Supporting information

# β-Chloroaldehydes from Trapping Zirconium Enolates Produced in Asymmetric 1,4-Additions

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## General procedures

All reactions, unless specified otherwise, were performed under a positive pressure of $N_2$ or Ar in flame dried glassware. Cooling to –78 ºC was achieved using dry ice and acetone, cooling to 0 ºC was achieved using ice and all other temperatures were attained using a Julabo FT902 immersion cooler. Heating was achieved using a hotplate coupled to Drysyn® heating blocks or sand baths.

Analytical thin-layer chromatography was performed on aluminium backed plates, pre-coated with silica gel (Silica Gel 60, $F_{254}$; Merck) unless otherwise specified. Visualisation was aided using UV light ($\lambda$ = 254 nm) and then stained using aqueous $KMnO_4$, aqueous cerium ammonium molybdate (CAM), acidic *p*-anisaldehyde in ethanol or vanillin where specified. Flash column chromatography was conducted using Merck 60 Å silica gel.

## Instrumentation

NMR spectra were acquired on Bruker DPX200 (200 MHz), DPX300 (300 MHz), AVIIIHD 400 nanobays (400 MHz) or AVII 500 (500 MHz) instruments in deuterated solvents. Chemical shifts ($\delta$) were referenced according to the residual solvent peak.[1] Coupling constants (*J*) were quoted to the nearest 0.1 Hz. Peaks were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), broad (br) and multiplet. Assignments of peaks were performed with the assistance of 2D NMR experiments including COSY, HSQC and HMBC.

Low resolution mass spectra were recorded on a Waters LCT with a time-of-flight detector for electrospray (ESI+) ionisation mode. High resolution mass spectra were recorded on a Bruker $\mu$TOF with a time-of-flight detector for electrospray (ESI+) ionization mode, Waters GCT classic GC-MS with a time-of-flight detector for electron impact (EI+) ionization mode at 70 eV or a Thermo Exactive spectrometer equipped with Waters Acquity liquid chromatography system (atmospheric pressure chemical ionization APCI+).

Infrared spectroscopy measurements were carried out using a Bruker Tensor 27 FTIR with internal calibration over the range of 4000 – 600 $cm^{-1}$. Optical rotations were recorded using a Schmidt Haensh Unipol L2000 Polarimeter.

Analytical and semi-preparatory HPLC were carried out using an Aglilent 1260 Infinity series normal phase unit equipped with an autosampler. Columns were protected by column guards and all solvents used were of HPLC quality.

Chiral SFC (supercritical fluid chromatography) separations were conducted on a Waters Acquity UPC system using the Empower software. Chiralpak® columns (150 mm x 3 mm, particle size 3$\mu$m)

were used as specified in the text. Solvents used were of HPLC grade (Fischer Scientific, Sigma Aldrich or Rathburn).

## Reagents

Dichloromethane ($CH_2Cl_2$), chloroform ($CHCl_3$), toluene (PhMe), diethyl ether ($Et_2O$), *n*-pentane, tetrahydrofuran (THF), dimethylformamide (DMF) and benzene (PhH) were obtained from a Braun solvent purifier system (SP-800) having been passed through a column of activated $Al_2O_3$. Methyl *tert*-butyl ether (MTBE) and 1,2-dichloroethane ($ClCH_2CH_2Cl$) were obtained commercially in an anhydrous state and stored over activated 3 Å molecular sieves. Other solvents were dried according to standard procedure.[2] Solvents were degassed either by bubbling a stream of $N_2$ through the solvent for 10 minutes or using the freeze-pump-thaw method. Petrol refers to 40 - 60 °C b.p. petroleum spirits.

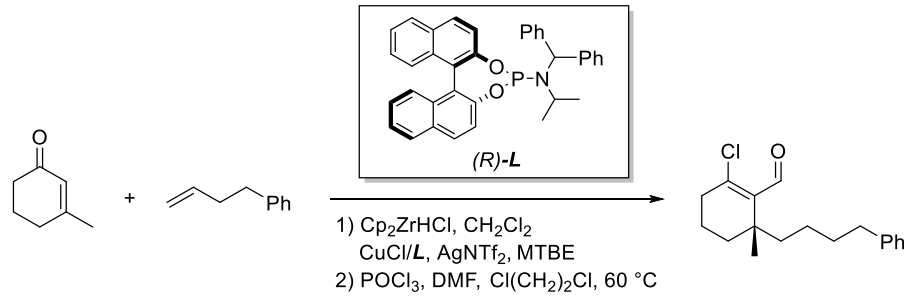
Commercially available chemicals were purchased at the highest commercial quality and used directly without intermediate purification. Molecular sieves were activated by heating with a flame under high vacuum, allowed to cool and then backfilled with $N_2$. The procedure was repeated 3 times.

Organometallic reagents were titrated using salicylaldehyde phenylhydrazone before use.[3] $MnO_2$ was activated prior to use in a glassware drying oven overnight.

The following chemicals were synthesised according to standard literature procedures: Bis(cyclopentadienyl)zirconium(IV) chloride hydride $Cp_2ZrHCl$ (Schwartz reagent),[4] Silver bis(trifluoromethanesulfonyl)imide $AgNTf_2$,[5] phosphoramidite ligand **L1**,[6] phosphoramidite ligand **L2**,[7] 3-ethyl-2-cyclohexen-1-one **I**,[8] (but-3-en-1-yloxy)(tert-butyl)dimethylsilane **II**,[9] tert-butyl((1-(4-chlorophenyl)but-3-en-1-yl)oxy)dimethylsilane **III**,[6] ((but-3-en-1-yloxy)methyl)benzene **IV**,[10] and 3-methyl-2-cyclohepten-1-one **V**.[8]

## Trapping reactions of zirconium enolates

### Representative procedure for the preparation of compound 9 (5 mmol scale)




CuCl (52 mg, 0.53 mmol, 0.10 mol equiv) and then ligand **L1** (290 mg, 0.054 mmol, 0.10 mol equiv) were added to a 50 mL flask equipped with a rubber septum and stirrer bar (flask **A**). Three cycles of vacuum and back filling with $N_2$ were then performed, after which methyl-*tert*-butylether (25 mL) was added by syringe and the solution allowed to stir for one hour in a darkened environment.

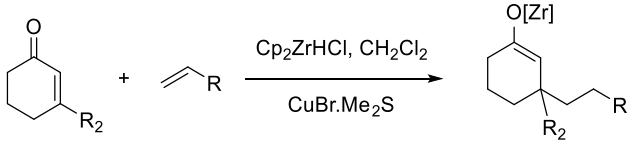
Concurrently, $Cp_2ZrHCl$ (2.32 g, 8.99 mmol, 1.70 mol equiv) was added to a separate 100 mL flask equipped with a stirrer bar and rubber septum (flask **B**). Three cycles of vacuum and back filling with $N_2$ were then performed, after which dry $CH_2Cl_2$ (4.0 mL) and then 4-phenyl-1-butene (1.6 mL, $\rho$ = 0.88 g.mL$^{-1}$, 11 mmol, 2.0 mol equiv) was added. After stirring for one hour, a clear orange solution was obtained.

After stirring for the allotted time, Silver bis(trifluoromethanesulfonyl)imide (310 mg, 0.80 mmol, 0.15 mol equiv) was tipped into flask **A** in one portion (minimising exposure to the atmosphere). After stirring for 10 minutes, the solution from flask **A** was then filtered (using a syringe filter) into flask **B** over a period of one minute. The resulting solution became dark within 10 seconds. After stirring for 5 minutes, 3-methyl-2-cyclohexenone was added dropwise at a rate of 1 drop every 2 seconds (0.60 mL, $\rho$ = 0.97 g.mL$^{-1}$, 5.3 mmol, 1.0 mol equiv). The reaction flask was then wrapped in foil and stirred at room temperature for 17 hours or until the reaction was complete, as monitored by TLC. An aliquot of the reaction mixture was loaded directly onto a small silica column (eluted with 10% $Et_2O$/*n*-pentane) in order to furnish a sample suitable for HPLC analysis (*ee* determination).

$POCl_3$ (5.5 mL, $\boldsymbol{\rho}$ = 1.64 g.mL$^{-1}$, 59 mmol, 11 mol equiv) was added in one portion to a stirred solution of *N*,*N*-dimethylformamide (4.1 mL, $\boldsymbol{\rho}$ = 0.944 g.mL$^{-1}$, 53 mmol, 10 mol equiv) in 1,2-dichloroethane (20 mL) at 0 °C under a $N_2$ atmosphere. After stirring for 5 minutes, the flask was warmed to room temperature, stirred for 15 minutes and then stirred at 60 °C for a further 5 minutes. The asymmetric conjugate addition reaction was then added by syringe and the dark brown solution was stirred for 2 hours at this temperature. The mixture was cooled to 0 °C and saturated $NaHCO_{3(aq)}$ (100 mL) was added drop wise using a separatory funnel under vigorous stirring. When the addition was complete, the slurry was stirred for an additional 15 minutes before the upper, solid-containing, aqueous phase

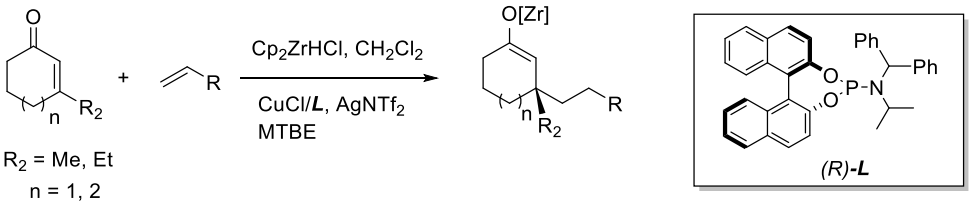
is extracted (5x) with $CH_2Cl_2$. The combined organic extracts were washed with water (2x), dried over $Na_2SO_4$, and concentrated *in vacuo*. The orange residue was purified by flash chromatography (5–10% $Et_2O$/pentane) to furnish the desired product as a yellow oil (789 mg, 2.71 mmol, 51% yield). Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step and submitting it to HPLC analysis using the conditions reported by Sidera et. al.[6] *ee* = 94%.

## General procedure A: Synthesis of racemic 1,4-addition products




Racemic samples for *ee* determination were prepared according to a literature procedure.[6] $Cp_2ZrHCl$ (113 mg, 0.438 mmol, 1.8 mol equiv) was added to a 7 mL vial equipped with a stirrer bar before a rubber septum and inert gas balloon were fitted. Dry $CH_2Cl_2$ (1.2 mL) and then alkene (0.50 mmol, 2.0 mol equiv) were added and the reaction stirred for 40 min (a clear yellow solution was obtained). $CuBr.Me_2S$ (52 mg, 0.25 mmol, 1.0 mol equiv) was then added, minimising exposure of the reaction to atmosphere and the black slurry stirred for 10 additional minutes. The enone (0.25 mmol) was added via syringe and stirring was allowed to continue overnight. At this point, TLC (30% $Et_2O$/n-pentane) showed complete consumption of the enone. The reaction was directly subjected to a trapping procedure (general procedures E to G).

## General procedure B: Copper catalysed 1,4-addition reactions to 3-substituted cyclohexenones




$R_2$ = Me, Et
n = 1, 2

1,4-addition reactions were performed according to a literature procedure.[6]

CuCl (5.2 mg, 0.053 mmol, 0.10 mol equiv) and then ligand **L1** (29 mg, 0.054 mmol, 0.10 mol equiv) were added to a 7 mL vial equipped with a rubber septum and stirrer bar (flask **A**). Three cycles of vacuum and back filling with $N_2$ were then performed, after which methyl-*tert*-butylether (2.5 mL) was added by syringe and the solution allowed to stir for one hour in a darkened environment.

Concurrently, $Cp_2ZrHCl$ (232 mg, 0.899 mmol, 1.70 mol equiv) was added to a separate 7 mL vial equipped with a stirrer bar and rubber septum (flask **B**). Three cycles of vacuum and back filling with $N_2$ were then performed, after which dry $CH_2Cl_2$ (0.4 mL) and then alkene (1.1 mmol, 2.1 mol equiv) were added. After stirring for one hour, a clear orange solution was obtained. In some instances

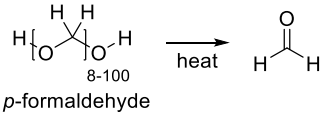
(dependent on the quality of alkene and Schwartz reagent used) hydrozirconation was not complete within the allotted time. In these situations, it was helpful to apply heat to the flask which usually resulted in the formation of a clear orange solution.

After stirring for the allotted time, Silver bis(trifluoromethanesulfonyl)imide (31 mg, 0.080 mmol, 0.15 mol equiv) was tipped into flask **A** in one portion (minimising exposure to the atmosphere). After stirring for 10 minutes, the solution from flask **A** was then filtered (using a syringe filter) into flask **B** over a period of one minute. The resulting solution became dark within 10 seconds. After stirring for 5 minutes, 3-methyl-2-cyclohexenone was added at a rate of 1 drop every 2 seconds (60 $\mu$L, $\rho$ = 0.97 g.mL$^{-1}$, 0.53 mmol, 1.0 mol equiv). The reaction flask was then wrapped in foil and stirred at room temperature for 17 hours or until the reaction was complete, as monitored by TLC. At this point, the reaction contents were subjected to a trapping procedure (general procedures E to G)

For the purpose of *ee* determination, an aliquot of the reaction mixture was loaded directly onto a small silica column (using a pipette) and eluted with 10% $Et_2O$/*n*-pentane.

Absolute stereochemical assignments were made based on analogy of existing compounds.[6]

## General procedure C: Cracking of *p*-formaldehyde to prepare monomeric formaldehyde solution

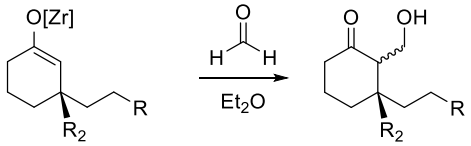


*p*-formaldehyde

The formaldehyde solution used in trapping procedure D should be prepared immediately before use and have low water content for optimal yields. This procedure for cracking the polymer is for a 0.53 mmol scale 1,4-addition reaction.

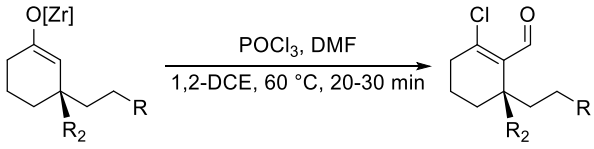
To a round bottom flask equipped with a stirrer bar was added *p*-formaldehyde (318 mg, monomer molecular weight 30, ~10.6 mmol monomer equivalent, 20 mol equiv). A Suba–Seal® and canula were then fitted and the canula was directed into another flask containing dry $Et_2O$ (15 mL). A nitrogen balloon was then fitted to the *p*-formaldehyde containing flask and a vent needle was inserted into the ether-containing flask. Care must be taken throughout these steps to prevent suck back of the solvent into the *p*-formaldehyde flask. Three cycles of vacuum and back filling with $N_2$ were then performed, after which the *p*-formaldehyde-containing flask was heated gently with a heat gun under a nitrogen stream (from the balloon) and the magnetic stirrer bar was occasionally agitated using a magnetic rod. When the white solid in the *p*-formaldehyde flask had vanished, the system was allowed to cool for 5 minutes and the formaldehyde/$Et_2O$ solution used immediately in the subsequent trapping reaction.

## General procedure D: Trapping with formaldehyde




Upon completion of the 1,4-addition reaction as judged by TLC, the contents of the asymmetric reaction were transferred via syringe into freshly prepared formaldehyde/$Et_2O$ solution. After stirring for 5 minutes TLC showed the formation of two new spots corresponding to the diastereomers of the hydroxymethylated product and untrapped 1,4-addition product. The reaction was quenched with 4 mL 1M $NH_4Cl_{(aq)}$ to form an emulsion after ~3 minutes which was diluted with $H_2O$ until two phases formed. The phases were partitioned and the aqueous phase was extracted three times with $Et_2O$. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The crude products were dry loaded onto celite and purified by flash chromatography.

## General procedure E: Trapping with chloroimine salt (Vilsmeier-Haack) reagent

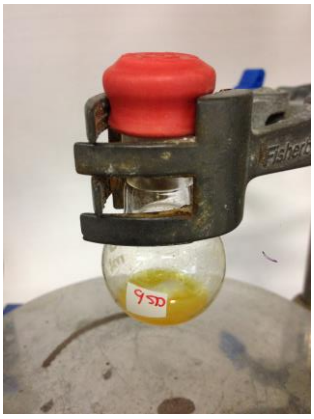



The following procedure is based on a 0.53 mmol scale 1,4-addition reaction.

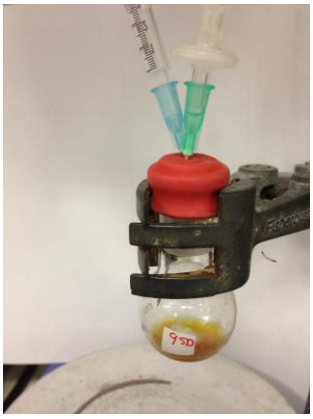
$POCl_3$ (1.1 mL, $\rho$ = 1.64 g.mL$^{-1}$, 12 mmol, 22 mol equiv) was added in one portion to a stirred, room temperature solution of *N*,*N*-dimethylformamide (0.82 mL, $\rho$ = 0.944 g.mL$^{-1}$, 11 mmol, 20 mol equiv) in 1,2-dichloroethane (7 mL) in a sealed round bottom flask under a $N_2$ atmosphere. On large scale, the addition should be performed at 0 °C and stirring continued for 5 minutes before warming to room temperature (to prevent thermal runaway). After stirring for 15 minutes, the flask was heated at 60 °C for a further 5 minutes before the contents of the 1,4-addition reaction (judged complete by TLC) were added by syringe. After 20 minutes stirring at 60 °C (TLC control) the reaction flask was cooled to 0 °C and the reaction mixture diluted with one-third volume $CH_2Cl_2$. Saturated $NaHCO_{3(aq)}$ (7 mL) was then added dropwise via syringe (on large scale use a dropping funnel) and the mixture was stirred vigorously for 15 minutes. An orange sludge is obtained, which was transferred to a separatory funnel. Upon standing, two phases are formed and the upper, solid-containing, aqueous phase is extracted (3x) with $CH_2Cl_2$. The combined organic extracts were washed with water twice, dried over $Na_2SO_4$, and concentrated *in vacuo*. The orange residue was purified by flash chromatography to furnish the desired products.

## Pictures of key experimental details

### Cu(I) catalysed 1,4-addition reactions to substituted cyclohexenones (general procedure B)



1. Zirconocene solution after complete hydrozirconation. Usually a clear, bright yellow, solution is obtained after 1 hour stirring at room temperature



2. Zirconocene solution just after Cu/Ag/L solution was added via a syringe filter.

3. The solution turns black within 10 seconds ($N_2$ inlet removed for clarity).

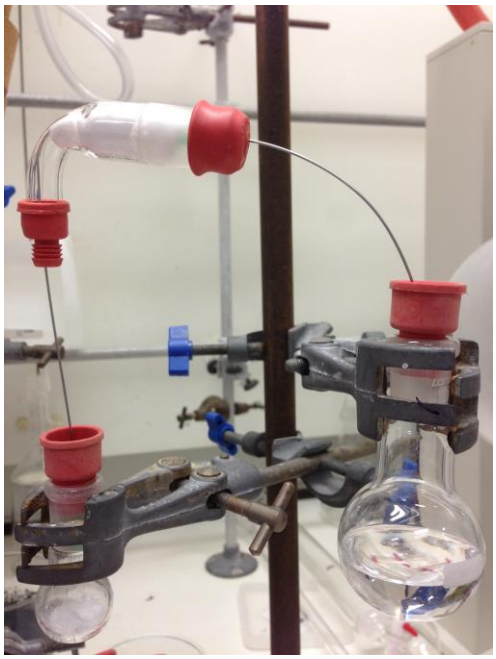
Additional notes:

- If the solution does not become clear yellow after 1 hour, it is usually a sign of poor quality Schwartz reagent.
- If the reaction does not go black immediately, the most likely cause is poor quality Schwartz (and incomplete hydrozirconation). Other likely causes include wet solvents (test via Karl-Fischer titration) or wet $AgNTf_2$ (dry under high vacuum at 40 °C overnight).

### Formaldehyde cracking (general procedure C)

A makeshift disposable canula that may be thrown away if blocked. Daisy-chained 120 mm/21G needles were used with an inline $P_2O_5$ filter. The filter was fashioned out of a B19 gas adaptor, glass wool, a no. 25 Suba–Seal® (Aldrich) and a no. 13 Suba–Seal® (Aldrich).

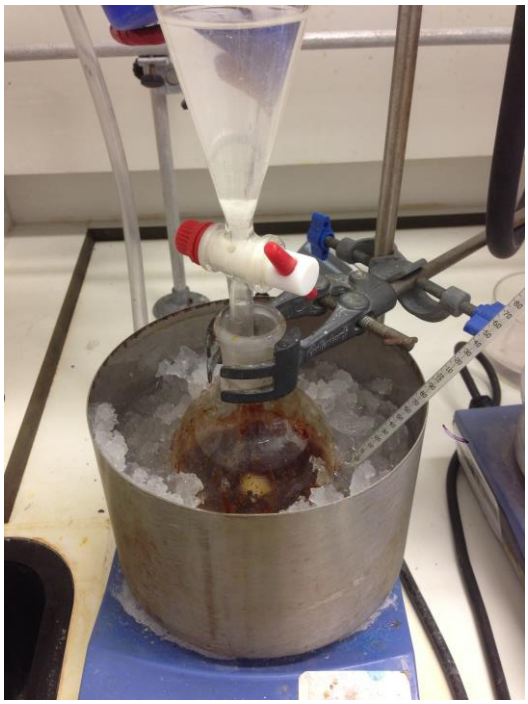
*p*-formaldehyde: $N_2$ balloon goes here to provide a positive pressure during the cracking procedure.



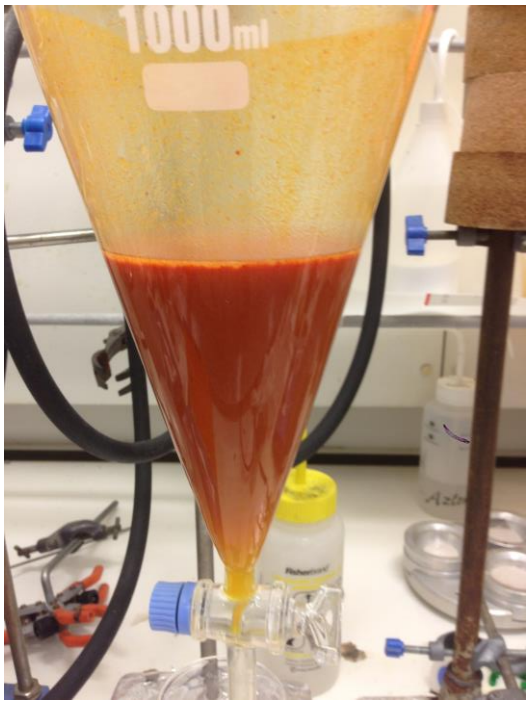
Receiver flask containing $Et_2O$. During the cracking, a vent needle (not shown here) should be used and the tip of the canula is immersed below the solution.

**Large scale quenching Vilsmeier trapping reaction (from general procedure E)**

1. Trapping reaction prior to quench



2. After cooling to 0 °C and diluting with $CH_2Cl_2$. Employ a separating funnel to slowly add $NaHCO_{3(aq)}$.

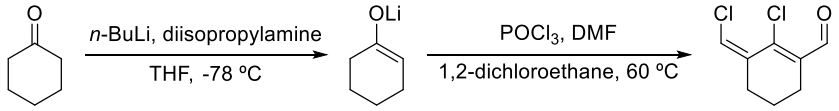



3. Orange sludge after vigorous stirring for 15 minutes and transfer to a separatory funnel.


4. Phase separation after dilution with $CH_2Cl_2$ (lower layer).

## Procedure for mechanistic studies

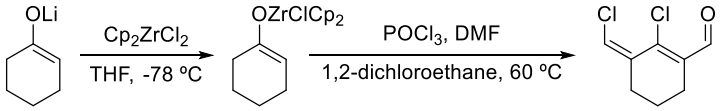
### Preparation of cyclohexanone lithium enolate and usage in trapping reaction




Cyclohexanone lithium enolate was prepared as follows. *n*-Butyllithium (0.45 mL of a 2.5 M solution in hexanes, 1.1 mmol, 1.1 mol equiv) was added to diisopropylamine (0.17 mL, $\rho$ = 0.717 g.mL$^{-1}$, 1.2 mmol, 1.2 mol equiv) in dry THF (3 mL) at –78 °C and then immediately warmed to room temperature. After stirring at room temperature for 10 minutes, the solution was cooled to –78 °C again, and cyclohexanone (0.10 mL, $\rho$ = 0.948 g.mL$^{-1}$, 1.0 mmol, 1.0 mol equiv) in dry THF (2 mL) was added by syringe. After stirring for 30 min, the enolate was subject to transmetalation with $Cp_2ZrCl_2$ or trapping procedure (general procedure E).

In the case where the trapping procedure was used, $^1$H NMR analysis (1,2-dichloroethane internal standard) showed that the doubly chlorinated product was obtained (10% yield, 0.10 mmol).

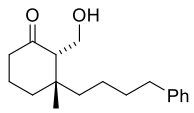
### Preparation of cyclohexanone zirconium enolate and usage in trapping reaction




$Cp_2ZrCl_2$ (321 mg, 1.1 mmol, 1.1 mol equiv) was dissolved in dry THF (6.8 mL). This solution was added to the cyclohexanone lithium enolate at –78 °C (as prepared above) and then immediately warmed to room temperature. After stirring for 30 min, the enolate was subject to trapping procedure (general procedure E). $^1$H NMR analysis (1,2-dichloroethane internal standard) showed that the doubly chlorinated product was obtained (48% yield, 0.48 mmol).

## Characterisation data

**(2S,3R)-2-(hydroxymethyl)-3-methyl-3-(4-phenylbutyl)cyclohexan-1-one 8**




*Trans* diastereomer. 1,4-addition reaction was conducted according to general procedure B on 0.53 mmol scale and using 4-phenyl-1-butene as the alkene. Trapping was conducted according to general procedure E. Flash chromatography (30% EtOAc/petrol) gave the product as a 1:1 separable mixture of diastereomers (colourless oil) with a combined mass of 68 mg (0.25 mmol, 50% total yield). Relative stereochemistry was assigned on the basis of NOE experiments. Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step and submitting it to HPLC analysis using the conditions reported by Sidera et. al.[6] *ee* = 94%.

**$R_f$** = 0.15 (50% EtOAc/petrol, stains orange with *p*-anisaldehyde);

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.32 – 7.27 (m, 3H), 7.23 – 7.14 (m, 2H), 4.03 (ddd, J = 11.4, 9.4, 4.1 Hz, 1H), 3.63 (td, J = 11.4, 9.8, 3.3 Hz, 1H), 2.69 – 2.55 (m, 2H), 2.49 – 2.28 (m, 2H), 2.42 – 2.35 (m, 1H), 1.96 – 1.64 (m, 2H), 1.83 – 1.52 (m, 2H), 1.62 – 1.55 (m, 2H), 1.21 (td, J = 8.4, 8.0, 5.0 Hz, 4H), 1.09 (s, 3H) ppm;

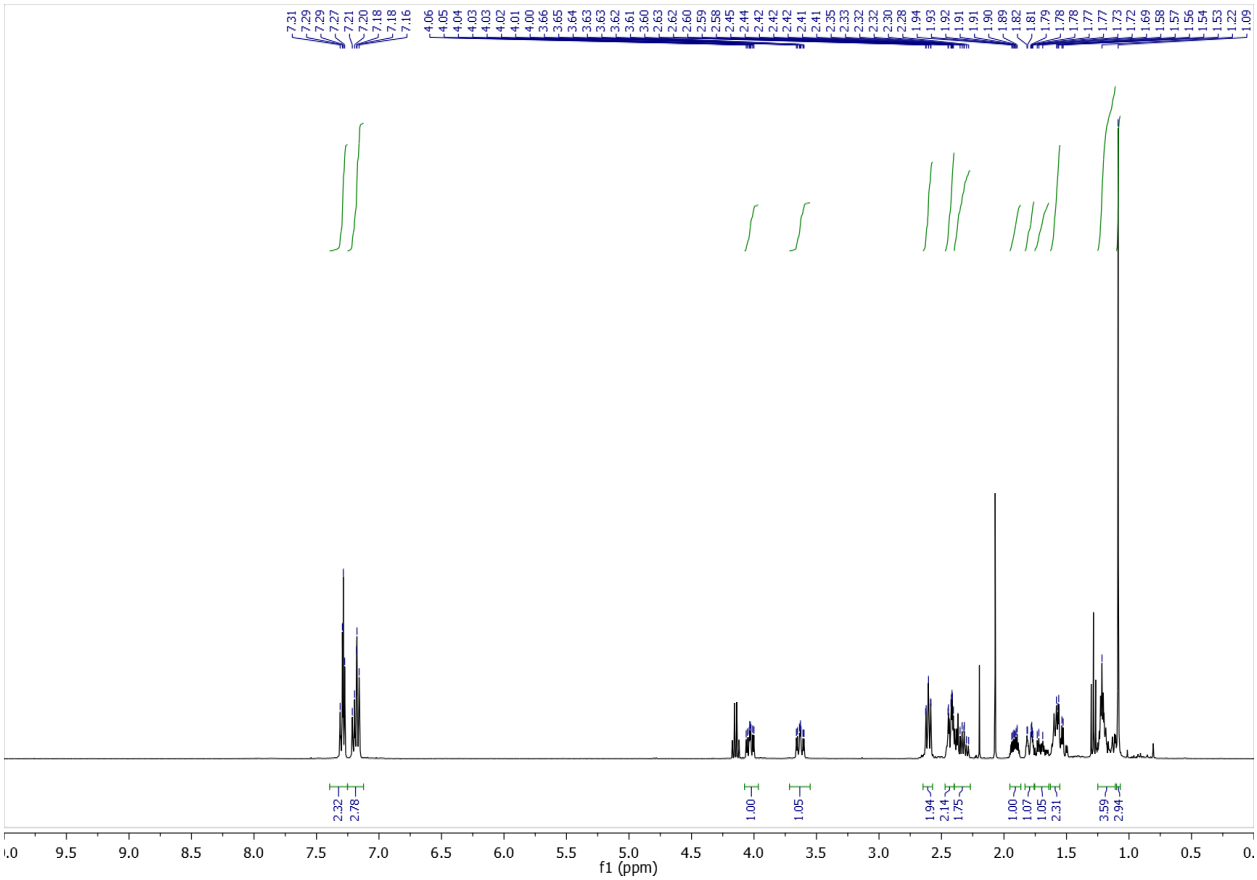
**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 215.0, 142.5, 128.5 (2C), 128.4 (2C), 125.8, 63.9, 58.4, 41.7, 41.0, 35.9, 35.7, 33.6 32.1, 26.1, 22.8, 22.0 ppm;

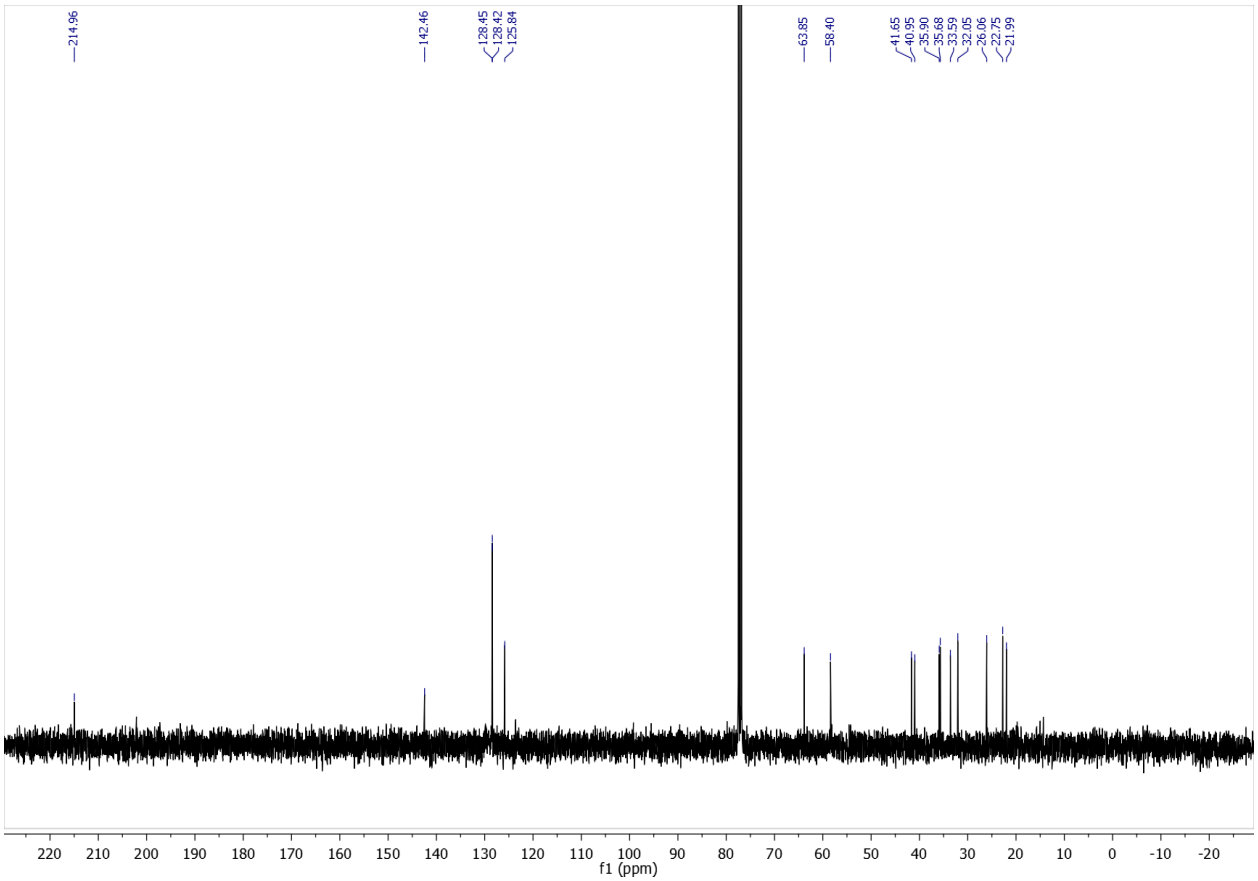
**FT-IR thin film, neat (ATR):** 3427, 3026, 2934, 2858, 2361, 1703, 1496, 1454, 1034 $cm^{-1}$;

**HRMS ($ESI^+$):** calculated for $C_{18}H_{26}O_2{}^{23}Na$, $[M+Na]^{+\bullet}$: 297.18250 found 297.18262 (Δ = 0.39 ppm);

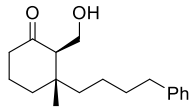
$[\alpha]_D^{25}$ **=** – 3.6º (*c* = 0.40, $CH_2Cl_2$), based on a sample of 94% *ee*;

## $^{1}H/^{13}C$ NMR


7.31 7.29 7.29 7.27 7.21 7.20 7.18 7.18 7.16
4.06 4.05 4.04 4.03 4.03 4.02 4.01 4.00 3.66 3.65 3.64 3.63 3.63 3.62 3.61 3.60 2.63 2.62 2.60 2.59 2.58 2.45 2.44 2.42 2.42 2.42 2.41 2.41 2.35 2.33 2.32 2.30 2.28 1.94 1.93 1.92 1.91 1.91 1.90 1.89 1.82 1.81 1.79 1.78 1.78 1.77 1.77 1.73 1.72 1.69 1.58 1.57 1.56 1.54 1.53 1.22 1.09
2.32 2.78 1.00 1.05 1.94 2.14 1.75 1.00 1.07 1.05 2.31 3.59 2.94
f1 (ppm)


214.96 142.46 128.45 128.42 125.84 63.85 58.40 41.65 40.95 35.90 35.68 33.59 32.05 26.06 22.75 21.99
f1 (ppm)

**(2R,3R)-2-(hydroxymethyl)-3-methyl-3-(4-phenylbutyl)cyclohexan-1-one 8'**




*Cis* diastereomer. The product was co-isolated with compound **8**. Relative stereochemistry was assigned on the basis of NOE experiments.

**$R_f$** = 0.25 (50% EtOAc/petrol, stains orange with *p*-anisaldehyde);

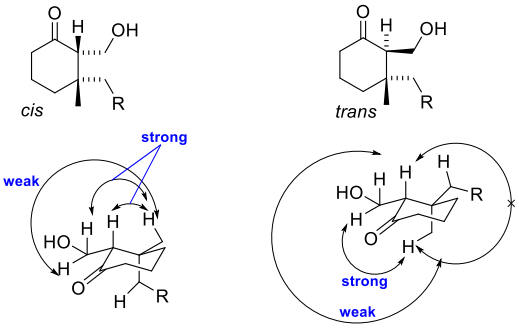
**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.31 – 7.26 (m, 2H), 7.21 – 7.16 (m, 3H), 3.92 (ddd, *J* = 11.5, 9.3, 4.1 Hz, 1H), 3.57 (ddd, *J* = 11.5, 10.0, 3.3 Hz, 1H), 2.63 (td, *J* = 7.5, 2.7 Hz, 2H), 2.49 (dd, *J* = 10.0, 4.1 Hz, 2H), 2.41 – 2.34 (m, 1H), 2.33 – 2.23 (m, 1H), 2.00 – 1.85 (m, 1H), 1.85 – 1.73 (m, 2H), 1.67 – 1.56 (m, 2H), 1.50 – 1.33 (m, 4H), 0.78 (s, 3H) ppm;

**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 215.8, 142.6, 128.5 (2C), 128.5 (2C), 125.9, 59.7, 58.5, 41.7, 41.4, 41.1, 36.5, 36.0, 32.2, 23.2, 22.3, 21.6 ppm;

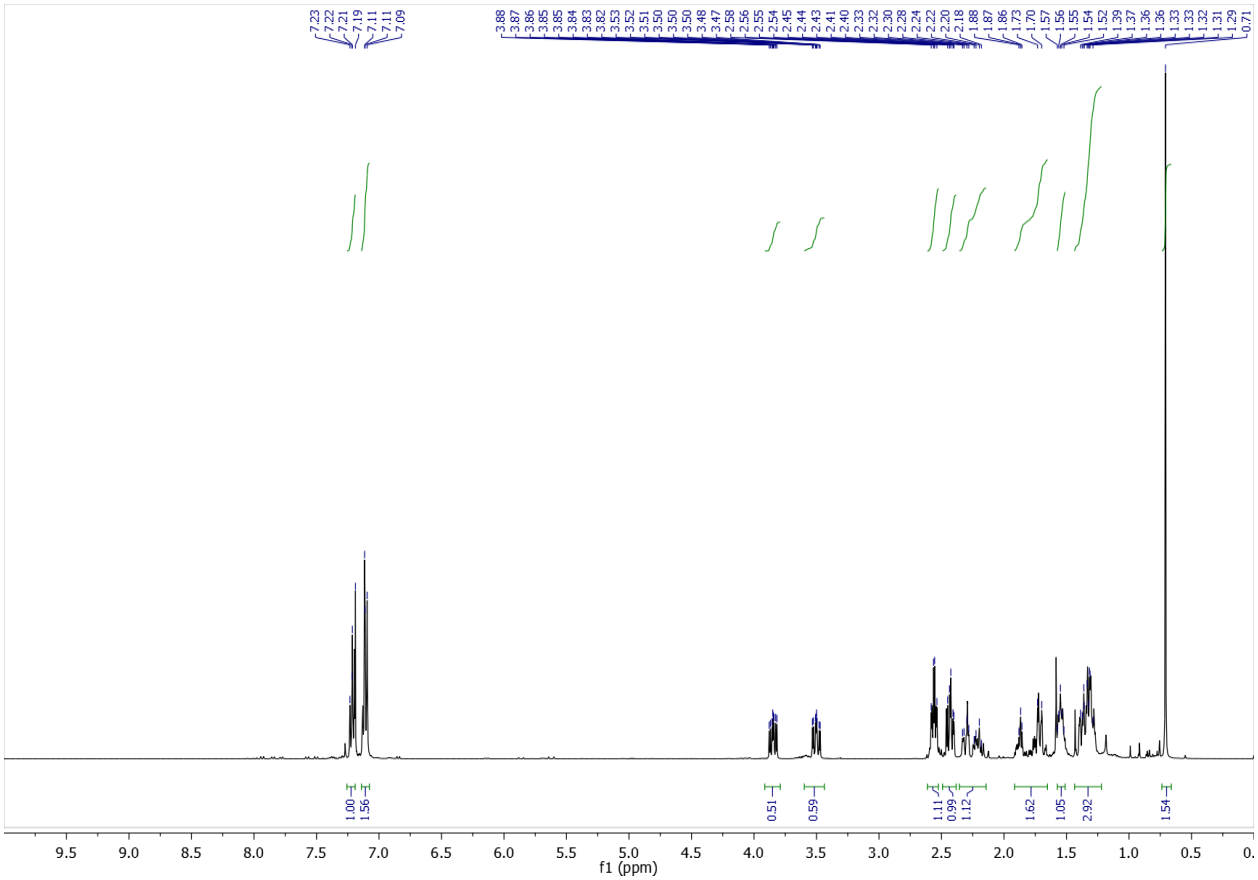
**FT-IR thin film, neat (ATR):** 3430, 3026, 2934, 2857, 1702, 1496, 1454, 1351, 1228, 1179, 1037 $cm^{-1}$;

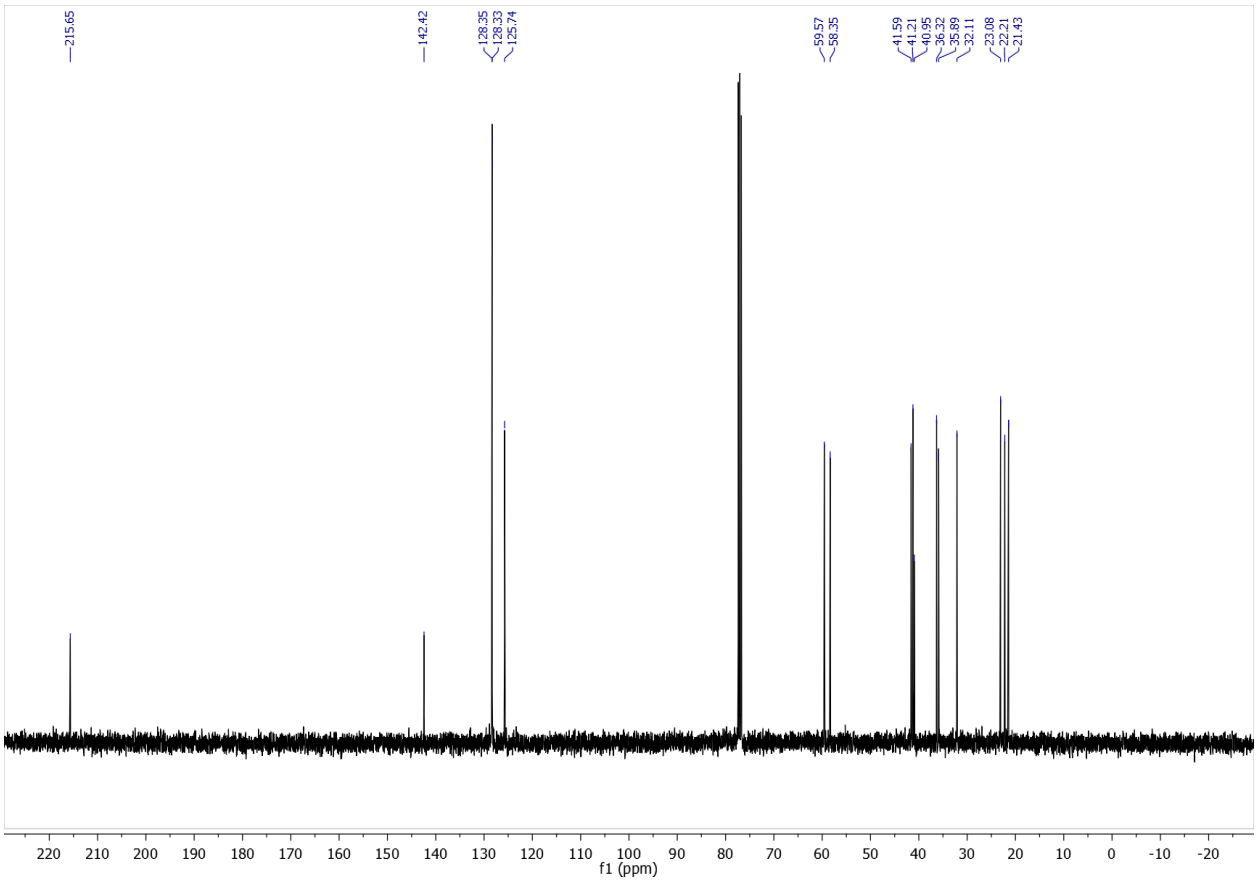
$[\alpha]_D^{25}$ **=** – 5.3° (*c* = 1.1, $CH_2Cl_2$), based on a sample of 94% *ee*;

**$^1$H/$^1$H NOE interactions:**

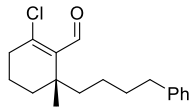


## $^{1}H/^{13}C$ NMR


7.23
7.22
7.21
7.19
7.11
7.11
7.09
3.88
3.87
3.86
3.85
3.85
3.84
3.83
3.82
3.53
3.52
3.51
3.50
3.50
3.50
3.48
3.47
2.58
2.56
2.55
2.54
2.45
2.44
2.43
2.41
2.40
2.33
2.32
2.30
2.28
2.24
2.22
2.20
2.18
1.88
1.87
1.86
1.73
1.70
1.57
1.56
1.55
1.54
1.52
1.39
1.37
1.36
1.36
1.33
1.33
1.32
1.31
1.29
0.71
1.00
1.56
0.51
0.59
1.11
0.99
1.12
1.62
1.05
2.92
1.54
f1 (ppm)


215.65
142.42
128.35
128.33
125.74
59.57
58.35
41.59
41.21
40.95
36.32
35.89
32.11
23.08
22.21
21.43
f1 (ppm)

**(R)-2-chloro-6-methyl-6-(4-phenylbutyl)cyclohex-1-ene-1-carbaldehydecarbaldehyde 9**




1,4-addition reaction was conducted according to general procedure B on 0.53 mmol scale and using 4-phenyl-1-butene as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure E. Flash chromatography (5% $Et_2O$/*n*-pentane) gave the title product as a yellow oil (87 mg, 0.30 mmol, 56% yield). Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step and submitting it to HPLC analysis using the conditions reported by Sidera et. al.[6] *ee* = 96%.

**$R_f$** = 0.54 (30% $Et_2O$/*n*-pentane, stains yellow with $KMnO_4$);

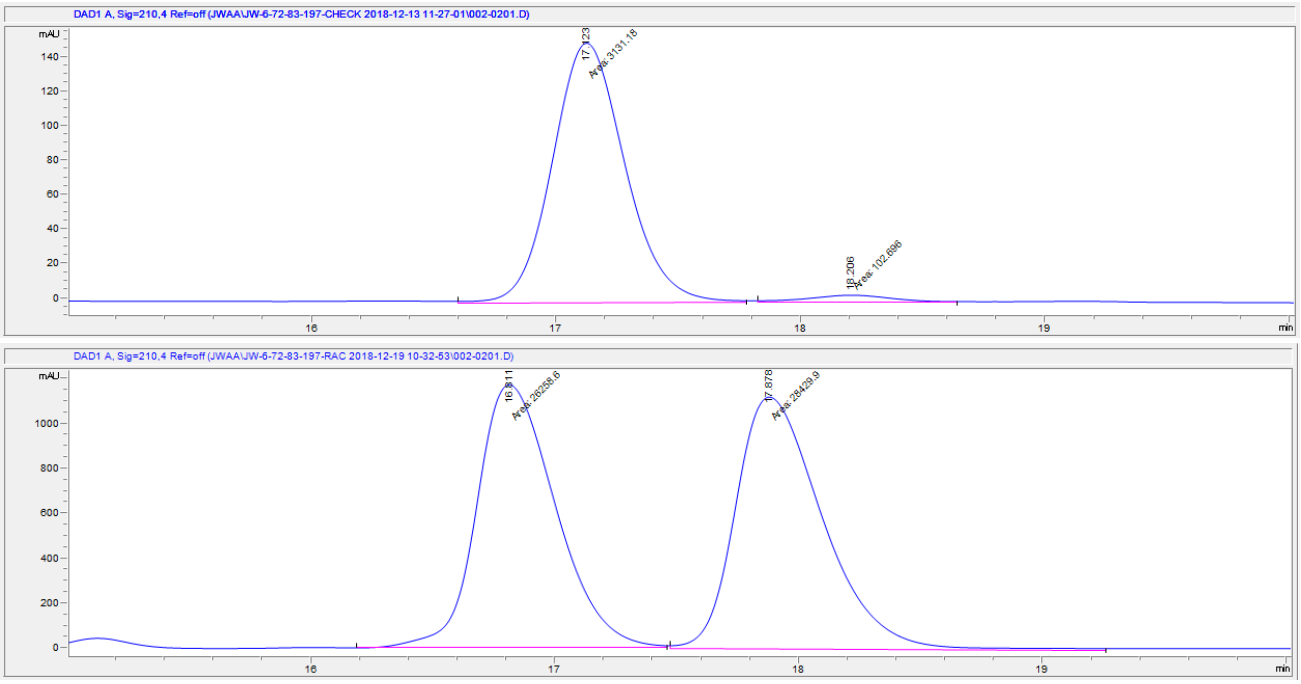
**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 10.23 (s, 1H), 7.34 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 2.69 – 2.60 (m, 2H), 2.39 – 2.23 (m, 2H), 2.49 – 2.25 (m, 2H), 1.68 – 1.57 (m, 2H), 1.46 (t, J = 6.5 Hz, 2H), 1.39 – 1.28 (m, 4H), 0.94 (s, 3H) ppm;

**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 191.2 , 150.6 , 142.6 , 132.5 , 128.5 (2C), 128.4 (2C), 125.8 , 48.5 , 41.1 , 36.0 , 34.0 , 32.3 , 32.0 , 24.4 , 23.2 , 21.3 ppm;

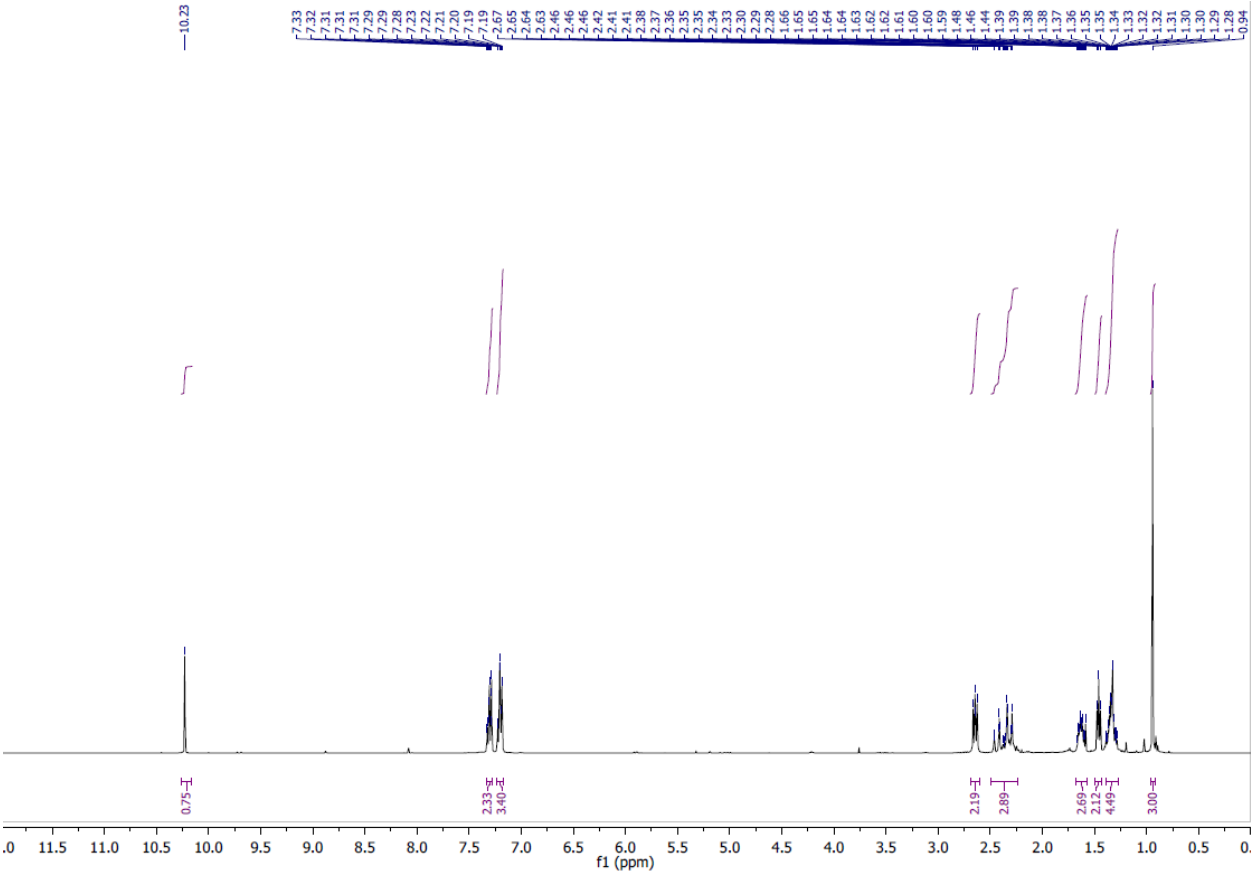
**FT-IR thin film, neat (ATR):** 2932, 2857, 1678, 1624 $cm^{-1}$;

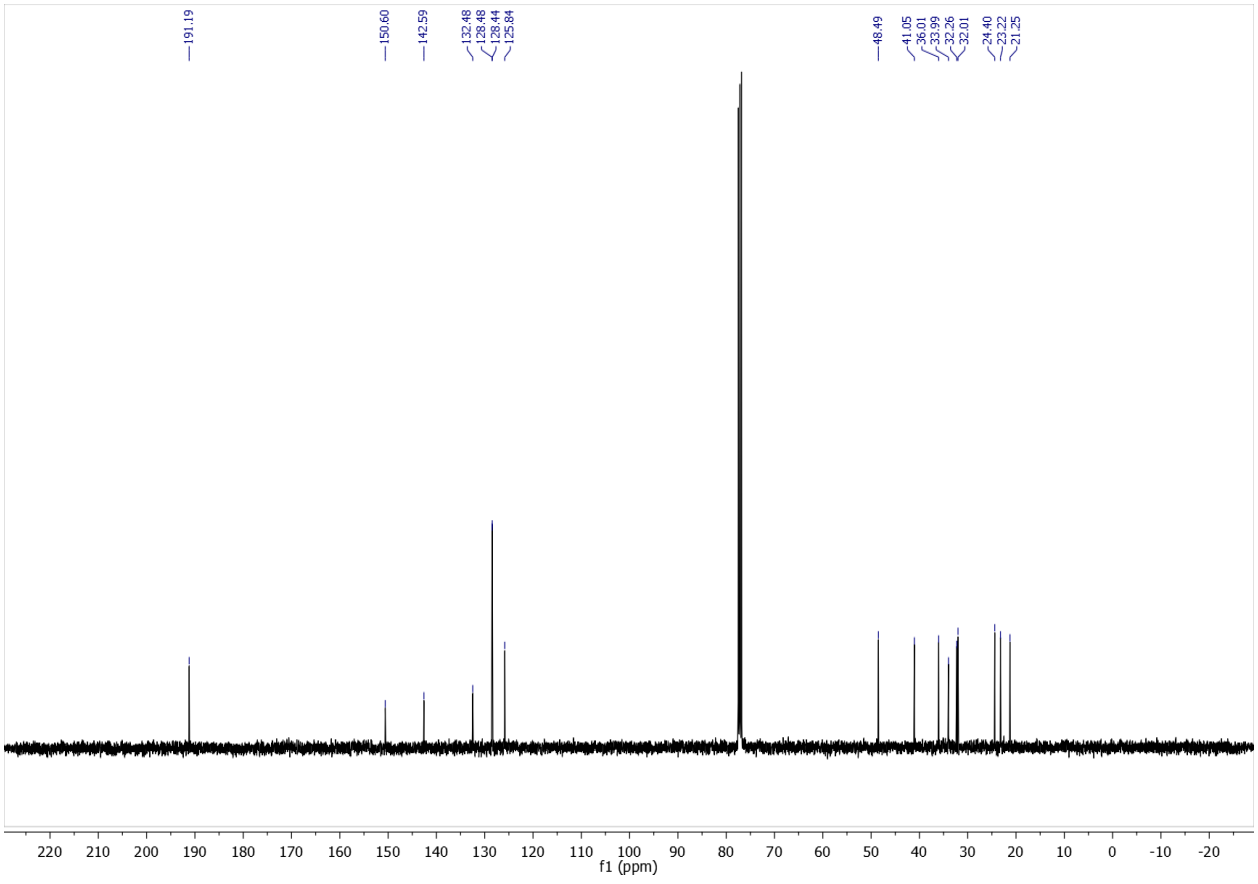
**HRMS ($ESI^+$):** calculated for $C_{18}H_{24}O^{35}Cl$, $[M+H]^{+\bullet}$: 291.15102 found 291.15112 (Δ = 0.36 ppm);

$[\alpha]_D^{25}$ **=** + 18º (*c* = 1.0, $CH_2Cl_2$), based on a sample of 96% *ee*;

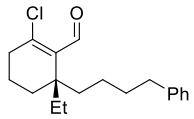


**$^{1}H/^{13}C$ NMR**


10.23
7.33 7.32 7.31 7.31 7.31 7.29 7.29 7.28 7.23 7.22 7.21 7.20 7.19 7.19 2.67 2.65 2.64 2.63 2.46 2.46 2.46 2.42 2.41 2.41 2.38 2.37 2.36 2.35 2.35 2.34 2.33 2.30 2.29 2.28 1.66 1.65 1.65 1.64 1.64 1.63 1.62 1.62 1.61 1.60 1.60 1.59 1.48 1.46 1.44 1.39 1.39 1.38 1.38 1.37 1.36 1.35 1.35 1.34 1.33 1.32 1.32 1.31 1.30 1.30 1.29 1.28 0.94
0.75
2.33
3.40
2.19
2.89
2.69
2.12
4.49
3.00
f1 (ppm)


191.19
150.60
142.59
132.48
128.48
128.44
125.84
48.49
41.05
36.01
33.99
32.26
32.01
24.40
23.22
21.25
f1 (ppm)

**(R)-2-chloro-6-ethyl-6-(4-phenylbutyl)cyclohex-1-ene-1-carbaldehyde 10**




1,4-addition reaction was conducted according to general procedure B using 3-ethyl-2-cyclohexenone **I**[8] (0.53 mmol) as the enone and 4-phenyl-1-butene as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure E. Flash chromatography (5% $Et_2O$/*n*-pentane) gave the title product as a yellow oil (66 mg, 0.22 mmol, 41% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak ID column 250 × 4.6 mm, 1-30% MeOH/$CO_2$ gradient over 5 min, 1.5 mL.min$^{-1}$): *ee* = 98% (minor enantiomer $t_R$ = 2.92 min, major enantiomer $t_R$ = 3.14 min).

**$R_f$** = 0.59 (30% $Et_2O$/*n*-pentane, stains yellow with $KMnO_4$);

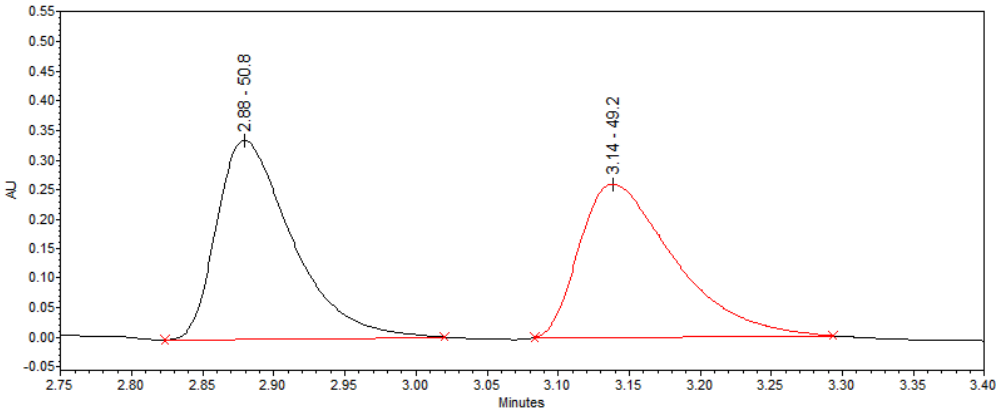
**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 10.12 (s, 1H), 7.23 – 7.17 (m, 2H), 7.10 (m, 3H), 2.54 (dd, J = 8.7, 6.8 Hz, 2H), 2.28 (t, J = 2.3 Hz, 2H), 2.18 (m, 2H), 1.58 – 1.47 (m, 2H), 1.37 (t, J = 6.4 Hz, 2H), 1.30 – 1.13 (m, 6H), 0.73 (t, J = 7.5 Hz, 3H) ppm;

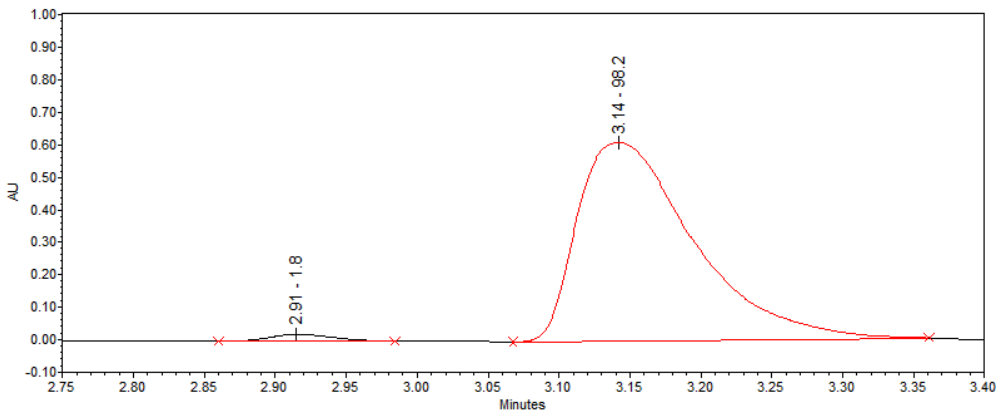
**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 191.0, 150.7, 142.4, 132.5, 128.3 (2C), 128.3 (2C), 125.7, 46.9, 36.3, 35.9, 35.8, 32.1, 29.5, 28.8, 22.6, 20.8, 7.5 ppm;

**FT-IR thin film, neat (ATR):** 2963, 2933, 2858, 1678, 1624 cm$^{-1}$;

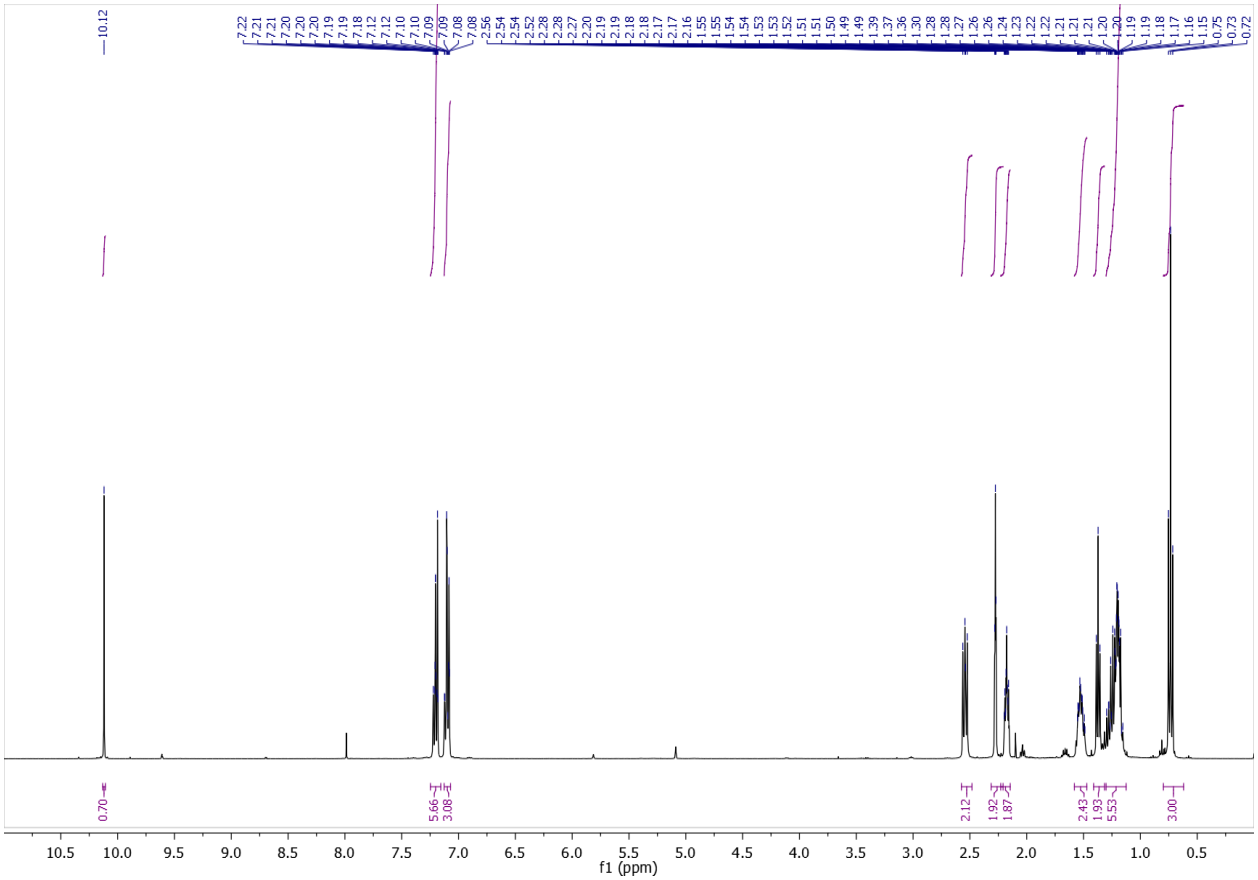
**HRMS (APCI$^+$):** calculated for $C_{19}H_{24}O^{35}Cl$, $[M+H]^{+\bullet}$: 303.15212 found 303.15173 (Δ = -1.26 ppm);

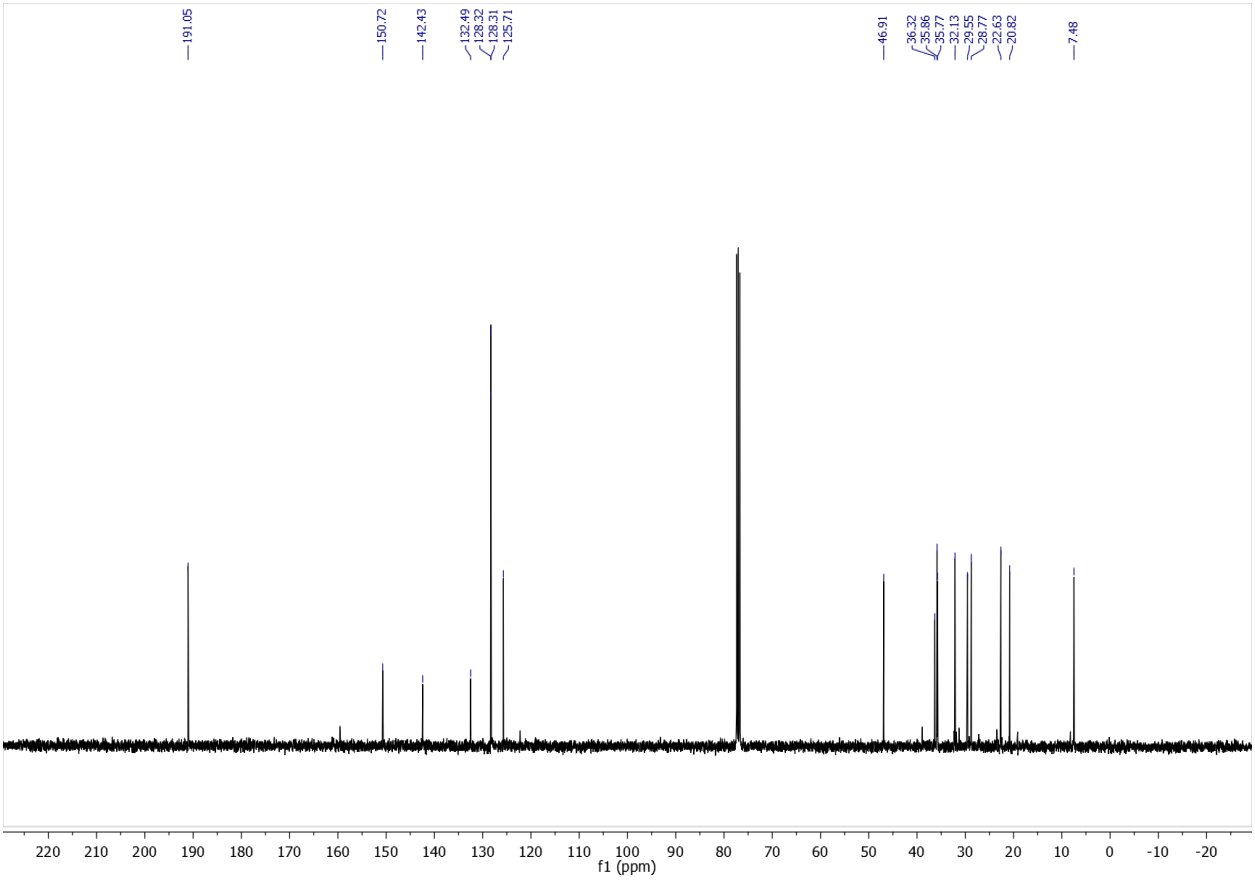
$[\alpha]_D^{25}$ **=** + 13° (*c* = 1.0, $CH_2Cl_2$), based on a sample of 98% *ee*;



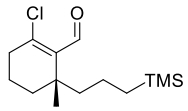



## $^{1}H/^{13}C$ NMR


10.12
7.22 7.21 7.21 7.20 7.20 7.20 7.19 7.19 7.18 7.12 7.12 7.10 7.10 7.09 7.09 7.08 7.08
2.56 2.54 2.54 2.52 2.28 2.28 2.27 2.20 2.19 2.19 2.18 2.18 2.17 2.17 2.16
1.55 1.55 1.54 1.54 1.53 1.53 1.52 1.51 1.51 1.50 1.49 1.49 1.39 1.37 1.36 1.30 1.28 1.28 1.27 1.26 1.26 1.24 1.23 1.22 1.22 1.21 1.21 1.21 1.20 1.20 1.19 1.19 1.18 1.17 1.16 1.15
0.75 0.73 0.72
0.70
5.66
3.08
2.12
1.92
1.87
2.43
1.93
5.53
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


191.05
150.72
142.43
132.49
128.32
128.31
125.71
46.91
36.32
35.86
35.77
32.13
29.55
28.77
22.63
20.82
7.48
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

**(S)-2-chloro-6-methyl-6-(3-(trimethylsilyl)propyl)cyclohex-1-ene-1-carbaldehyde 11**




1,4-addition reaction was conducted according to general procedure B on 0.53 mmol scale and using allyl trimethylsilane as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure E. Flash chromatography (5% $Et_2O$/*n*-pentane) gave the product as a yellow oil (66 mg, 0.24 mmol, 46% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak IF column 250 × 4.6 mm, 1-30% MeOH/$CO_2$ gradient over 5 min, 1.5 mL.min$^{-1}$): *ee* = 96% (minor enantiomer $t_R$ = 1.54 min, major enantiomer $t_R$ = 1.60 min).

**$R_f$** = 0.91 (30% $Et_2O$/*n*-pentane, stains yellow with $KMnO_4$);

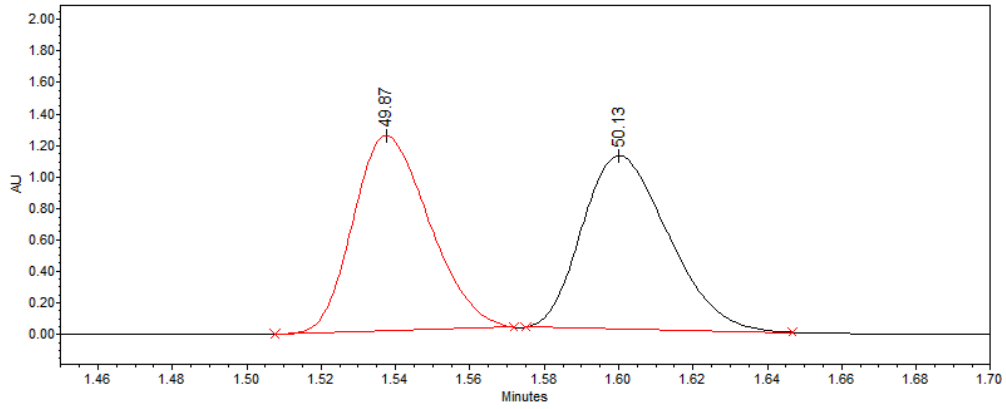
**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 10.20 (s, 1H), 2.46 – 2.22 (m, 2H), 2.32 – 2.25 (m, 2H), 1.44 (dd, J = 7.3, 5.8 Hz, 2H), 1.28 (ddd, J = 6.5, 4.5, 1.6 Hz, 4H), 0.92 (s, 3H), 0.49 – 0.41 (m, 2H), -0.02 (s, 9H) ppm;

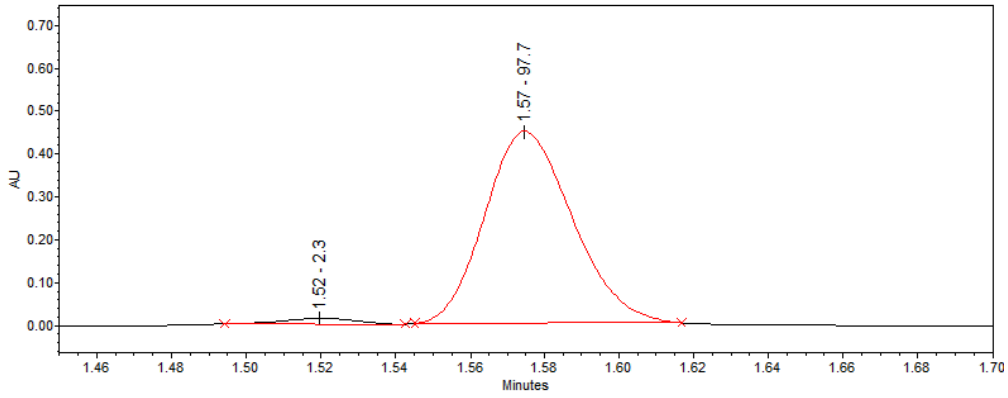
**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 191.2 , 150.7 , 132.5 , 48.5 , 45.6 , 34.2 , 32.0 , 24.4 , 21.3 , 17.9 , 17.6 , -1.4 (3C) ppm;

**FT-IR thin film, neat (ATR):** 2932, 2861, 1681, 1625 cm$^{-1}$;

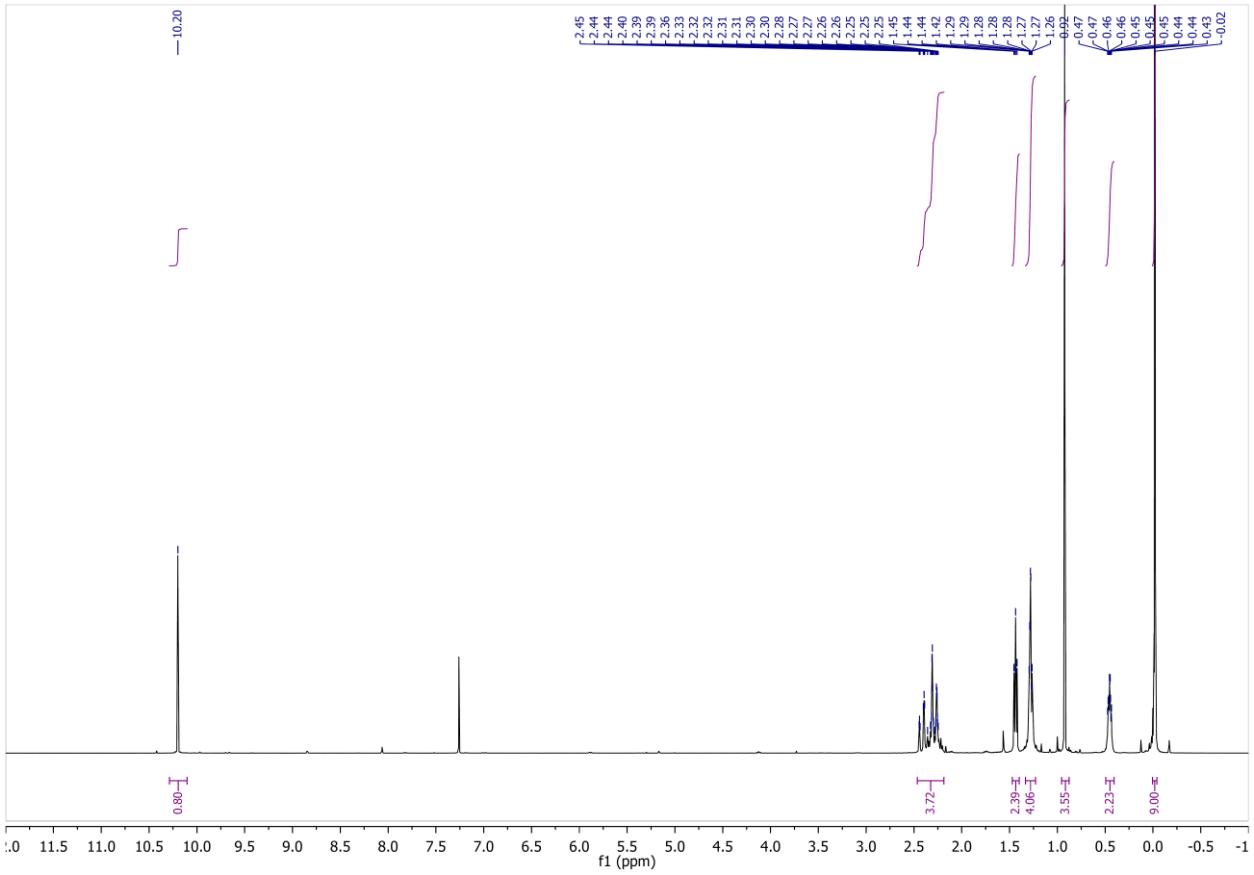
**HRMS (APCI$^-$):** calculated for $C_{14}H_{24}O^{35}Cl^{28}Si$, $[M\text{-}H]^{+\bullet}$: 271.12795 found 271.12872 (Δ = 2.87 ppm);

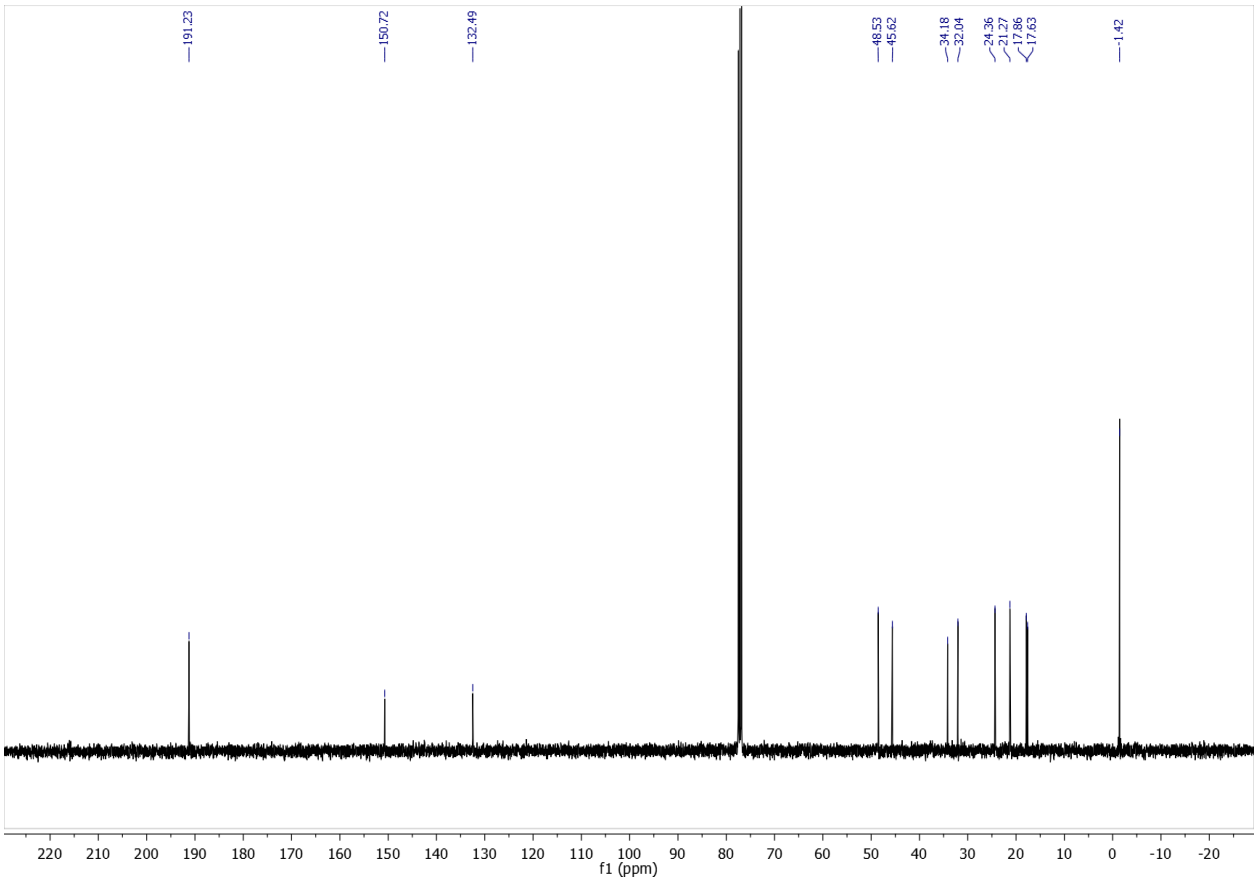
$[\alpha]_D^{25}$ **=** + 20° (*c* = 1.0, $CH_2Cl_2$), based on a sample of 96% *ee*;



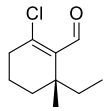



## $^{1}H/^{13}C$ NMR


10.20
0.80
3.72
2.39
4.06
3.55
2.23
9.00
f1 (ppm)


191.23
150.72
132.49
48.53
45.62
34.18
32.04
24.36
21.27
17.86
17.63
-1.42
f1 (ppm)

**(R)-2-chloro-6-ethyl-6-methylcyclohex-1-ene-1-carbaldehyde 12**




1,4-addition reaction was conducted according to general procedure B on 0.5 mmol scale. An ethylene-filled balloon was attached directly to the $Cp_2ZrHCl/CH_2Cl_2$ mixture for the hydrozirconation step. All other procedures remain unchanged. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure E. Flash chromatography (5% $Et_2O$/*n*-pentane) gave the title product as a yellow oil (61 mg, 0.31 mmol, 62% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak IF column 250 × 4.6 mm, 1-30% MeOH/$CO_2$ gradient over 5 min, 1.5 mL.min$^{-1}$): *ee* = 98% (major enantiomer $t_R$ = 2.00 min, minor enantiomer $t_R$ = 1.91 min).

**$R_f$** = 0.60 (30% $Et_2O$/*n*-pentane, stains yellow with $KMnO_4$);

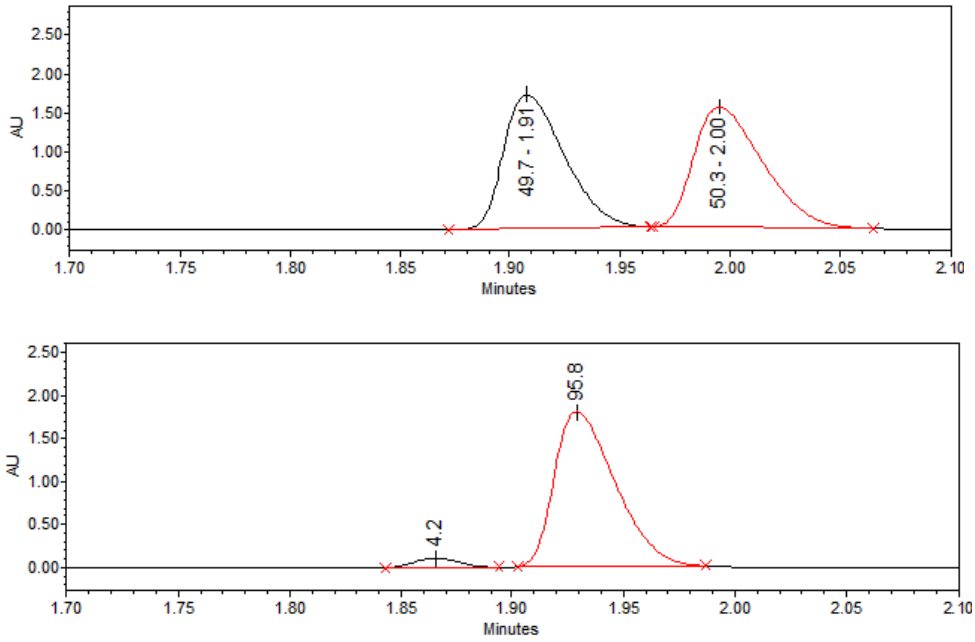
**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 10.20 (s, 1H), 2.44 – 2.20 (m, 2H), 2.33 – 2.23 (m, 2H), 1.43 (dd, J = 7.3, 5.8 Hz, 2H), 1.32 (qd, J = 7.5, 3.8 Hz, 2H), 0.91 (s, 3H), 0.87 (t, J = 7.5 Hz, 3H) ppm;

**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 191.2, 150.7, 132.5, 48.1, 34.0, 33.5, 31.6, 23.8, 21.3, 7.9 ppm;

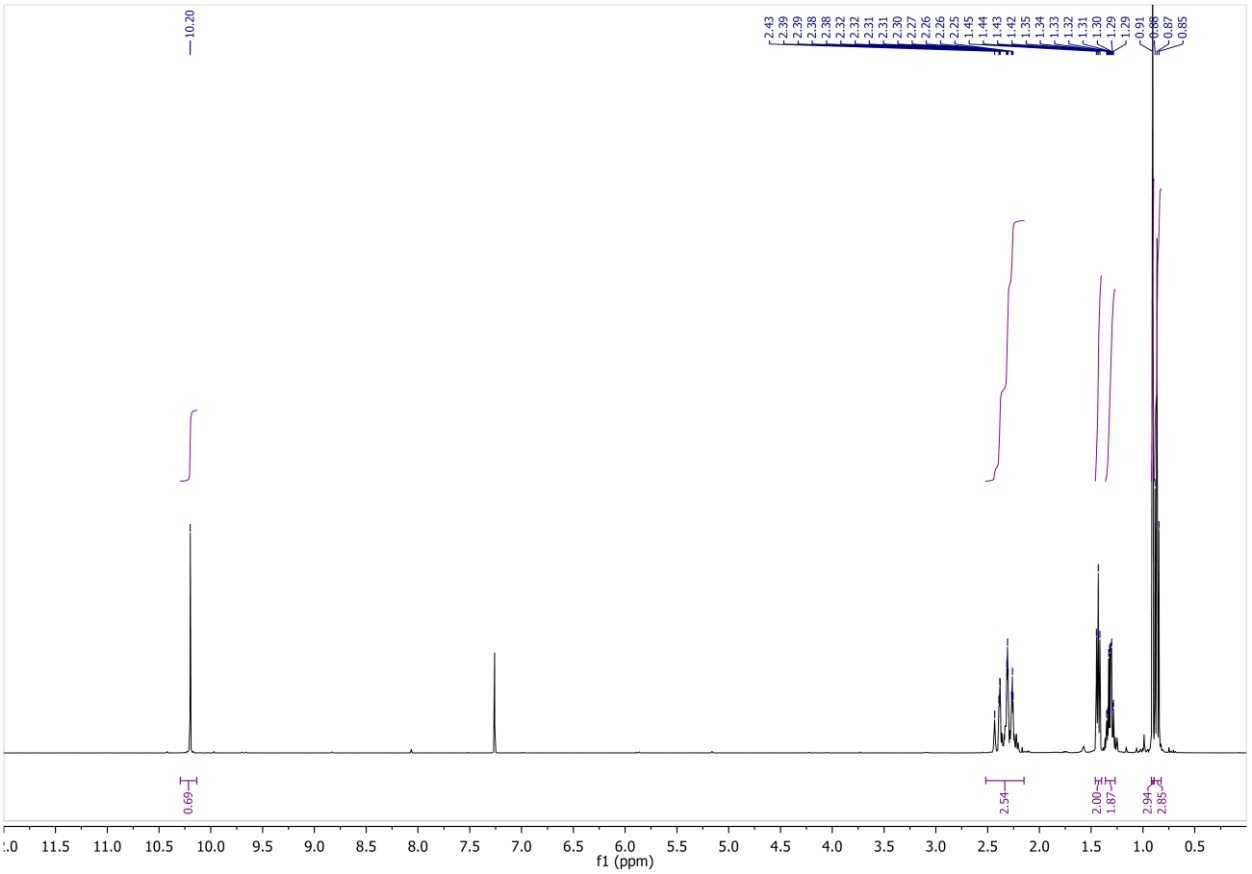
**FT-IR thin film, neat (ATR):** 2964, 2926, 2879, 1678, 1623 cm$^{-1}$;

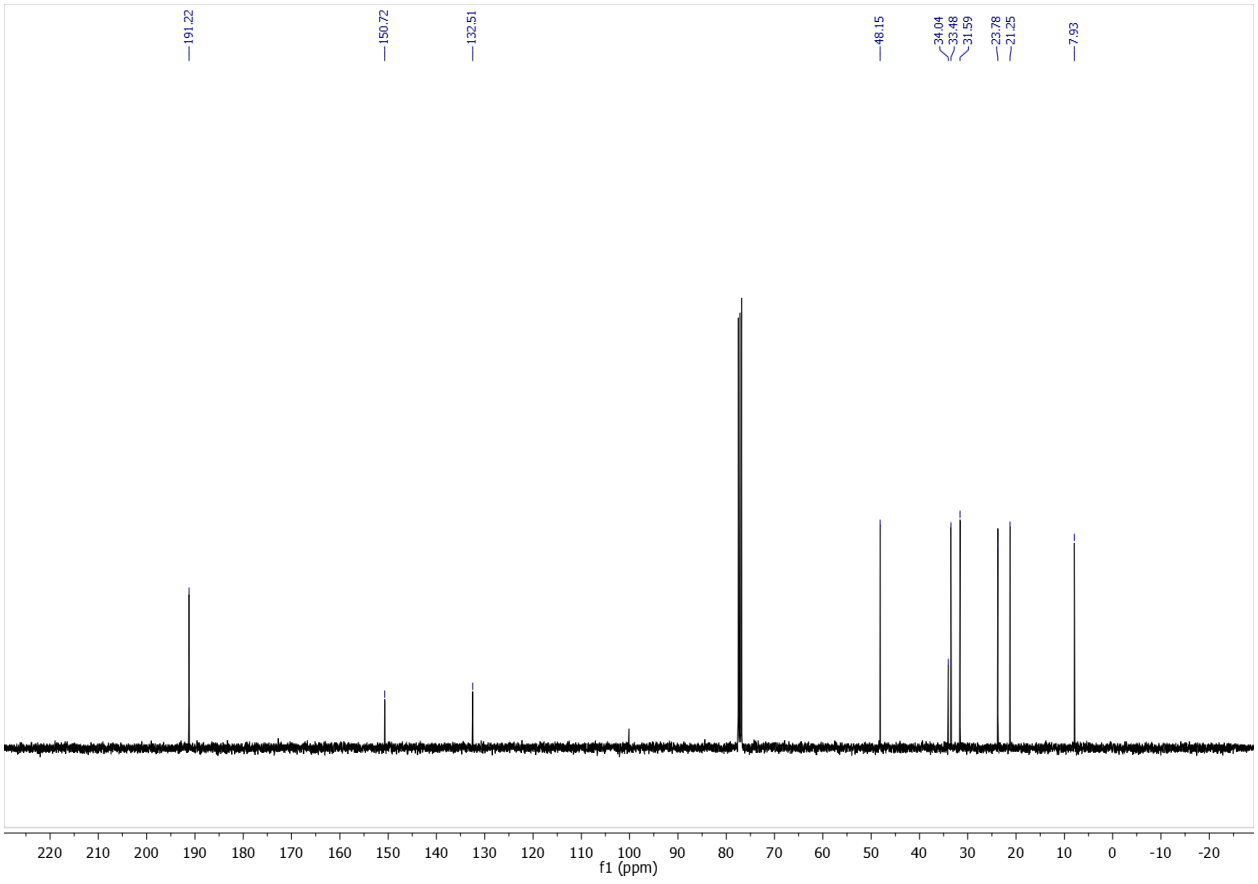
**HRMS (APCI$^+$):** calculated for $C_{10}H_{16}O^{35}Cl$, $[M+H]^{+\bullet}$: 187.08842 found 187.08850 (Δ = 0.44 ppm);

$[\alpha]_D^{25}$ **=** + 14° (*c* = 1.0, $CH_2Cl_2$), based on a sample of 92% *ee*;

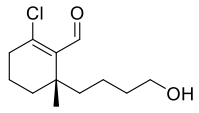


## $^{1}H/^{13}C$ NMR


10.20
2.43
2.39
2.39
2.38
2.38
2.32
2.31
2.31
2.30
2.27
2.26
2.26
2.25
1.45
1.44
1.43
1.42
1.35
1.34
1.33
1.32
1.31
1.30
1.29
1.29
0.91
0.88
0.87
0.85
0.69
2.54
2.00
1.87
2.94
2.85
f1 (ppm)


191.22
150.72
132.51
48.15
34.04
33.48
31.59
23.78
21.25
7.93
f1 (ppm)

**(R)-2-chloro-6-(4-hydroxybutyl)-6-methylcyclohex-1-ene-1-carbaldehyde 13a**




1,4-addition reaction was conducted according to general procedure B on 0.53 mmol scale and using (but-3-en-1-yloxy)(tert-butyl)dimethylsilane **II**[9] as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure E. Flash chromatography (5-20% $Et_2O$/*n*-pentane gradient, silica column) gave the title product as a colourless oil (16 mg, 0.069 mmol) as well as the formate ester **13b** (colourless oil 46 mg, 0.17 mmol). The total yield of the reaction was thus 45%. Enantiomeric excess was determined by comparison with an authentic racemic sample. HPLC (Chiralpak IB column 250 × 4.6 mm, 1% $^{i}$PrOH/*n*-hexane, 1.0 mL.min$^{-1}$): *ee* = 94% (major enantiomer $t_R$ = 13.19 min, minor enantiomer $t_R$ = 12.59 min).

**$R_f$** = 0.54 (30% $Et_2O$/*n*-pentane, stains yellow with $KMnO_4$);

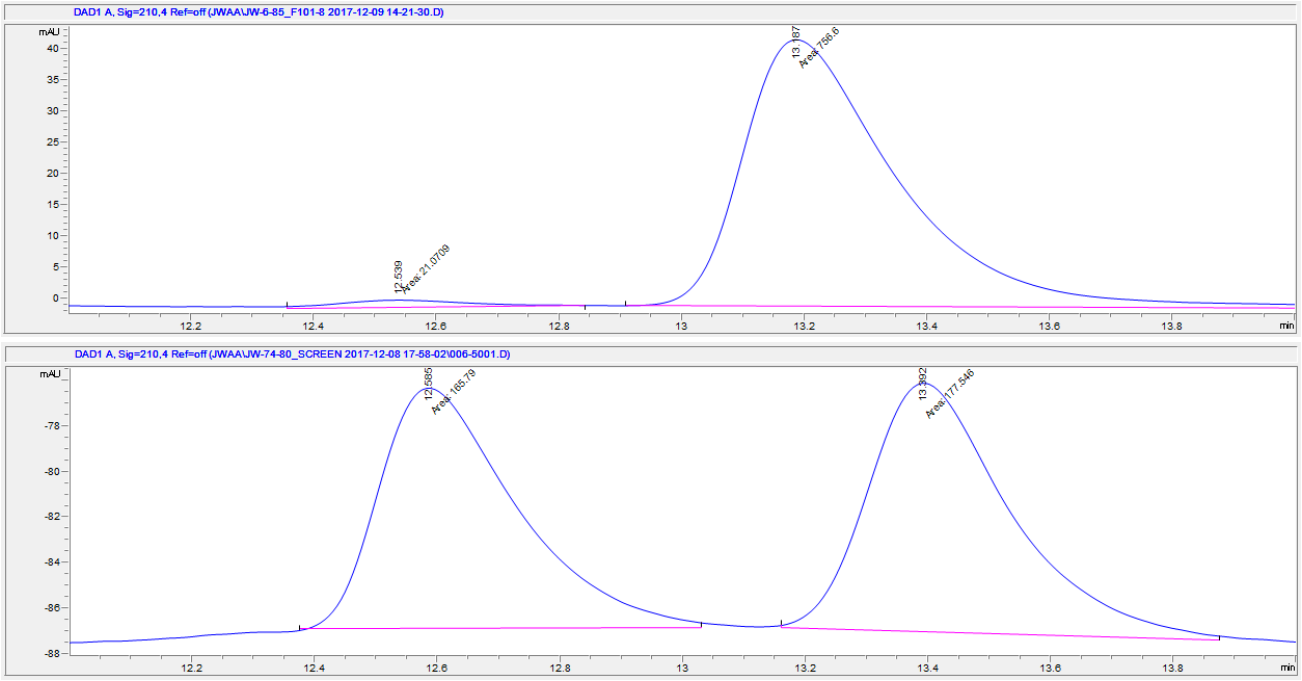
**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 10.29 (s, 1H), 3.64 (t, J = 6.5 Hz, 2H), 2.58 – 2.34 (m, 2H), 2.45 – 2.33 (m, 2H), 1.91 – 1.79 (m, 2H), 1.60 – 1.51 (m, 4H), 1.41 – 1.30 (m, 2H), 1.03 (s, 3H) ppm;

**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 191.1, 150.3, 132.4, 48.4, 45.0, 40.4, 34.0, 33.2, 31.9, 24.3, 21.2, 20.9 ppm;

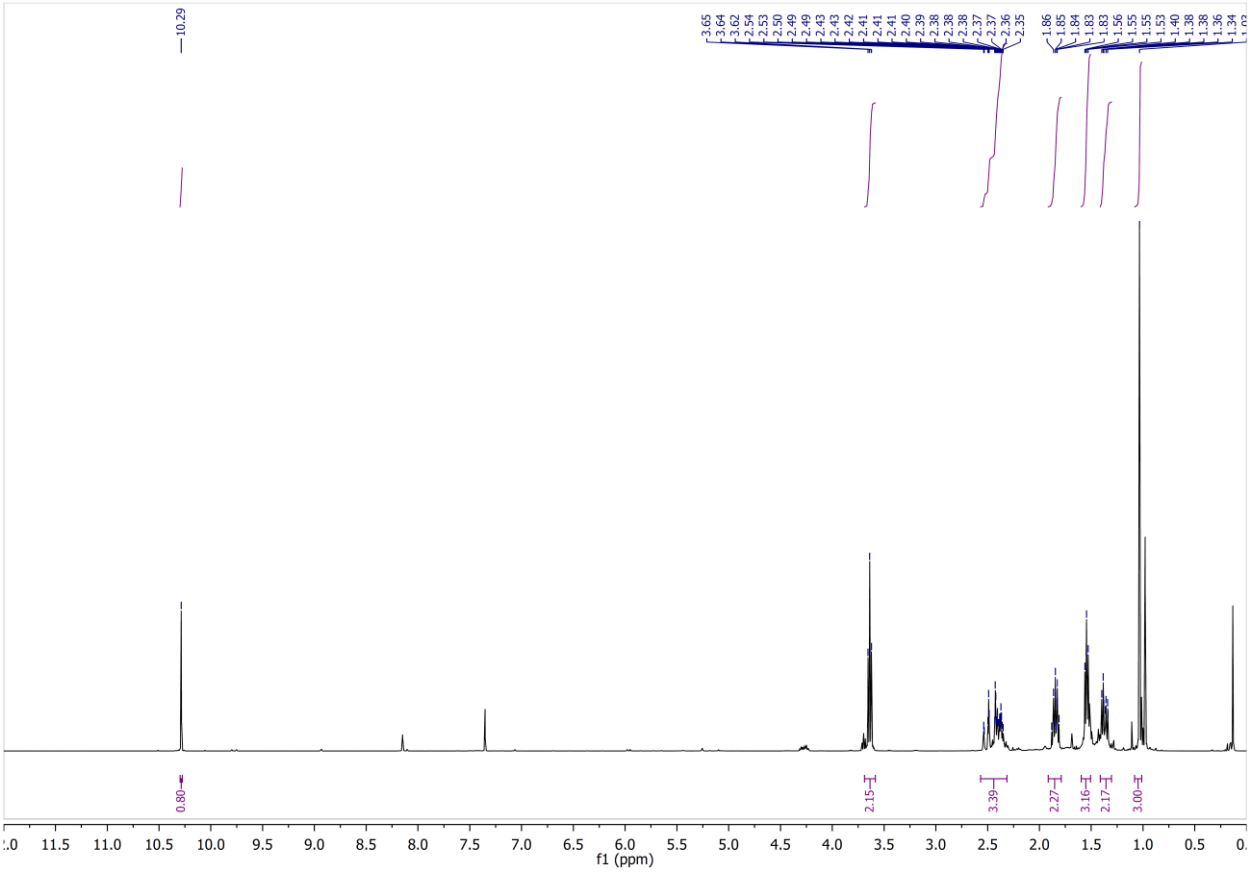
**FT-IR thin film, neat (ATR):** 2931, 2858, 1678, 1624, 1229 cm$^{-1}$;

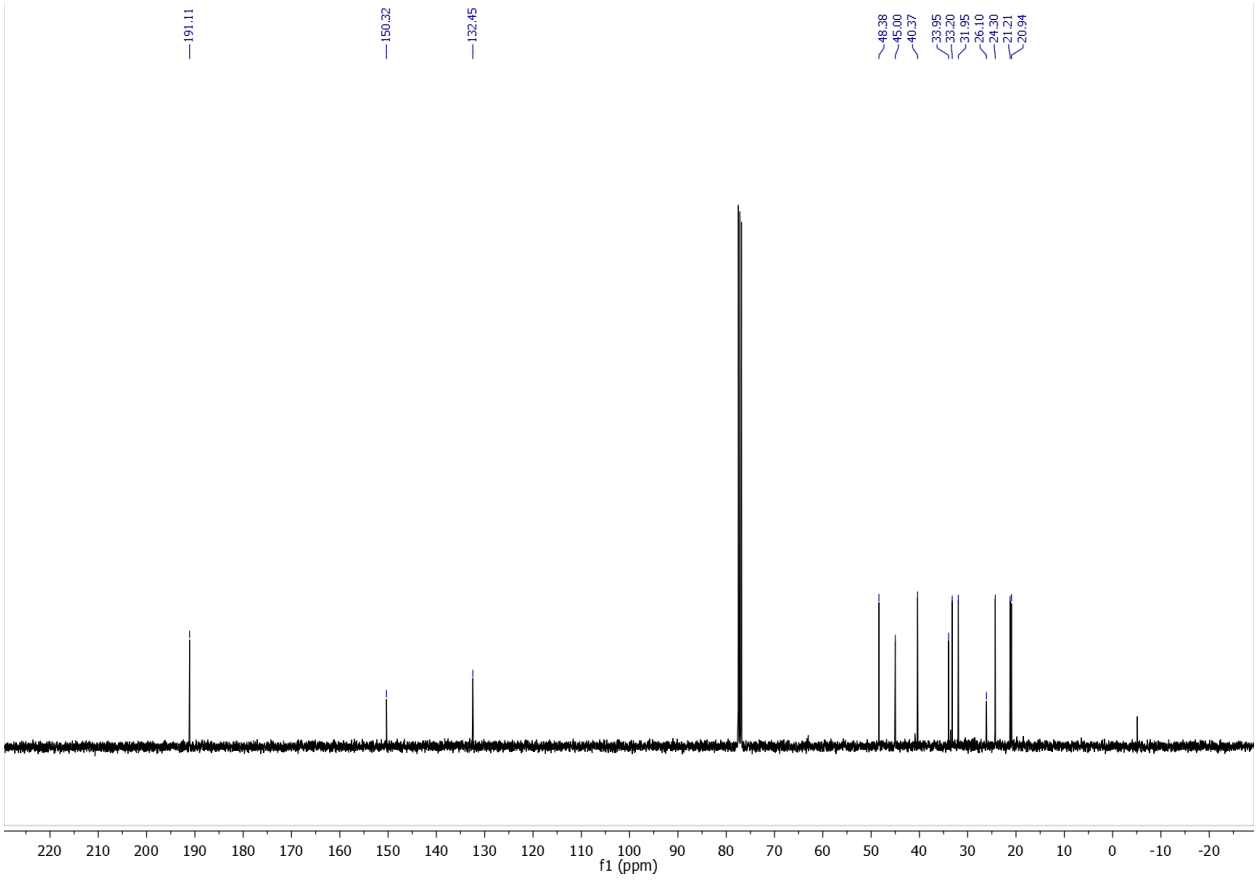
**HRMS (APCI$^+$):** calculated for $C_{13}H_{24}O_3{}^{35}Cl$, $[M+CH_3OH+H]^{+\bullet}$: 263.14085 found 263.14064 (Δ = 0.78 ppm);

$[\alpha]_D^{25}$ **=** + 18º (*c* = 1.0, $CH_2Cl_2$), based on a sample of 94% *ee*;

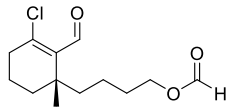


## $^{1}H/^{13}C$ NMR


10.29
3.65
3.64
3.62
2.54
2.53
2.50
2.49
2.49
2.43
2.43
2.42
2.41
2.41
2.41
2.40
2.39
2.38
2.38
2.38
2.37
2.37
2.36
2.35
1.86
1.85
1.84
1.83
1.83
1.56
1.55
1.55
1.53
1.40
1.38
1.38
1.36
1.34
0.80
2.15
3.39
2.27
3.16
2.17
3.00
f1 (ppm)


191.11
150.32
132.45
48.38
45.00
40.37
33.95
33.20
31.95
26.10
24.30
21.21
20.94
f1 (ppm)

**(R)-4-(3-chloro-2-formyl-1-methylcyclohex-2-en-1-yl)butyl formate 13b**



The product was co-isolated with compound **13a**.

**$R_f$** = 0.32 (30% $Et_2O$/*n*-pentane, stains yellow with $KMnO_4$);

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 10.19 (s, 1H), 8.06 (d, J = 0.8 Hz, 1H), 4.17 (td, J = 6.6, 0.8 Hz, 2H), 2.46 – 2.25 (m, 2H), 2.35 – 2.23 (m, 2H), 1.65 (dq, J = 7.8, 6.6 Hz, 2H), 1.45 (dd, J = 7.2, 5.9 Hz, 2H), 1.40 – 1.24 (m, 4H), 0.93 (s, 3H) ppm;

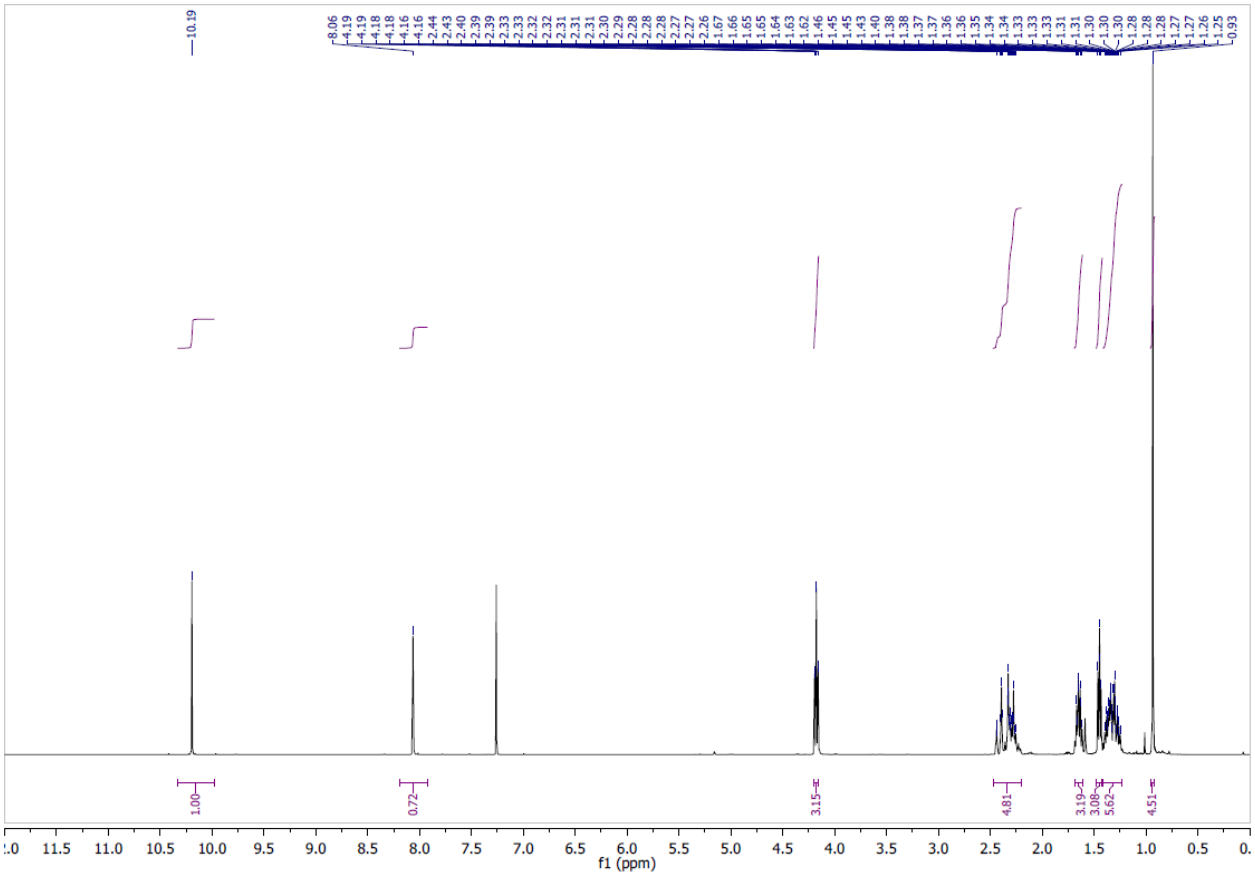
**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 191.1, 161.2, 150.3, 132.4, 63.9, 48.4, 40.8, 33.9, 31.9, 29.3, 24.3, 21.2, 20.0 ppm;

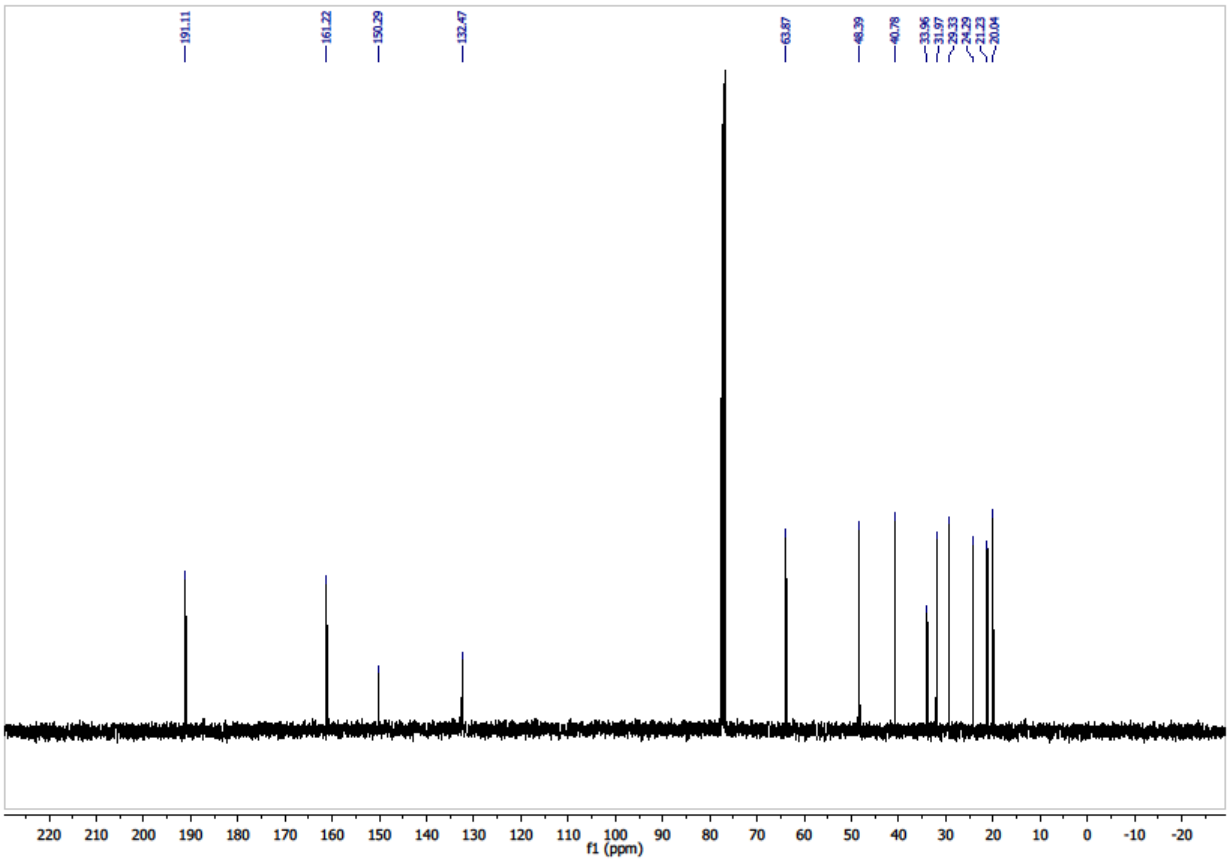
**FT-IR thin film, neat (ATR):** 2933, 2870, 1724, 1677, 1624, 1170 $cm^{-1}$;

**HRMS ($ESI^+$):** calculated for $C_{13}H_{19}O_3{}^{35}Cl^{23}Na$, $[M+Na]^{+\bullet}$: 281.09149 found 281.09143 (Δ = -0.22 ppm);

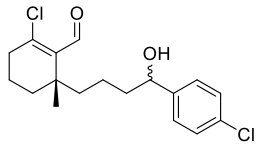
$[\alpha]_D^{25}$ **=** + 22º (*c* = 0.78, $CH_2Cl_2$), based on a sample of 94% *ee*;

**$^{1}H/^{13}C$ NMR**


10.19
8.06
4.19
4.19
4.18
4.18
4.16
4.16
2.44
2.43
2.40
2.39
2.39
2.33
2.33
2.32
2.31
2.31
2.30
2.29
2.28
2.28
2.28
2.27
2.27
2.26
1.67
1.66
1.65
1.64
1.63
1.62
1.46
1.45
1.45
1.43
1.40
1.38
1.38
1.37
1.36
1.36
1.35
1.34
1.34
1.33
1.33
1.31
1.31
1.30
1.30
1.30
1.28
1.28
1.28
1.27
1.27
1.26
1.25
0.93
1.00
0.72
3.15
4.81
3.19
3.08
5.62
4.51
f1 (ppm)


191.11
161.22
150.29
132.47
63.87
48.39
40.78
33.96
31.97
29.33
24.29
21.23
20.04
f1 (ppm)

**(6R)-2-chloro-6-(4-(4-chlorophenyl)-4-hydroxybutyl)-6-methylcyclohex-1-ene-1-carbaldehyde 14**




1,4-addition reaction was conducted according to general procedure B on 0.53 mmol scale and using *tert*-butyl((1-(4-chlorophenyl)but-3-en-1-yl)oxy)dimethylsilane **III**[6] as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure E. Flash chromatography (5% $Et_2O$/*n*-pentane gradient, silica column) gave the title product as a mixture of diastereomers (103 mg yellow oil, 0.30 mmol, 57% yield). Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step, hydrolyzing the *tert*-butyldimethylsilyl group using TBAF and submitting it to HPLC analysis according to the conditions reported by Sidera et. al.[6] *ee* = 90%.

**$R_f$** = 0.52 (30% $Et_2O$/*n*-pentane, stains yellow with $KMnO_4$);

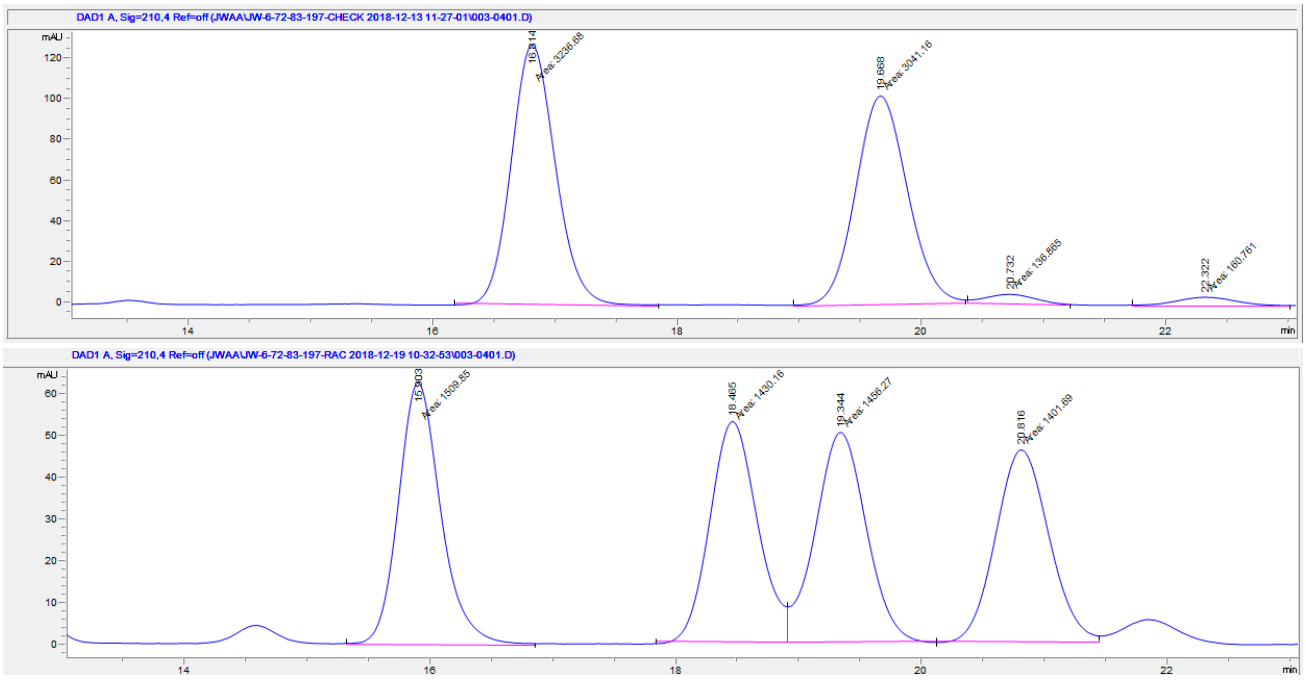
**$^1$H NMR (500 MHz, $CDCl_3$):** $\delta$ 10.22 (s, 1H), 4.84 (t, J = 7.4 Hz, 1H), 2.45 – 2.26 (m, 3H), 2.33 – 2.23 (m, 3H), 2.14 – 1.91 (m, 3H), 1.57 – 1.41 (m, 4H), 1.40 – 1.21 (m, 4H), 0.94 (s, 3H) ppm;

**$^{13}$C NMR (126 MHz, $CDCl_3$)** $\delta$ 191.1, 150.2, 140.4, 140.4, 134.2, 132.4, 129.0 (2C), 128.4 (2C), 62.7, 48.3, 40.6, 40.4, 40.3, 33.9, 31.9, 31.9, 24.3, 24.3, 21.2 ppm;

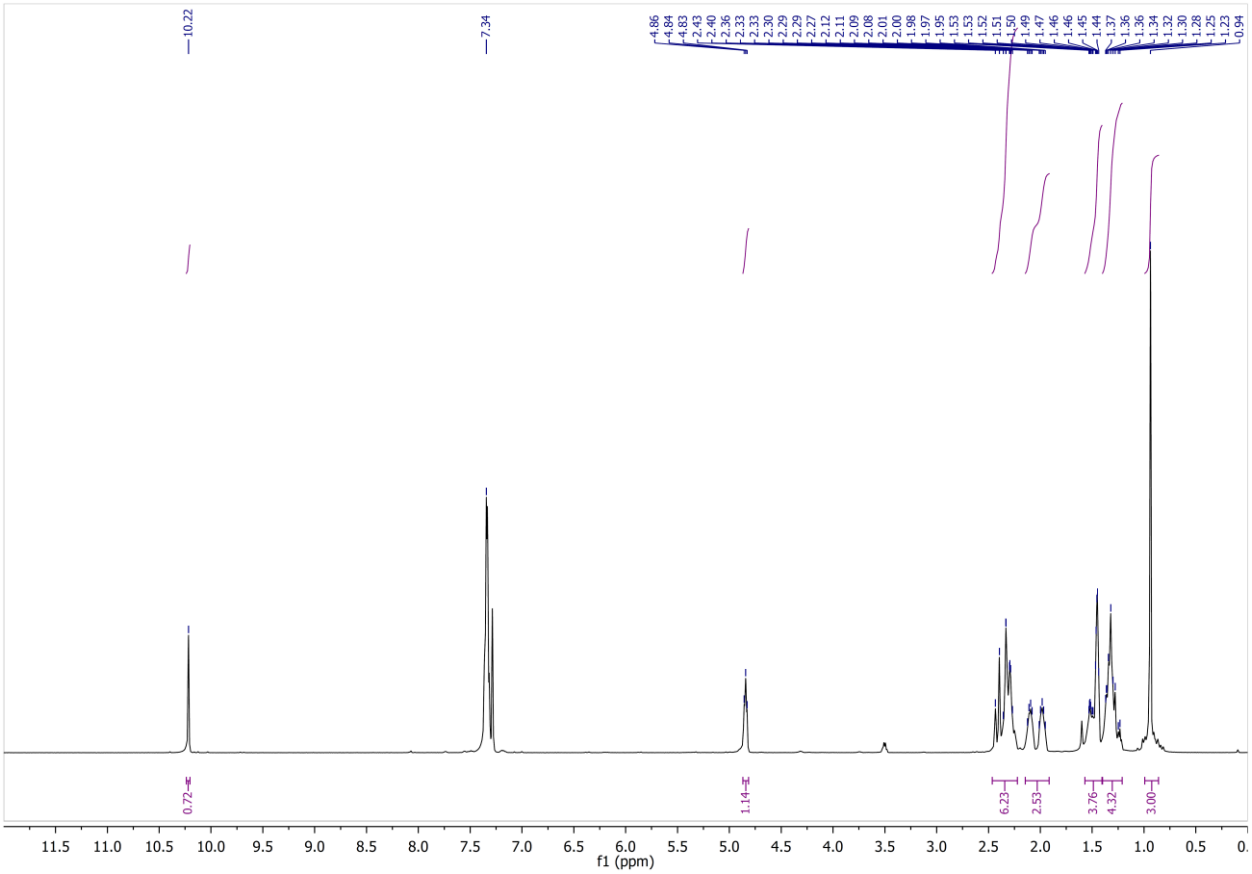
**FT-IR thin film, neat (ATR):** 2930, 2869, 1677, 1624, 1493, 1230, 1092, 1015, 821 $cm^{-1}$;

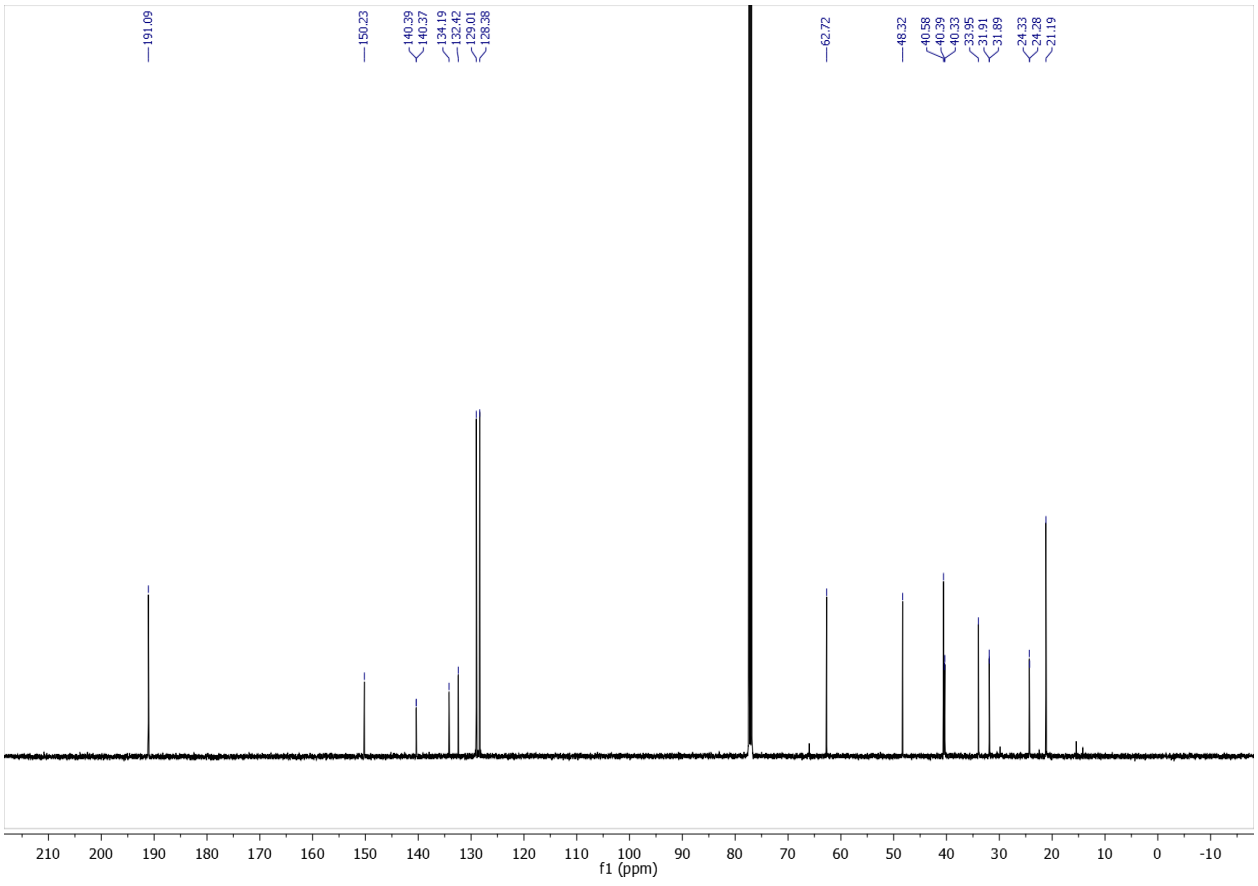
**HRMS (APCI$^+$):** calculated for $C_{18}H_{21}O^{35}Cl_2$, $[M\text{-}OH]^{+\bullet}$: 323.09640 found 323.09638 (Δ = 0.05 ppm);

$[\alpha]_D^{25}$ **=** + 13º (*c* = 1.0, $CH_2Cl_2$), based on a sample of 90% *ee*;

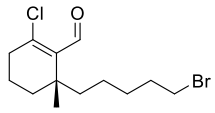


## $^{1}H/^{13}C$ NMR


10.22
7.34
4.86
4.84
4.83
2.43
2.40
2.36
2.33
2.33
2.30
2.29
2.29
2.27
2.12
2.11
2.09
2.08
2.01
2.00
1.98
1.97
1.95
1.53
1.52
1.51
1.50
1.49
1.47
1.46
1.46
1.45
1.44
1.37
1.36
1.36
1.34
1.32
1.30
1.28
1.25
1.23
0.94
0.72
1.14
6.23
2.53
3.76
4.32
3.00
f1 (ppm)


191.09
150.23
140.39
140.37
134.19
132.42
129.01
128.38
62.72
48.32
40.58
40.39
40.33
33.95
31.91
31.89
24.33
24.28
21.19
f1 (ppm)

**(R)-6-(5-bromopentyl)-2-chloro-6-methylcyclohex-1-ene-1-carbaldehyde 15**




1,4-addition reaction was conducted according to general procedure B on 0.53 mmol scale and using 5-bromo-1-pentene as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure E. Flash chromatography (0–5% $Et_2O$/*n*-pentane) gave the title product as a yellow oil (78 mg, 0.25 mmol, 48% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak IA column 250 × 4.6 mm, 1-30% MeOH/$CO_2$ gradient over 5 min, 1.5 mL.min$^{-1}$): *ee* = 80% (major enantiomer $t_R$ = 2.91 min, minor enantiomer $t_R$ = 2.49 min).

**$R_f$** = 0.64 (30% $Et_2O$/*n*-pentane, stains yellow with $KMnO_4$);

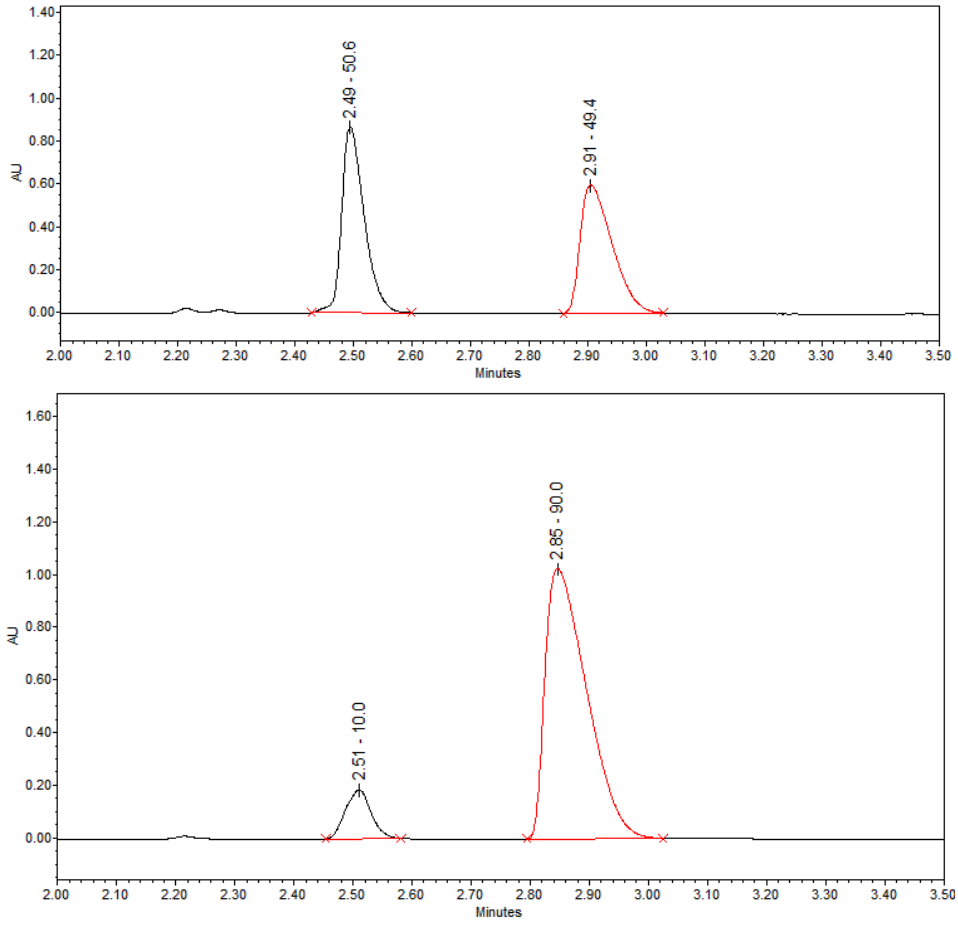
**$^1$H NMR (500 MHz, $CDCl_3$):** $\delta$ 10.20 (s, 1H), 3.40 (t, J = 6.8 Hz, 2H), 2.45 – 2.21 (m, 4H), 1.91 – 1.82 (m, 2H), 1.48 – 1.37 (m, 4H), 1.35 – 1.24 (m, 4H), 0.93 (s, 3H) ppm;

**$^3$C NMR (126 MHz, $CDCl_3$)** $\delta$ 191.2, 150.5, 132.4, 48.5, 41.0, 33.9, 33.9, 32.85, 32.0, 29.0, 24.4, 22.8, 21.2 ppm;

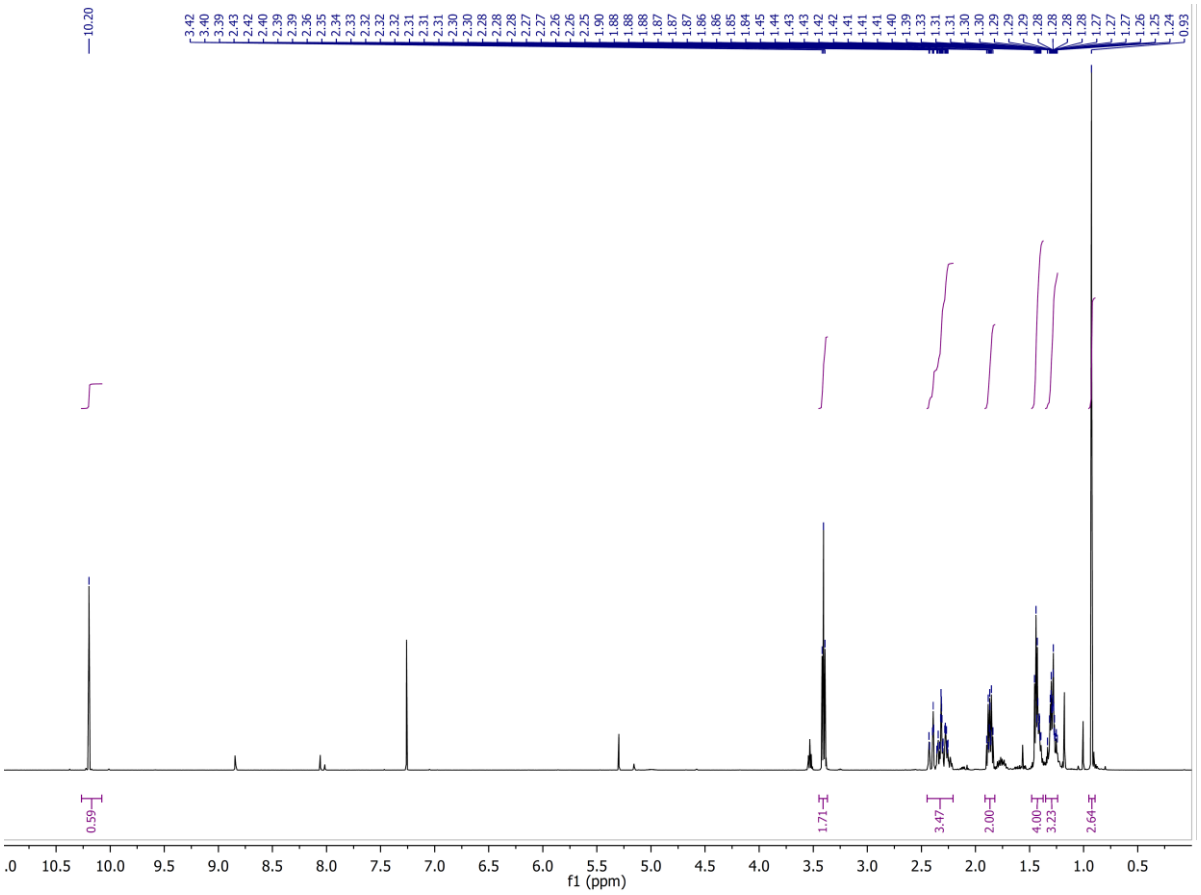
**FT-IR thin film, neat (ATR):** 2933, 2858, 1678, 1624, 1228 cm$^{-1}$;

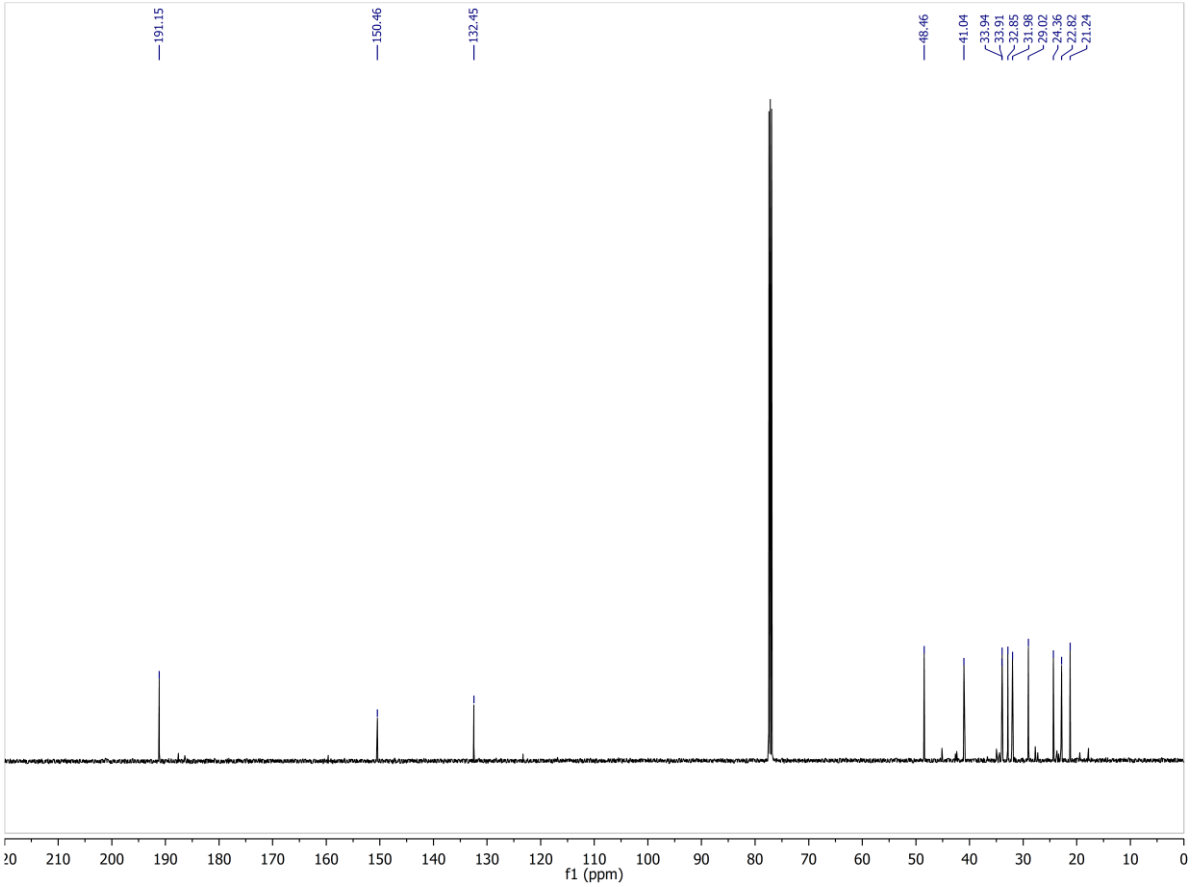
**HRMS (ESI$^+$):** calculated for $C_{13}H_{21}O^{79}Br^{35}Cl$, $[M+H]^{+\bullet}$: 307.04588 found 307.04605 (Δ = 0.55 ppm);

$[\alpha]_D^{25}$ **=** + 17° (*c* = 1.0, $CH_2Cl_2$), based on a sample of 80% *ee*;

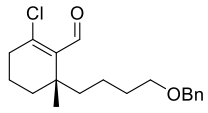


## $^{1}H/^{13}C$ NMR


10.20
0.59
1.71
3.47
2.00
4.00
3.23
2.64
f1 (ppm)


191.15
150.46
132.45
48.46
41.04
33.94
33.91
32.85
31.98
29.02
24.36
22.82
21.24
f1 (ppm)

**(R)-6-(4-(benzyloxy)butyl)-2-chloro-6-methylcyclohex-1-ene-1-carbaldehyde 16**




1,4-addition reaction was conducted according to general procedure B on 0.53 mmol scale and using ((but-3-en-1-yloxy)methyl)benzene **IV**[10] as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure E. Flash chromatography (5% $Et_2O$/*n*-pentane) gave the title product as a yellow oil (77 mg, 0.23 mmol, 43% yield). Enantiomeric excess was determined by taking an aliquot of the reaction mixture prior to the trapping step and submitting it to HPLC analysis using the conditions reported by Sidera et. al.[6] *ee* = 86%.

**$R_f$** = 0.55 (30% $Et_2O$/*n*-pentane, stains yellow with $KMnO_4$);

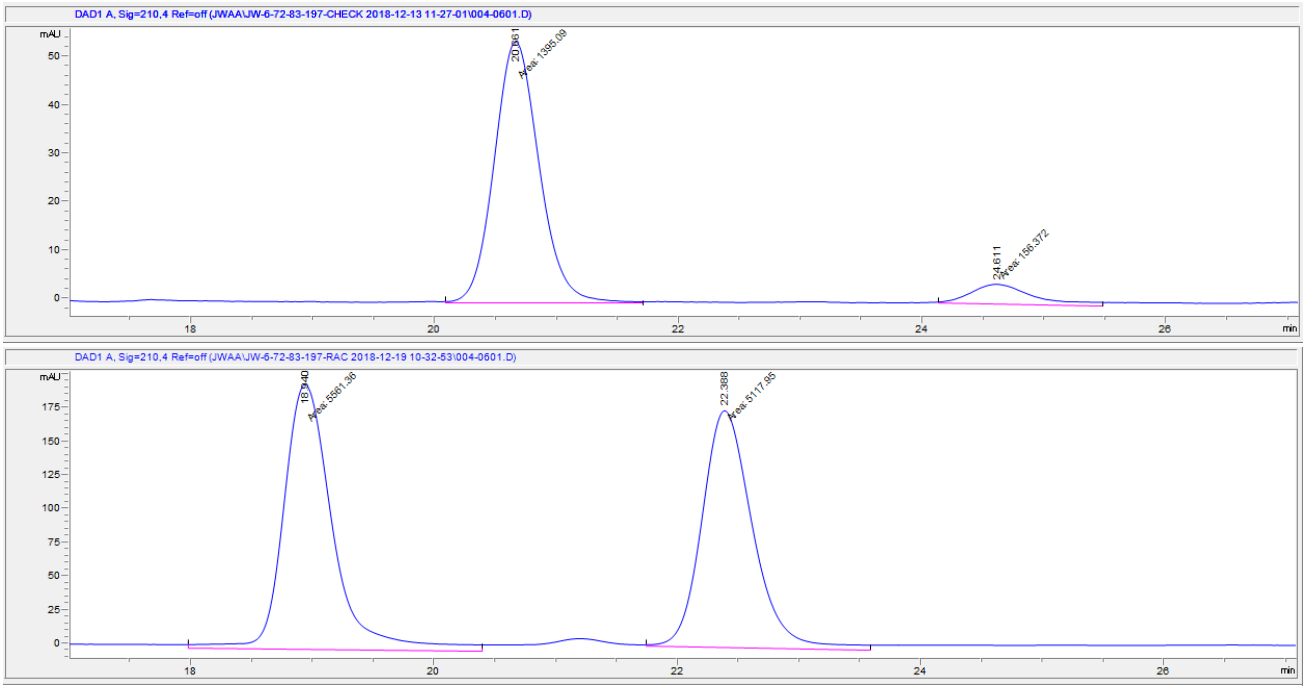
**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 10.12 (s, 1H), 7.31 – 7.26 (m, 3H), 7.23 – 7.17 (m, 2H), 4.43 (s, 2H), 3.40 (dd, J = 6.8, 5.8 Hz, 2H), 2.39 – 2.30 (m, 2H), 2.28 – 2.11 (m, 2H), 1.57 – 1.46 (m, 2H), 1.36 (dd, J = 7.1, 5.9 Hz, 2H), 1.32 – 1.24 (m, 2H), 1.23 – 1.17 (m, 2H), 0.85 (s, 3H) ppm;

**$^3$C NMR (101 MHz, $CDCl_3$)** $\delta$ 191.2, 150.6, 138.7, 132.5, 128.5 (2C), 127.8 (2C), 127.7, 73.1, 70.3, 48.5, 41.1, 34.0, 32.0, 30.6, 24.3, 21.2, 20.3 ppm;

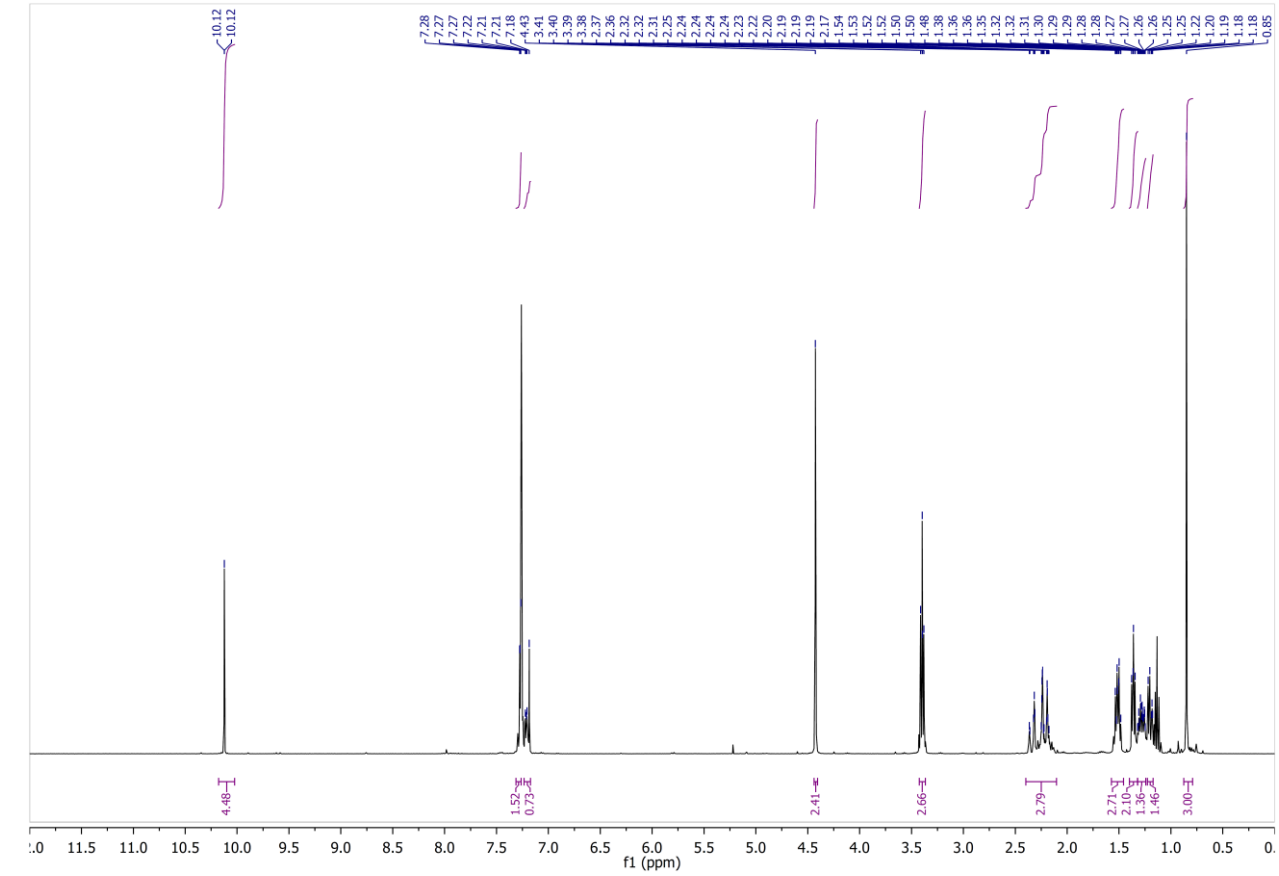
**FT-IR thin film, neat (ATR):** 2934, 2857, 1678, 1624, 1103 $cm^{-1}$;

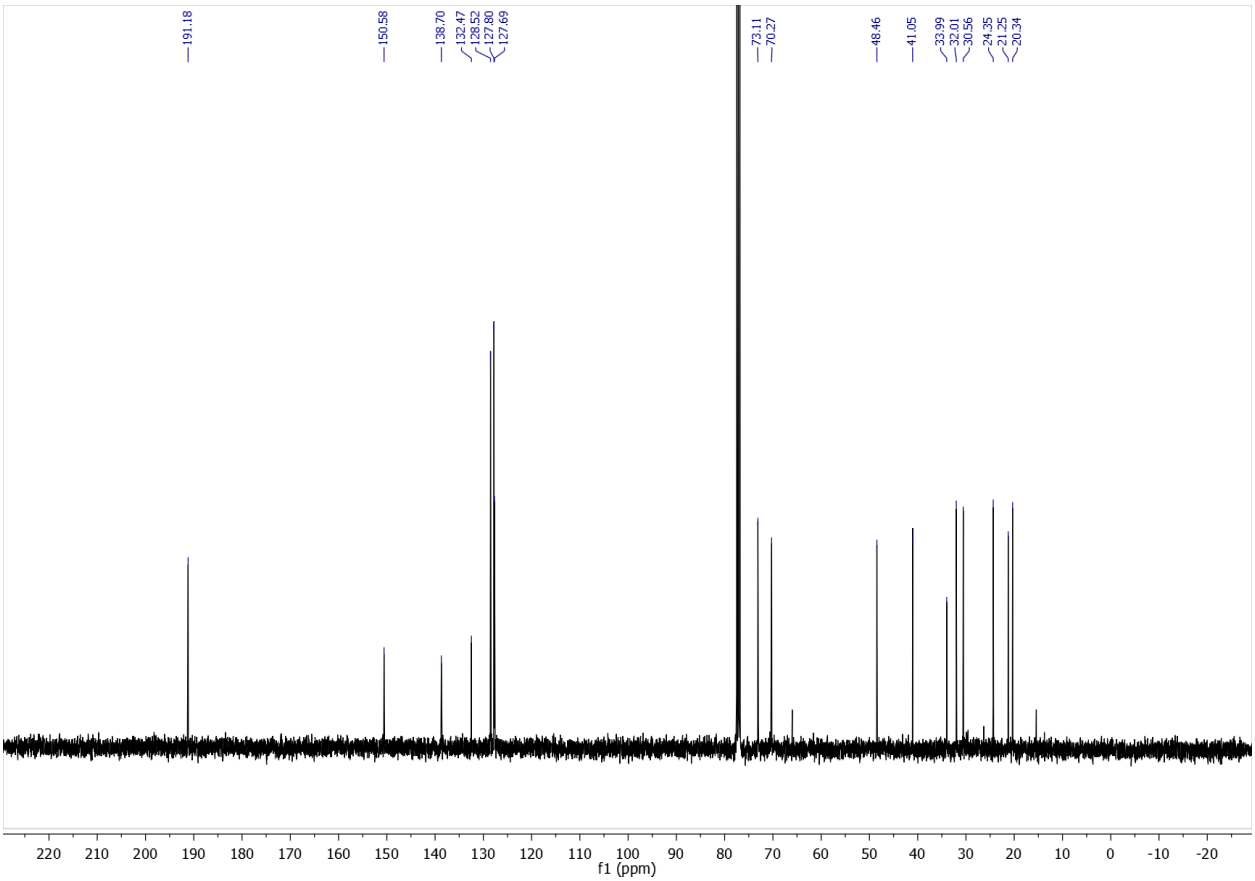
**HRMS ($ESI^+$):** calculated for $C_{19}H_{25}O_2{}^{35}Cl^{23}Na$, $[M+Na]^{+\bullet}$: 343.14353 found 343.14355 ($\Delta$ = 0.08 ppm);

$[\alpha]_D^{25}$ **=** + 12° (*c* = 1.0, $CH_2Cl_2$), based on a sample of 86% *ee*;

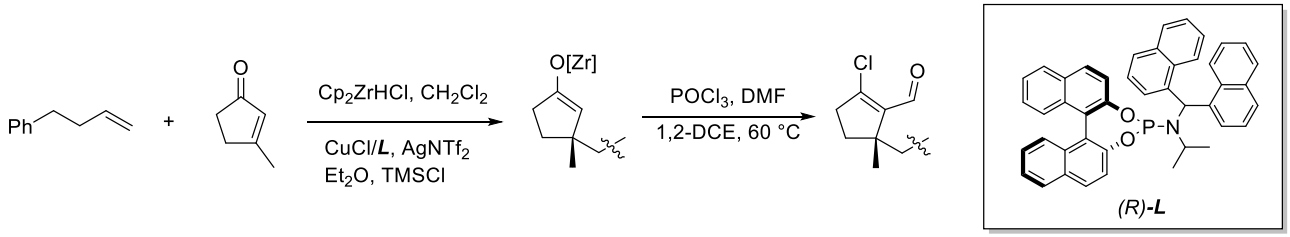


## $^{1}H/^{13}C$ NMR


10.12
10.12
7.28
7.27
7.27
7.22
7.21
7.21
7.18
4.43
3.41
3.40
3.39
3.38
2.37
2.36
2.32
2.32
2.31
2.25
2.24
2.24
2.24
2.23
2.22
2.20
2.19
2.19
2.19
2.17
1.54
1.53
1.52
1.52
1.50
1.50
1.48
1.38
1.36
1.36
1.35
1.32
1.32
1.31
1.30
1.29
1.29
1.28
1.28
1.27
1.27
1.26
1.26
1.25
1.25
1.22
1.20
1.19
1.18
1.18
0.85
4.48
1.52
0.73
2.41
2.66
2.79
2.71
2.10
1.36
1.46
3.00
f1 (ppm)


191.18
150.58
138.70
132.47
129.52
127.80
127.69
73.11
70.27
48.46
41.05
33.99
32.01
30.56
24.35
21.25
20.34
f1 (ppm)

**(R)-2-chloro-5-methyl-5-(4-phenylbutyl)cyclopent-1-ene-1-carbaldehyde 17**




The 1,4-addition reaction was performed according to a literature procedure.[7] CuCl (4.0 mg, 0.040 mmol, 0.10 mol equiv) and then ligand **L2** (28 mg, 0.044 mmol, 0.11 mol equiv) were added to a 5 mL round bottom flask equipped with a rubber septum and stirrer bar (flask **A**). Three cycles of vacuum and back filling with $N_2$ were then performed after which $Et_2O$ (2.0 mL) was added by syringe and the solution allowed to stir for one hour in a darkened environment. Concurrently, $Cp_2ZrHCl$ (206 mg, 0.798 mmol, 2.0 mol equiv) was added to a separate 5 mL round bottom flask equipped with a rubber septum and stirrer bar (flask **B**). Three cycles of vacuum and back filling with $N_2$ were then performed, after which dry $CH_2Cl_2$ (0.4 mL) and then alkene (0.15 mL, 1.0 mmol, 2.5 mol equiv) were added. After stirring for one hour, a clear orange solution was obtained.

Silver bis(trifluoromethanesulfonyl)imide (22 mg, 0.057 mmol, 0.14 mol equiv) was tipped into flask **A** in one portion (minimizing exposure to the atmosphere). After stirring for 10 minutes, the solution from flask **A** was then filtered (using a syringe filter) into flask **B** over a period of one minute. The resulting solution became dark within 10 seconds. After stirring for 20 minutes, chlorotrimethylsilane (0.25 mL, $\rho$ = 0.86 g.mL$^{-1}$, 2.0 mmol, 4.9 mol equiv) was added in one portion then 3-methyl-2-cyclopentenone was added at a rate of 1 drop every 2 seconds (40 $\mu$L, $\rho$ = 0.97 g.mL$^{-1}$, 0.40 mmol, 1.0 mol equiv). The reaction flask was then wrapped in foil and stirred at room temperature for 17 hours or until the reaction was complete, as monitored by TLC. At this point, the reaction contents were subjected to trapping procedure B with quantities scaled appropriately (0.40 mmol scale). Flash chromatography (5% $Et_2O$/*n*-pentane) gave the title product as a colourless oil (45 mg, 0.16 mmol, 41% yield). Enantiomeric excess determined by taking an aliquot of the reaction mixture prior to trapping and submitting it to HPLC analysis.[7] *ee* = 90%.

**$R_f$** = 0.64 (30% $Et_2O$/*n*-pentane, stains yellow with $KMnO_4$);

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 9.91 (s, 1H), 7.24 – 7.18 (m, 2H), 7.13 – 7.07 (m, 3H), 2.58 – 2.50 (m, 2H), 2.68 – 2.37 (m, 2H), 2.38 – 2.19 (m, 2H), 1.59 – 1.48 (m, 2H), 1.40 – 1.33 (m, 2H), 1.28 – 1.16 (m, 2H), 1.01 (s, 3H) ppm;

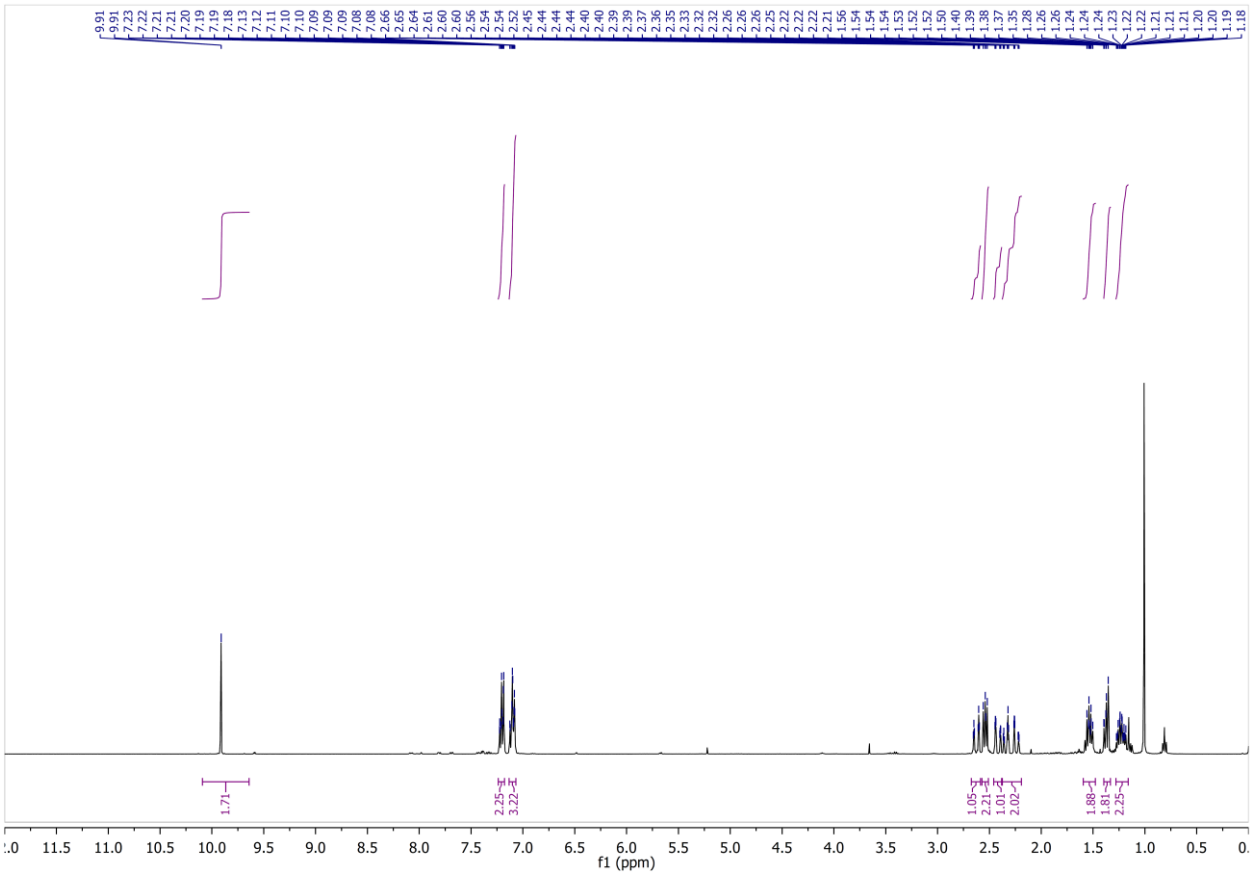
**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 187.9, 149.3, 142.4, 136.2, 128.3 (2C), 128.3 (2C), 125.7, 53.3, 42.1, 41.8, 39.7, 35.9, 32.0, 27.3, 24.6 ppm;

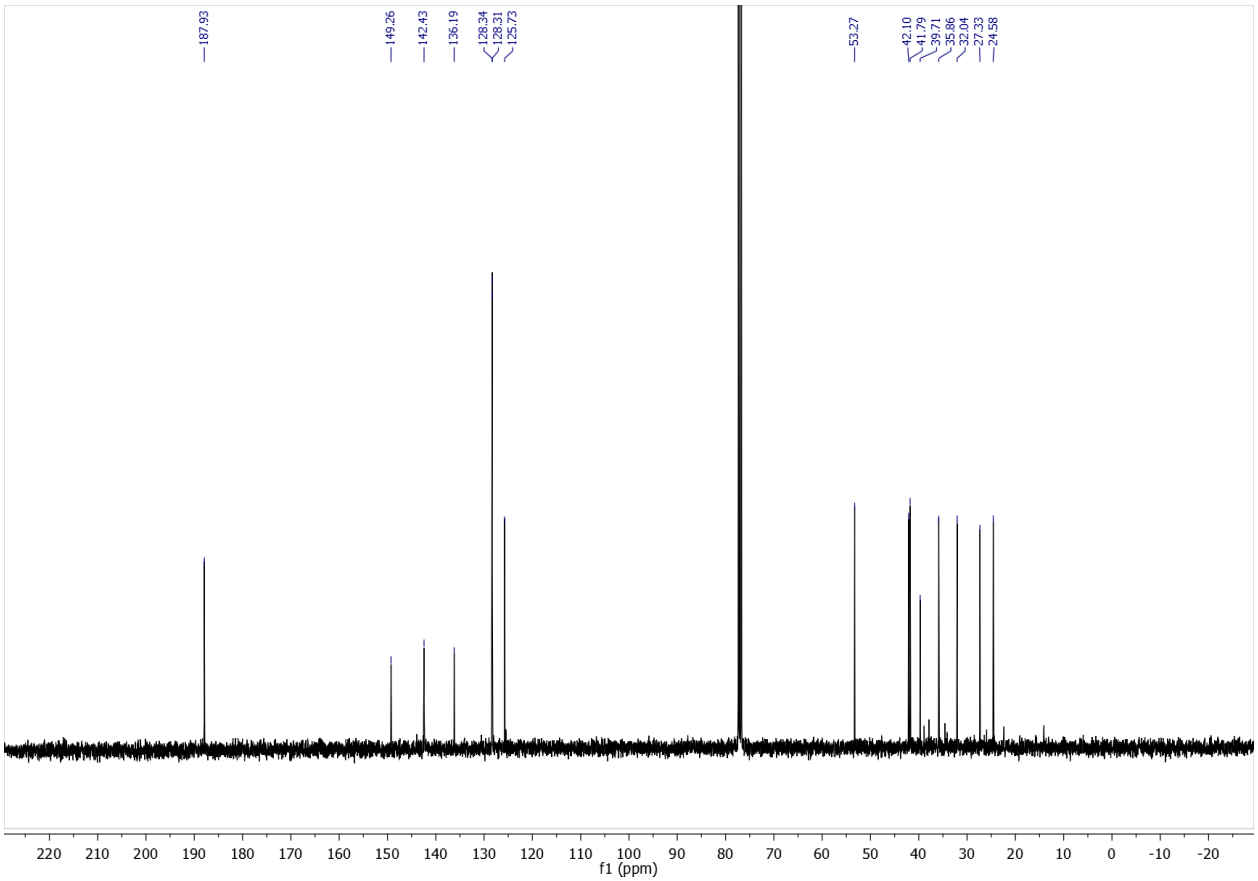
**FT-IR thin film, neat (ATR):** 2930, 2856, 1726, 1672, 1614 cm$^{-1}$;

**HRMS (APCI$^+$):** calculated for $C_{17}H_{22}O^{35}Cl$, $[M+H]^{+\bullet}$: 277.13537 found 277.13541 ($\Delta$ = 0.13 ppm);

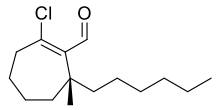
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ **=** + 13º (*c* = 1.0, $CH_2Cl_2$), based on a sample of 90% *ee*;

## $^{1}H/^{13}C$ NMR


f1 (ppm)


187.93
149.26
142.43
136.19
128.34
128.31
125.73
53.27
42.10
41.79
39.71
35.86
32.04
27.33
24.58
f1 (ppm)

**(R)-2-chloro-7-hexyl-7-methylcyclohept-1-ene-1-carbaldehyde 18**




1,4-addition reaction was conducted according to general procedure B using 3-ethyl-2-cycloheptenone **IV**[8] (0.53 mmol) as the enone and 1-hexene as the alkene. Trapping of the metal enolate using Vilsmeier's reagent was performed according to general procedure E. Flash chromatography (5% $Et_2O$/*n*-pentane) gave the title product as a yellow oil (59 mg, 0.23 mmol, 43% yield). Enantiomeric excess was determined by comparison with an authentic racemic sample. SFC (Chiralpak IF column 250 × 4.6 mm, 1-30% MeOH/$CO_2$ gradient over 5 min, 1.5 mL.min$^{-1}$): *ee* = 96% (major enantiomer $t_R$ = 3.51 min, minor enantiomer $t_R$ = 2.47 min).

**$R_f$** = 0.67 (30% $Et_2O$/*n*-pentane, stains yellow with $KMnO_4$);

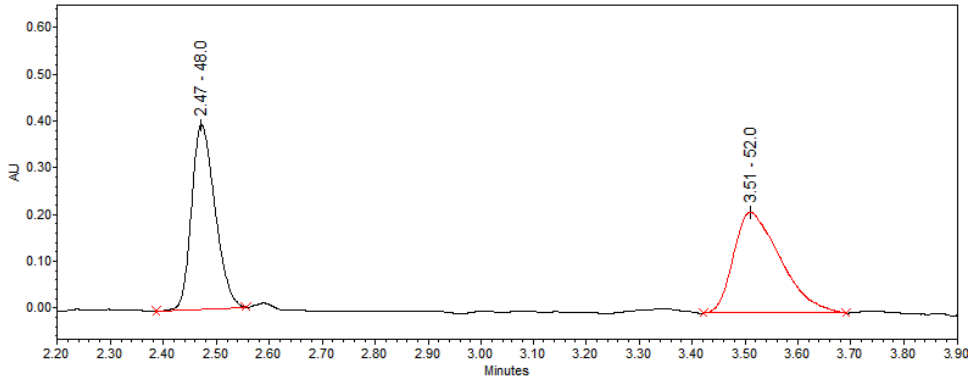
**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 10.13 (s, 1H), 2.79 – 2.63 (m, 2H), 2.44 (m, 2H), 1.69 – 1.50 (m, 2H), 1.49 – 1.41 (m, 2H), 1.33 – 1.23 (m, 10H), 0.95 (s, 3H), 0.92 – 0.85 (m, 3H) ppm;

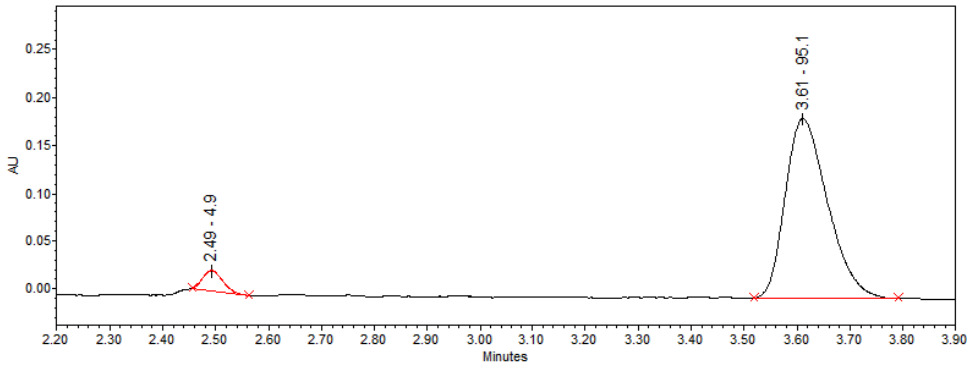
**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 190.6, 153.6, 138.3, 52.4, 43.4, 41.3, 34.2, 32.0, 30.2, 25.3, 24.8, 23.7, 22.8, 21.3, 14.2 ppm;

**FT-IR thin film, neat (ATR):** 2955, 2928, 2858, 1723, 1676, 1612 cm$^{-1}$;

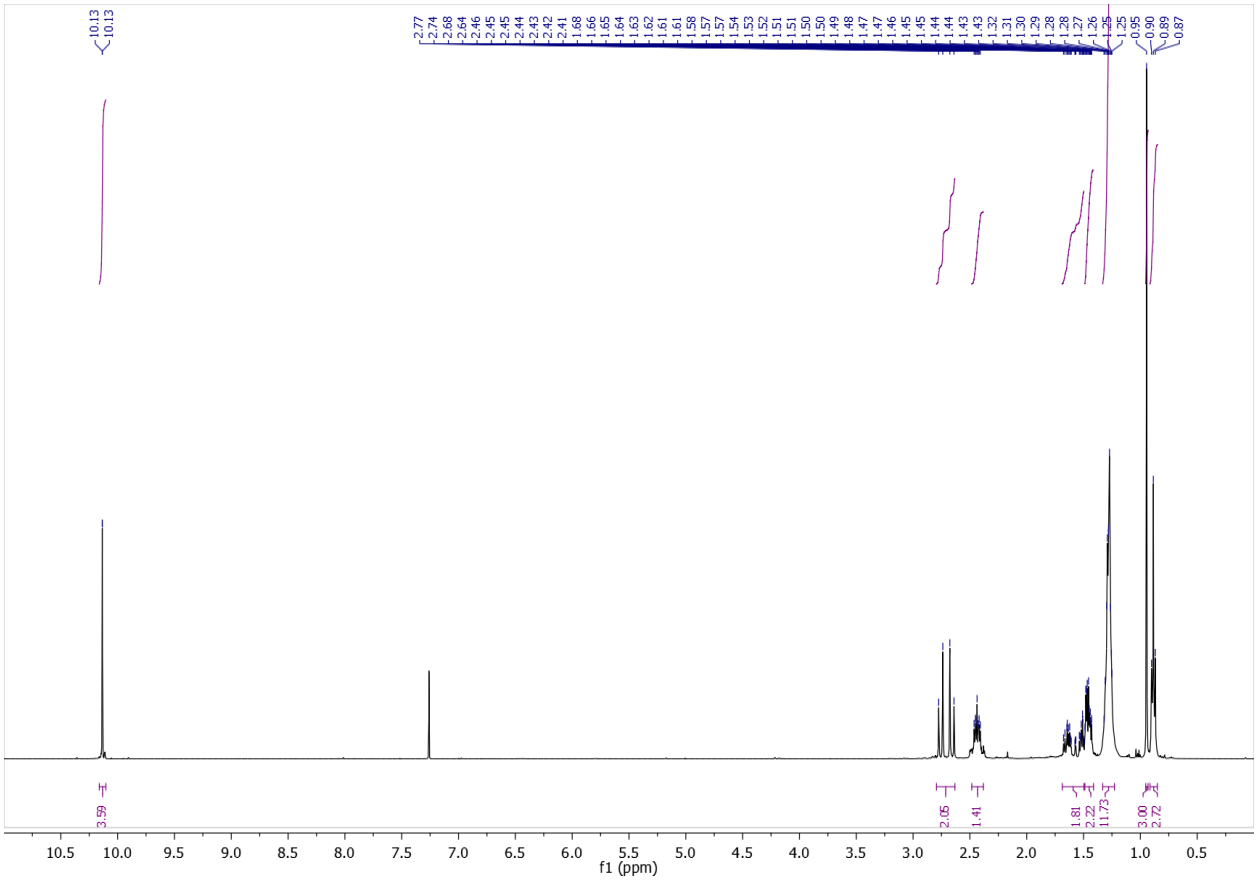
**HRMS (ESI$^+$):** calculated for $C_{15}H_{26}O^{35}Cl$, $[M+H]^{+\bullet}$: 257.16667 found 257.16681 (Δ = 0.54 ppm);

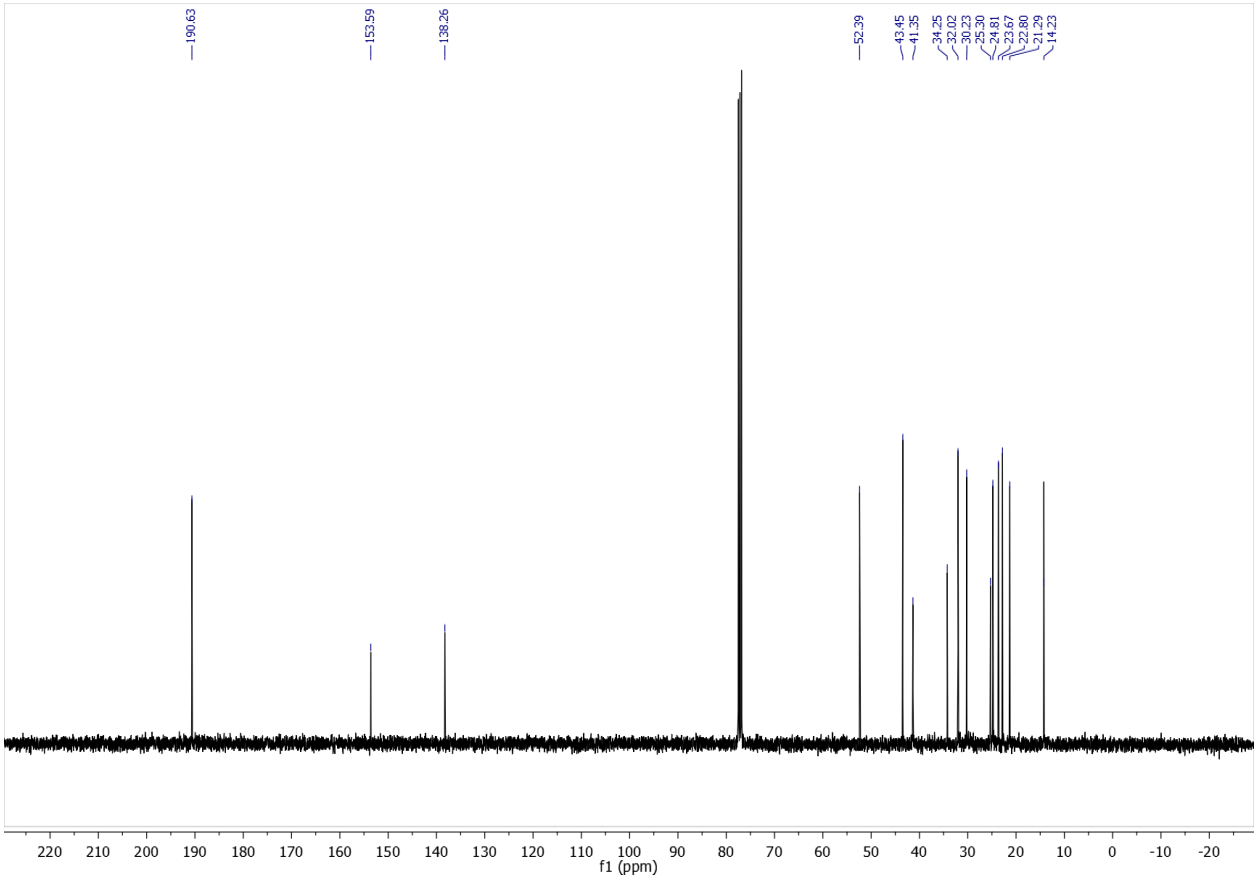
$[\alpha]_D^{25}$ = + 7.1° (*c* = 1.0, $CH_2Cl_2$), based on a sample of 90% *ee*;



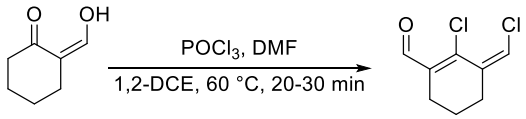



## $^{1}H/^{13}C$ NMR


10.13
10.13
2.77
2.74
2.68
2.64
2.46
2.45
2.45
2.44
2.43
2.42
2.41
1.68
1.66
1.65
1.64
1.63
1.62
1.61
1.61
1.58
1.57
1.57
1.54
1.53
1.52
1.51
1.51
1.50
1.50
1.49
1.48
1.47
1.47
1.46
1.45
1.45
1.44
1.44
1.43
1.32
1.31
1.30
1.29
1.28
1.28
1.27
1.26
1.25
1.25
0.95
0.90
0.89
0.87
3.59
2.05
1.41
1.81
2.22
11.73
3.00
2.72
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


190.63
153.59
138.26
52.39
43.45
41.35
34.25
32.02
30.23
25.30
24.81
23.67
22.80
21.29
14.23
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

**(Z)-2-chloro-3-(chloromethylene)cyclohex-1-ene-1-carbaldehyde 19**




Keto enol **19** was prepared according to a literature procedure.[12]

$POCl_3$ (0.90 mL, 9.6 mmol, 19.2 mol equiv) was added in one portion to a stirred solution of DMF (0.75 mL, 9.7 mmol, 19.4 mol equiv) in 1,2-dichloroethane (7 mL) in a round bottom flask at room temperature. After 15 minutes, the flask was heated at 60 °C for a further 5 minutes before **18** (58$\mu$L, $\rho$ = 1.08 g.mL$^{-1}$, 0.50 mmol, 1.0 mol equiv) was added by syringe. After stirring for 20 minutes (TLC control) at 60 °C, the reaction was quenched at 0 °C by careful addition of saturated $NaHCO_{3(aq)}$ solution. After transferring to a separating funnel, the aqueous phase was extracted (3x) with $CH_2Cl_2$. The combine organic extracts were washed with water (2x), dried ($Na_2SO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (5% $Et_2O$/*n*-pentane, silica column) to give the title compound as yellow crystals (73 mg, 0.38 mmol, 76% yield).

**$R_f$** = 0.55 (30% $Et_2O$/*n*-pentane, stains yellow with $KMnO_4$);

**$^1$H NMR (500 MHz, $CDCl_3$):** $\delta$ 10.33 (s, 1H), 7.12 (d, J = 2.0 Hz, 1H), 2.70 – 2.62 (m, 2H), 2.47 – 2.41 (m, 2H), 1.75 (p, J = 6.2 Hz, 2H) ppm;

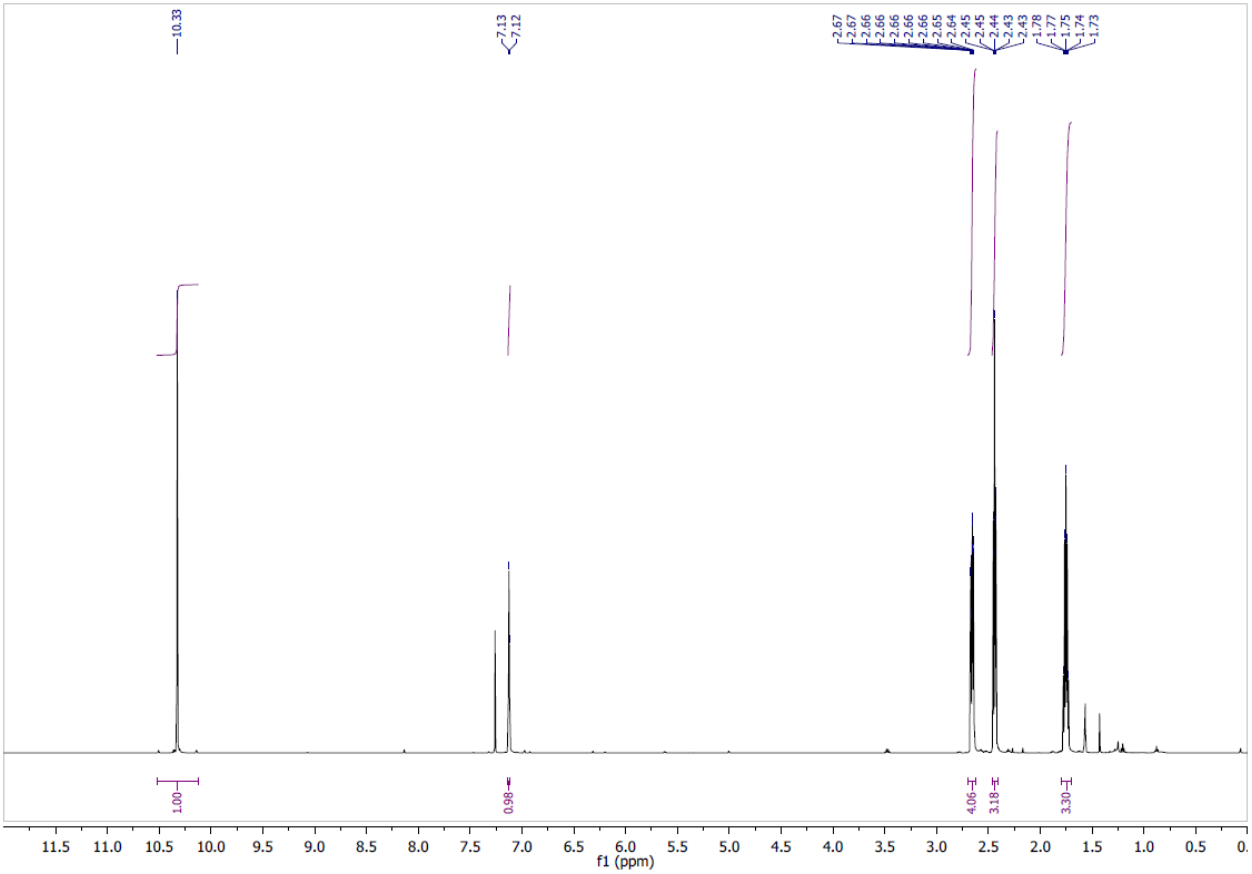
**$^3$C NMR (126 MHz, $CDCl_3$)** $\delta$ 191.1, 142.9, 135.8, 134.2, 124.9, 27.6, 24.7, 20.4 ppm;

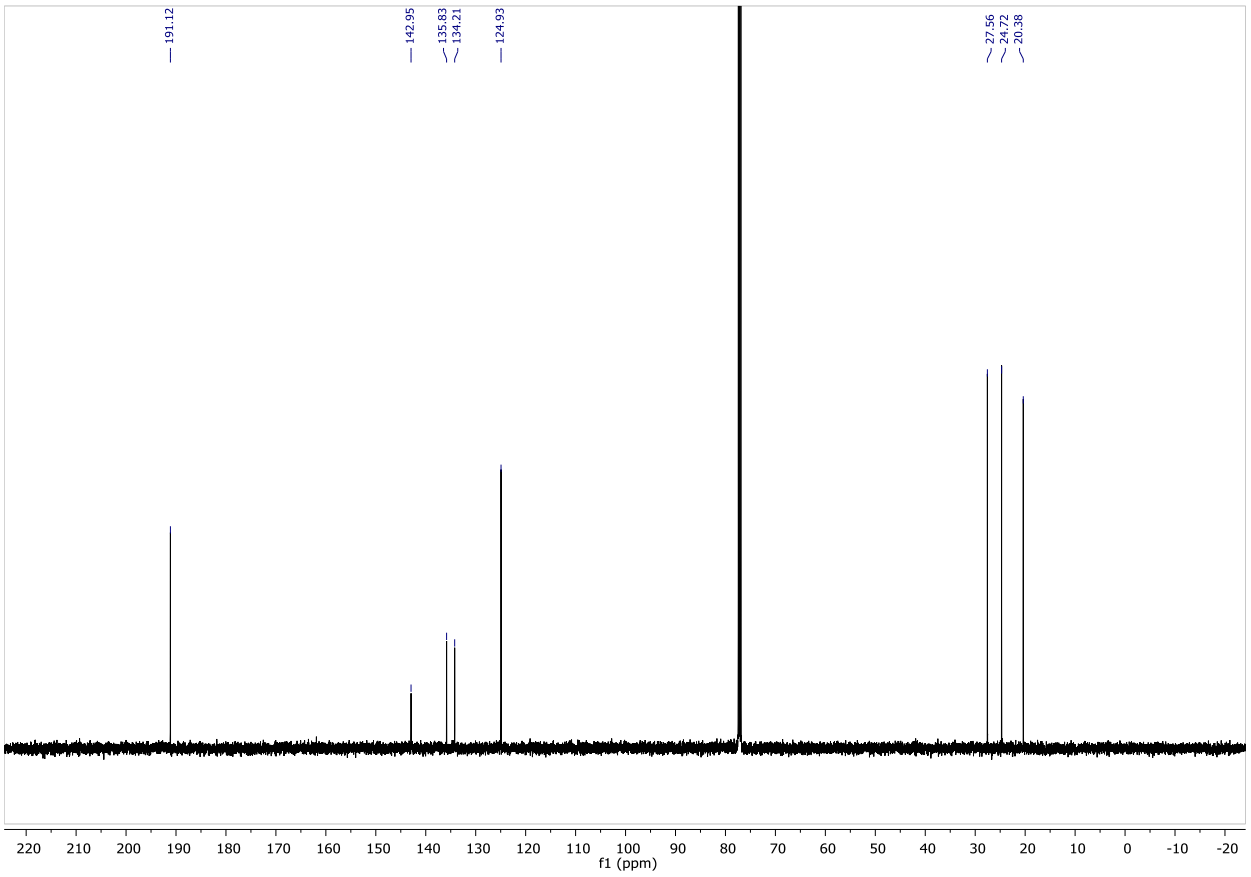
**FT-IR thin film, neat (ATR):** 3074, 2950, 1667, 1569, 1345, 1312, 1245 cm$^{-1}$;

**HRMS (EI$^+$):** calculated for $C_8H_8OCl_2$, $[M+]^{+\bullet}$: 189.9947 found 189.9949 ($\Delta$ = -1.2 ppm);

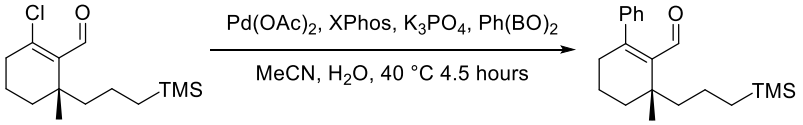
**Melting Point:** 38 – 42 °C

## $^{1}H/^{13}C$ NMR


10.33
7.13
7.12
2.67
2.67
2.66
2.66
2.66
2.66
2.65
2.64
2.45
2.45
2.44
2.43
2.43
1.78
1.77
1.75
1.74
1.73
1.00
0.98
4.06
3.18
3.30
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


191.12
142.95
135.83
134.21
124.93
27.56
24.72
20.38
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

**(S)-3-methyl-3-(3-(trimethylsilyl)propyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carbaldehyde 26**




Phenylboronic acid (27 mg, 0.22 mmol, 1.1 mol equiv), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.050 mol equiv) and XPhos (5.0 mg, 0.010 mmol, 0.050 mol equiv) were added to a 7 mL vial equipped with a stir bar and a rubber septum. Three cycles of vacuum and back filling with $N_2$ were then performed before chloroaldehydes **11** (55 mg, 0.20 mmol, 1.0 mol equiv) and degassed acetonitrile (0.5 mL) were added. A solution of degassed $K_3PO_4$ was added (0.30 mL of a 2M solution in $H_2O$, 0.60 mmol, 3.0 mol equiv) and the reaction stirred for 4.5 hours at 40 ºC, or until the reaction was complete, as monitored by TLC. After cooling to room temperature, the reaction mixture was diluted with $Et_2O$ and saturated $NH_4Cl_{(aq)}$ added. The contents were transferred to a separating funnel and the aqueous phase was extracted (3x) with $Et_2O$. The combined organic extracts were dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash chromatography (2-4% $Et_2O$/*n*-pentane gradient, silica column) to give the title compound as a yellow oil (31.9 mg, 0.10 mmol, 56% yield). Enantiomeric excess is based off that of the starting material (92% *ee*).

**$R_f$** = 0.65 (30% $Et_2O$/*n*-pentane, stains blue with CAM);

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 9.49 (s, 1H), 7.40 – 7.34 (m, 3H), 7.22 – 7.18 (m, 2H), 2.46 – 2.24 (m, 2H), 2.47 – 2.20 (m, 2H), 1.51 (td, J = 6.8, 6.4, 1.6 Hz, 2H), 1.37 – 1.26 (m, 4H), 0.96 (s, 3H), 0.47 (tdd, J = 7.0, 3.5, 1.8 Hz, 2H), -0.02 (s, 7H) ppm;

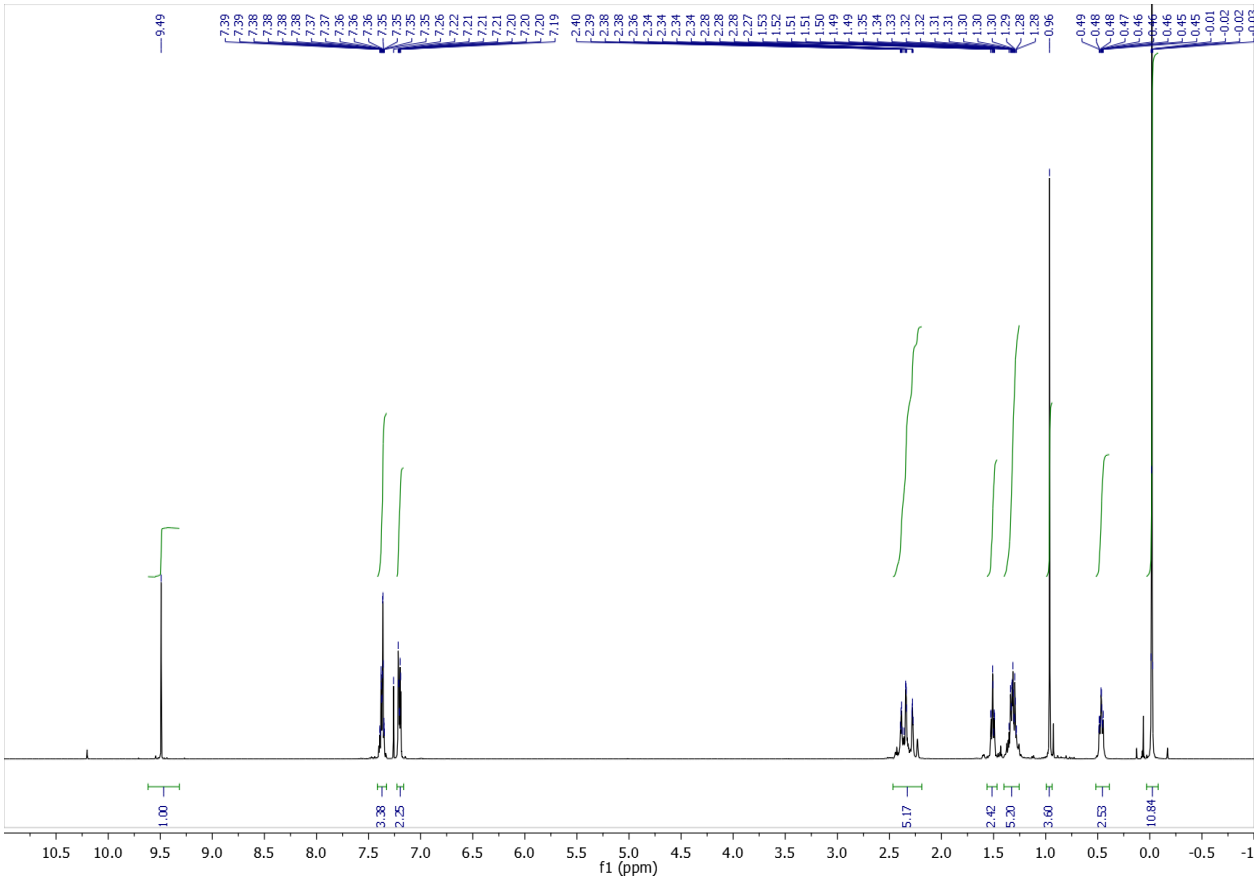
**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 193.7, 158.7, 139.8, 134.8, 128.7 (2C), 128.3 (2C), 128.3, 47.1, 45.8, 32.4, 32.2, 24.6, 20.0, 17.9, 17.8, -1.4 (3C) ppm;

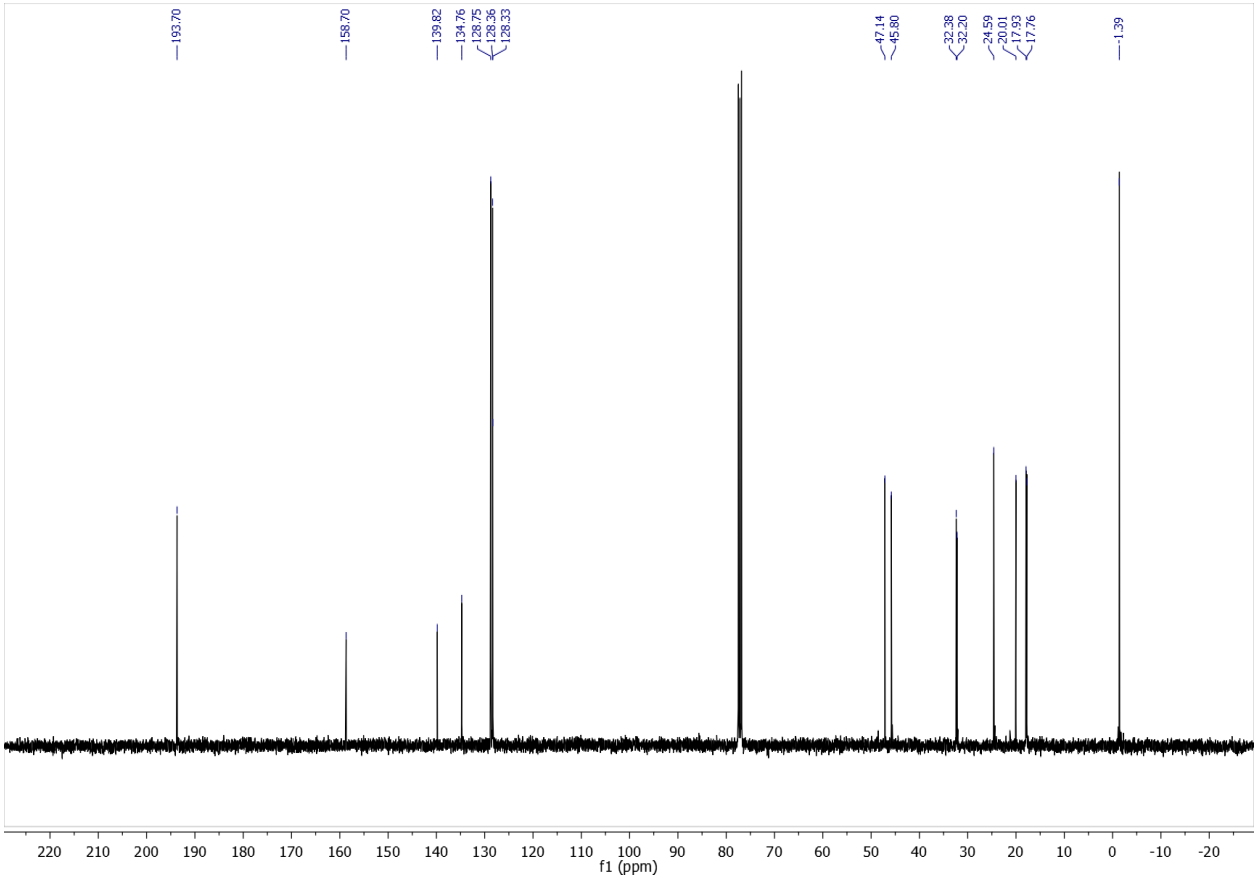
**FT-IR thin film, neat (ATR):** 2952, 2923, 2859, 1671, 1247 $cm^{-1}$;

**HRMS (APCI$^+$):** calculated for $C_{20}H_{31}O^{28}Si$, $[M+H]^{+\bullet}$: 315.21387 found 315.21396 ($\Delta$ = 0.29 ppm);

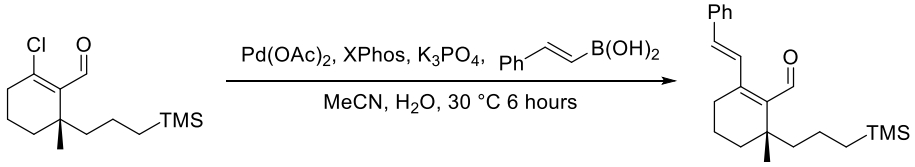
$[\alpha]_D^{25}$ **=** + 16º (*c* = 1.0, $CH_2Cl_2$), based on a sample of 92% *ee*;

## $^{1}H/^{13}C$ NMR


9.49
7.39
7.38
7.37
7.36
7.35
7.26
7.22
7.21
7.20
7.19
2.40
2.39
2.38
2.36
2.34
2.28
2.27
1.53
1.52
1.51
1.50
1.49
1.35
1.34
1.33
1.32
1.31
1.30
1.29
1.28
0.96
0.49
0.48
0.47
0.46
0.45
-0.01
-0.02
1.00
3.38
2.25
5.17
2.42
5.20
3.60
2.53
10.84
f1 (ppm)


193.70
158.70
139.82
134.76
128.75
128.36
128.33
47.14
45.80
32.38
32.20
24.59
20.01
17.93
17.76
-1.39
f1 (ppm)

**(S,E)-6-methyl-2-styryl-6-(3-(trimethylsilyl)propyl)cyclohex-1-ene-1-carbaldehyde 27**




*trans*-2-phenylvinylboronic acid (65 mg, 0.44 mmol, 1.1 mol equiv), $Pd(OAc)_2$ (4.4 mg, 0.020 mmol, 0.050 mol equiv) and XPhos (9.5 mg, 0.020 mmol, 0.050 mol equiv) were added to a 7 mL vial equipped with a stir bar and a rubber septum. Three cycles of vacuum and back filling with $N_2$ were then performed before chloroaldehydes **11** (109 mg, 0.40 mmol, 1.0 mol equiv) and degassed acetonitrile (1.0 mL) were added. A solution of degassed $K_3PO_4$ was added (0.60 mL of a 2M solution in $H_2O$, 1.2 mmol, 3.0 mol equiv) and the reaction stirred for 6 hours at room temperature and then jan addition 4 hours at 30 ºC. After cooling to room temperature, the reaction mixture was diluted with $Et_2O$ and saturated $NH_4Cl_{(aq)}$ added. The contents were transferred to a separating funnel and the aqueous phase was extracted (3x) with $Et_2O$. The combined organic extracts were dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash chromatography (20-50% $CH_2Cl_2$/*n*-pentane gradient, silica column) to give the title compound as a yellow oil (99 mg, 0.29 mmol, 72% yield). Enantiomeric excess is based off that of the starting material (92% *ee*).

**$R_f$** = 0.58 (30% $Et_2O$/*n*-pentane, stains blue with CAM);

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 10.47 (s, 1H), 7.76 (d, J = 15.9 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.40 – 7.35 (m, 2H), 7.34 – 7.29 (m, 1H), 6.87 (d, J = 15.9 Hz, 1H), 2.47 – 2.24 (m, 4H), 1.47 (ddd, J = 7.8, 6.2, 1.5 Hz, 2H), 1.39 – 1.28 (m, 4H), 0.95 (s, 3H), 0.54 – 0.38 (m, 2H), 0.00 (s, 9H) ppm;

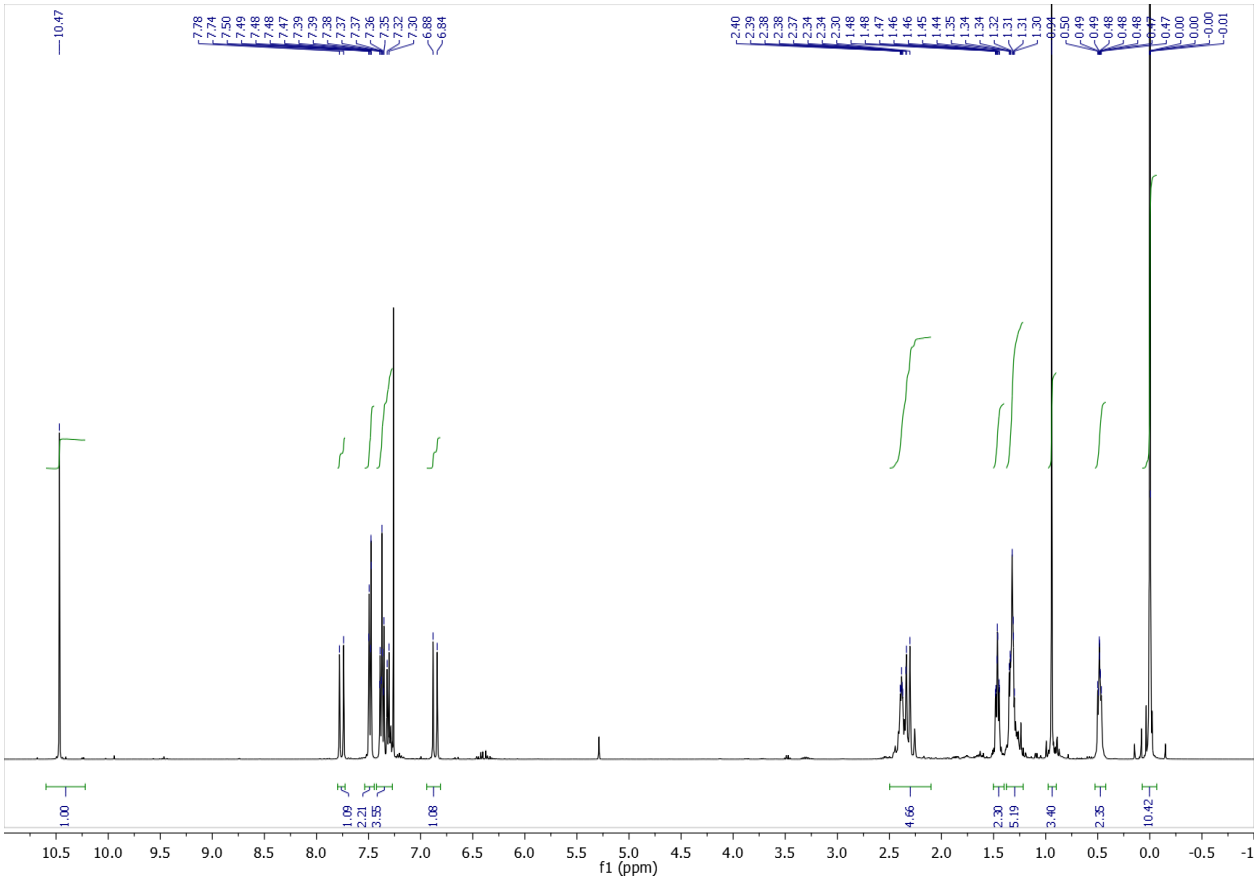
**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 190.5, 150.9, 136.7, 134.8, 133.6, 129.0 (2C), 128.8, 127.1 (2C), 123.7, 45.7, 40.5, 32.1, 31.7, 24.9, 20.9, 17.9, 17.7, -1.4 (3C) ppm;

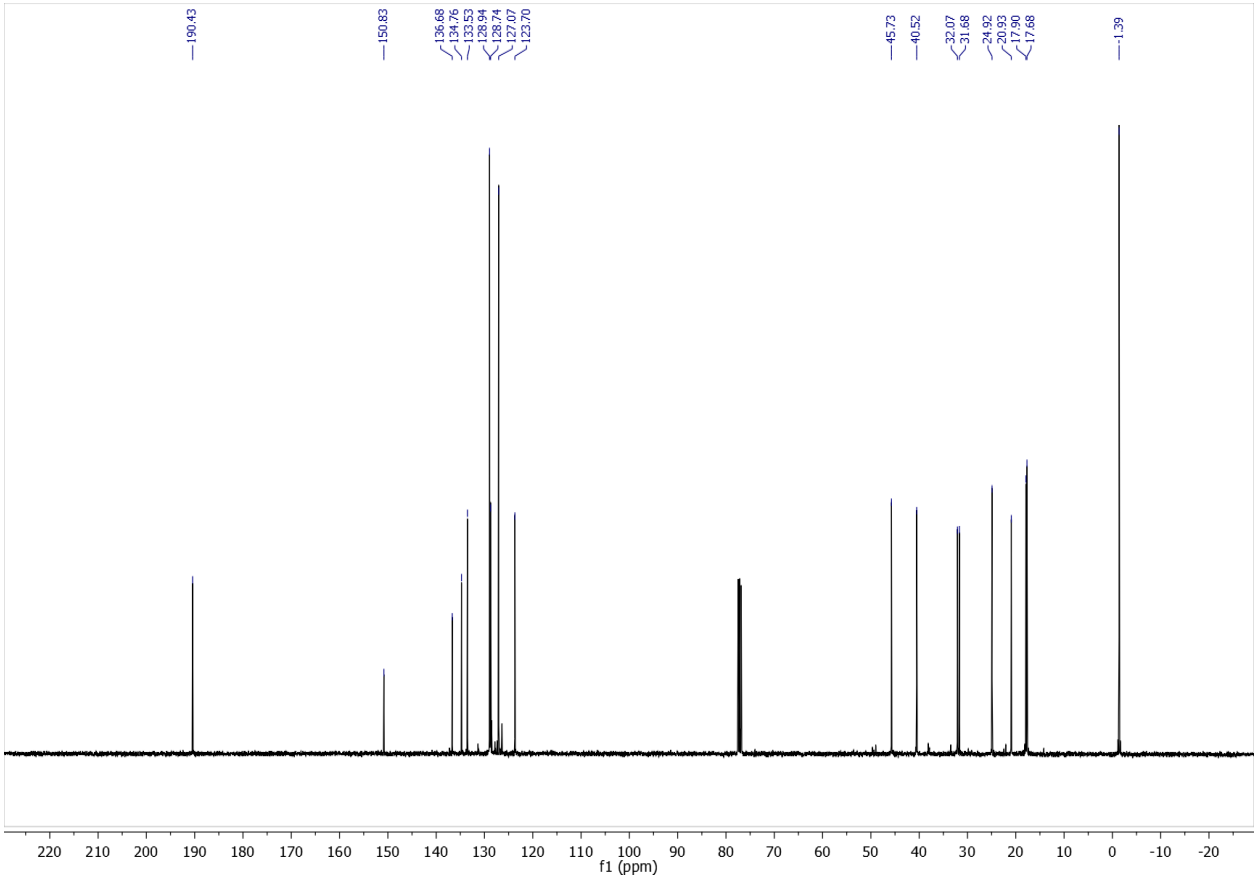
**FT-IR thin film, neat (ATR):** 3058, 2952, 1659, 1247 $cm^{-1}$;

**HRMS ($ESI^+$):** calculated for $C_{22}H_{33}O^{28}Si$, $[M+H]^{+\bullet}$: 341.22952 found 341.22955 ($\Delta$ = 0.1 ppm);

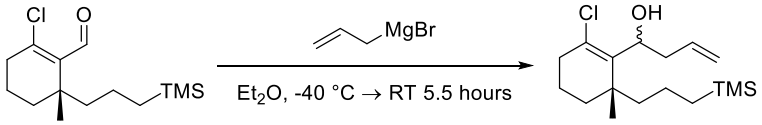
$[\alpha]_D^{25}$ **=** + 3.0º (*c* = 1.0, $CH_2Cl_2$), based on a sample of 92% *ee*;

## $^{1}H/^{13}C$ NMR


10.47
7.78
7.74
7.50
7.49
7.48
7.48
7.47
7.39
7.39
7.38
7.37
7.37
7.36
7.35
7.32
7.30
6.88
6.84
2.40
2.39
2.38
2.38
2.37
2.34
2.34
2.30
1.48
1.48
1.47
1.46
1.46
1.45
1.44
1.35
1.34
1.34
1.32
1.31
1.31
1.30
0.04
0.50
0.49
0.49
0.48
0.48
0.48
0.47
0.47
0.00
0.00
-0.00
-0.01
1.00
1.09
2.21
3.55
1.08
4.66
2.30
5.19
3.40
2.35
10.42
f1 (ppm)


190.43
150.83
136.68
134.76
133.53
128.94
128.74
127.07
123.70
45.73
40.52
32.07
31.68
24.92
20.93
17.90
17.68
-1.39
f1 (ppm)

**1-((S)-2-chloro-6-methyl-6-(3-(trimethylsilyl)propyl)cyclohex-1-en-1-yl)but-3-en-1-ol 28**




Chloroaldehyde **11** (51 mg, 0.19 mmol, 1.0 mol equiv) and $Et_2O$ (0.23 mL) were added to a 7 mL vial equipped with a stir bar and a rubber septum. Allylmagnesium bromide (0.23 mL of a 1M solution in $Et_2O$, 0.23 mmol, 1.2 mol equiv) was added dropwise at –40 ºC. The cooling bath was removed immediately after the addition and stirring was continued at room temperature for 5.5 hours. The reaction was quenched with wet $Et_2O$ and then concentrated *in vacuo*. The residue was purified by flash chromatography (10-15% $Et_2O$/*n*-pentane gradient, silica column) to give the product as a 1:1 separable mixture of diastereomers (colourless oil) with a combined mass of 42 mg (0.13 mmol, 71% total yield). Enantiomeric excess is based off that of the starting material (92% *ee*).

**$R_f$** = 0.46 (30% $Et_2O$/*n*-pentane, stains blue with CAM);

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 5.80 (ddt, J = 17.2, 10.2, 7.0 Hz, 1H), 5.19 – 5.07 (m, 2H), 4.90 (ddd, J = 7.8, 6.0, 3.4 Hz, 1H), 2.40 – 2.28 (m, 2H), 2.26 – 1.99 (m, 4H), 1.43 – 1.37 (m, 2H), 1.31 – 1.24 (m, 4H), 0.87 (s, 3H), 0.45 (tdd, J = 5.3, 4.2, 1.6 Hz, 2H), -0.02 (s, 9H) ppm;

**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 134.5, 133.1, 127.4, 118.1, 70.2, 46.6, 46.4, 39.3, 34.0, 33.1, 23.9, 21.7, 17.8, 17.7, -1.4 (3C) ppm;

**FT-IR thin film, neat (ATR):** 3354, 2924, 1248 $cm^{-1}$;

**HRMS (APCI$^+$):** calculated for $C_{17}H_{31}OSi$, $[M\text{-}Cl]^{+\bullet}$: 279.21387 found 279.21386 (Δ = 0.03 ppm);

$[\alpha]_D^{25}$ **=** + 3.7º (*c* = 0.54, $CH_2Cl_2$), based on a sample of 92% *ee*;

<u>Second diastereomer</u> (NOE studies did not afford conclusive insight into relative configuration)

**$R_f$** = 0.37 (30% $Et_2O$/*n*-pentane, stains blue with CAM);

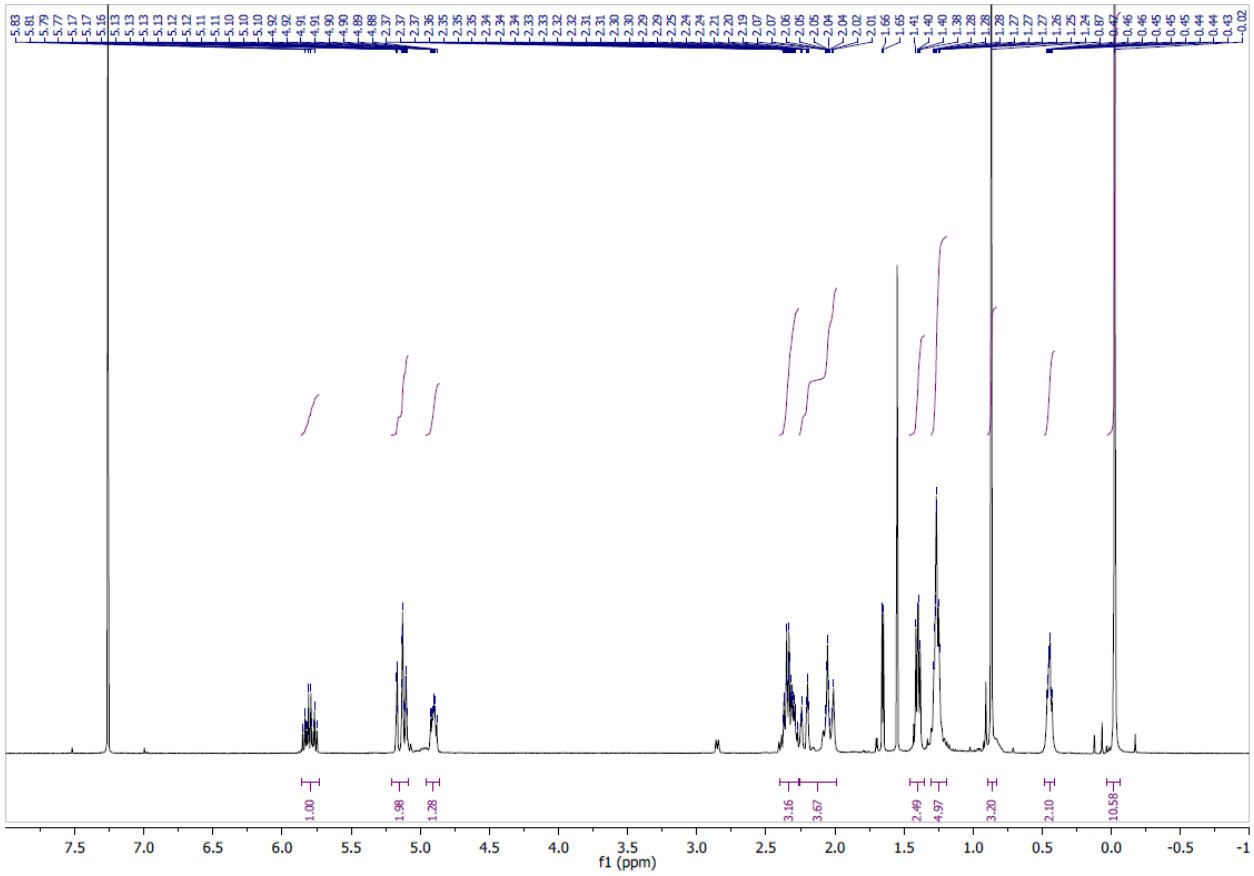
**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 5.81 (ddt, J = 17.3, 10.1, 7.1 Hz, 1H), 5.20 – 5.10 (m, 2H), 4.88 (td, J = 7.0, 3.5 Hz, 1H), 2.39 – 2.31 (m, 2H), 2.26 – 2.00 (m, 2H), 2.12 – 2.02 (m, 2H), 1.47 – 1.34 (m, 2H), 1.32 – 1.23 (m, 4H), 0.91 (s, 3H), 0.44 (ddd, J = 7.6, 5.7, 2.5 Hz, 2H), -0.02 (d, J = 1.0 Hz, 9H) ppm;

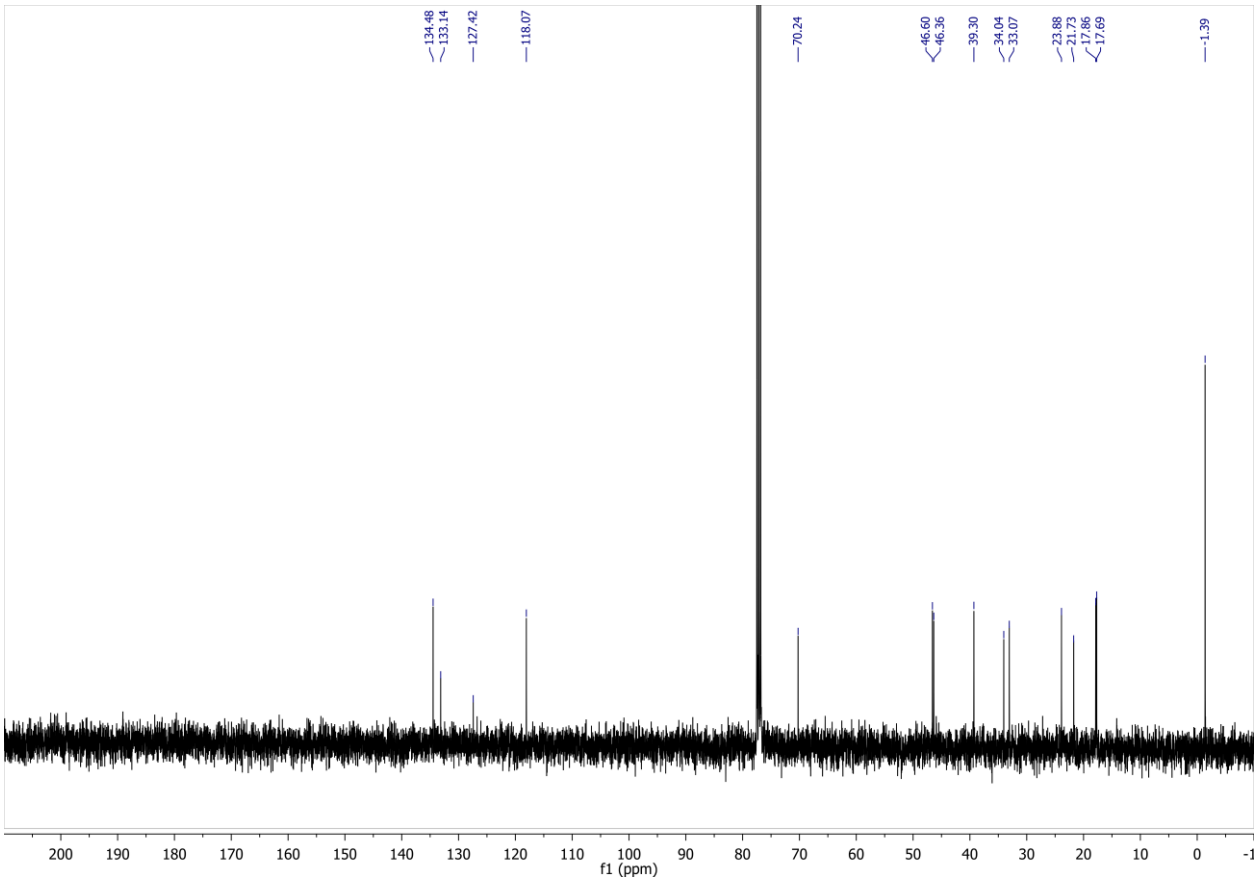
**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 134.5, 133.3, 127.0, 118.2, 70.3, 46.7, 45.4, 39.4, 34.0, 33.1, 24.6, 22.0, 17.9, 17.7, -1.4 (3C) ppm;

**FT-IR thin film, neat (ATR):** 3348, 29234, 1274, 860, 837 $cm^{-1}$;

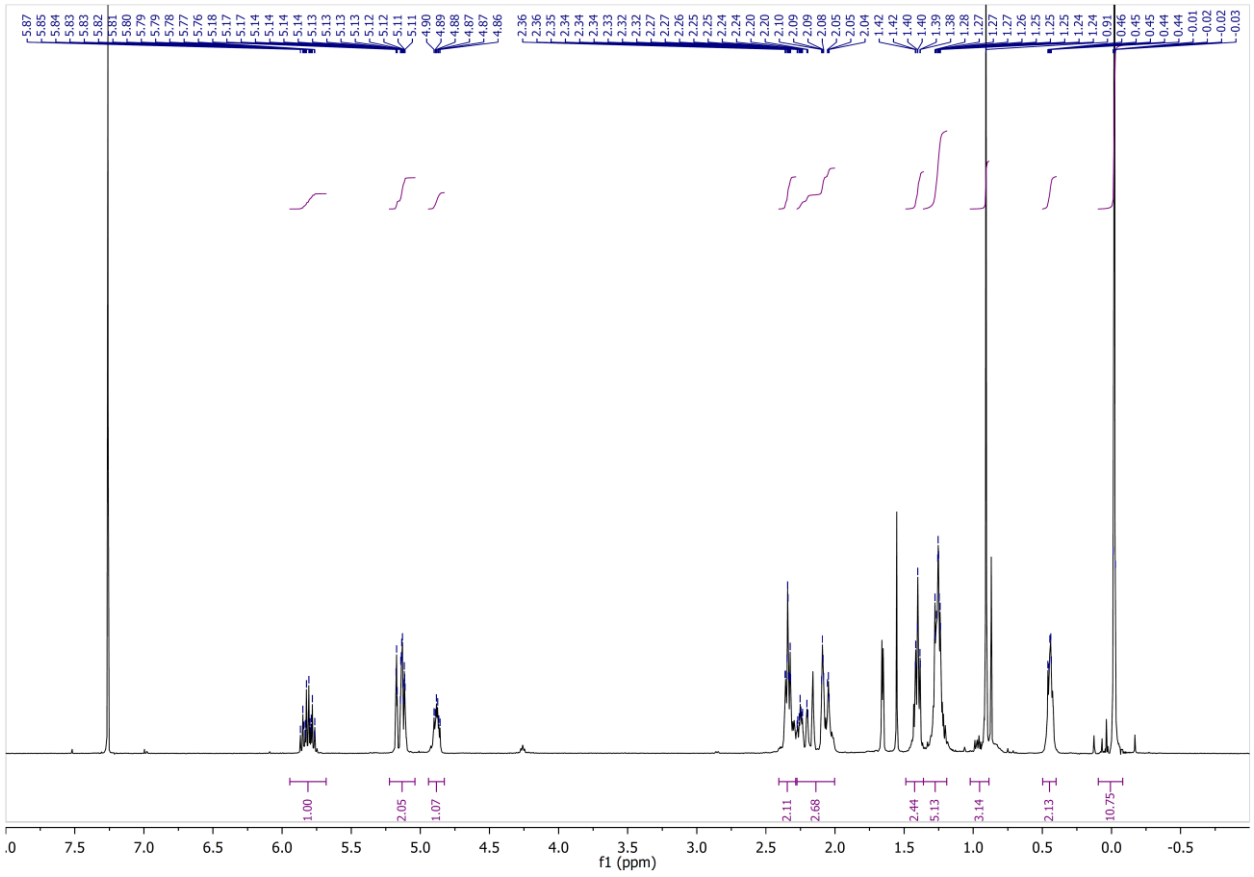
$[\alpha]_D^{25}$ **=** + 9.0º (*c* = 1.0, $CH_2Cl_2$), based on a sample of 92% *ee*;

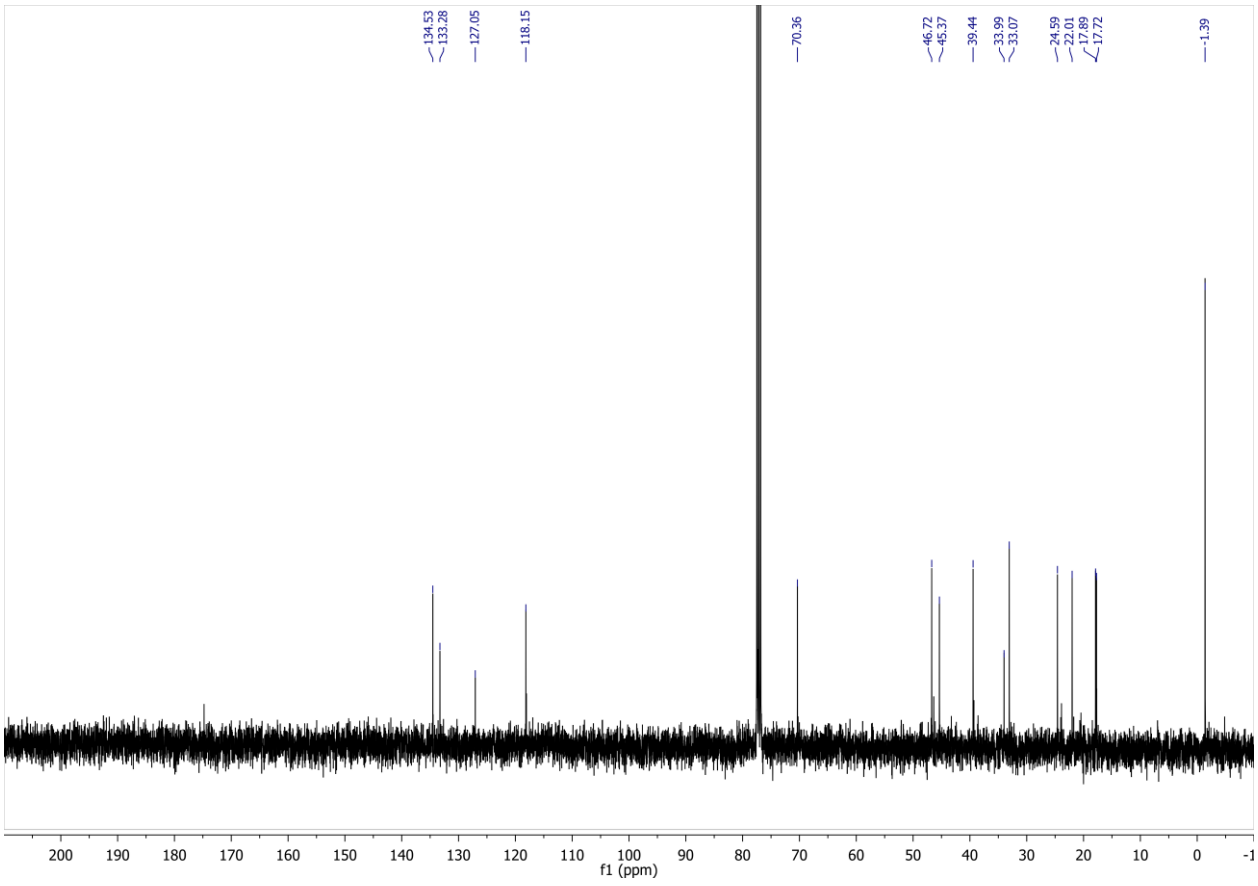
**$^{1}$H/$^{13}$C NMR** (First diastereomer):



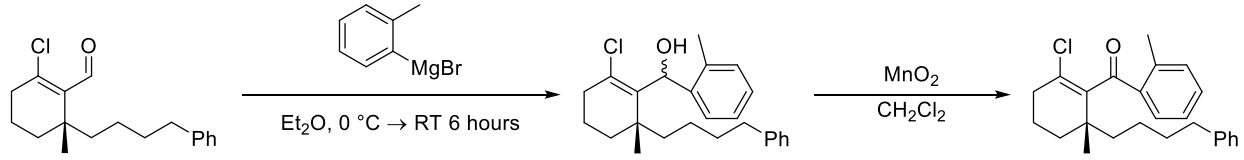



**$^{1}H/^{13}C$ NMR** (Second diastereomer):



**((R)-2-chloro-6-methyl-6-(4-phenylbutyl)cyclohex-1-en-1-yl)(o-tolyl)methanol 29**




Chloroaldehyde **9** (58 mg, 0.20 mmol, 1.0 mol equiv) and $Et_2O$ (0.23 mL) were added to a 7 mL vial equipped with a stir bar and a rubber septum *o*-Tolylmagnesium bromide (0.24 mL of a 1M solution in tetrahydrofuran, 0.24 mmol, 1.2 mol equiv) was added dropwise at 0 ºC. The cooling bath was removed after the addition and stirring was continued at room temperature for 50 minutes. The reaction was diluted with $Et_2O$ and quenched with saturated $NH_4Cl$ solution. After transferring the contents to a separating funnel, the aqueous phase was extracted (3x) with $Et_2O$. The combined organic extracts were washed (2x) with water, dried ($Na_2SO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-10% $Et_2O$/*n*-pentane gradient, silica column, $R_f$ = 0.52 30% $Et_2O$/*n*-pentane, stains with $KMnO_4$) to give the title compound as a 1:1 inseparable mixture of diastereomers (colorless oil, combined mass of 51 mg, 0.13 mmol, 67% yield). Enantiomeric excess is based off that of the starting material (94% *ee*).

For characterisation purposes, the alcohol (15 mg, 0.039 mmol, 1.0 mol equiv) was treated with $MnO_2$ (133 mg, 1.53 mmol, 39 mol equiv) in $CH_2Cl_2$ (0.15 mL). After stirring for 20 hours, the mixture was filtered through celite and the filter cake was washed (5x) with $CH_2Cl_2$. Concentration of the mixture in vacuo followed by flash chromatography(0-30% $Et_2O$/*n*-pentane gradient, silica column) afforded the ketone product as a colorless oil (7.9 mg, 0.021 mmol, 53% yield).

**$R_f$** = 0.60 (30% $Et_2O$/*n*-pentane, stains with $KMnO_4$);

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.55 (dd, J = 7.2, 1.1 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.32 – 7.24 (m, 4H), 7.21 – 7.16 (m, 3H), 2.64 (dd, J = 8.7, 6.8 Hz, 2H), 2.56 (s, 3H), 2.46 – 2.37 (m, 2H), 2.34 – 2.11 (m, 2H), 1.69 – 1.60 (m, 2H), 1.54 – 1.47 (m, 2H), 1.41 – 1.33 (m, 4H), 1.01 (s, 3H) ppm;

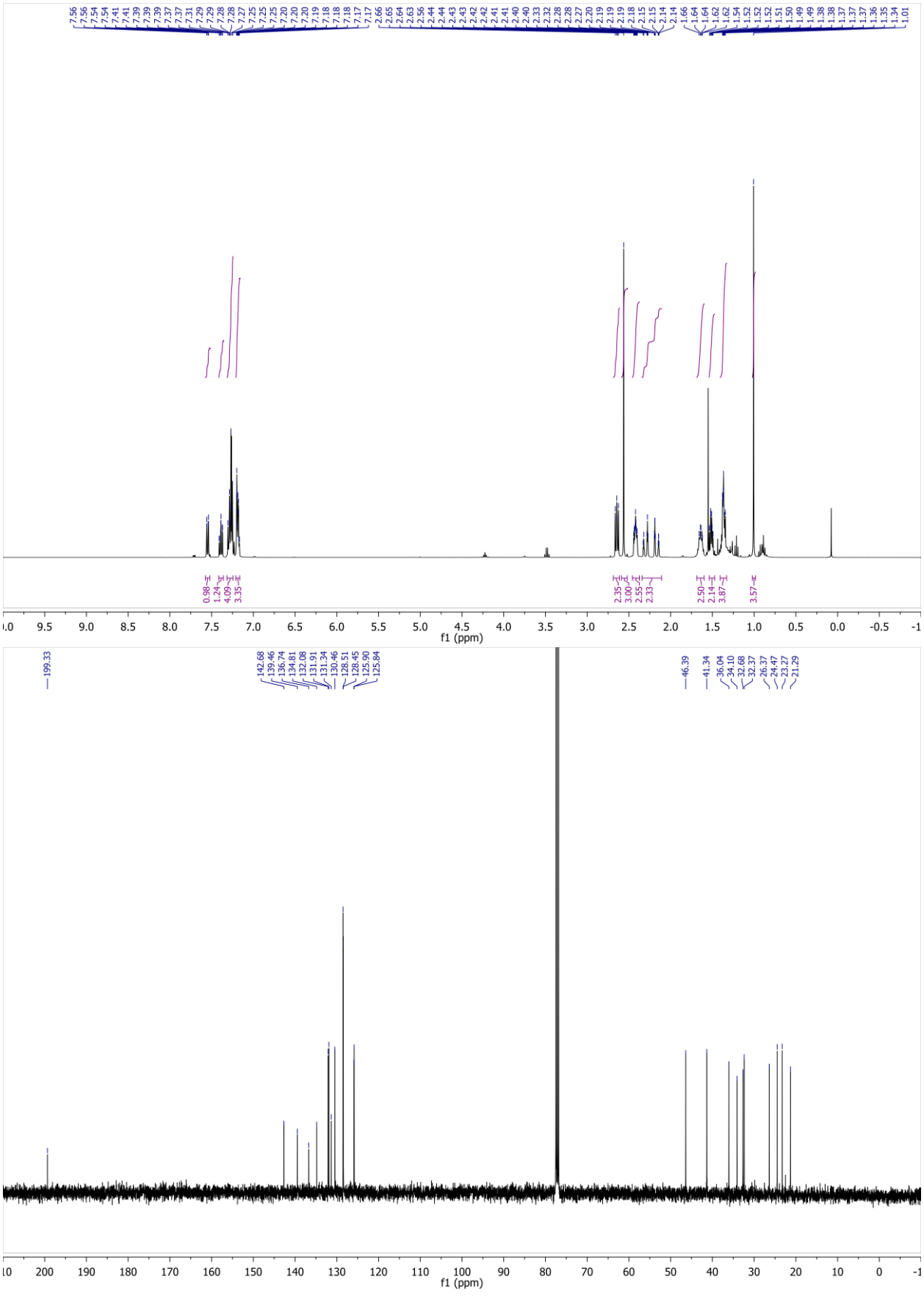
**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 199.3, 142.7, 139.5, 136.7, 134.8, 132.1, 131.9, 131.3, 130.5, 128.5(2C), 128.4(2C), 125.9, 125.8, 46.4, 41.3, 36.0, 34.1, 32.7, 32.4, 26.4, 24.5, 23.3, 21.3 ppm;

**FT-IR thin film, neat (ATR):** 2930, 2360, 1666, 1455, 1250 $cm^{-1}$;

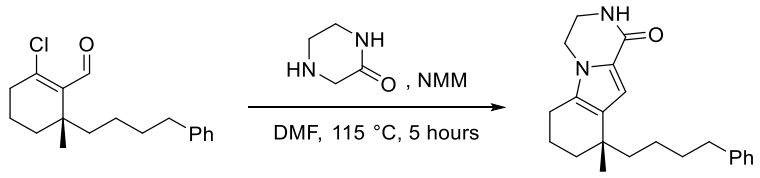
**HRMS ($ESI^+$):** calculated for $C_{25}H_{30}O^{35}Cl$, $[M+1]^{+\bullet}$: 381.19797 found 381.19803 (Δ = 0.15 ppm);

$[\alpha]_D^{25}$ **=** + 4.3º (*c* = 1.0, $CH_2Cl_2$), based on a sample of 94% *ee*;

**$^{1}$H/$^{13}$C NMR** (ketone):



**(R)-9-methyl-9-(4-phenylbutyl)-2,3,6,7,8,9-hexahydropyrazino[1,2-a]indol-4(1H)-one 30**




The condensation reaction was performed according to a literature procedure.[13] Chloroaldehyde **9** (174 mg, 0.60 mmol, 1.5 mol equiv) and 2-oxopiperazine (40 mg, 0.50 mmol, 1.0 mol equiv) were added to a 7 mL vial equipped with a rubber septum and stirring bar. Three cycles of vacuum and back filling with $N_2$ were then performed, after which *N,N*-dimethylformamide (1 mL) and *N*-methylmorpholine (60 mg, 0.6 mmol, 1.5 mol equiv) were added and the reaction mixture was heated at 115 ºC for 5 hours. The reaction mixture was allowed to cool, diluted with $CH_2Cl_2$, washed (2x) with water, dried ($Na_2SO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (0-7.5% MeOH/$CH_2Cl_2$ slow gradient, silica) to furnish the title compound as a white foam (56 mg, 0.17 mmol, 34% yield). Enantiomeric excess is based off that of the starting material (94% *ee*).

**$R_f$** = 0.31 (10% MeOH/$CH_2Cl_2$, stains yellow with $KMnO_4$);

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ 7.31 – 7.24 (m, 2H), 7.20 – 7.13 (m, 3H), 6.73 (s, 1H), 6.41 (t, J = 2.7 Hz, 1H), 3.88 (td, J = 5.5, 1.8 Hz, 2H), 3.64 (td, J = 6.7, 5.5, 2.8 Hz, 2H), 2.62 (dd, J = 8.7, 6.7 Hz, 2H), 2.50 (t, J = 6.3 Hz, 2H), 2.37 – 2.17 (m, 2H), 1.66 – 1.56 (m, 2H), 1.52 (q, J = 6.2 Hz, 2H), 1.42 – 1.29 (m, 4H), 0.96 (s, 3H) ppm;

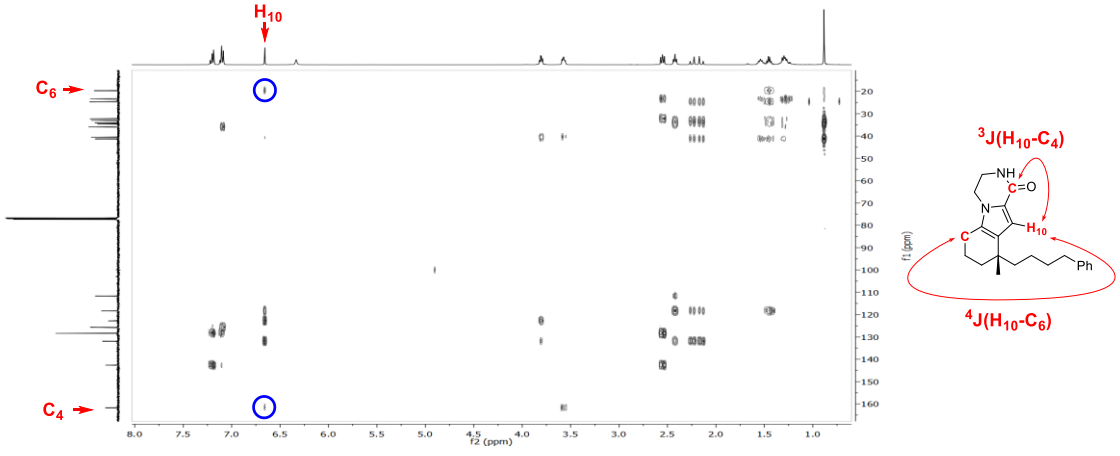
**$^{13}$C NMR (101 MHz, $CDCl_3$)** $\delta$ 161.9, 142.8, 132.0, 128.5 (2C), 128.4 (2C), 125.8, 122.9, 118.4, 111.8, 41.4, 40.7, 40.6, 36.0, 34.8, 34.3, 33.1, 32.4, 24.8, 23.5, 19.8 ppm;

**FT-IR thin film, neat (ATR):** 3280, 2927, 2854, 1649, 1499, 1345 $cm^{-1}$;

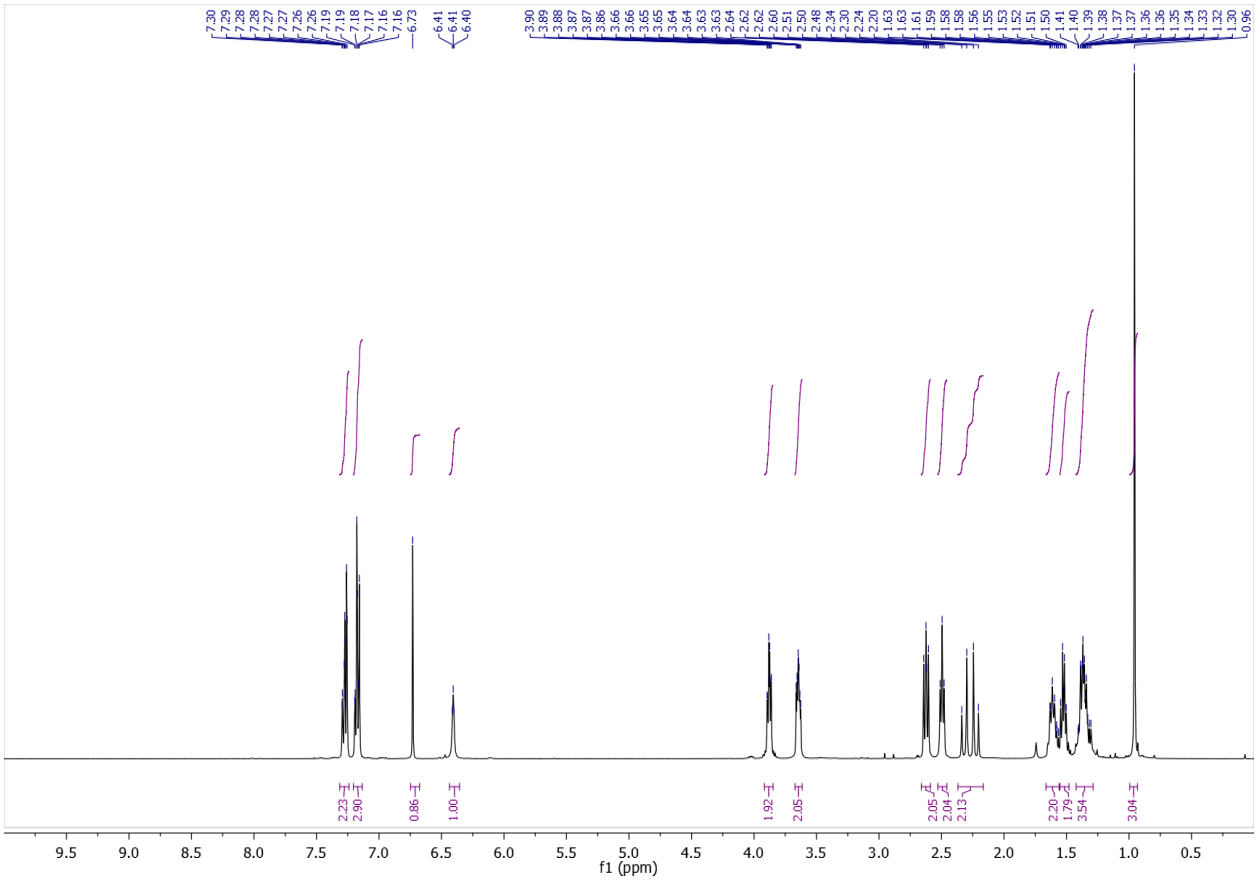
**HRMS (APCI$^+$):** calculated for $C_{22}H_{29}ON_2$, $[M+H]^{+\bullet}$: 337.22744 found 337.22726 (Δ = -0.52 ppm);

$[\alpha]_D^{25}$ **=** – 18º (*c* = 1.0, $CH_2Cl_2$), based on a sample of 94% *ee*;

**$^1$H/$^{13}$C HMBC assignment**



# $^{1}H/^{13}C$ NMR


7.30
7.29
7.28
7.28
7.27
7.27
7.26
7.26
7.19
7.19
7.18
7.17
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7.16
6.73
6.41
6.41
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3.89
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1.00
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2.20
1.79
3.54
3.04
9.5
9.0
8.5
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7.5
7.0
6.5
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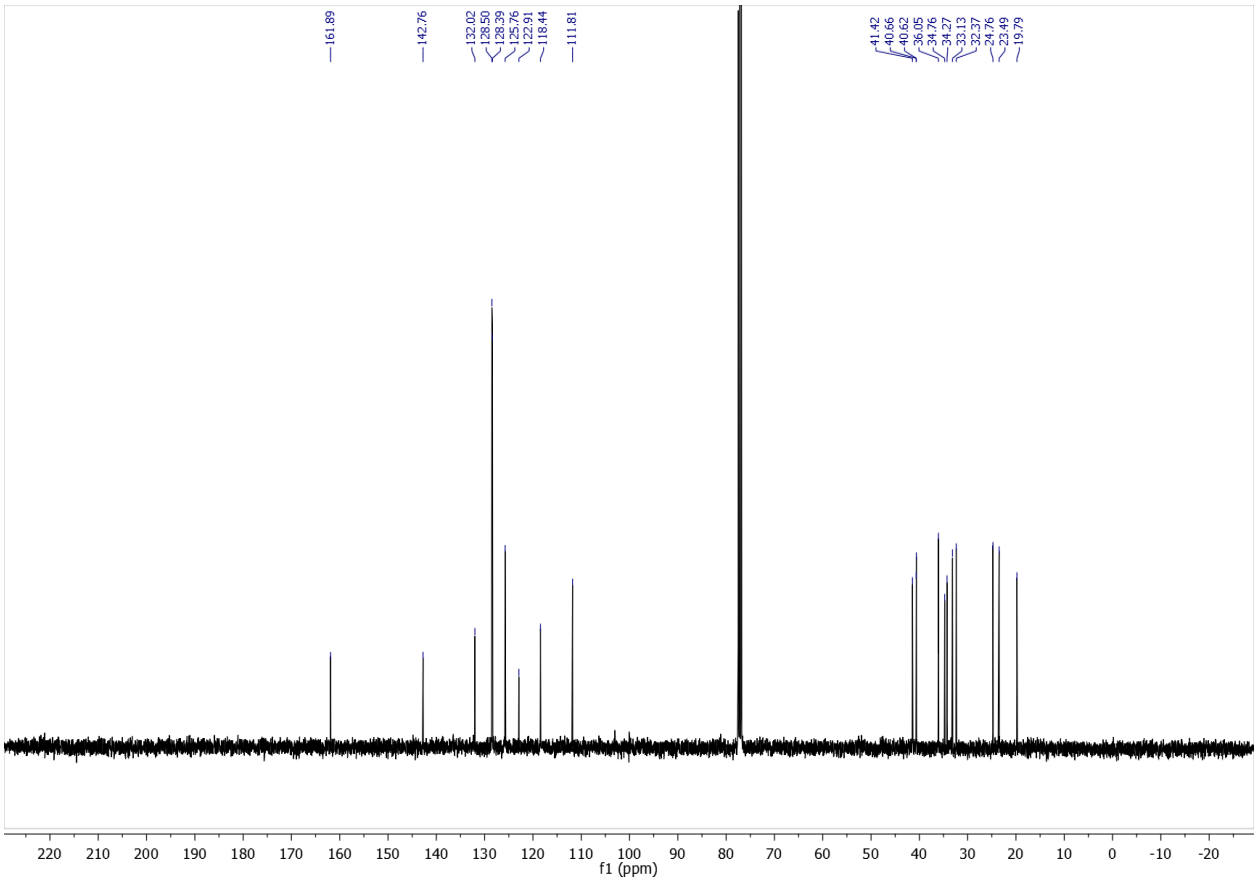
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


161.89
142.76
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128.50
128.39
125.76
122.91
118.44
111.81
41.42
40.66
40.62
36.05
34.76
34.27
33.13
32.37
24.76
23.49
19.79
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210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

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