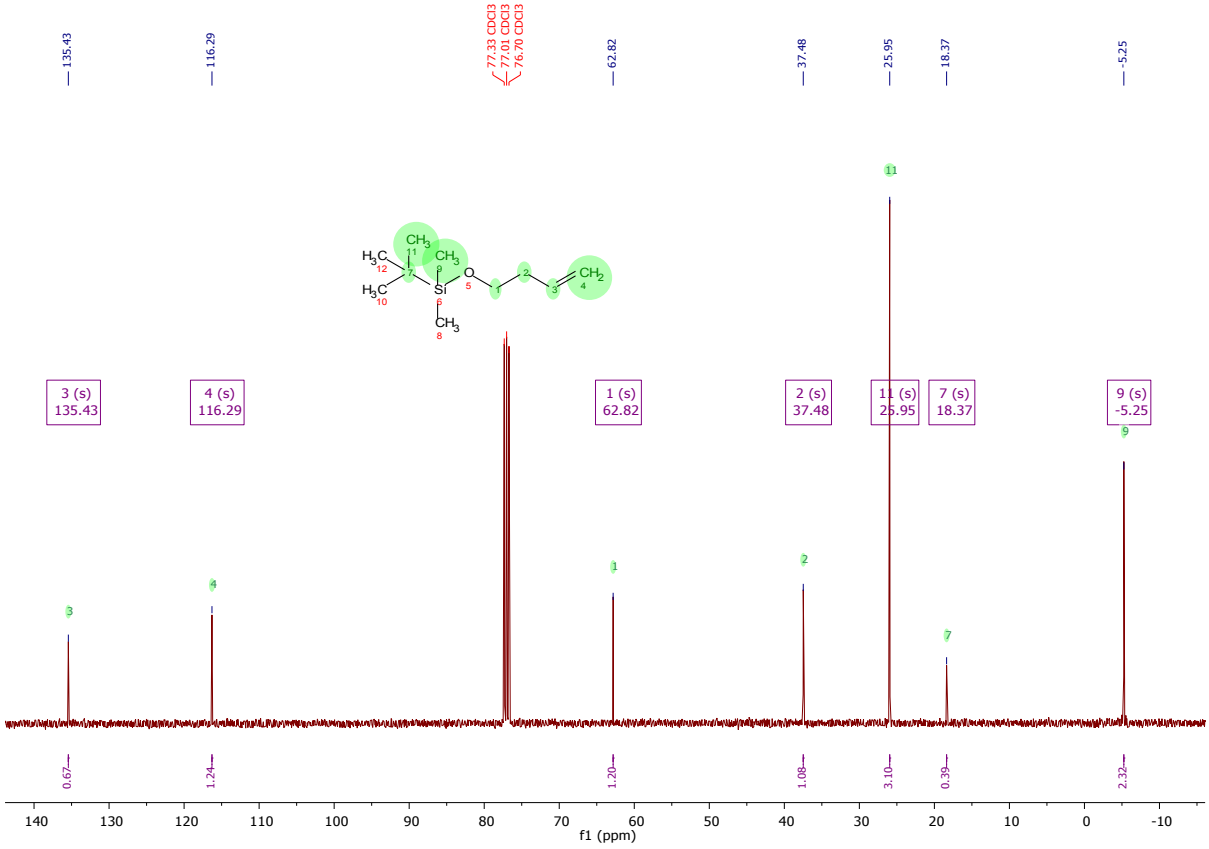
In a flame dried flask was added but-3-en-1-ol (0.3 mL, 3.486 mmol, 1.0 eq.) and imidazole (474.7mg, 6.973 mmol, 2.0 eq.) in 5 mL CH_2Cl_2, followed by TBSCl (536.0 mg, 3.556 mmol, 1.02 eq.) under an Ar atmosphere with a strong stirring. The reaction was stirred at room temperature for 48 h before water (5mL) was added to it. The aqueous layer was extracted with pentanes (2 × 10 mL). The combined organic layers were dried on anhydrous sodium sulfate, filtered and concentrated in vacuum. *(Note: product is a bit volatile. Use an ice bath if needed).* The crude product was passed through a short column of silica gel, flushed with pentanes to afford a clear oil (510 mg, 2.719 mmol, 78%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.76 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.07 – 4.92 (m, 2H), 3.60 (t, *J* = 6.8 Hz, 2H), 2.22 (qt, *J* = 6.8, 1.3 Hz, 2H), 0.84 (s, 9H), 0.00 (s, 6H).

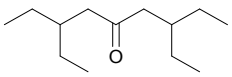
^{13}C NMR (101 MHz, Chloroform-*d*) δ 135.4, 116.3, 62.8, 37.5, 25.9 (3 C), 18.4, -5.2 (2 C).

Analytical data are in agreement with the literature.[12]


7.21 CDCl3
B (ddt) 5.76
A (m) 4.99
1 (t) 3.60
2 (qt) 2.22
11 (s) 0.84
9 (s) 0.00
f1 (ppm)


135.43
116.29
77.33 CDCl3
77.01 CDCl3
76.70 CDCl3
62.82
37.48
25.95
18.37
-5.25
3 (s) 135.43
4 (s) 116.29
1 (s) 62.82
2 (s) 37.48
11 (s) 25.95
7 (s) 18.37
9 (s) -5.25
f1 (ppm)

3,7-diethylnonan-5-one



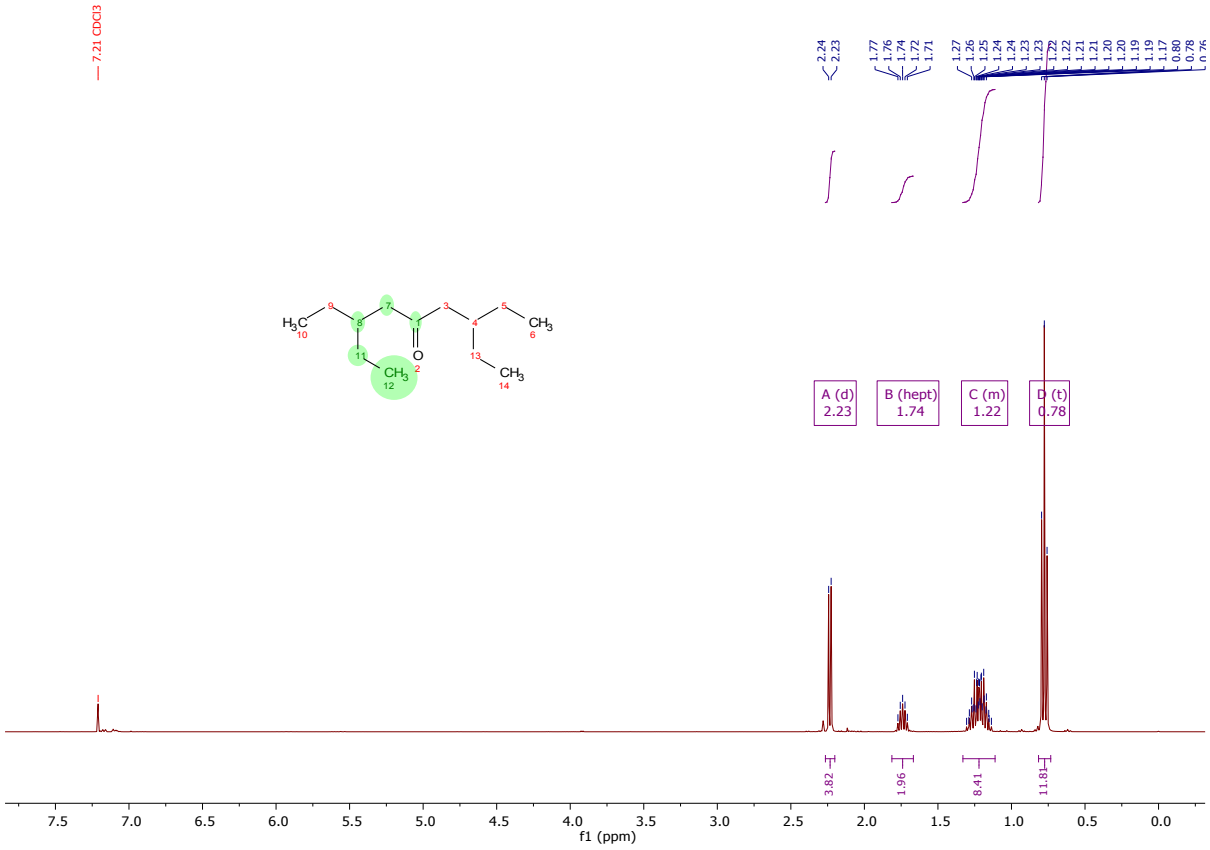
Mg (352 mg, 14.479 mmol, 1.45 eq.) was added into flask and the latter was flame dried. THF (15 mL) was added to immerse the magnesium and one piece of I_2 was poured to activate it. The solution turned brown, and then became clear again after a while. A solution of 3-(bromomethyl)pentane (1.68 mL, 11.982 mmol, 1.2 eq.) dissolved in THF (15 mL) was added and the mixture was heated at reflux for at least 3 h. Meanwhile, 3-ethylpentanoic acid (1300 mg, 9.985 mmol, 1.0 eq.) was diluted in CH_2Cl_2 (2 mL) and oxalyl chloride (0.84 mL, 9.985 mmol, 1.0 eq.) was added dropwise at rt. The reaction was stirred for 2 h and monitored. After cooling down at rt then 0 °C, the Grignard was added dropwise to a solution of CuI (2282 mg, 11.982 mmol, 1.2 eq.) dissolved in THF (10 mL) at 0 °C. The mixture was stirred for 30 min then it was cooled down at -78 °C. The freshly prepared acyl chloride was added dropwise. The reaction was then stirred for at least 2 h. Upon completion, the reaction was quenched with aq. HCl 1M (10 mL). After 30 min, the organic and aqueous layers were partitioned and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. After column chromatography (Hexane, SiO_2), 3,7-diethylnonan-5-one was obtained as a pale yellow oil (402 mg, 1.997 mmol, 20%).

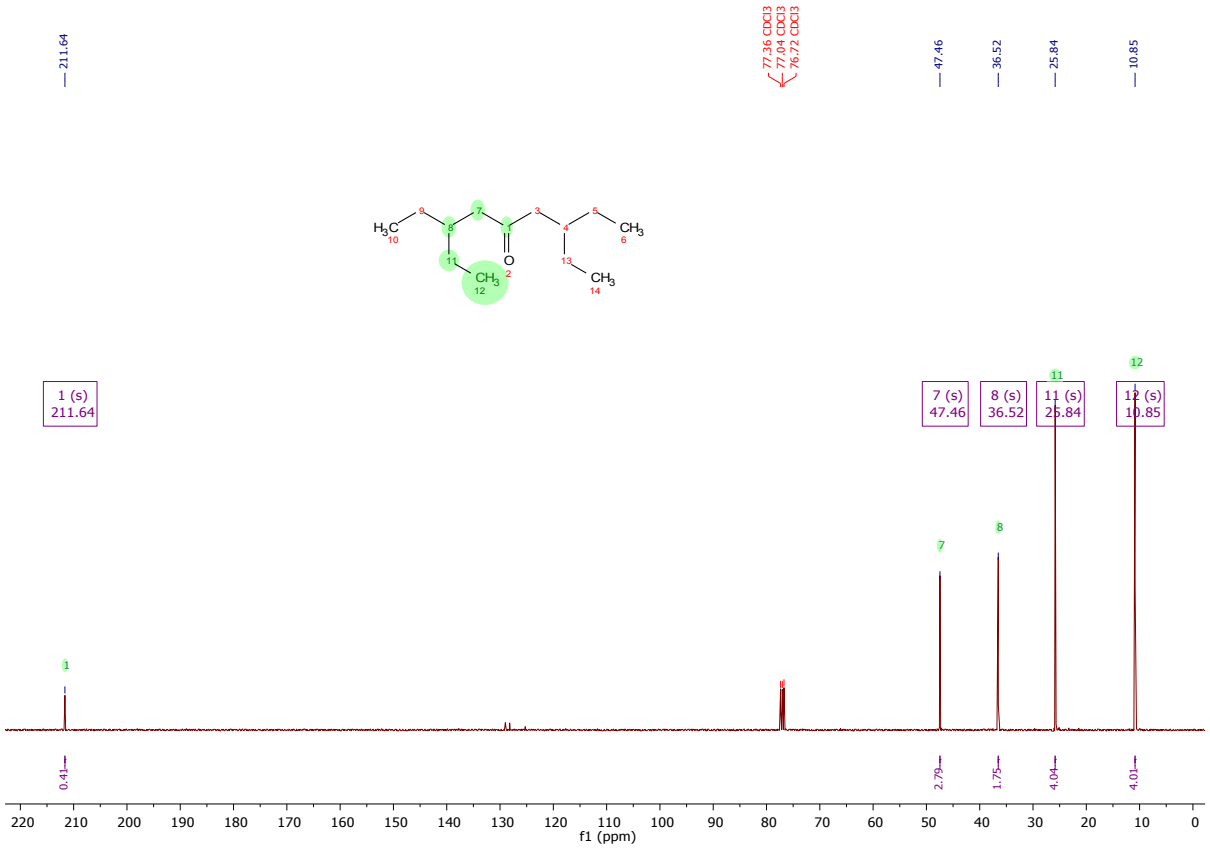
^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.23 (d, *J* = 6.7 Hz, 2H), 1.74 (hept, *J* = 6.4 Hz, 1H), 1.33 – 1.11 (m, 4H), 0.78 (t, *J* = 7.5 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 211.6, 47.5 (2 C), 36.5 (2 C), 25.8 (4 C), 10.8 (4 C).

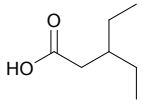
IR υ_{max} (film): 2962, 2931, 1712, 1460, 1380, 1152, 1056.

HRMS (EI) *m/z* calcd for $C_{13}H_{27}O$ $[M+H]^+$: 199.2056, found 199.2058.


7.21 CDCl3
A (d) 2.23
B (hept) 1.74
C (m) 1.22
D (t) 0.78
3.82
1.96
8.41
11.81
f1 (ppm)


211.64
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
47.46
36.52
25.84
10.85
1 (s) 211.64
7 (s) 47.46
8 (s) 36.52
11 (s) 25.84
12 (s) 10.85
0.41
2.79
1.75
4.04
4.01
f1 (ppm)

3-ethylpentanoic acid



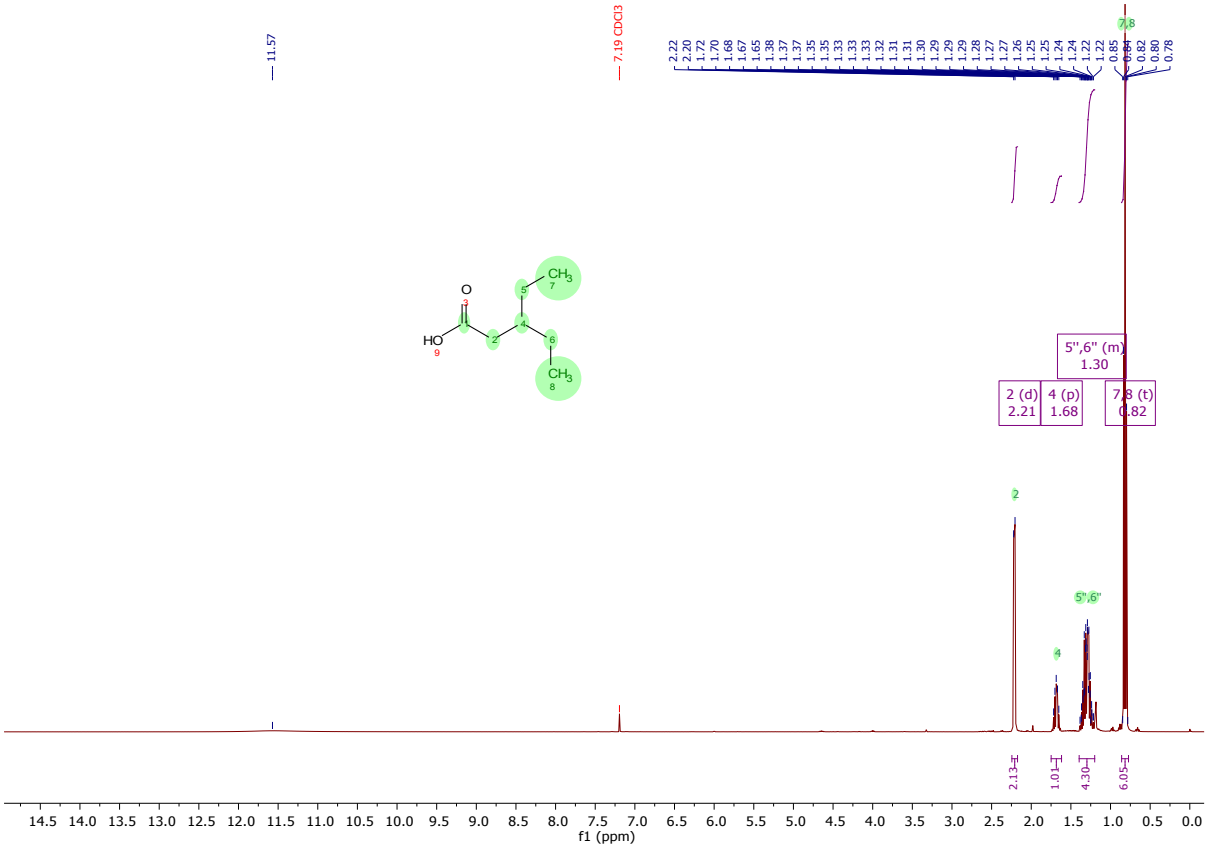
Methyl 3-ethylpentanoate (100 mg, 0.693, 1.0 eq.) was added to a solution of MeOH (10 mL) followed with aq. NaOH 2M (10 mL). The mixture was stirred overnight at rt then quenched with NH_4Cl (aq. sat., *ca* 20 mL). The organic and aqueous layers were partitioned and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a colorless oil (90 mg, 0.686 mmol, 99%). No further purification was needed.

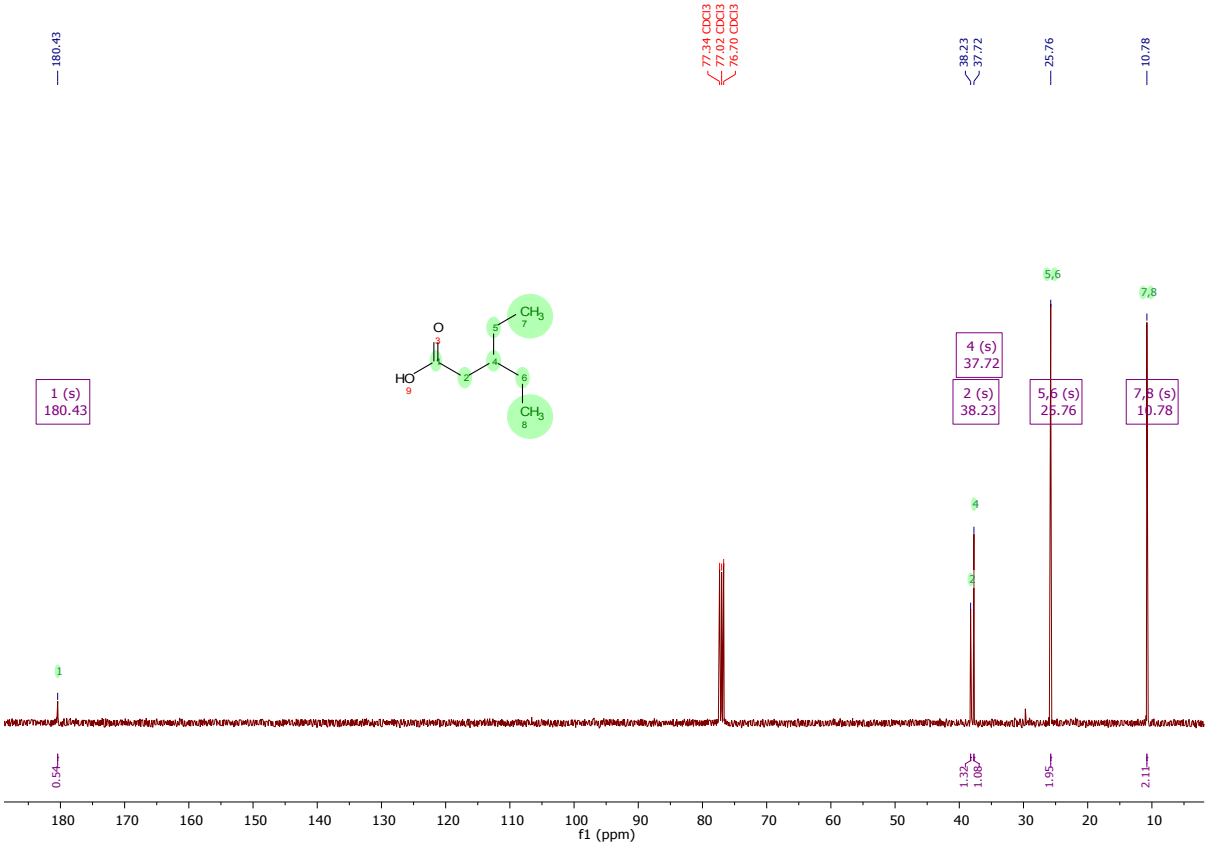
^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.21 (d, *J* = 7.0 Hz, 2H), 1.68 (p, *J* = 6.6 Hz, 1H), 1.40 – 1.20 (m, 5H), 0.82 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 180.4, 38.2, 37.7, 25.8 (2 C), 10.8 (2 C).

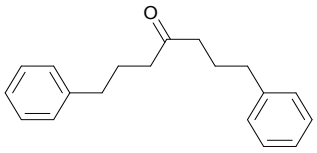
IR υ_{max} (film): 2963, 1704, 1460, 1285.

HRMS (EI) *m/z* calcd for $C_7H_{13}O_2$ $[M+H]^+$: 129.0921, not found.


11.57
7.19 CDCl3
7,8
5'',6'' (m)
1.30
2 (d)
2.21
4 (p)
1.68
7,8 (t)
0.82
2
5'',6''
4
2.13
1.01
4.30
6.05
f1 (ppm)


180.43
77.34 CDCl3
77.02 CDCl3
76.70 CDCl3
38.23
37.72
25.76
10.78
1 (s)
180.43
4 (s)
37.72
2 (s)
38.23
5,6 (s)
25.76
7,8 (s)
10.78
5,6
7,8
4
2
1
0.54
1.32
1.08
1.95
2.11
f1 (ppm)

1,7-diphenylheptan-4-one



Mg (21.1 mg, 0.868 mmol, 1.8 eq.) was added into a flask and the latter was flame dried. THF (5 mL) was added to immerse the magnesium and one piece of I_2 was poured to activate it. The solution turned brown, and then became clear again after a while. A solution of (3-bromopropyl)benzene (0.11 mL, 0.724 mmol, 1.5 eq.) dissolved in THF (3 mL) was added and the mixture was heated at reflux for at least 3 h. After cooling down at rt then -78 °C, the Grignard was added dropwise to a solution of N-methoxy-N-methyl-4-phenylbutanamide (100 mg, 0.482 mmol, 1.0 eq.) in THF (10 mL) at -78 °C. The mixture was stirred for 6 h and finally quenched with aq. NaOH 2 M (10 mL). After 30 min, the organic and aqueous layers were partitioned and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. After column chromatography (Hexane, SiO_2), 1,7-diphenylheptan-4-one was obtained as a pale yellow oil (63 mg mg, 0.236 mmol, 49%).

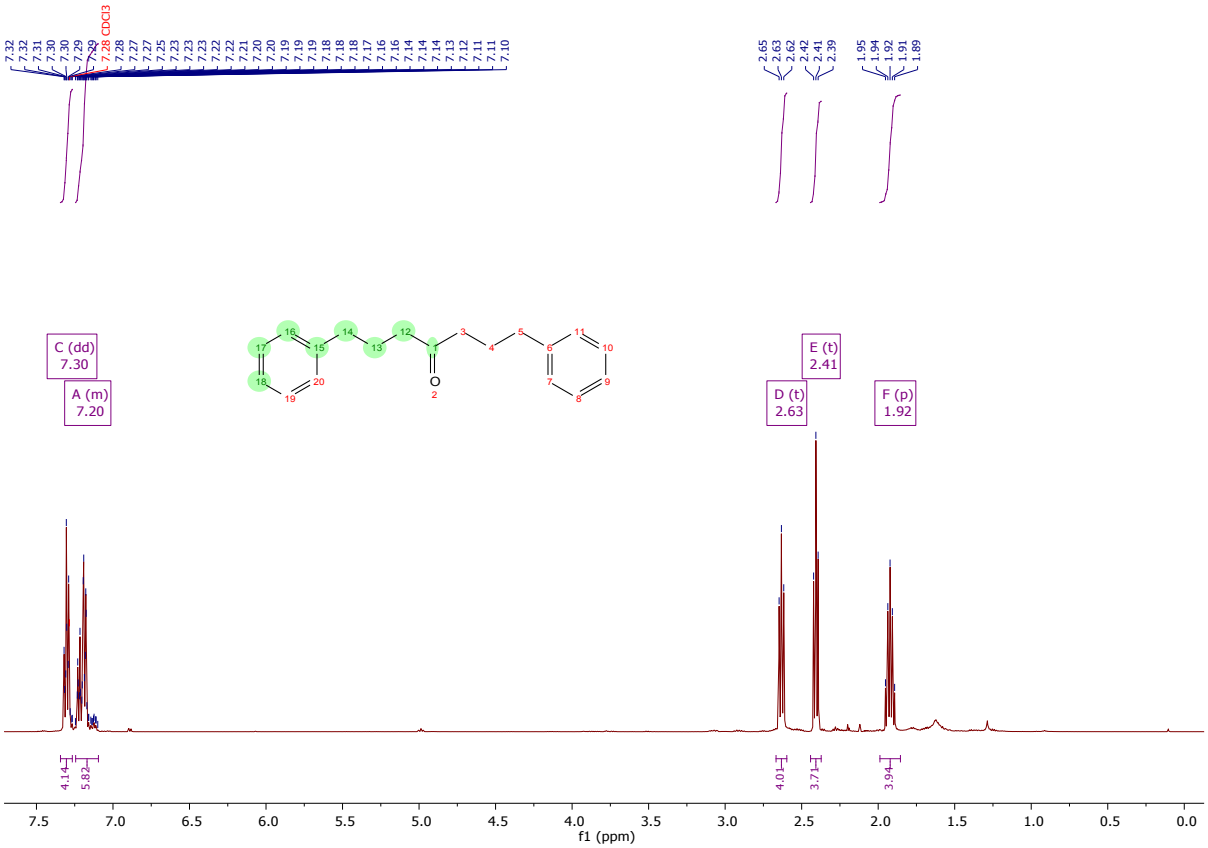
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 (dd, *J* = 8.2, 6.8 Hz, 4H), 7.24 – 7.10 (m, 6H), 2.63 (t, *J* = 7.6 Hz, 4H), 2.41 (t, *J* = 7.4 Hz, 4H), 1.92 (p, *J* = 7.5 Hz, 4H).

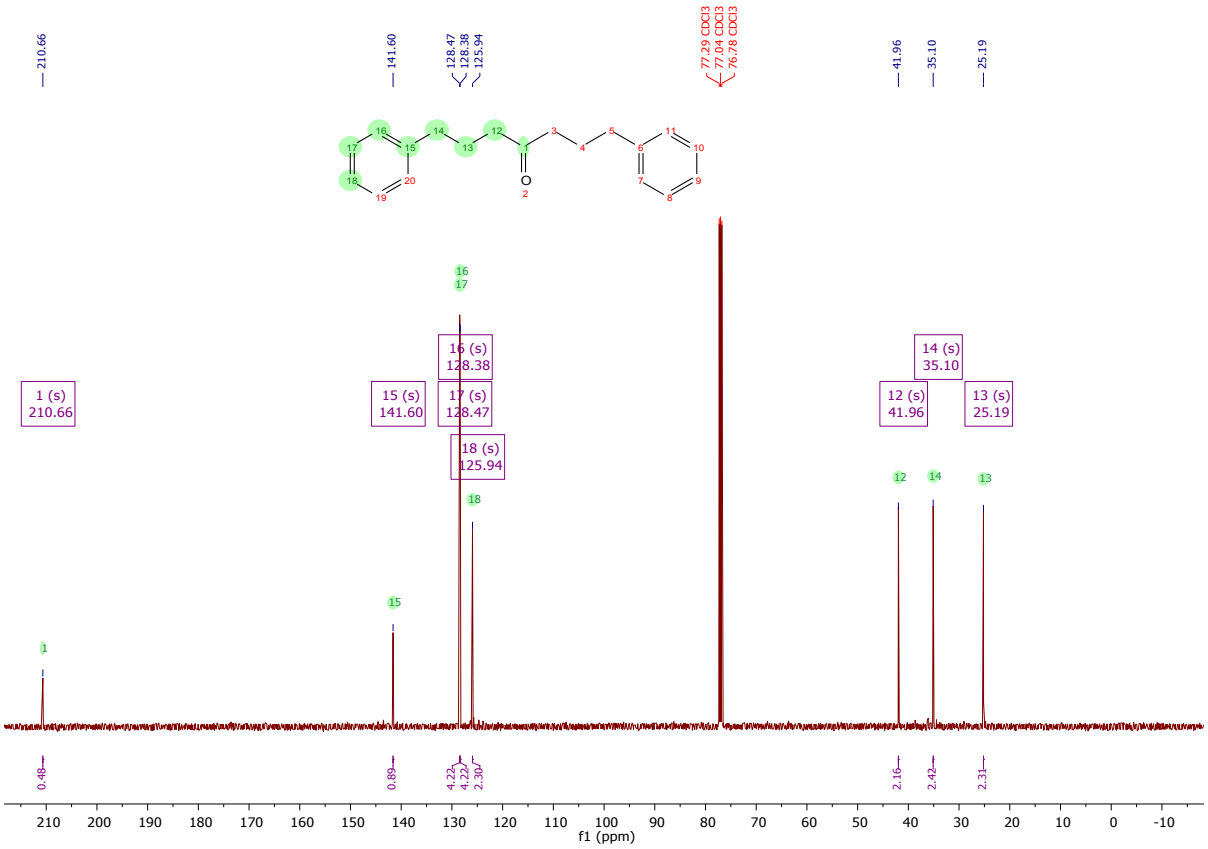
^{13}C NMR (126 MHz, Chloroform-*d*) δ 210.7, 141.6 (2 C), 128.5 (4 C), 128.4 (4 C), 125.9 (2 C), 42.0 (2 C), 35.1 (2 C), 25.2 (2 C).

IR υ_{max} (film): 3026, 1712, 1453, 1372, 1154.

HRMS (GCMS Methane Cl) *m/z* calcd for C_{19} H_{23} O $[M+H]^+$: 267.1743, found 267.1743.

Analytical data are in agreement with the literature.[13]


7.32 7.32 7.31 7.30 7.30 7.29 7.29 7.28 CDCl3 7.28 7.28 7.27 7.27 7.25 7.23 7.23 7.23 7.22 7.22 7.21 7.20 7.20 7.19 7.19 7.19 7.18 7.18 7.18 7.17 7.16 7.16 7.14 7.14 7.14 7.13 7.12 7.11 7.11 7.10
2.65 2.63 2.62 2.62 2.42 2.41 2.39
1.95 1.94 1.92 1.92 1.91 1.89
C (dd) 7.30
A (m) 7.20
E (t) 2.41
D (t) 2.63
F (p) 1.92
4.14 5.82 4.01 3.71 3.94
f1 (ppm)


210.66 141.60 128.47 128.38 125.94 77.29 CDCl3 77.04 CDCl3 76.78 CDCl3 41.96 35.10 25.19
1 (s) 210.66
15 (s) 141.60
16 (s) 128.38
17 (s) 128.47
18 (s) 125.94
12 (s) 41.96
14 (s) 35.10
13 (s) 25.19
0.48 0.89 4.22 4.22 2.30 2.16 2.42 2.31
f1 (ppm)

II. Computational Section

1. General Information

The QSSR studies were realised using the R package (R version 3.5.1, 2018-07-02).[14] Scatter plots were produced with *ggplot2* and *ggrepel* libraries, installed via the CRAN project (*https://cran.r-project.org/).* 3D molecular graphics were generated by open-source Pymol Version 1.8.6.0. wSterimol,[15] Mopac version 2016 for semi-empirical calculations[16] and Gaussian 09[17] for DFT calculations were used in this study. wSterimol calculations were carried out on a laptop (processor Intel(R) Core(TM) i7-7600U CPU @ 2.80GHz, 16.0 GB installed memory (RAM), 64-bit Operating System, Windows 7 enterprise) except for the DFT optimisation using Gaussian 09 that were done on a Linux cluster. AlogPS values were calculated online, at the Virtual Computational Chemistry Laboratory (http://www.vcclab.org/lab/alogps/).[18] Spartan (Version 16, 2.0.10) was also used to generate several parameters at the semi-empirical level of theory.[19] Distances, angles and dihedrals were generated semi-automatically within Pymol with the help of in-house scripts.

2. Quantitative Structure – Selectivity Relationship (QSSR)

This section is aimed to explain the model development process into details and choices that were made. The code used to generate all the models is provided in the supplementary ZIP file. The reader is directed toward it to reproduce any and all figures. A detailed workflow is explained in Figure S1.

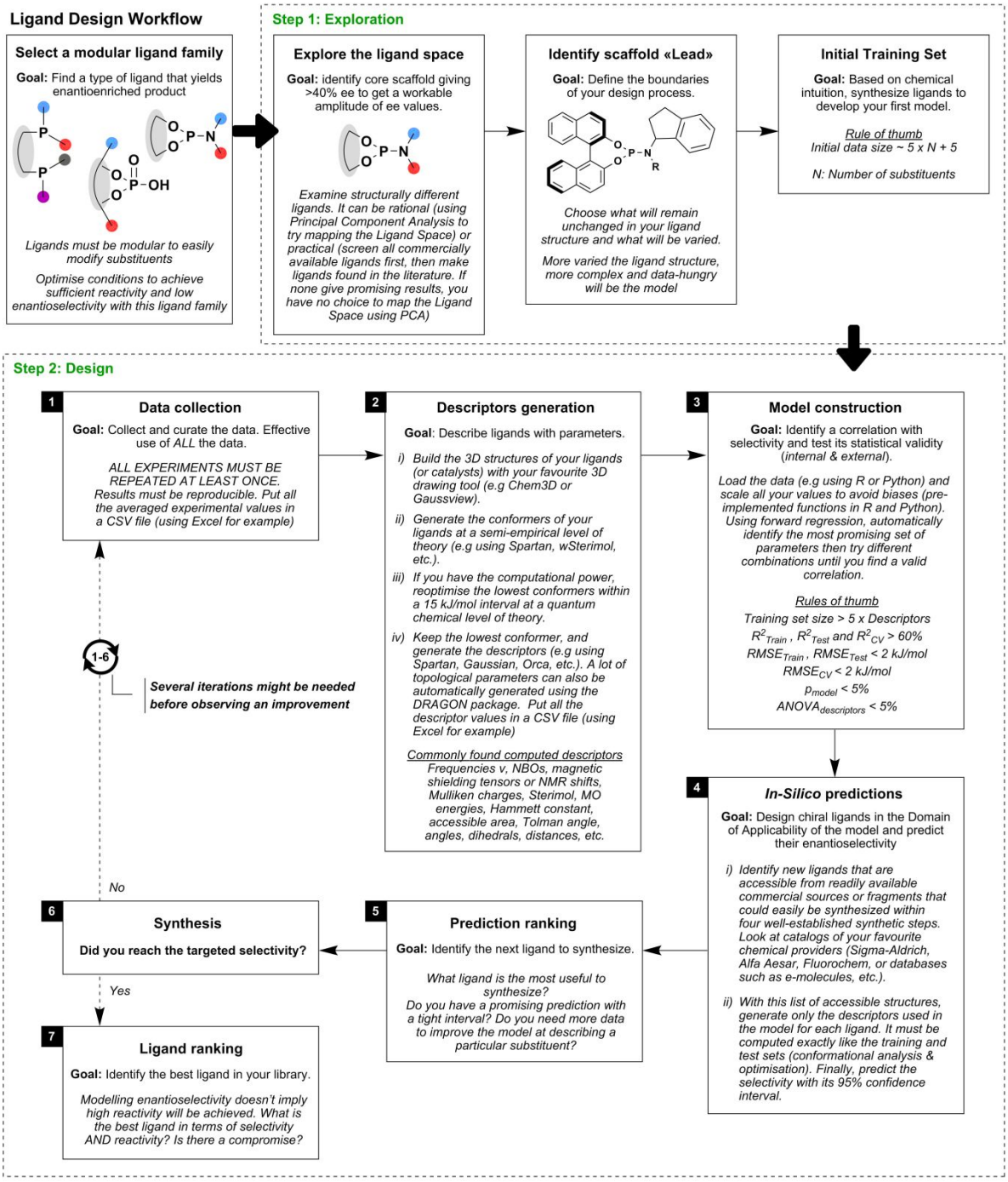


Figure S1. Detailed Ligand design workflow used in this work.

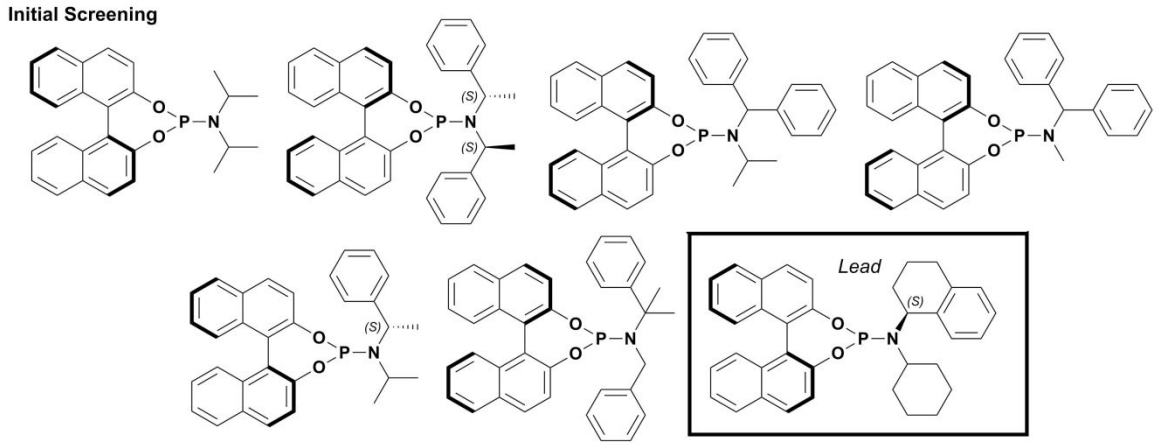
1. Step 1: Exploration of the Ligand Space

After optimising the reaction conditions in terms of yield and enantioselectivity, one needs to identify a (modular) core structure of the ligand from which different substitution patterns allow to achieve higher enantioinduction. The initial screening is therefore of tremendous importance to identify a "lead" structure. We define this here as a core scaffold giving >40% ee, that will subsequently be optimized. Finding a "lead" structure in the chemical space of possible ligands is challenging, since this space contains all conceivable structures that possess different steric and electronic features. To increase the chance of finding a good starting point for optimization, screening should be done as systematically as possible. In this regard, several approaches can be envisaged:

- Intuition: One tries different ligands based on chemical intuition until a promising enantioselectivity is obtained. This classic approach is heavily based on chance and screening but allows the identification of completely novel structures.
- Pragmatic: Based on the commercial availability of ligands or the easy preparation of the precursors, one tries easily accessible ligands that are *subjectively* structurally as different as possible. This approach is self-limited to what is known: a completely new scaffold won't be explored but it allows for a quick screening of previously successful ligands.
- Mapping: One tries to rationally map the ligands according to their features (sterics, electronics) using dimensionality reduction algorithms and clustering (e.g. Principal Component Analysis, followed by *k*-means or Kennard Stone methods) in order to map the explorable Ligand Space in fewer dimensions. This approach generally requires some kind of "featurization", wherein molecular descriptors (*e.g* Sterimol, NBO, etc.) are chosen to differentiate between different structures. *A priori*, the relative importance of a given feature descriptor is unknown. Therefore it can lead to the exploration of unimportant feature space. An important synthetic effort must also be realised to get the ligands that will (likely) have never been made before. However one can be certain with this approach that the Ligand Space will have been rationally explored *within the chosen features*.

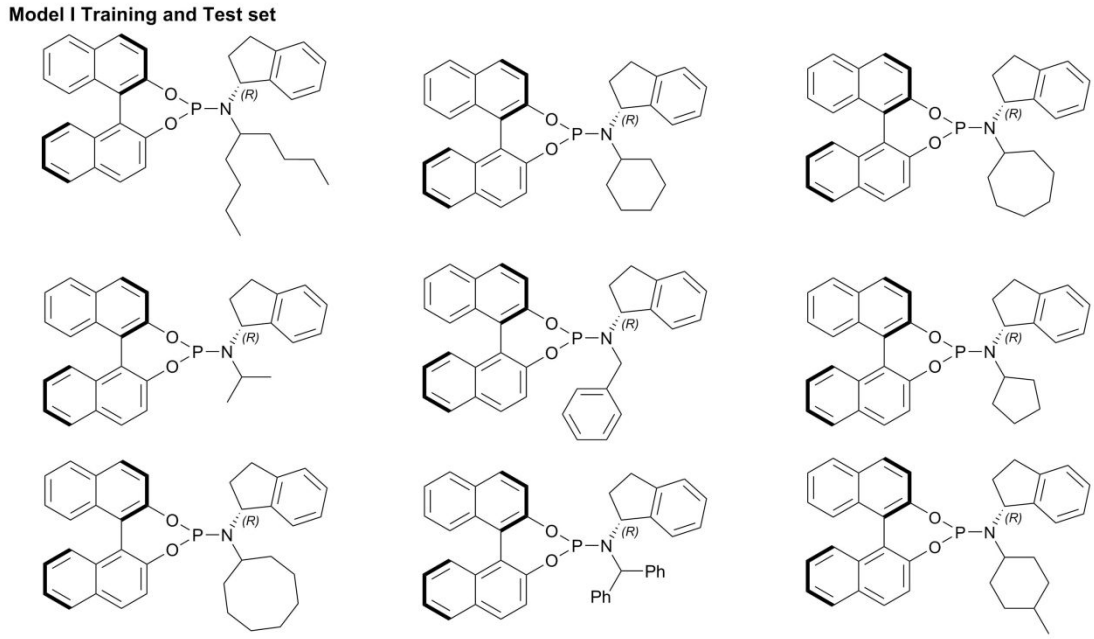
From all the different possibilities, the mapping approach remains the best in order to explore the Ligand Space, particularly if the optimum ligand is within the chosen feature space.[20] However the synthesis of ligands in this work remains the bottleneck of the design process and there is little appeal to investing considerable resources (*e.g* time, money) to prepare many ligands just to identify a "lead". We were also not sure that all these very diverse ligand structures would behave correctly in linear multivariate modelling and might not be used outside nonlinear parametric models.

Here we decided to start with the pragmatic approach and come back to the mapping approach if necessary. Among 150 phosphoramidite ligands in our ligand database, 7 structurally diverse phosphoramidite structures known to be relevant in the copper-catalysed conjugate addition were chosen (Scheme S1).



Scheme S1. List of seven structurally diverse phosphoramidite ligand used to quickly explore the Phosphoramidite Ligand Space known to be relevant in the copper-catalysed conjugate addition.

The initial exploration allowed the discovery of the most promising structure circled in black (90% yield, 71% ee), that we called a ligand "lead". Nine other ligands similar in structure to the "lead" were synthesized if necessary and tested (Scheme S2), which led to a better understanding of the structure selectivity relationship presented in Scheme 2A.



Scheme S2. List of ligands used to analyse the structure selectivity relationship and later used to generate Model I for the training and external sets.

2. Step 2: Multivariate modelling construction

Applying chemical intuition to the preliminary structure-selectivity relationship, the syntheses of many different ligands could be envisaged. In order to prioritize the different syntheses in a rational way, multivariate modelling was carried out in accordance with the workflow presented in Scheme 2B, and using the ligands shown in Scheme S2.

Note that all ligands were modelled as *(S,S)*, and only the magnitude of enantioselectivity was considered as a result.

The first step in multivariate construction is usually the selection of a list of descriptors to explore. The list tends to increase rapidly and it can quickly become time-consuming. One should aim for the most meaningful parameters as possible, particularly when building models and synthesizing in parallel over time. Packages (such as Dragon or its online version E-Dragon [http://www.vcclab.org/lab/edragon/]) exist to quickly generate a large amount of data. However, for this work, we prioritized a relatively small number of descriptors obtained from electronic structure theory that explicitly take into account molecular conformation, and which also capture the subtleties of stereoelectronic effects. We focused on using DFT generated parameters, or semi-empirically generated descriptors when the enormous amount of conformers possible with our ligands did not allow us to use DFT level of theory. Benchmarking of DFT calculations against X-ray structures was performed to identify the best level of theory (see DFT section). The ligands were modelled in 3 different ways (substituents, ligand or catalyst) and the descriptors were usually calculated for the three of them.

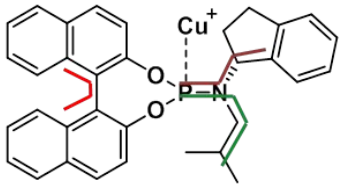
Conformational analysis was performed as follows: The copper catalyst of the corresponding ligand was built in GaussView, and then optimised at the ωB97XD/6-31G(d) (C, H, P, O, N) and ωB97XD/LANL2DZ (Cu) level of theory. The 3D coordinates were simplified to keep only the structure of interest (substituent only, ligand only or full catalyst). The wSterimol script was used to generate the different conformers by performing a systematic evaluation of the torsional space for each structure. In the case of the ligand only or full catalyst, note that the backbone and indanyl group were not explored as DFT calculations suggested it was already minimised. Each generated conformer was then optimised at the PM7 semi-empirical level of theory. Note that the longer chains could take ***days*** of computing power in order to go through the different possibilities at the PM7 semi-empirical level of theory. The most favoured conformer was then re-optimised at the ωB97XD/6-31G(d) (C, H, P, O, N) (and ωB97XD/LANL2DZ (Cu) if relevant) level of theory. This structure was then used to generate the different descriptors.

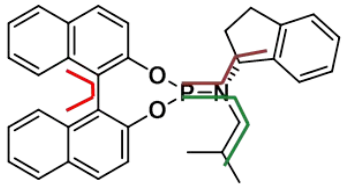
In the case of wSterimol parameter, Boltzmann-averaged ensemble values where generated at the PM7 level of theory due to the large amount of conformers.

All the parameters generated in this work are presented in the Table S2.

Table S2. List of descriptors generated for the construction of Model I.

	L	B1	B5	Dihedrals red	Dihedral green	Dihedral brown	logP	logS	NBO_P	NBO_C
Substituent	x	x	x				x	x		
Ligand	x	x	x	x	x	x			x	x
Catalyst	x	x	x	x	x	x			x	x





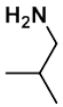


Table S3. List of descriptors generated for the construction of Model II.

	wL	wB1	wB5	minL	minB1	minB5	maxL	maxB1	maxB5	Dihedrals red	Dihedral green	Dihedral brown	logP	logS
Substituent	x	x	x	x	x	x	x	x	x				x	x
Ligand	x	x	x	x	x	x	x	x	x	x	x	x		
Catalyst	x	x	x	x	x	x	x	x	x	x	x	x		

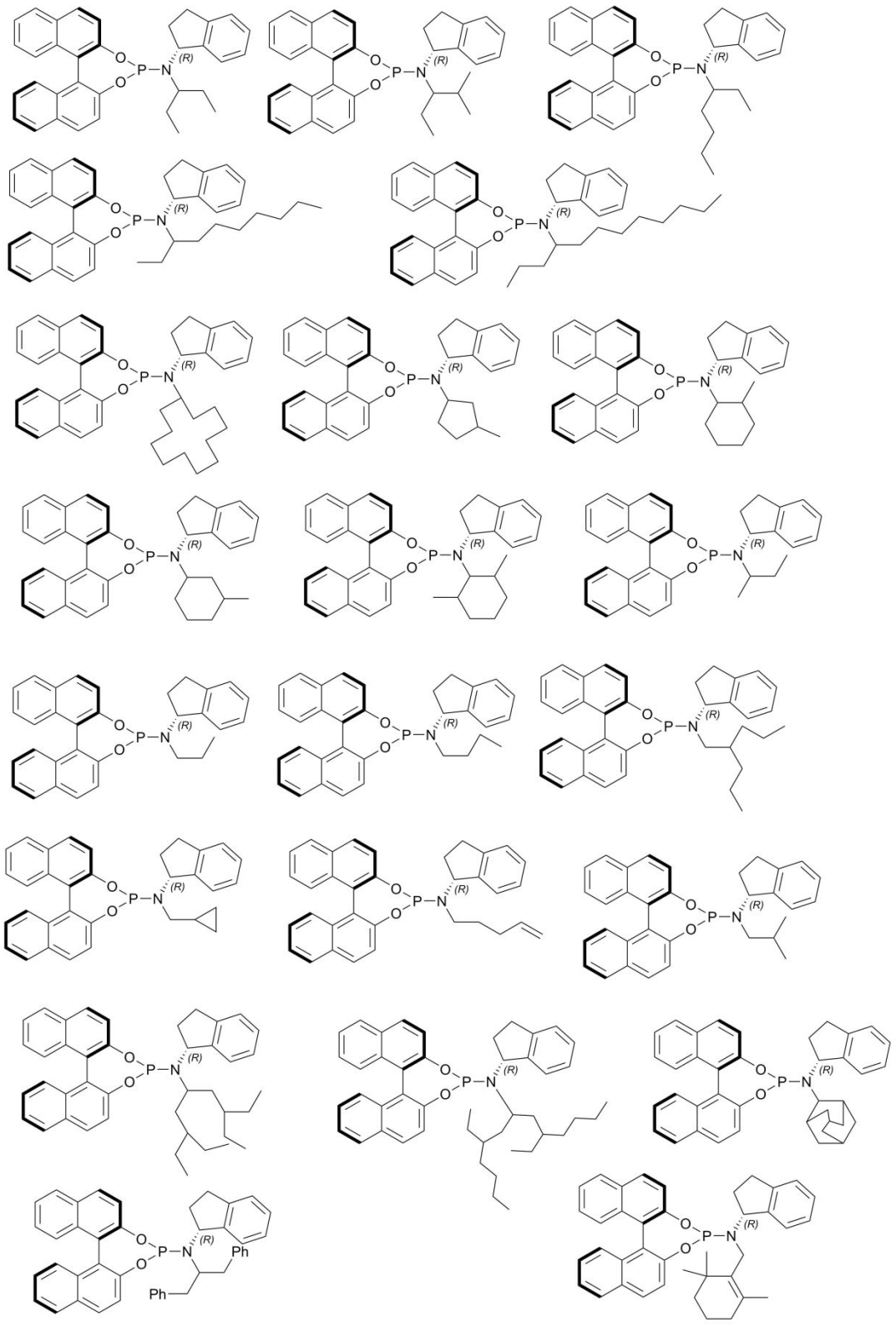
	$Area_{CPK}$	V_{CPK}	PSA	$Ovality_{CPK}$	Pol.	E_{HOMO}	E_{LUMO}	MW	Dipole	Polar Area	Acc. Area	Energy	NBO_P	NBO_C
Substituent														
Ligand	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Catalyst						x	x	x				x	x	x

With descriptors in hand, we started by identifying the confounded parameters (above 75%). The Pearson coefficient was used as this is already implemented in R. Being careful not to put together confounded parameters, forward regression was used to rapidly identify interesting model formula. Cross-terms were also tried when meaningful: for instance, there could be a synergy between wB1 and wB5, hence wB1 x wB5 cross term. However we observed that forward regression tended to over fit the training set, and the external test set very often failed. Therefore forward regression was a start with new descriptors, but was rarely the final form of the model. Combinations of promising parameters identified with the forward regression were indeed tried manually on the training set until a model could pass the external test, ANOVA and then internal cross validation. We always targeted a model with as few descriptors as possible.

An example of model development has also been well explained by Sigman.[21]

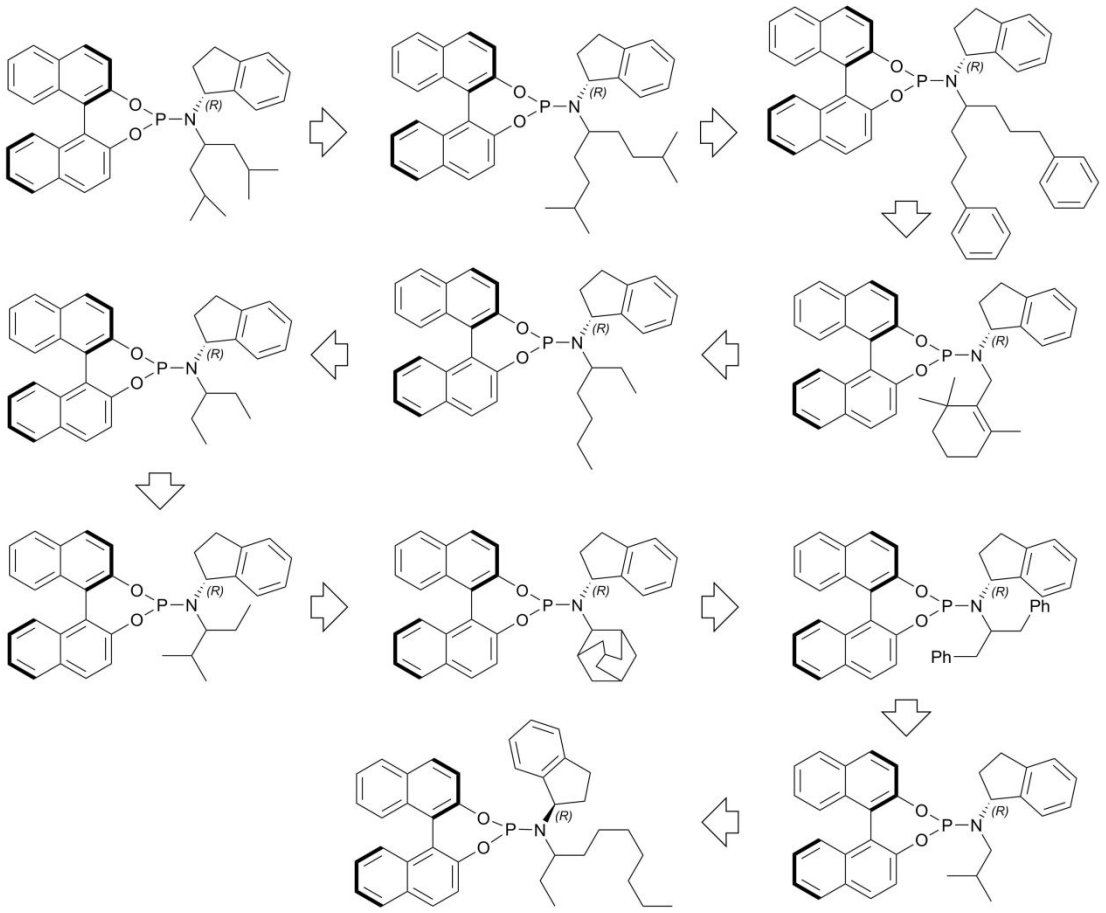
Once the initial model was validated, we tried to come up with easily accessible precursors of the ligands looking at catalogs from Sigma-Aldrich, Alfa Aesar, Fluorochem or e-molecules. In total, twenty-two *in-silico* ligands shown in Scheme S3 were considered to be synthetically accessible and their corresponding descriptors were computed.

***In silico* ligands**



Scheme S3. List of ligands predicted *in-silico* by using Model I.

As explained in the main text of the manuscript, eleven ligands were then synthesized one after each other and the model was always re-trained (Scheme S4).

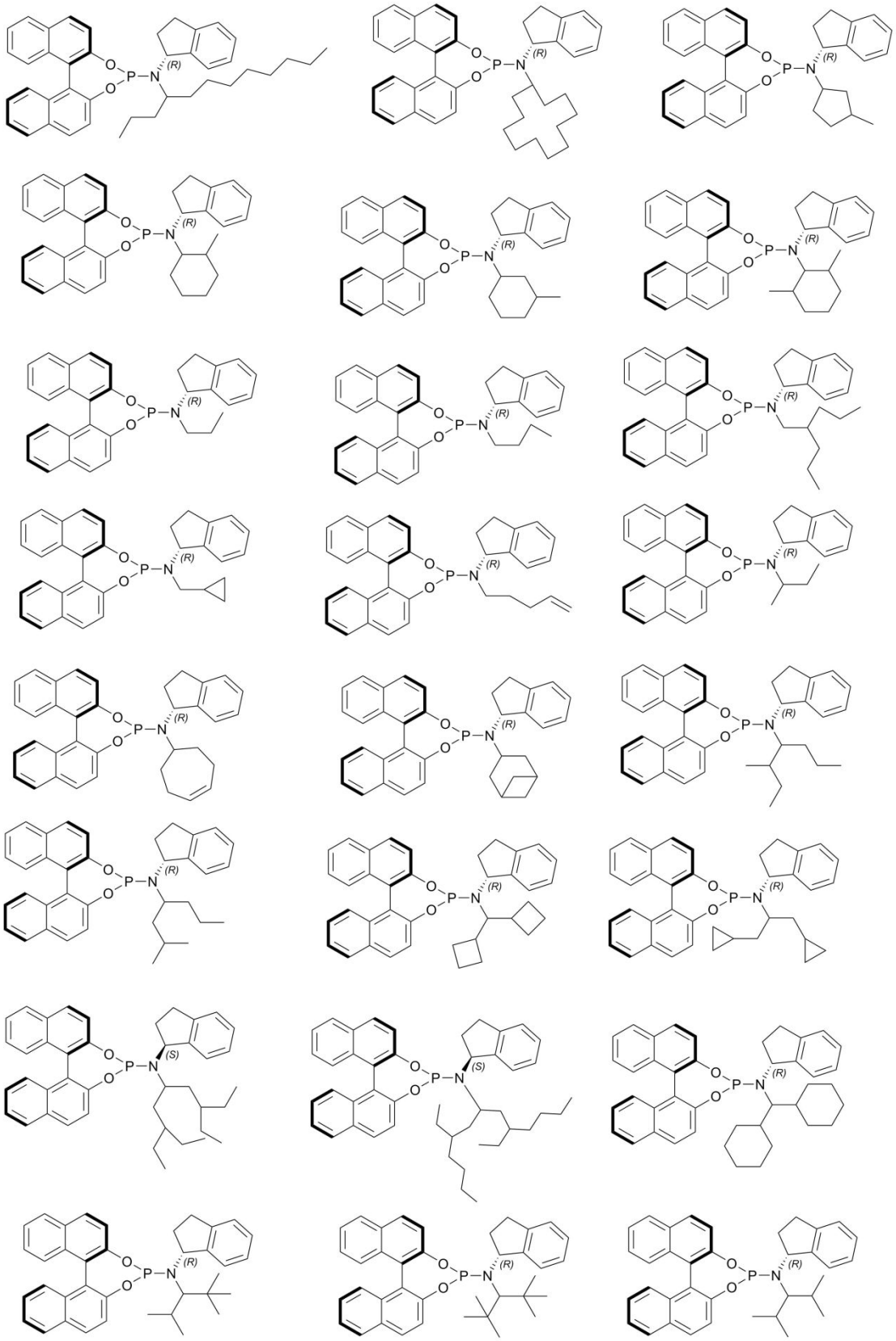


Scheme S4. List of phosphoramidite ligands synthesized one after another, which were later used to build Model II.

The ligands presented in Scheme S4 were all used to build the final Model II and the full list of parameters tried is presented in Table S3. We tried to test the minimum conformer and the entire Boltzman ensemble. Inspired from Doyle's work, a lot of descriptors were generated from Spartan 16. However calculations could not be realised on a Linux cluster and it therefore had to be realised on a local computer (iMac). Even though we tried to generate the descriptors on Spartan at the ωB97XD/6-31G(d) level of theory, we quickly realised that the time frame was not realistic for twenty ligands, plus all the other *in-silico* ligands that we would need later. That is why the semi-empirical PM6 level of theory was used instead of DFT for the parameters generated with Spartan.

Following the same workflow explained in Model I, we found Model II to be statistically valid. This allowed the *in-silico* analysis of twenty-four new structures that could be easily accessible in few steps according to commercial availability of the reagents (Scheme S5). Unfortunately, none of these structures showed any promise according to Model II.

Model II: Calculated but not synthesized ligands



Scheme S5. List of ligands predicted *in-silico* by using Model II.

3. Note on the importance of conformational sampling

As explained in the previous section (Multivariate modelling construction), a conformational search was realised. In this work, conformation is important due to the presence of very long and floppy alkyl chains. Using only the nine first ligands used in Model I, one can see that no significant correlation (which gets worse with more ligands) is obtained with wSterimol parameters as shown in Figure S2. The most striking feature is the interval that can be reached with wSterimol parameters because of the different conformers.

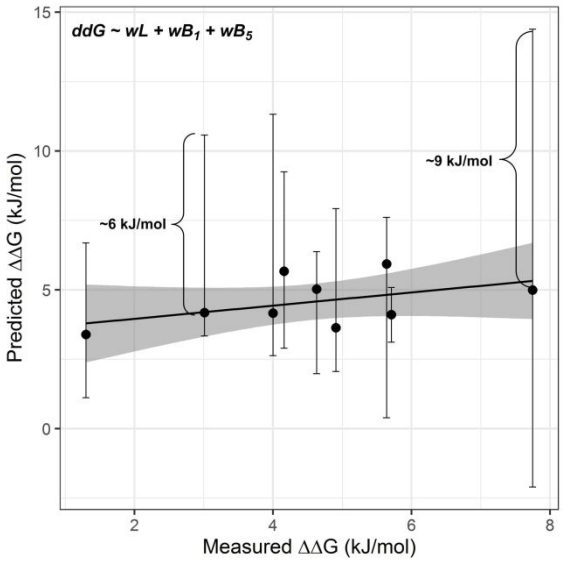


Figure S2. Showcase the importance of conformational sampling in this work, with prediction uncertainty due to conformers. Gray area represents standard error of the model at the 95% confidence interval. Error bars represent the range of Sterimol values of the conformers within a 5.0 kcal/mol window.

4. Note on the importance of multivariate modelling

Note: this section was added to openly explain concerns of one of the referees and detail our reasoning.

The first step, consisting in exploring the Ligand Space, allowed us to examine sixteen ligands among which ligand **L6** afforded 92% ee and 63% yield. From this initial pool of ligands, the second step (multivariate modelling) allowed us to directly predict and synthesize **L12** (94% ee). From 92% to 94% ee, this can retrospectively represent a rather small ee difference but is actually a significant ~1 kJ/mol increase that the model successfully predicted. At that point in time, it was a step in the right direction but we wanted more accurate predictions and a more robust model. Further efforts in improving the model with less symmetrical and more complicated R substituents made it break (**L16-L18**). The model was reformulated by introducing new descriptors and re-validated using new ligands (**L19-L22**). This new robust model then showed that none of our *in-silico* predictions could exceed our previously synthesized ligands, putting a halt to the ligand design.

One could therefore question the importance of multivariate modelling in the design of better ligands.

The synthesis of ligands is the bottleneck of the design process. It is not coming up with new ligand designs that is complicated, the issue is the time required to test these ideas. The value in developing a multivariate model is in all the ligands that were not synthesized.

If we contrast the data-driven approach against chemical intuition and/or serendipity, we would argue that there are two major advantages: the first, is that the use of descriptors can provide suggestions for structures that are not obvious based purely on chemical intuition. A second advantage is that potential structures can be prioritized based on their predicted performance, or their value upon improving the coverage of chemical space that is being surveyed. We would argue that since there are many logical modifications that could be made to a ligand in principle, there is value in prioritizing synthetic effort to ensure that sufficient structural and electronic variations have been surveyed, and that this is done as efficiently as possible. Without some descriptors of the ligand properties, it is difficult to quantify whether an optimization program has surveyed important (and perhaps neglected) areas of chemical space.

On the point of complexity, we have endeavoured to provide a detailed description of the methods followed to allow others to reproduce our approach. The descriptors were calculated using standard and widely-available computational tools (e.g. Gaussian and Spartan), and they are also re-usable across different projects. Indeed, one of our overriding goals has been to reduce the time and synthetic effort involved in a challenging optimization campaign. The advantage of this approach lies in the fact that all these ideas can be tested *in-silico* before synthesis, to prioritize only the most useful ligands. Moreover, the final model suggested stopping the ligand design because no more improvement could be achieved according to the *in-silico* predictions, which was valuable to us. Finally, interpretation of the multivariate model also allowed us to gain mechanistic insights as shown in Figure 2A, and helped developing an understanding about our successful ligand.

Could our best ligand have been found without the model, following intuitive modifications of the R substituents? Likely, after systematically testing all our ligand ideas one by one. Chance might make you test the best one first, or at the end. Even for cases where structures could be developed using chemical intuition alone, the overall reduction in non-value added ligand syntheses is a critical component in the acceleration of the ligand design process.

3. Density functional theory (DFT) calculations

1. Benchmarking

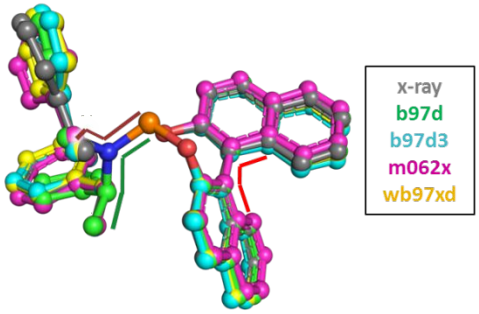
From the CSD database, a crystal structure of Feringa's ligand (ID: WAJSAC) could be obtained.[22] The x-ray geometry was then optimised using four different density functionals in order to probe the effect of the level of theory on the ligand structure. Three dihedrals were selected for their importance in the final structure, which will impact the different parameters that could be generated from it (Figure S3).

Pair-alignment and angle analysis led to the conclusion that ωB97XD/6-31g(d) was the best level of theory from those examined.

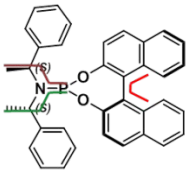
A

CCSD: WAJSAC		Gas					
		Dihedral (°)	Dihedral (°)	Dihedral (°)	rms_align (Å)	rms_pair_fit (Å)	rms_cur (Å)
xray		-69.2	119.7	-58.7	0.0	0.0	0.0
M06-2X	6-31g(d)	-67.4	117.7	-56.3	0.15	0.017	0.681
wb97x-d	6-31g(d)	-74.0	119.4	-57.4	0.13	0.016	0.357
B97-D	6-31g(d)	-76.4	120.0	-56.6	0.44	0.038	0.647
B97-D3	6-31g(d)	-77.1	119.5	-56.6	0.15	0.037	0.335

B



C



D

	RMSD (scaled)
xray	0.00
M06-2X	1.72
wb97x-d	**0.98**
B97-D	1.71
B97-D3	1.55

Figure S3. A. Angles and alignment RMS of the x-ray crystal structure (CSD ID: WAJSAC) of Feringa's ligand were obtained at different levels of theory. **B.** 3D representation of the ligand was optimised at different levels of theory and pair-fitted on the pyramidal structure of the phosphoramidite moeity. **C.** 2D representation of the x-ray crystal structure is annotated with the studied dihedrals. **D.** RMSD is calculated from vectors of all the scaled parameters of each level of theory showed in the table. ωB97XD is the best density functional.

2. Copper interaction with indane

As shown in one of our previous work,[23] the copper interacts strongly with the Phosphorous lone pair but can also interact with π orbitals of aromatics rings. Here, we envisaged that similar behaviour might appear with the indane moiety, which led to the DFT optimisation of several ligands at the (SMD, Et_2O) ωB97XD/6-31G(d) (C, H, P, O, N) and ωB97XD/LANL2DZ (Cu) level of theory. Satisfactorily, all of them showed similar behaviour with the copper-arene interactions (Figure S4), which seem somehow important in order to reach high enantioselectivity and reactivity. Unfortunately, distances and NBO analysis around the copper did not lead to any useful parameters that correlated to the observed enantioselectivities.

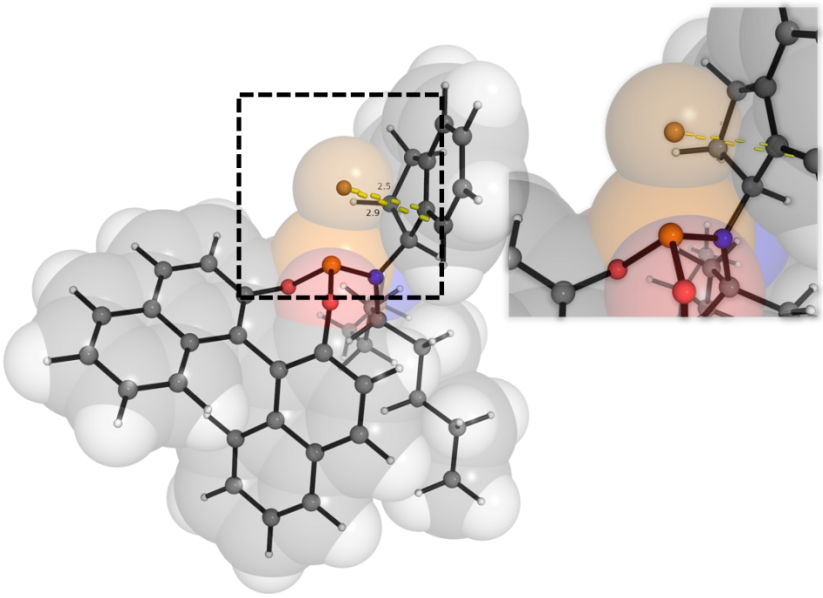


Figure S4. Ligand L6 optimisation with copper catalyst displaying a copper-arene interaction.

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