Asymmetric addition of Grignard reagents to ketones: culmination of the ligand-mediated methodology allows modular construction of chiral tertiary alcohols

Supporting Information

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Materials and methods

General information

(*R*,*R*)-1,2-Diaminocyclohexane monohydrochloride (*R*,*R*)-**4·HCl** and (*S*,*S*)-1,2-diaminocyclohexane monohydrochloride (*S*,*S*)-**4·HCl** were purchased from Arran Chemical Company Ltd. All other reagents were purchased from Sigma-Aldrich, Acros Organics and Fluorochem Ltd. and used as supplied, unless otherwise stated. Toluene, tetrahydrofuran and diethyl ether were dried with a Grubbs-type Pure Solv-400-3-MD solvent purification system supplied by Innovative Technology Inc. Dichloromethane was dried over 4Å molecular sieves. Dry solvents were stored in J Young flasks over 4Å molecular sieves under N_2. The water content in all solvents was monitored before use by titration on an Aquamax KF instrument. The solvents used in palladium-catalyzed cross-coupling reactions were degassed before use via 3 freeze-pump-thaw cycles. Oxygen-free nitrogen was obtained from BOC gases and passed over dry 4Å molecular sieves. Flash column chromatography was performed on Davisil silica with particle size 40-63 µm. Thin layer chromatography was performed on Merck pre-coated Kieselgel $60F_{254}$ aluminium plates with UV realisation.

NMR spectra were recorded on Varian VNMRS 400, 500 and 600 spectrometers at 25 °C. Assignments were based on standard ^{1}H-^{1}H and ^{1}H-^{13}C two-dimensional techniques. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^{1}H and ^{13}C NMR (^{1}H-NMR: 7.26 ppm and ^{13}C NMR: 77.16 ppm for $CDCl_3$). Coupling constants (*J*) are in Hz. Multiplicities are reported as follow: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet and br = broad. HPLC analyses were performed on Agilent Technologies 1260 Infinity system equipped with auto-sampler and Agilent UV-Vis detector operating at 210, 230 and 254 nm. Enantiomers were separated on chiral stationary phases Daicel Chiralpak® IA, IB, IC, AS-H, Daicel Chiracel® OJ-H, OB-H and Regis (S,S)-Whelk-O® 1, 250 mm L x 4.6 mm ID, 5 µm particle size, coupled to a guard column 50 mm L x 4.6 mm ID. Specific rotations were measured with a PerkinElmer Model 343 polarimeter, reported as [$100 \cdot deg \cdot dm^{-1} \cdot cm^3 \cdot g^{-1}$] and are uncorrected for enantiomeric excess. HRMS analyses were performed with a LCT mass spectrometer Micromass/Waters corp. USA and a Waters GC/MS GCT premier mass spectrometer.

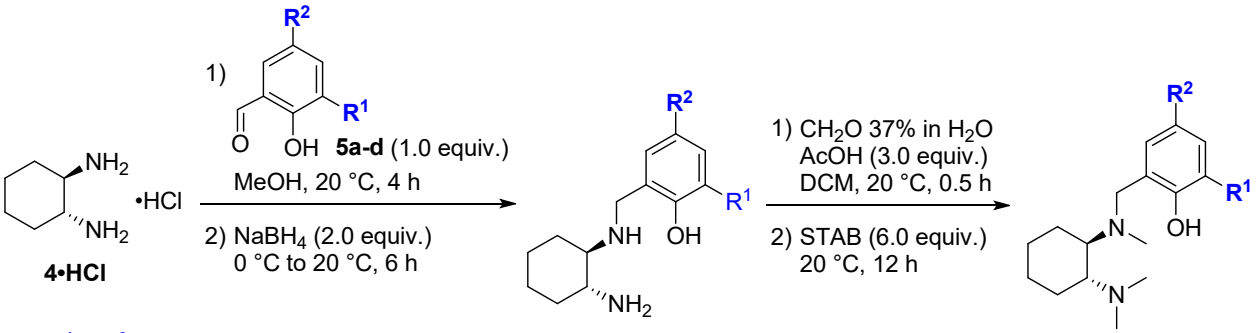
Commercially available Grignard reagent solutions (MeMgBr 3.0 M in Et_2O, MeMgI 3.0 M in Et_2O, EtMgBr 3.0 M in Et_2O, PhMgBr 3.0 M in Et_2O, *para*-chlorophenylmagnesium bromide 1.0 M in Et_2O, *para*-fluorophenylmagnesium bromide 2.0 M in Et_2O, *para*-methoxyphenylmagnesium bromide 0.5 M in Et_2O, *para*-tolylmagnesium bromide 0.5 M in Et_2O) were purchased from Sigma-Aldrich. The non-commercially available Grignard reagents were prepared from the corresponding alkyl bromides/aryl bromides and magnesium turnings in dry Et_2O, using 1,2-dibromoethane as activating agent, and stored in J Young flasks under N_2. Grignard reagents solutions were titrated before use with a 1.0 M (-)-menthol solution in dry toluene, using 1,10-phenantroline as indicator.[1] Hygroscopic ketones were pre-dried over 4Å molecular sieves and used as 0.5 M solution in dry toluene, stored in J Young flasks under N_2.

Ligand (*R*,*R*)-**L0'** was prepared according to our previously reported procedure.[2]

Experimental procedures and characterization

Preparation of 1,2-DACH-derived tridentate ligands

Improved 2-step synthetic route for the preparation of alkyl ligands L0-L3



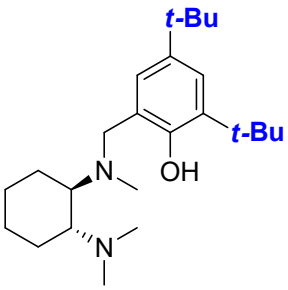
5a R^1 = R^2 = *t*-Bu
5b R^1 = *t*-Bu; R^2 = H
5c R^1 = Me; R^2 = *t*-Bu
5d R^1 = Me; R^2 = H

To a solution of (*R*,*R*)-1,2-diaminocyclohexane monohydrochloride **4·HCl** (2.0 g, 13.28 mmol) in MeOH (50 mL) was added aldehyde **5a-d** (13.28 mmol, 1.0 equiv.) in one portion at 20 °C. The mixture was stirred for 4 hours at 20 °C, then cooled to 0 °C with an ice bath, and sodium borohydride (0.949 g, 25.08 mmol) was added portionwise over 1 hour. The ice bath was removed, and the suspension was stirred at 20 °C for 6 hours. The reaction was quenched with saturated sodium bicarbonate (100 mL) and the resulting mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with H_2O (3 x 50 mL) and brine (50 mL), dried over sodium sulfate, filtered and the solvent removed under reduced pressure to yield **6a-d** that were used in the next step without further purification.

The crude product **6a-d** was dissolved in DCM (150 mL) at 20 °C and treated, under vigorous stirring, with formaldehyde 37% aqueous solution (8.0 equiv.) followed by glacial acetic acid (3.0 equiv.). The mixture was stirred for 20 minutes. Sodium triacetoxyborohydride (6.0 equiv.) was then added portionwise and the mixture was stirred for 12 hours. The reaction was quenched with $NaHCO_3$ sat. (200 mL) and extracted with DCM (3 x 100 mL). The combined organic phases were washed with H_2O (3 x 100 mL) and brine (100 mL), dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure to obtain crude ligands **L0-L3**. The crude products were purified via recrystallization from MeOH to obtain pure ligands **L0-L3** as crystalline solids.

It should be noted that the purification of the crude products **L0-L3** via recrystallization, despite the operational simplicity, entailed a substantial loss of material, thus affecting the overall yield of the preparations. To address this issue, an alternative two-stage purification strategy was developed for **L0**, the best performing ligand of the series **L0-L3**. The crude product was first purified by column chromatography on silica gel eluting with DCM/acetone (0% to 10% acetone), followed by recrystallization from MeOH or *i*-PrOH/H_2O 85:15.

2,4-Di-*tert*-butyl-6-((((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)(methyl)amino)methyl)phenol, L0



L0

White solid, 75% yield (over 2 steps)

Purification: two-stage, column chromatography on silica gel eluting with DCM/acetone 0% to 10%, followed by recrystallization from EtOH/H_2O.

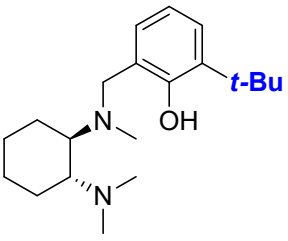
Alternatively, single-stage purification via recrystallization from MeOH (no column chromatography), 54% yield.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 2.5 Hz, 1H), 6.84 (d, *J* = 2.5 Hz, 1H), 3.93 (br d, *J* = 12.6 Hz, 1H), 2.62 – 2.60 (m, 1H), 2.55 – 2.50 (m, 1H), 2.27 (s, 6H), 2.21 (s, 3H), 2.02 – 1.99 (m, 1H0, 1.91 – 1.89 (m, 1H), 1.82 – 1.80 (m, 2H), 1.43 (s, 9H), 1.29 (s, 9H), 1.23 – 1.14 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 154.7, 139.2, 135.5, 124.6, 123.3, 122.7, 64.2, 64.0, 54.2 br, 39.6 br, 38.0 br, 35.4, 34.2, 31.0, 29.0, 25.9, 25.7, 24.0, 22.2.

Analytical data for **L0** were in accordance with our previously reported results.[3]

2-(*Tert*-butyl)-6-((((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)(methyl)amino)methyl)phenol, L1



L1

White solid, 61% yield (over 2 steps).

Purification: recrystallization from MeOH.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.85 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.66 (t, *J* = 7.5, 1H), 3.93 (d, *J* = 12.8 Hz, 1H), 3.24 (br s, 1H), 2.64 – 2.61 (m, 1H), 2.56 – 2.51 (m, 1H), 2.29 (s, 6H), 2.21 (s, 3H), 2.03 – 2.00 (m, 1H), 1.93 – 1.91 (m, 1H), 1.83 – 1.8175 (m, 2H), 1.44 (s, 9H), 1.28 – 1.15 (m, 4H).

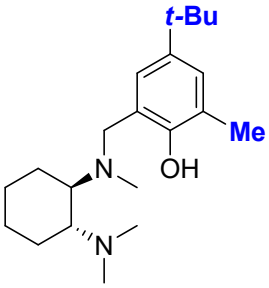
^{13}C-NMR (101 MHz, $CDCl_3$) δ 157.3, 136.6, 127.9, 125.7, 124.3, 117.2, 64.2, 64.0 br, 53.4 br, 39.6 br, 38.1 br, 35.0, 29.7, 25.9, 25.7, 24.0, 22.2.

HRMS (ESI) calculated for $C_{20}H_{35}N_2O$ ($[M+H]^+$) 319.2754, found 319.2749.

Elemental analysis calculated for $C_{20}H_{34}N_2O$: C, 75.42; H, 10.76; N, 8.80. Found C, 75.33; H, 10.89; N, 8.75.

m.p. = 122-123 °C.

4-(*Tert*-butyl)-2-((((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)(methyl)amino)methyl)-6-methylphenol, L2



L2

White solid, 50% yield (over 2 steps).

Purification: recrystallization from MeOH.

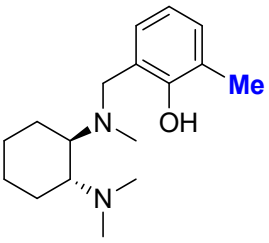
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 2.2 Hz, 1H), 6.81 (d, *J* = 2.2 Hz, 1H), 3.91 (d, *J* = 12.8 Hz, 1H), 3.14 (br s, 1H), 2.63 – 2.61 (m, 1H), 2.56 – 2.51 (m, 1H), 2.28 (s, 6H), 2.24 (s, 3H), 2.20 (s, 3H), 2.04 – 2.02 (m, 1H), 1.93 – 1.91 (m, 1H), 1.83 – 1.81 (m, 2H), 1.27 (s, 9H), 1.23 – 1.15 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 153.7, 140.1, 126.7, 124.4, 124.3, 122.6, 64.5, 64.2, 53.4 br, 39.6 br, 38.3 br, 33.8, 31.8, 25.9, 25.7, 23.6, 22.0, 16.6.

HRMS (ESI) calculated for $C_{21}H_{37}N_2O$ ($[M+H]^+$) 333.2892, found 333.2906.

m.p. = 72-73 °C.

2-((((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-6-methylphenol, L3



L3

White solid, 40% yield (over 2 steps).

Purification: recrystallization from MeOH.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 7.3 Hz, 1H), 6.82 (d, *J* = 7.3 Hz, 1H), 6.63 (t, *J* = 7.4 Hz, 1H), 3.91 (d, *J* = 12.8 Hz, 1H), 3.15 (br s, 1H), 2.64 – 2.62 (m, 1H), 2.56 – 2.54 (m, 1H), 2.29 (s, 6H), 2.24 (s, 3H), 2.19 (s, 3H), 2.04 – 2.01 (m, 1H), 1.94 – 1.91 (m, 1H), 1.83 – 1.81 (m, 2H), 1.26 – 1.12 (m, 4H).

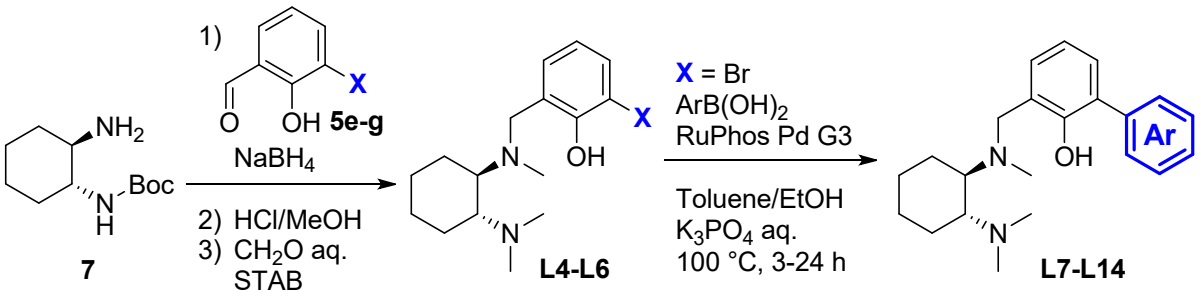
^{13}C-NMR (101MHz, $CDCl_3$) δ 156.1, 129.9, 127.6, 125.3, 123.4, 117.6, 64.5, 64.2, 52.8 br, 39.6 br, 38.4 br, 25.9, 25.7, 23.5, 22.0, 16.3.

HRMS (ESI) calculated for $C_{17}H_{29}N_2O$ ($[M+H]^+$) 277.2268, found 277.2280.

Elemental analysis calculated for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21; N, 10.13. Found C, 73.78; H, 10.28; N, 10.03.

m.p. = 88-89 °C.

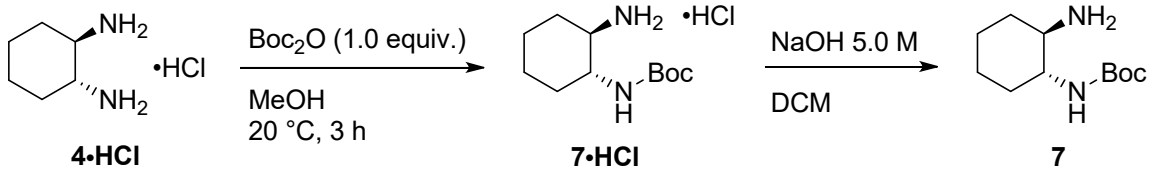
Divergent synthesis of biaryl ligands via late-stage Suzuki-Miyaura coupling



5e X = F
5f X = Cl
5g X = Br

L4 X = F
L5 X = Cl
L6 X = Br

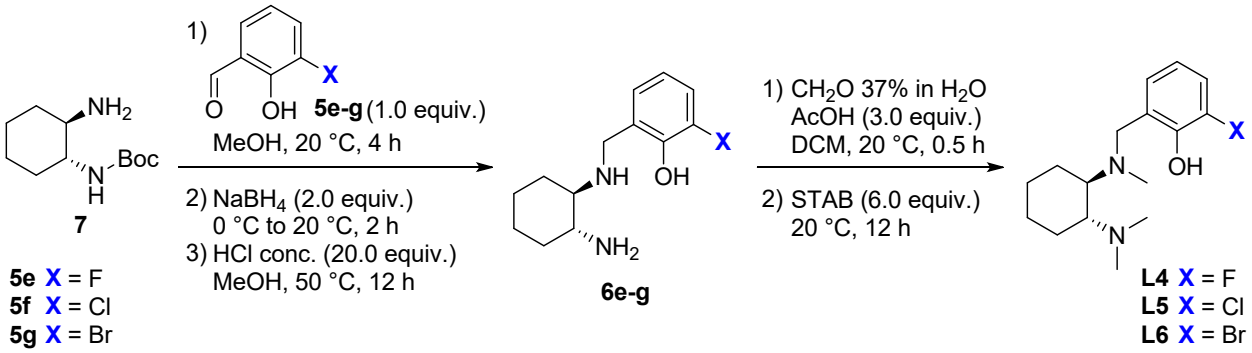
i) Preparation of (*R*,*R*)-N-Boc-1,2-DACH 7 from (*R*,*R*)-DACH 4·HCl



To a solution of (*R*,*R*)-1,2-diaminocyclohexane monohydrochloride **4·HCl** (5.0 g, 33.19 mmol) in MeOH (50 mL) was added a solution of di-*tert*-butyl dicarbonate (7.24 g, 33.19 mmol) in MeOH (10 mL), dropwise at 20 °C. The mixture was stirred for 3 hours. The solvent was removed under reduced pressure and the solid residue was washed with Et_2O (3 x 30 mL) and then dried under vacuum to obtain pure monohydrochloride salt **7·HCl** as white solid (7.91 g, 95% yield).

7·HCl (7.90 g, 31.53 mmol) was suspended in DCM (60 mL) and treated with NaOH 5.0 M (12 mL). The biphasic mixture was vigorously stirred at room temperature for 30 minutes, the phases were separated and the aqueous phase extracted with DCM (2 x 20 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over sodium sulfate, filtered and the solvent removed under reduced pressure to obtain the free-base product **7** (6.42 g, 95% yield), which was used in the following step without further purification (it is advisable to keep the free-base **7** under N_2 atmosphere and use it immediately in the following step, whereas the bench-stable hydrochloride salt **7·HCl** should be preferred for long-term storage).

ii) Preparation of halogenated ligands L4-L6



To a solution of (*R*,*R*)-N-Boc-1,2-DACH **7** (2.0 g, 9.33 mmol) in MeOH (50 mL) was added the aldehyde **5e-g** (9.33 mmol, 1.0 equiv.) in one portion at 20 °C. The mixture was stirred for 2 hours at 20 °C, then cooled to 0 °C with an ice bath, and sodium borohydride (0.706 g, 18.66 mmol) was added portionwise over 1 hour. The ice bath was removed, and the suspension was stirred at 20 °C for 2 hours. The reaction was quenched with saturated sodium bicarbonate (100 mL) and the resulting mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with H_2O (3 x 50 mL) and brine (50 mL), dried over sodium sulfate, filtered and the solvent removed under reduced pressure.

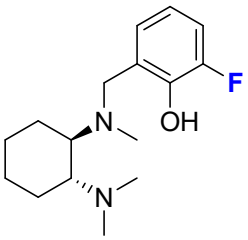
The solid residue was transferred to a 250 mL two-neck round bottom flask equipped with reflux condenser and dissolved in MeOH (100 mL). HCl 37% (20.0 equiv.) was added to the solution under stirring at 20 °C. The mixture was heated to 50 °C and stirred for 12 hours at that temperature. After cooling to room temperature, the pH of the solution was adjusted to 7-8 by slow addition of NaOH 5.0 M. The nature of the *ortho*-halogen functionality of the phenol greatly influenced the solubility of compounds **6e-g**. Specifically, unlike **6e** and **6f**, the solubility of the bromo-derivative **6g** sensibly decreased upon neutralization, making it necessary to develop two different work-up procedures:

i) 6e and **6f work-up***:* following neutralization with NaOH 5.0 M, DCM (50 mL) was added and the phases separated. The aqueous layer was extracted with DCM (3 x 30 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude products **6e** and **6f** were used in the following step without the need for further purification.

ii) 6g work-up*:* neutralization of the acid with NaOH 5.0 M, to pH = 7-8, resulted in the precipitation of a white solid. The mixture was left standing for 30 minutes, then filtered under reduced pressure on a Buchner filter and the precipitate collected to obtain **6g** as an off-white solid. The solid crude product was used in the following step without further purification.

The intermediate **6e-g** was dissolved in DCM (150 mL) at 20 °C and formaldehyde 37% aqueous solution (8.0 equiv.) was added, followed by glacial acetic acid (3.0 equiv.), and the mixture was stirred for 20 minutes under vigorous stirring. Sodium triacetoxyborohydride (6.0 equiv.) was then added portionwise and the mixture stirred for 12 hours at 20 °C. The reaction was quenched with $NaHCO_3$ sat. (200 mL) and extracted with DCM (3 x 100 mL). The combined organic phases were washed with H_2O (3 x 100 mL) and brine (100 mL), dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure to obtain crude ligands (*R*,*R*)-**L4-L6**. The crude products were purified via recrystallization from EtOH/H_2O or MeOH to obtain pure ligands (*R*,*R*)-**L4-L6** as crystalline solids.

2-((((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-6-fluorophenol, L4



L4

White solid, 40% yield (over 3 steps).

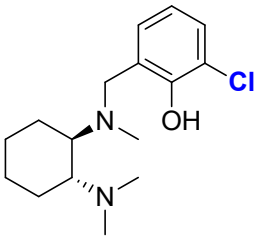
Purification: recrystallization from EtOH/H_2O.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.95 (ddd, *J* = 11.1, 8.1, 1.5 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.60 (td, *J* = 7.8, 4.8 Hz, 1H), 3.91 (d, *J* = 12.8 Hz, 1H), 3.02 (br d, *J* = 12.8 Hz, 1H), 2.70 – 2.64 (m, 1H), 2.54 – 2.48 (m, 1H), 2.30 (br s, 6H), 2.17 (s, 3H), 2.06 – 2.01 (m, 1H), 1.98 – 1.92 (m, 1H), 1.85 – 1.79 (m, 2H), 1.23 – 1.11 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 152.3 (d, *J* = 241.1 Hz), 146.2 (d, *J* = 10.8 Hz), 127.2 , 125.1 (d, *J* = 2.5 Hz), 117.1 (d, *J* = 7.4 Hz), 115.2 (d, *J* = 19.0 Hz), 64.7, 64.1, 51.5 br, 39.5 (hsqc only) br, 39.0 br, 25.7, 25.7, 23.1, 21.9.

^{19}F-NMR (376 MHz, $CDCl_3$) δ - 137.7 (dd, *J* = 11.0 Hz, 4.0 Hz).

2-Chloro-6-((((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)(methyl)amino)methyl)phenol, L5



L5

Pale yellow solid, 36% yield (over 3 steps).

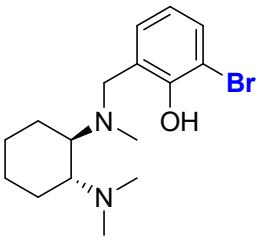
Purification: recrystallization from MeOH.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.86 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.62 (t, *J* = 7.7, 1H), 3.90 (d, *J* = 12.9 Hz, 1H), 3.08 (br d, *J* = 12.9 Hz, 1H), 2.68 – 2.62 (m, 1H), 2.56 – 2.50 (m, 1H), 2.30 (br s, 6H), 2.17 (s, 3H), 2.05 – 2.01 (m, 1H), 1.96 – 1.91 (m, 1 H), 1.88 – 1.77 (m, 2H), 1.23 – 1.13 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 154.1, 129.2, 128.5, 126.1, 121.5, 118.1, 64.6, 64.2, 52.4 br, 39.6 br, 38.7 br, 25.8, 25.7, 23.4, 22.0.

Elemental analysis calculated for $C_{16}H_{25}ClN_2O$: C, 64.75; H, 8.49; N, 9.44. Found C, 64.36; H, 8.51; N, 9.27.

2-Bromo-6-((((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)(methyl)amino)methyl)phenol, L6



L6

White solid, 38% yield (over 3 steps).

Purification: recrystallization from MeOH.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.90 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.57 (t, *J* = 7.7, 1H), 3.90 (d, *J* = 12.9 Hz, 1H), 3.09 (br d, *J* = 12.9 Hz, 1H), 2.65 – 2.64 (m, 1H), 2.55 – 2.53 (m, 1H), 2.30 (s, 6H), 2.18 (s, 3H), 2.04 – 2.01 (m, 1H), 1.94 – 1.92 (m, 1H), 1.83 – 1.82 (m, 2H), 1.21 – 1.16 (m, 4H).

^{13}C NMR (101MHz, $CDCl_3$) δ 155.03, 132.2, 129.2, 126.0, 118.6, 111.3, 64.5, 64.1, 52.6 br, 39.7 br, 38.7 br, 25.8, 25.7, 23.5, 22.0.

HRMS (ESI) calculated for $C_{16}H_{26}N_2OBr$ ($[M+H]^+$) 341.1221, found 341.1228.

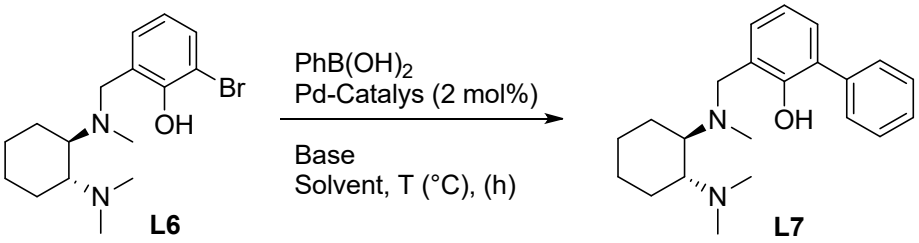
Elemental analysis calculated for $C_{16}H_{25}N_2O$: C, 56.31; H, 7.34; N, 8.21. Found C, 56.25; H, 7.44; N, 8.33.

iii) Preparation of biaryl ligands L7-L14

Screening of conditions for the coupling of L6 with phenylboronic acid

A preliminary screening of palladium catalysts for the Suzuki-Miyaura coupling of aryl bromides showed catalysts $Pd(OAc)_2$ and $Pd(dppf)Cl_2$ to be ineffective in the coupling of (*R*,*R*)-**L6** with phenylboronic acid, providing no conversion even after prolonged reaction time (Table S1, entries 1 and 2). On the contrary, the use of RuPhos Pd G3 pre-catalyst in the presence of K_3PO_4 aq. in THF at 50 °C provided moderate conversion of **L6** to **L7** (Table S1, entry 3). Replacing THF with a toluene/EtOH mixture and increasing the temperature to 100 °C provided full conversion of **L6** after 6 hours (Table S1, entries 4 and 5). The purification of crude products (*R*,*R*)-**L7-L14** were carried out by column chromatography on alumina or silica gel, followed by recrystallization from EtOH/H_2O or MeOH.

Table S1 Screening of conditions for the Suzuki-Miyaura coupling of **L6** with phenylboronic acid.

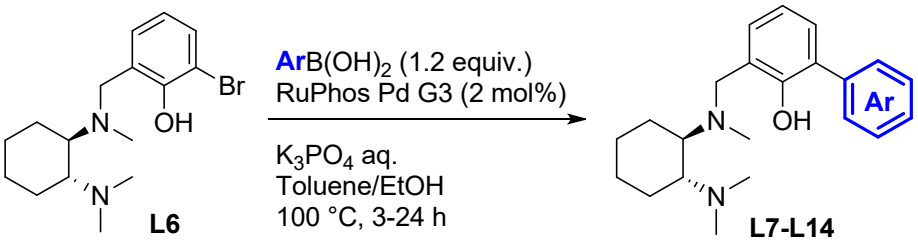


L6 **L7**

Entry	Pd-Catalyst	Base	Solvent	T (°C)	Time (h)	L7 conv. (%)[a]	L7 yield (%)[b]
1	$Pd(OAc)_2$	*i*-Pr_2NH	THF/H_2O	50	48	-	-
2	$Pd(dppf)Cl_2$	K_2CO_3 aq. or K_3PO_4 aq.	Toluene/EtOH	100	48	-	-
3	RuPhos Pd G3	K_3PO_4 aq.	THF	50	24	50	-
4	RuPhos Pd G3	K_3PO_4 aq.	Toluene/EtOH	100	12	>95	-
5[c]	RuPhos Pd G3	K_3PO_4 aq.	Toluene/EtOH	100	6	>95	72

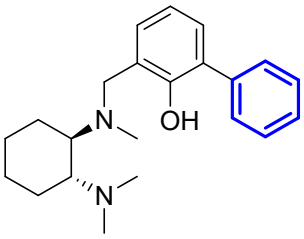
[a] Conversion determined by ^{1}H-NMR analysis of the crude reaction mixture; [b] Isolated yields;
[c] RuPhos Pd G2 pre-catalyst showed similar performances.

General procedure for the synthesis of ligands L7-L14 via Suzuki-Miyaura coupling[4]



An oven-dried 10 mL crimp top vial equipped with a stirrer bar was charged with (*R*,*R*)-**L6** (0.5 mmol), arylboronic acid (0.6 mmol, 1.2 equiv.) and RuPhos G3 palladacycle (2 mol%). The vial was sealed and flushed with nitrogen. Degassed toluene (1 mL) and ethanol (1 mL) were added, followed by K_3PO_4 solution 0.5 M (degassed, 4 mL). This mixture was heated to 100 °C and stirred vigorously for 3-24 hours. The reaction progress was monitored *via* LRMS by taking a small aliquot (0.1 mL) of the organic layer and diluting with MeOH. When no peak for the starting material could be observed, the reaction mixture was filtered through a pad of Celite™ eluting with ethyl acetate. The phases were separated and the aqueous phase extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The resulting product was purified by column chromatography followed by recrystallization, see conditions below, to obtain pure ligands (*R*,*R*)-**L7-L14**.

3-((((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-[1,1'-biphenyl]-2-ol, L7



L7

White solid, 72% yield. Reaction time = 6 hours.

Purification: column chromatography on alumina, cyclohexane/Et_3N 98:2.

Further purification via recrystallization from MeOH.

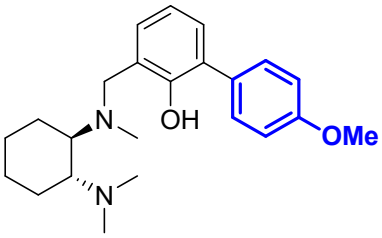
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.34 – 7.25 (m, 2H), 7.00 (dd, *J* = 7.3, 1.6 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 4.02 (d, *J* = 13.0 Hz, 1H), 3.32 (br d, *J* = 13.0 Hz, 1H), 2.68 – 2.55 (m, 2H), 2.28 (s, 6H), 2.27 (s, 3H), 2.09 – 2.02 (m, 1H), 1.97 – 1.91 (m, 1H), 1.85 – 1.83 (m, 2H), 1.28 – 1.15 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 155.4, 139.6, 130.0, 129.8, 129.3, 128.8, 127.8, 126.3, 124.6, 118.0, 64.3, 64.2, 53.6 br, 39.6 br, 38.1 br, 25.8, 25.7, 23.9, 22.1.

HRMS (ESI) calculated for $C_{22}H_{31}N_2O$ ($[M+H]^+$) 339.2450, found 339.2436.

Elemental analysis calculated for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found C, 78.05; H, 8.99; N, 8.26.

3-((((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-4'-methoxy-[1,1'-biphenyl]-2-ol, L8



L8

White solid, 83% yield. Reaction time = 12 hours.

Purification: column chromatography on silica gel, DCM/ Et_3N 99:1.

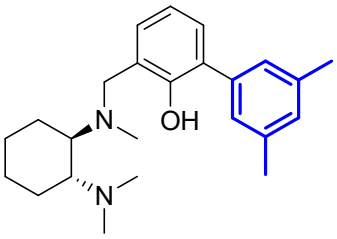
Further purification via recrystallization from MeOH.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 2H), 7.23 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.96 – 6.92 (m, 3H), 6.77 (t, *J* = 7.6, 1H), 3.98 (d, *J* = 13.0 Hz, 1H), 3.84 (s, 3H), 3.29 (br d, *J* = 13.0 Hz, 1H), 2.70 – 2.52 (m, 2H), 2.25 (s, 6H), 2.23 (s, 3H), 2.05 – 2.01 (m, 1H), 1.92 – 1.89 (m, 1H), 1.83 – 1.81 (m, 2H), 1.29 – 1.14 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 158.3, 155.4, 132.0, 130.8, 129.7, 128.8, 128.4, 124.5, 118.0, 113.4, 64.3, 64.2, 55.4, 53.8 br, 39.6 br, 38.2 br, 25.9, 25.7, 24.0, 22.1.

HRMS (ESI) calculated for $C_{23}H_{33}N_2O_2$ ($[M+H]^+$) 369.2527, found 369.2542.

3-((((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-3',5'-dimethyl-[1,1'-biphenyl]-2-ol, L9



L9

White solid, 18% yield. Reaction time = 12 hours.

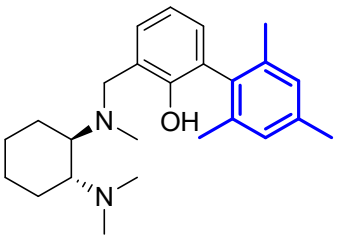
Purification: column chromatography on alumina, cyclohexane/Et_3N 98.5:1.5.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30 (br s, 2H), 7.24 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.77 (t, *J* = 7.6 Hz, 1H), 3.99 (d, *J* = 13.0 Hz, 1H), 3.31 (d, *J* = 13.0 Hz, 1H), 2.66 – 2.51 (m, 2H), 2.36 (s, 6H), 2.25 (s, 6H,), 2.24 (s, 3H), 2.05 – 2.01 (m, 1H), 1.92 – 1.90 (m, 1H), 1.83 – 1.81 (m, 2H), 1.27 – 1.14 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 155.5, 139.4, 137.1, 130.0, 129.0, 129.0, 128.1, 127.7, 124.5, 117.9, 64.3, 64.2, 53.9 br, 39.7 br, 38.1 br, 25.9, 25.7, 24.2, 22.1, 21.6.

HRMS (ESI) calculated for $C_{24}H_{35}N_2O$ ($[M+H]^+$) 367.2749, found 367.2749.

3-((((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-2',4',6'-trimethyl-[1,1'-biphenyl]-2-ol, L10



L10

White solid, 66% yield. Reaction time = 12 hours.

Purification: column chromatography on silica gel, DCM/acetone/Et_3N 100:0:1 to 96:3:1.

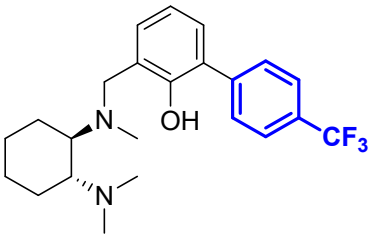
Further purification via recrystallization from MeOH.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.97 (dd, *J* = 7.3, 1.7 Hz, 1H), 6.92 – 6.90 (m, 3H), 6.75 (t, *J* = 7.3 Hz, 1H), 4.03 (d, *J* = 13.1 Hz, 1H), 3.39 (d, *J* = 13.1 Hz, 1H), 2.70 – 2.63 (m, 1H), 2.61 – 2.49 (m, 2H), 2.32 (s, 3H), 2.23 (s, 3H), 2.19 (s, 6H), 2.07 (s, 3H), 2.04 (s, 3H), 2.00 – 1.96 (m, 1H), 1.91 – 1.85 (m, 1H), 1.80 – 1.78 (m, 2H), 1.20 – 1.10 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 155.5, 136.9, 136.8, 136.4, 135.9, 130.2, 128.6, 128.1, 127.9, 127.9, 124.1, 117.7, 64.2, 63.8, 54.2 br, 39.6 br, 37.7, 25.9, 25.7, 24.9, 22.1, 21.3, 20.6, 20.5.

HRMS (ESI) calculated for $C_{25}H_{37}N_2O$ ($[M+H]^+$) 381.2913, found 381.2906.

3-((((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-ol, L11



L11

White solid, 76% yield. Reaction time = 12 hours.

Purification: column chromatography on silica gel, cyclohexane/Et_3N 98:2.

Further purification via recrystallization from MeOH.

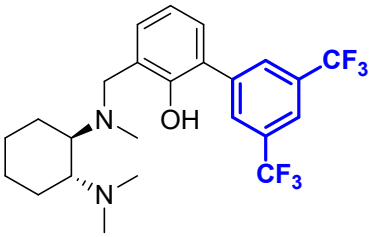
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.24 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.01 (dd, *J* = 7.3, 1.5 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 3.98 (d, *J* = 13.0 Hz, 1H), 3.23 (br s, 1H), 2.67 – 2.53 (m, 2H), 2.25 (s, 6H), 2.23 (s, 3H), 2.06 – 2.00 (m, 1H), 1.96 – 1.88 (m, 1H), 1.83 – 1.79 (m, 2H), 1.25 – 1.12 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 155.6, 143.4, 130.2 br, 130.0, 129.8, 128.20 (q, *J* = 32.2 Hz), 125.0 br, 124.8 (q, *J* = 273 Hz), 124.7 (q, *J* = 3.7 Hz), 118.2, 64.5, 64.2, 53.1, 38.4 br, 25.8, 25.7, 23.7, 22.1, 8.25.

^{19}F-NMR (376 MHz, $CDCl_3$) δ - 62.3.

HRMS (ESI) calculated for $C_{23}H_{30}N_2OF_3$ ($[M+H]^+$) 407.2307, found 407.2310.

3-((((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-ol, L12



L12

Yellow solid, 68% yield. Reaction time = 3 hours.

Purification: recrystallisation from EtOH/H_2O.

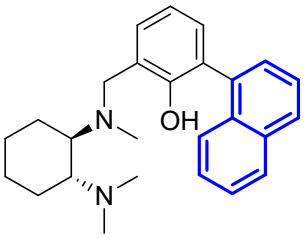
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19 (br s, 2H), 7.75 (br s, 1H), 7.29 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.06 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.83 (t, *J* = 7.5 Hz, 1H), 3.97 (d, *J* = 12.9 Hz, 1H), 3.06 (br s, 1H), 2.68 (br s, 1H), 2.56 – 2.52 (m, 1H), 2.24 (s, 3H), 2.23 (s, 6H), 2.06 – 2.03 (m, 1H), 1.94 – 1.92 (m, 1H), 1.85 – 1.83 (m, 2H), 1.26 – 1.18 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 155.7, 141.6, 131.0, 130.9 (q, *J* = 32.2 Hz), 130.0 (q, *J* = 3.0 Hz), 129.4, 125.8, 123.9 (q, *J* = 272.4 Hz), 119.8 (h, J = 3.7 Hz), 118.3, 64.8, 64.1, 51.5 br, 39.7 br, 39.4 br, 25.8, 25.7, 23.4, 22.2.

^{19}F-NMR (376 MHz, $CDCl_3$) δ - 62.9.

Elemental analysis calculated for $C_{24}H_{28}F_6N_2O$: C, 60.75; H, 5.95; F, 24.02; N, 5.90. Found C, 60.58; H, 5.92; F, 24.10; N, 5.82.

2-((((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-6-(naphthalen-1-yl)phenol, L13



L13

White solid, 60% yield. Reaction time = 24 hours.

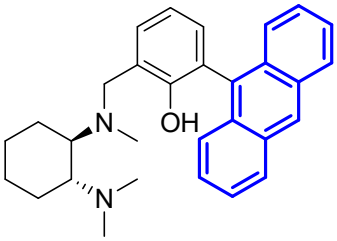
Purification: column chromatography on alumina, cyclohexane/EtOAc 100:0 to 85:15.

^{1}H-NMR (400 MHz, $CDCl_3$) (Dynamic mixture of two rotamers present in 55:45 ratio. The peaks of the two rotamers are joined by "and") δ 7.8 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.77 – 7.74 (d, *J* = 8.4 Hz and d, *J* = 8.4 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.44 (t, *J* = 7.1 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.23 – 7.17 (d, *J* = 7.8 Hz and d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.84 (t, *J* = 7.9 Hz, 1H), 4.14-3.98 (d, *J* = 13.3 Hz and d, *J* = 12.8 Hz, 1H), 3.47-3.21 (d, *J* = 13.3 Hz and d, *J* = 12.8 Hz, 1H), 2.66 – 2.51 (m, 2H), 2.31 – 2.30 (s and s, 3H), 2.13 – 2.09 (s and s, 6H), 2.03 – 2.00 (m, 1H), 1.88 – 1.79 (m, 3H), 1.27 – 1.08 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 156.0 and 155.8, 138.5 and 138.2, 133.7, 132.4 and 132.2, 131.3 and 131.25, 129.7 and 129.3, 128.5 and 128.1, 128.0 and 127.99, 127.7 and 127.5, 127.6, 127.2, 125.6 and 125.5, 125.4 and 125.3, 125.2 and124.0, 125.2 and 125.1, 117.8 and 117.7, 64.5 and 64.3, 64.1 and 63.6, 54.3 and 52.9, 39.5 br and 39.2 br, 38.6 and 38.0, 25.9 and 25.8, 25.7, 24.6 and 24.1, 22.2 and 22.0.

HRMS (ESI) calculated for $C_{26}H_{33}N_2O$ ($[M+H]^+$) 389.2575, found 389.2593.

2-(Anthracen-9-yl)-6-((((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)(methyl)amino)methyl)phenol, L14



L14

Yellow oil, >95% yield. Reaction time = 3 hours.

Purification: column chromatography on alumina, cyclohexane/Et_3N 100:0 to 95:5.

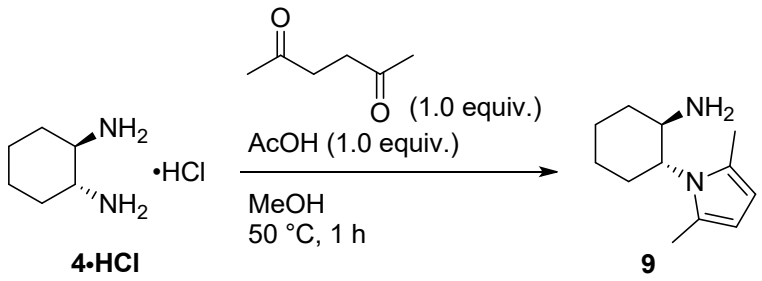
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 2H), 7.75 (dd, *J* = 15.7, 8.5 Hz, 2H), 7.43 – 7.40 (m, 2H), 7.33 – 7.31 (m, 2H), 7.16 (dd, *J* = 14.6, 8.2 Hz, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 4.12 (d, *J* = 13.1 Hz, 1H), 3.46 (br d, *J* = 13.1 Hz, 1H), 2.59 – 2.51 (m, 2H), 2.34 (s, 3H), 2.03 (s, 6H), 2.01 – 1.98 (m, 1H), 1.84 – 1.78 (m, 3H), 1.26 – 1.07 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 156.8, 132.2, 131.7, 131.7, 130.6, 130.5, 129.6, 128.4, 128.3, 127.7, 127.7, 126.1, 125.9, 125.0, 124.9, 124.8, 124.7, 117.7, 64.2, 63.7, 54.0, 38.0, 25.9, 25.7, 25.5, 24.9, 22.1.

HRMS (ESI) calculated for $C_{30}H_{35}N_2O$ ($[M+H]^+$) 439.2739, found 439.2749.

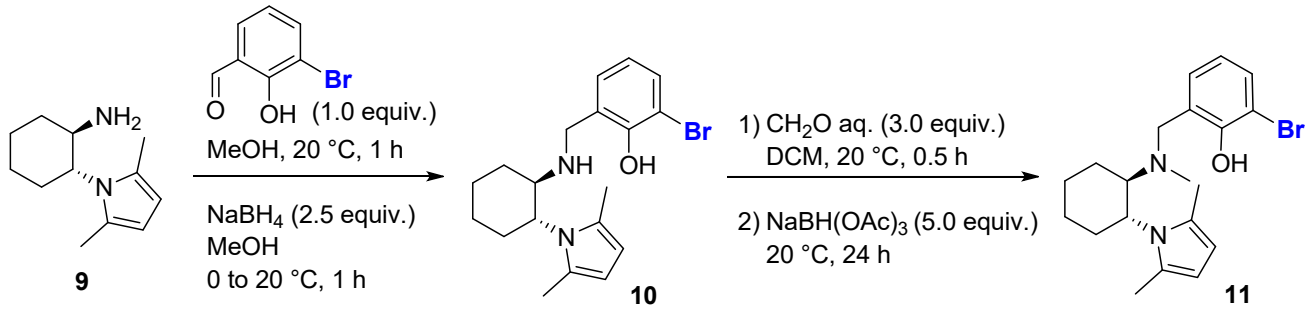
Preparation of *N*-pyrrolidyl analogue ligand L12'

i) Preparation of (*R*,*R*)-*N*-pyrrolidyl-1,2-DACH 9[2]



To a solution of (*R*,*R*)-1,2-diaminocyclohexane monohydrochloride **4·HCl** (5.0 g, 33.19 mmol) in MeOH (150 mL) were sequentially added glacial acetic acid (1.90 mL, 33.19 mmol) and hexane-2,5-dione (3.90 mL, 33.19 mmol), and the mixture was heated to 50 °C for 1 hour. The solvent was removed under reduced pressure and the residue partitioned between DCM (150 mL) and NaOH 4.0 M (200 mL), the phases separated, and the aqueous layer extracted with DCM (3 x 50 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to obtain **9** as an orange oil (6.10 g, >95% yield), which was used without further purification.

ii) Preparation of *N*-pyrrolidyl brominated intermediate 11

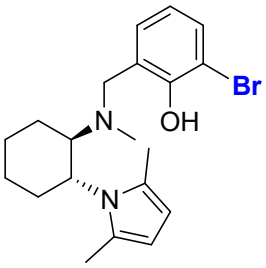


3-Bromo-2-hydroxybenzaldehyde (3.10 g, 15.44 mmol) was dissolved in methanol (150 mL) (*R*,*R*)-2-(2,5-Dimethylpyrrol-1-yl)-cyclohexylamine **9** (2.97 g, 15.44 mmol) was added and the solution was stirred at room temperature for 1 hour. The solution was cooled to 0 °C and sodium borohydride (2.5 equiv.) was added in two portions. The solution was allowed to warm to room temperature and was stirred for 1 hour. The solvent was evaporated under reduced pressure and to the residue were added diethyl ether (100 mL) and $NaHCO_3$ sat. (100 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to obtain (*R*,*R*)-**10** as a sticky yellow solid (5.15 g, 88% yield), which was used without further purification.

Under a nitrogen atmosphere, (*R*,*R*)-**10** (5.15 g, 13.6 mmol) was dissolved in dichloromethane (250 mL). Formaldehyde 37% in H_2O (3.2 mL, 40.8 mmol) was added and the solution was stirred for 10 minutes (compared to the standard procedure, in this case a shorter reaction time and the exclusion of glacial acetic acid were required to prevent degradation of the substrate via polymerization). Sodium triacetoxyborohydride (14.3 g, 68.0 mmol) was added and the solution was stirred for 24 hours. The reaction was quenched with $NaHCO_3$ sat. (150 mL) and the product was

extracted in dichloromethane (4 x 50 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified via a short silica plug, eluting with DCM, to obtain (*R*,*R*)-**11** as a white solid (4.38 g, 82% yield).

2-Bromo-6-((((1*R*,2*R*)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)cyclohexyl)(methyl)amino)methyl)phenol, 11



11

White solid, 82% yield (over 2 steps).

Purification: short silica plug, eluting with DCM 100%.

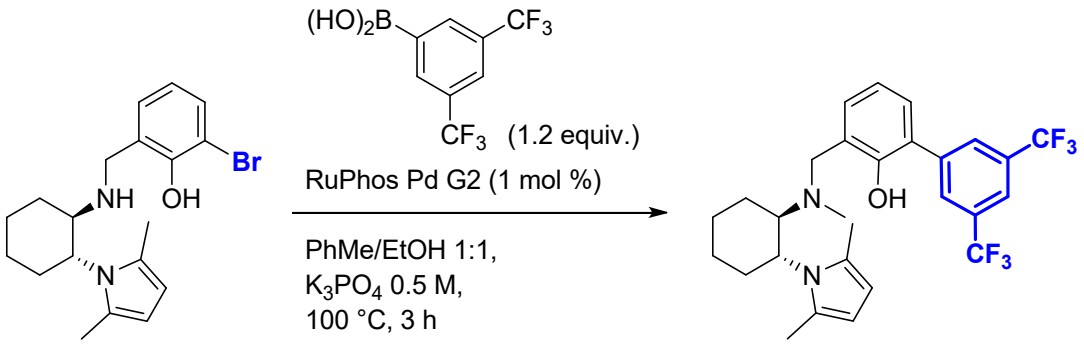
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.80 – 6.76 (m, 1H), 6.59 (t, *J* = 7.7 Hz, 1H), 5.84 (s, 1H), 5.83 (s, 1H), 4.01 – 3.91 (m, 1H), 3.71 (d, *J* = 14.0 Hz, 1H), 3.46 – 3.36 (m, 2H), 2.33 (s, 3H), 2.26 (s, 3H), 2.20 (s, 3H), 2.15 – 2.07 (m, 1H), 1.97 – 1.79 (m, 4H), 1.54 – 1.43 (m, 1H), 1.38 – 1.26 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 155.1, 132.1, 127.9, 127.8, 127.1, 123.2, 119.7, 110.2, 109.1, 106.9, 63.2, 57.9, 56.6, 35.5, 33.1, 28.2, 26.0, 25.5, 15.7, 13.7.

HRMS (ESI) Calculated for $C_{21}H_{27}BrN_2O$ ($[M+H]^+$) 391.1385; found 391.1374.

IR (film) 2930, 1455, 1393, 1292, 1020, 729 cm^{-1}.

iii) Synthesis of ligand L12' via Suzuki-Miyaura coupling

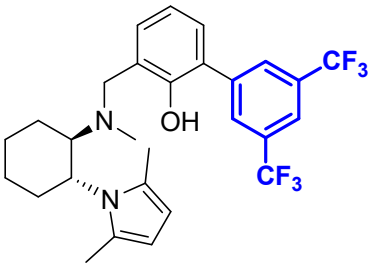


11 **L12'**

(*R*,*R*)-**11** (3.50 g, 8.94 mmol), RuPhos Pd G2 (1 mol %) and 3,5-bis-(trifluoromethyl)benzeneboronic acid (2.77 g, 10.73 mmol) were added to a flame-dried 25 mL crimp-top vial. The vial was sealed and placed under a nitrogen atmosphere. Degassed toluene (18 mL) and ethanol (18 mL) were added followed by K_3PO_4 0.5 M solution (degassed, 70 mL). The biphasic mixture was heated to 100 °C for 3 hours under vigorous stirring. The reaction mixture was cooled to room temperature and filtered through a pad of Celite™ eluting with ethyl acetate, yielding a clear yellow solution. Water

was added, the phases were separated, and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with water, then brine and dried over Na_2SO_4. Removal of the solvent yielded the crude product which was purified via a silica plug eluting with dichloromethane, to obtain (*R*,*R*)-**L12'** as a yellow solid (4.05 g, 86% yield). The product was further purified via recrystallization from ethanol to obtain pure (*R*,*R*)-**L12'** as a white solid (2.82 g, 60% yield).

3-((((1*R*,2*R*)-2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)cyclohexyl)(methyl)amino)methyl)-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-ol, L12'



L12'

White solid, 86% yield.

Purification: column chromatography on silica gel, DCM 100%.

Further purification via recrystallization from EtOH (60% yield).

^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.10 (br s, 2H), 7.77 (br s, 1H), 7.27 – 7.26 (m, 1H), 6.96 (d, *J* = 7.0 Hz, 1H), 6.83 (t, *J* = 7.0 Hz, 1H), 5.82 (br s, 2H), 4.06 – 4.02 (m, 1H), 3.91 (d, *J* = 13.9 Hz, 1H), 3.66 (br d, *J* = 13.9 Hz, 1H), 3.45 (td, *J* = 11.3, 3.5 Hz, 1H), 2.35 (s, 3H), 2.26 (s, 3H), 2.25 (s, 3H), 2.16 – 2.13 (m, 1H), 1.98 – 1.87 (m, 4H), 1.48 – 1.35 (m, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$) δ 155.9, 140.6, 131.2 (q, *J* = 32.8 Hz), 129.8 – 129.7 (m), 129.5, 129.3, 128.2, 126.57, 125.2, 123.9 (q, *J* = 272.7 Hz), 122.5, 120.2 (h, *J* = 3.4 Hz), 119.2, 109.3, 106.9, 64.3, 57.6 br, 57.0, 36.0 br, 33.2, 26.2, 25.7, 25.5, 15.6, 13.6.

^{19}F-NMR (470 MHz, $CDCl_3$) δ - 62.72.

HRMS (ESI) Calculated for $C_{29}H_{30}F_6N_2O$ ($[M+H]^+$) 525.2341; found 525.2327.

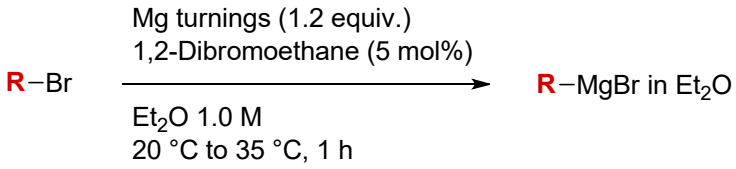
IR (film) 2934, 1376, 1277, 1124, 745 cm^{-1}.

m.p. = 140-143 °C

Asymmetric Grignard synthesis of chiral tertiary alcohols

General procedure for the preparation of Grignard reagents in Et_2O

The Grignard reagents which were not commercially available as Et_2O solutions, were prepared from the corresponding alkyl bromides or aryl bromides and magnesium turnings in dry Et_2O, using 1,2-dibromoethane as activating agent, following the general procedure described below (in contrast with the established preparations of Grignard reagents in THF, the use of Et_2O has been sparsely reported in the literature. The different physical-chemical properties of the two ethers made it necessary to develop a new procedure for the preparation of Grignard reagents in Et_2O, since the standard THF one showed generally poor performances).



To a flame dried 25 mL Schlenk flask under N_2, were added Mg turnings (54 mg, 2.2 mmol, 1.1 equiv.). Mg was subjected to 3 cycles of heating (heatgun, T = 350 °C, under N_2)/vacuum (<0.1 mbar). In the meanwhile, in a flame dried 25 mL Schlenk flask under N_2, was prepared a 1.0 M solution of dry bromide (2.0 mmol, 1.0 equiv.) in dry Et_2O (**Note 1**). The magnesium turnings were covered with the minimum volume of dry Et_2O (0.3 - 0.5 mL) and 10% of the bromide solution was added at room temperature, under slow stirring. 1,2-Dibromoethane (10 µL, 0.1 mmol, 5 mol%) was added to the reaction mixture via a gas-tight micro syringe (**Note 2**), resulting in the immediate start of the reaction, at which point the stirring rate was increased to 800-1000 rpm (**Note 3**). The remaining bromide solution was then added dropwise, at such a rate to maintain a gentle reflux. At the end of the addition, the mixture was stirred for 1 hour at room temperature, until most of the magnesium turnings had been consumed. The resulting cloudy solution was then transferred in a dry J Young flask under N_2 to remove the remaining magnesium turnings and titrated.

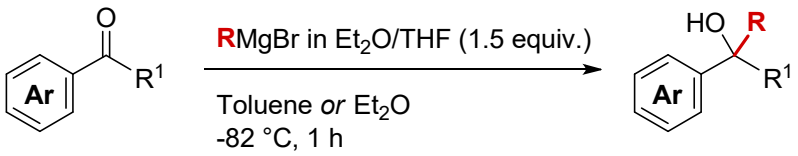
Titration with menthol/1,10-phenanthroline: in a dry 10 mL Schlenk flask under N_2 the freshly prepared Grignard reagent in Et_2O (500 µL) was diluted with dry toluene (2 mL), and the solution stirred at room temperature. 1,10-Phenanthroline (5 mg) was added, and the resulting purple mixture was titrated with a (-)-menthol solution (1.0 M in dry toluene).

Note 1: the bromide was pre-dried over 4Å molecular sieves, to ensure the exclusion of water from the system, as it was noted that the presence of residual water had a significant impact over the induction period of the reaction, affecting the reaction outcome and, in turn, the reproducibility of the transformation.

Note 2: I_2 could be used in place of 1,2-dibromoethane as activating agent. After the heating/vacuum cycles, to the dried magnesium turnings a crystal of I_2 was added, followed by dry Et_2O. Addition of 10% of the bromide solution caused the reaction to start, as indicated by the discoloration of the dark solution.

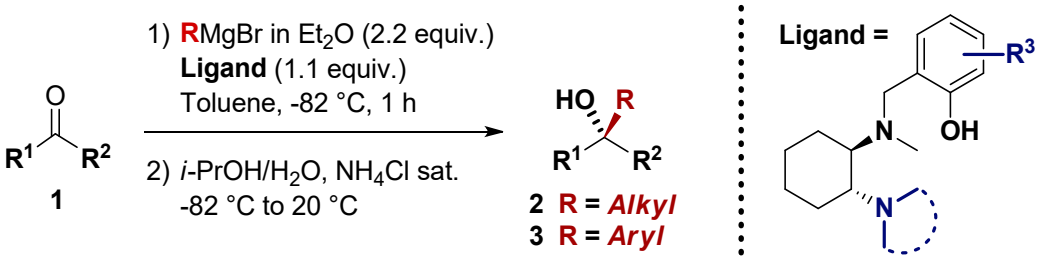
Note 3: In the eventuality that the reaction did not start after adding 1,2-dibromoethane, the mixture was heated gently, a few seconds at a time, by using a heat gun (T = 80 °C) or a water bath (T = 80-90 °C), taking care to avoid excessive refluxing of the ether solvent.

General procedure for the preparation of racemic tertiary alcohols



In a 50 mL flame-dried Schlenk flask under nitrogen was prepared a solution of ketone (3.0 mmol) in dry toluene or dry Et_2O (10 mL). The solution was cooled to -82 °C and the Grignard reagent (4.5 mmol, solution in Et_2O or THF) was added dropwise. The mixture was stirred at -82 °C for 1 hour and then quenched with NH_4Cl sat. (3 mL) and H_2O (3 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel, eluting with pentane/Et_2O 95:5 to 80:20 to obtain the pure tertiary alcohol.

General procedure for the asymmetric Grignard synthesis of chiral tertiary alcohols



To a 25 mL flame-dried Schlenk flask, under nitrogen, was added the ketone **1** (0.1 mmol, **Note 1**) followed by dry toluene (1.2 mL). The DACH-derived ligand (0.11 mmol, 1.1 equiv.) was added, the solution stirred at 600-750 rpm for 5 minutes at room temperature and then cooled to -82 °C with a EtOAc/liquid N_2 cold bath. The Grignard reagent in Et_2O (0.22 mmol, 2.2 equiv.) was diluted with dry toluene (400 µL) in a 1 mL syringe (**Note 2**). The resulting solution was added to the ketone/ligand solution dropwise at -82 °C, over 15 minutes (ca 1 drop/5 seconds). The reaction mixture was stirred at -82 °C for 1 hour and then quenched at that temperature with a solution of *i*-PrOH/H_2O 1:1 (0.3 mL), followed by NH_4Cl sat. (0.3 mL) and diluted with heptane (1 mL). The cooling bath was removed, and the mixture allowed to warm up to room temperature under vigorous stirring. The layers were separated, and the aqueous phase was extracted with heptane (3 x 10 mL). The combined organic phases were washed with H_2O (2 x 10 mL) and brine (10 mL), dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel, eluting with pentane/Et_2O 95:5 to 80:20 to obtain the pure scalemic tertiary alcohol. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase. The conversion was determined either via HPLC or NMR analysis of the crude reaction mixture after work-up.

Chiral ligand recovery: a slight modification of the work-up allowed recovery of the ligand from the crude reaction mixture, without interfering with the isolation of the tertiary alcohol product. Following the extraction of the crude reaction mixture with heptane (3 x 10 mL), the combined organic phases were first washed with a solution of AcOH in H_2O (20% (v/v), 2 x 10 mL). The work-up was then continued as described above for isolating the alcohol product, by washing with H_2O (2 x 10 mL) and brine (10 mL). To recover the ligand, the combined AcOH washings were neutralized with NaOH 5.0 M and extracted with Et_2O (3 x 10 mL) or DCM (3 x 10 mL). The combined organic phases were washed

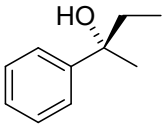
with H_2O (10 mL) and brine (10 mL), dried over sodium sulfate, filtered and the solvent removed under reduced pressure to obtain the pure ligand, which could be further purified by recrystallization from MeOH or EtOH/H_2O.

Note 1: Liquid and/or hygroscopic ketones were used as 0.5 M solutions in dry toluene: the ketone was pre-dried over 4Å molecular sieves and then dissolved in dry toluene to obtain a 0.5 M solution, which was stored in a J Young flask under N_2. On the other hand, solid and non-hygroscopic ketones did not require the preparation of 0.5 M solutions in toluene and were added to the reaction flask as solids.

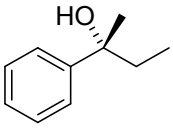
Note 2. Diluting the Grignard reagent in Et_2O with dry toluene: *Small scale preparations:* the Grignard reagent was diluted with dry toluene in the 1 mL syringe, by sequentially withdrawing ca. 400 µL of dry toluene, followed by the exact volume of Grignard reagent (e.g. for EtMgBr 3.0 M, 0.22 mmol = 73 µL), and the remaining volume of the syringe filled with N_2 gas to a total volume of ca. 0.9 – 1.0 mL (withdrawn from the N_2 atmosphere above the Grignard solution. Specifically, after withdrawing the Grignard solution, the needle was raised out of the solution into the N_2 atmosphere). The resulting mixture was cautiously mixed in the syringe by gently shaking it 4-5 times, taking care to maintain the solution under inert atmosphere. 1 mL plastic syringes (stopperless) provided optimal results and excellent reproducibility, representing a cost-effective and easy-to-handle alternative to the use of gas-tight glass syringes.
Large scale preparations: the Grignard reagent was diluted with dry toluene in a separate 10-20 mL Schlenk flask, pre-dried and under N_2.

Addition of *alkyl* Grignard reagents to ketones

2-Phenylbutan-2-ol, 2a



(*S*)-**2a**
Acetophenone + EtMgBr
or
Methyl ethyl ketone + PhMgBr



(*R*)-**2a**
Propiophenone + MeMgBr

Colourless oil.

(*S*)-**2a** 63% yield, 87% *ee*, (*R*,*R*)-**L12** (acetophenone + EtMgBr).

(*R*)-**2a** 82% yield, 92% *ee*, (*R*,*R*)-**L12** (propiophenone + MeMgBr).

(*S*)-**2a** 66% yield, 54% *ee*, (*R*,*R*)-**L12** (methyl ethyl ketone + PhMgBr).

The absolute configuration of **2a** was determined by comparison with our previous results and literature data.[2]

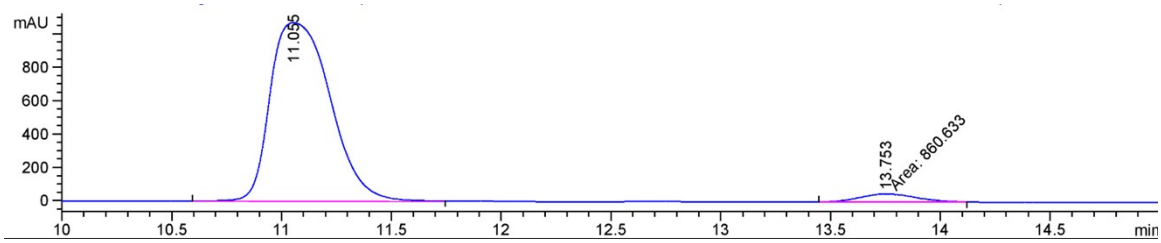
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.37 – 7.30 (m, 2H), 7.28 – 7.20 (m, 1H), 1.84 (qd, *J* = 7.4, 4.1 Hz, 2H), 1.69 (s, 1H), 1.55 (s, 3H), 0.80 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 147.7, 128.1, 126.5, 124.9, 74.9, 36.7, 29.7, 8.3.

Analytical data was in accordance with literature reported results.[3]

HPLC analysis on chiral stationary phase: Chiralcel® OJ-H column, 95/5 heptane/EtOH, 1 mL/min., 20 °C, 210 nm.

a) (*R*)-**2a** 92% *ee*, retention times: t_M = 11.06 min. and t_m = 13.75 min. (propiophenone + MeMgBr; (*R*,*R*)-**L12**).

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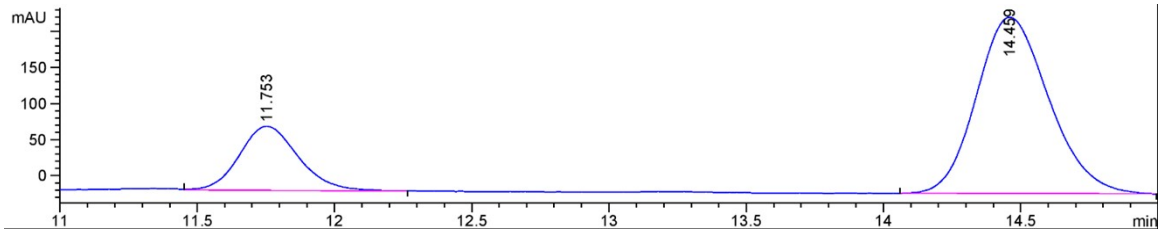
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.055 VB    0.3048 2.04648e4  1071.84814  95.9643
   2  13.753 MM    0.2961  860.63348   48.43842   4.0357

Totals :                  2.13255e4  1120.28656
```

b) (*S*)-**2a** 54% *ee*, retention times: t_m = 11.75 min and t_M = 14.46 min. (methyl ethyl ketone + PhMgBr; (*R*,*R*)-**L12**).

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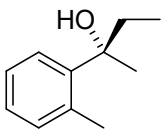
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.753 VB    0.2264 1327.75342   88.83912  22.8544
   2  14.459 BBA   0.2839 4481.85498  244.49513  77.1456

Totals :                  5809.60840  333.33425
```

2-(*o*-Tolyl)butan-2-ol, 2b



Colourless oil.

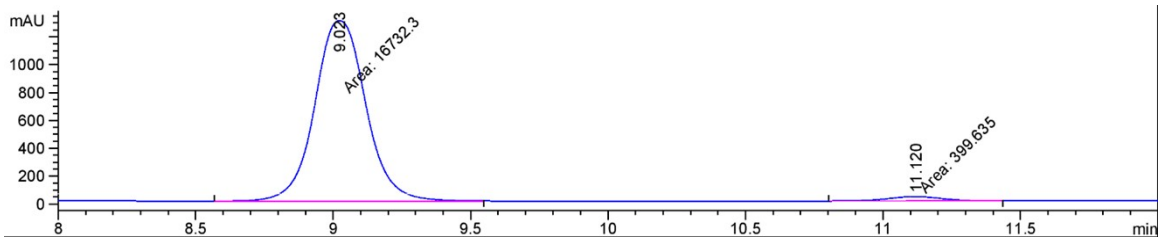
67% yield, 95% *ee*, (*R*,*R*)-**L12**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.39 (m, 1H), 7.20 – 7.09 (m, 3H), 2.61 (s, 3H) 2.08 – 1.83 (m, 2H), 1.62 (s, 3H), 0.80 (t, *J* = 7.5 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 144.6, 135.4, 132.4, 126.7, 126.7, 125.3, 76.0, 34.4, 28.7, 22.2, 8.4.

Analytical data were in accordance with literature reported results.[3]

HPLC analysis on chiral stationary phase: Chiralpak® IA column, 98/2 heptane/ethanol, 1 mL/min., 20 °C, 210 nm, retention times: t_M = 9.02 min and t_m = 11.12 min.

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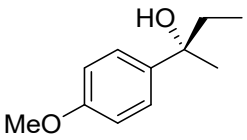
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   9.023 MM    0.2149 1.67322e4  1297.52917  97.6673
   2  11.120 MM    0.2196  399.63528   30.33572   2.3327

Totals :                  1.71319e4  1327.86489
```

4-Methoxyphenyl-butan-2-ol, 2c



Colourless liquid.

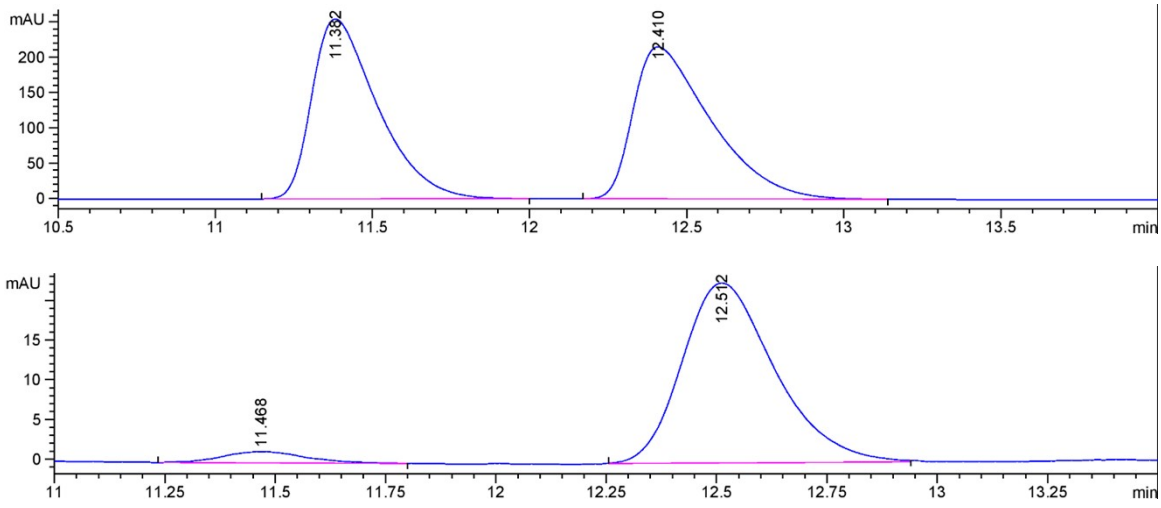
87% yield, 90% *ee*, (*R*,*R*)-**L12**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 1.81 (m, 2H), 1.52 (s, 3H), 0.79 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 158.1, 139.9, 126.1, 113.3, 74.6, 55.2, 36.7, 29.5, 8.5.

Analytical data was in accordance with literature reported results.[3]

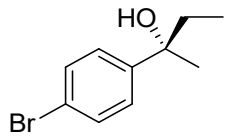
HPLC analysis on chiral stationary phase: Chiralpak® IB column, 99/1 heptane/ethanol, 1 mL/min., 20 °C, 254 nm, retention times: t_m = 11.47 min. and t_M = 12.51 min.



Signal 1: DAD1 A, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.467	MM	0.2085	279.43683	22.34037	4.9262
2	12.512	MM	0.2440	5392.99561	368.42416	95.0738
Totals :				5672.43243	390.76454	

2-(4-Bromophenyl)butan-2-ol, 2d



Colourless oil.

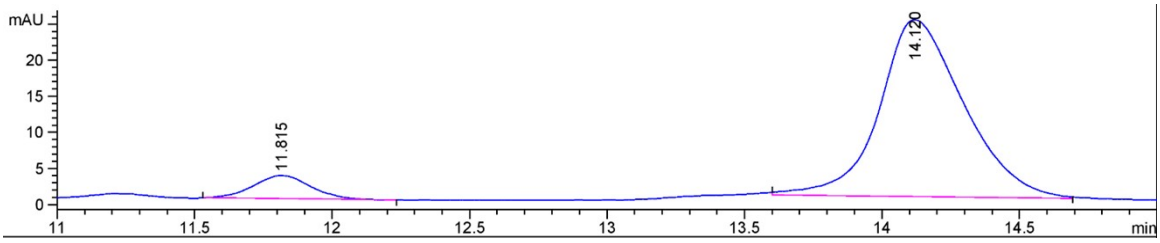
65% yield, 84% *ee*, (*R*,*R*)-**L12**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.7 Hz), 7.30 (d, *J* = 8.7 Hz), 1.88 – 1.73 (m, 2H), 1.68 (broad s, 1H), 1.52 (s, 3H), 0.79 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 146.9, 131.3, 127.0, 120.6, 74.9, 36.8, 29.9, 8.3.

Analytical data was in accordance with literature reported results.[5]

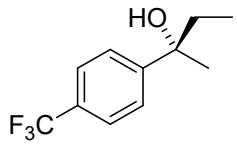
HPLC analysis on chiral stationary phase: Chiralpak® IA column, 98/2 heptane/ethanol, 1 mL/min., 20 °C, 254 nm, retention times: t_m = 11.81 min. and t_M = 14.12 min.



Signal 1: DAD1 A, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.815	BB	0.2187	45.72985	3.20049	8.0124
2	14.120	BB	0.3181	525.00873	24.49507	91.9876
Totals :				570.73858	27.69556	

2-(4-(Trifluoromethyl)phenyl)butan-2-ol, 2e



Colourless oil.

87% yield, 60% *ee*, (*R*,*R*)-**L12**.

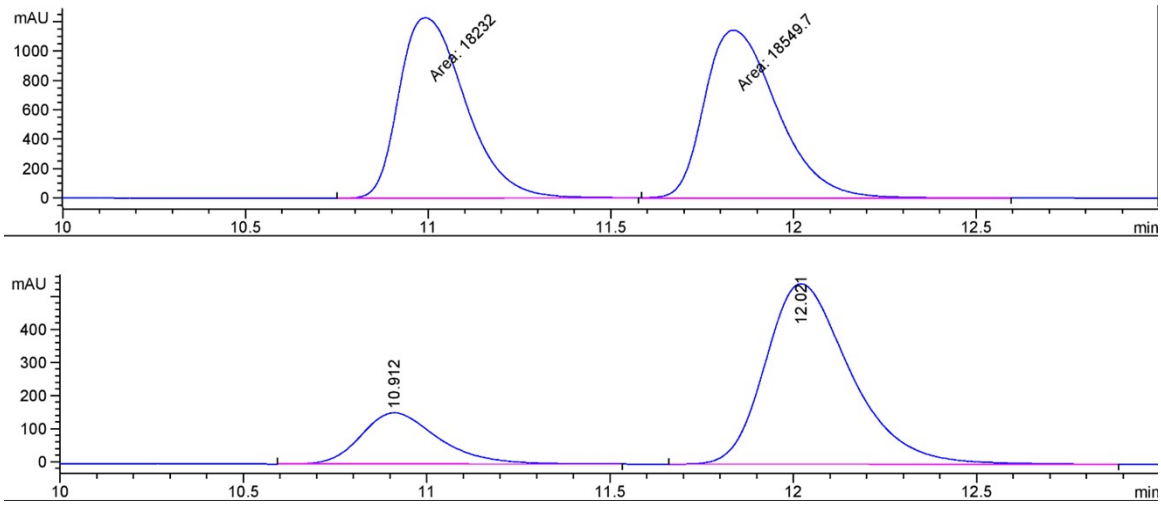
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.46 (m, 4H), 1.90 – 1.87 (m, 2H), 1.56 (s, $3H_3$), 0.80 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 151.7, 125.3, 125.1, 125.0, 125.0, 125.0, 120.2, 74.8, 36.6, 29.8, 8.1.

^{19}F-NMR (376 MHz, $CDCl_3$) δ -62.4.

Analytical data was in accordance with literature reported results.[3]

HPLC analysis on chiral stationary phase: Chiracel® OJ-H column, 99/1 heptane/ethanol, 1 mL/min., 20 °C, 210 nm, retention times: t_m = 10.91 min. and t_M = 12.02 min.

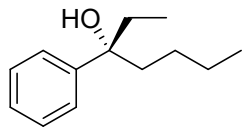



```
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.912 BB    0.2233 2271.54004  154.72166  20.4248
   2  12.021 BB    0.2473 8849.95605  545.36005  79.5752

Totals :                 1.11215e4   700.08171
```

3-Phenylheptan-3-ol, 2f



Colourless oil.

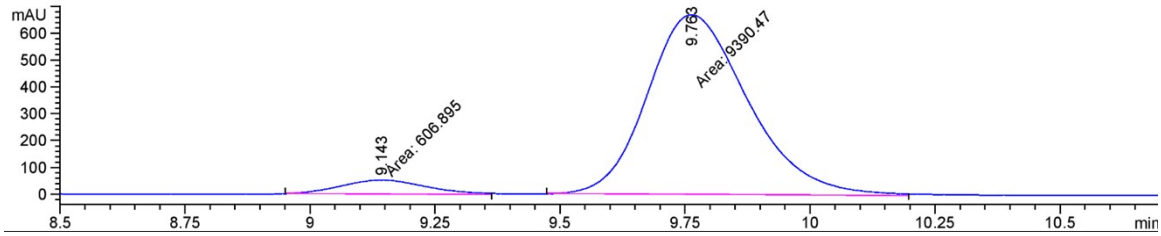
52% yield, 87% *ee*, (*R*,*R*)-**L12**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.25 – 7.21 (m, 1H), 1.91 – 1.74 (m, 4H), 1.70 (s, 1H), 1.30 – 1.22 (m, 3H), 1.06 – 1.02 (m, 1H), 0.84 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.4 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 146.3, 128.1, 126.3, 125.5, 77.3, 42.4, 35.5, 25.8, 23.2, 14.2, 7.9.

Analytical data was in accordance with literature reported results.[6]

HPLC analysis on chiral stationary phase: Chiracel® OJ-H column, 99/1 heptane/ethanol, 1 mL/min., 20 °C, 210 nm, retention times: t_m = 9.14 min. and t_M = 9.76 min.

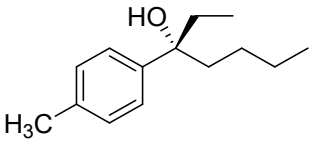



```
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   9.143 MM    0.1951  606.89514   51.84236   6.0705
   2   9.763 MM    0.2331 9390.47168  671.39478  93.9295

Totals :                  9997.36682  723.23713
```

3-(*p*-Tolyl)heptan-3-ol, 2g



Colourless liquid.

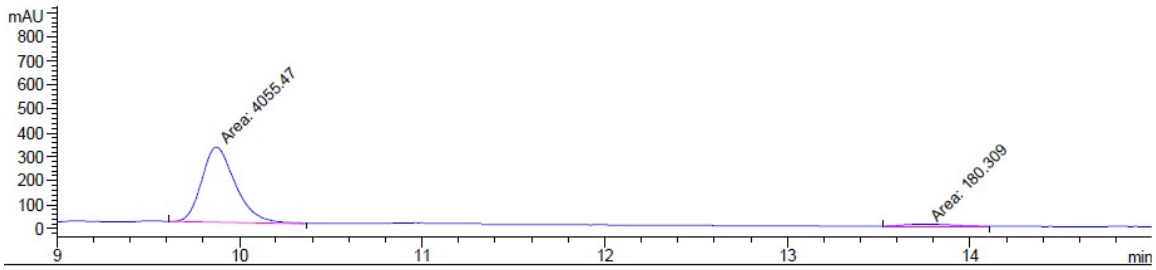
67% NMR conversion, 90% *ee*, (*R*,*R*)-**L12**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 2.32 (s, 3H), 1.90 – 1.72 (m, 4H), 1.29 – 1.17 (m, 3H), 1.09 – 0.96 (m, 1H), 0.82 (t, *J* = 7.2 Hz, 3H), 0.74 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 143.1, 135.7, 128.8, 125.1, 77.3, 43.0, 35.5, 25.7, 23.0, 21.0, 14.1, 8.0.

Analytical data was in accordance with literature reported results.[6]

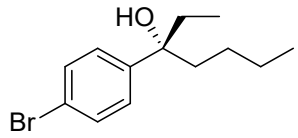
HPLC analysis on chiral stationary phase: Chiracel® OJ-H column, 99.5/0.5 heptane/ethanol, 1 mL/min., 20 °C, 210 nm, retention times: t_M = 9.82 min. and t_m = 13.67 min.



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.874	MM	0.2147	4055.46704	314.87766	95.7432
2	13.763	MM	0.3251	180.30898	9.24491	4.2568
Totals :				4235.77602	324.12256	

3-(4-Bromophenyl)heptan-3-ol, 2h



Colourless oil.

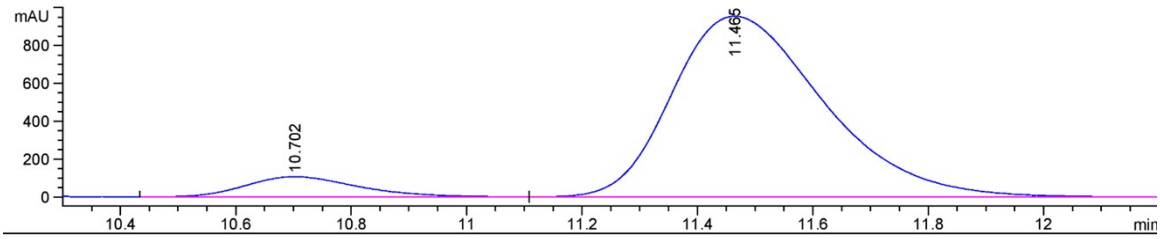
74% yield, -85% *ee*, (*R*,*R*)-**L12**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 1.90 – 1.71 (m, 4H), 1.60 (bs, 1H), 1.28 – 1.22 (m, 4H), 0.83 (t, *J* = 7.1 Hz, 3H), 0.74 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 145.3, 131.2, 127.5, 120.3, 77.2, 42.5, 35.6, 25.7, 23.2, 14.1, 7.8.

Analytical data was in accordance with literature reported results.[6]

HPLC analysis on chiral stationary phase: Chiracel® OJ-H column, 99.5/0.5 heptane/ethanol, 1 mL/min., 20 °C, 230 nm, retention times: t_m = 10.70 min. and t_M = 11.47 min.

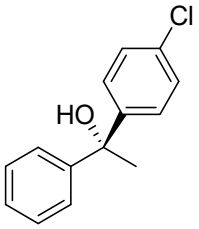


Signal 3: DAD1 D, Sig=230,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.702	VV	0.2075	1428.27148	105.82086	7.5654
2	11.465	VB	0.2834	1.74507e4	954.14191	92.4346
Totals :				1.88790e4	1059.96277	

Addition of *aryl* Grignard reagents to ketones

1-(4-Chlorophenyl)-1-phenylethan-1-ol, 3a



Colourless oil.

73% yield, 94% *ee*, (*R*,*R*)-**L12** (acetophenone + *p*-Cl-C_6H_4MgBr).

60% yield, 70% *ee*, (*R*,*R*)-**L12** (4'-chloroacetophenone + PhMgBr).

5% NMR conversion, 20% *ee*, (*R*,*R*)-**L12** (4'-chlorobenzophenone + MeMgBr).

44% conversion, 82% *ee*, (*R*,*R*)-**L12'** (acetophenone + *p*-Cl-C_6H_4MgBr).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.23 (m, 9H), 2.16 (s, 1H), 1.93 (s, 3H).

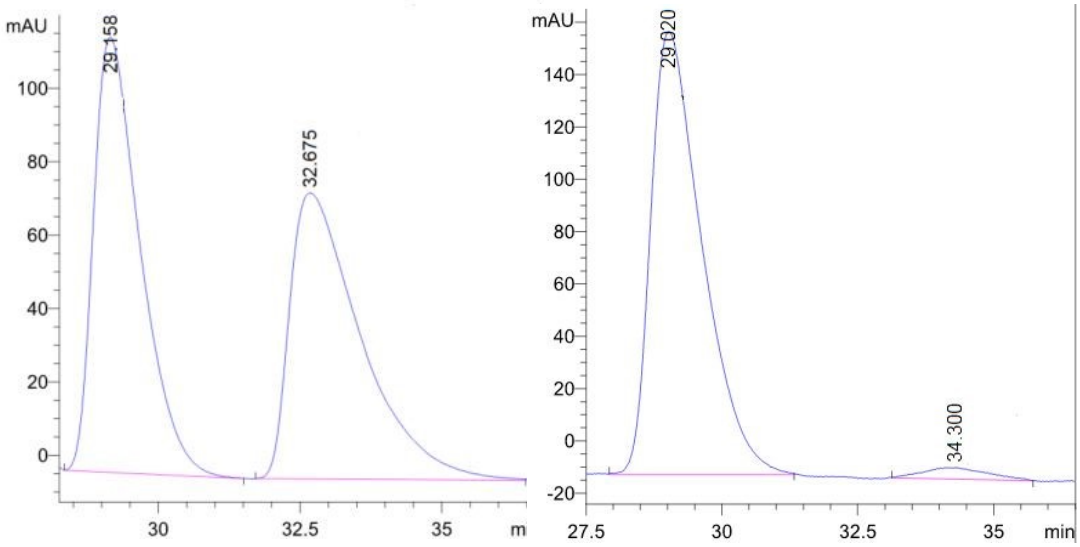
^{13}C-NMR (126 MHz, $CDCl_3$) δ 147.6, 146.7, 132.9, 128.5, 128.4, 127.5, 127.4, 125.9, 76.0, 31.0.

Analytical data were in accordance with literature reported results.[7]

$[\alpha]_D^{25}$: -15.2 (c 0.8, $CHCl_3$). Lit. $[\alpha]_D^{22}$: -11.2 (c 1.9, $CHCl_3$).[8]

HPLC analysis on chiral stationary phase: Chiralcel® OB-H column, 99/1 heptane/EtOH, 1 mL/min., 20 °C, 210 nm.

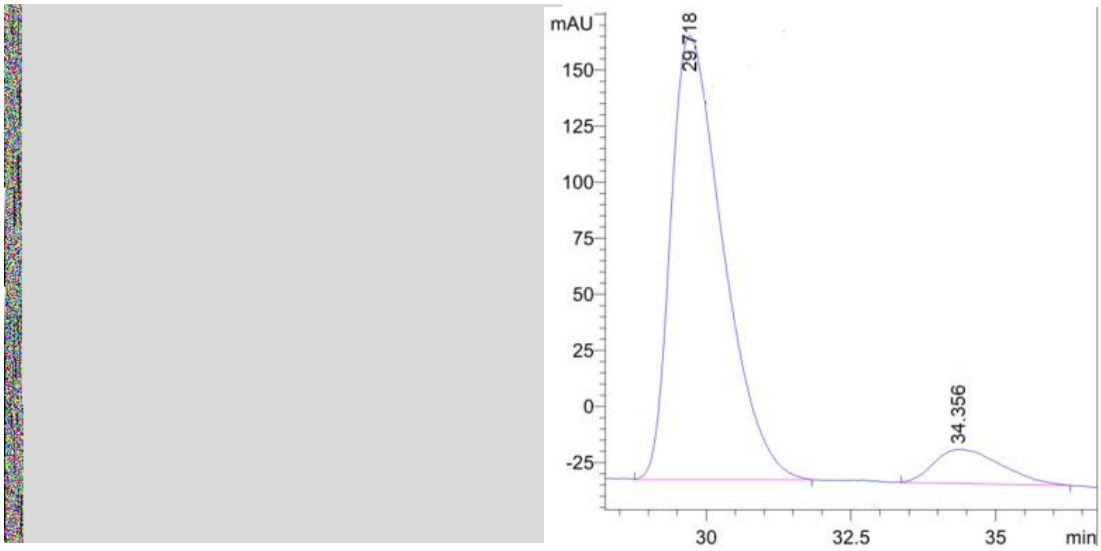
a) (*R*)-**3a** 94% *ee*, retention times: t_M = 29.02 min. and t_m = 34.30 min. (acetophenone + *p*-Cl-C_6H_4MgBr; (*R*,*R*)-**L12**).



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.020	MM	1.0941	1.11132e4	169.28648	96.8131
2	34.300	MM	1.3706	365.82666	4.44845	3.1869
Totals :				1.14790e4	173.73493	

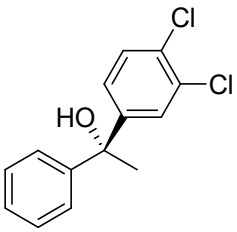
b) (*R*)-**3a** 82% *ee*, retention times: t_M = 29.72 min. and t_m = 34.36 min. (acetophenone + *p*-Cl-C_6H_4MgBr; (*R*,*R*)-**L12'**).



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.718	MM	1.0442	1.24173e4	198.18518	90.9790
2	34.356	MM	1.3466	1231.23413	15.23876	9.0210
Totals :				1.36485e4	213.42394	

1-(3,4-Dichlorophenyl)-1-phenylethan-1-ol, 3b



Colourless oil.

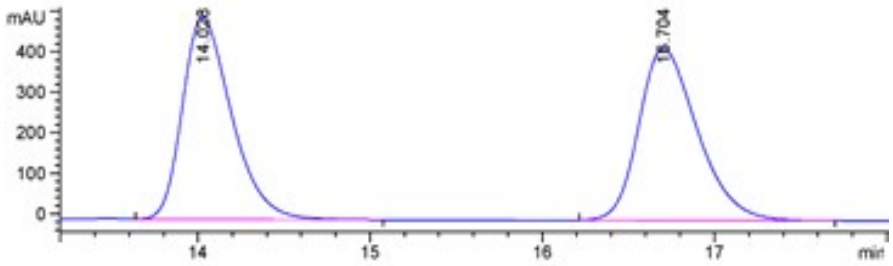
76% yield, 78% *ee*, (*R*,*R*)-**L12**.

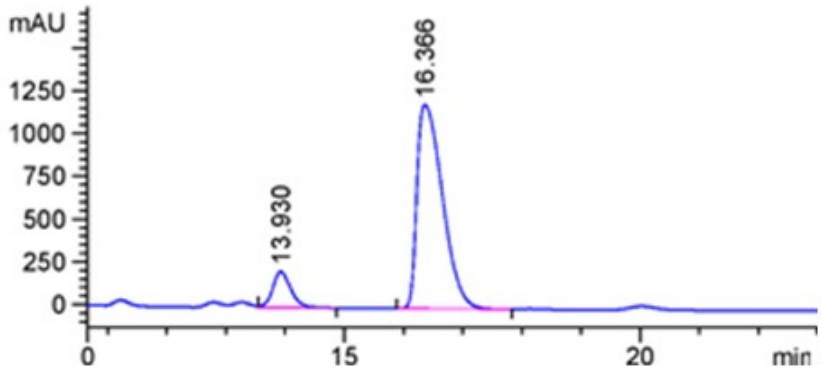
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.55 (m, 1H), 7.41 – 7.32 (m, 5H), 7.29 – 7.25 (m, 1H), 7.22 – 7.19 (m, 2H), 3.48 (s, 1H), 1.93 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 148.5, 146.9, 132.4, 131.0, 130.2, 128.6, 128.1, 127.6, 125.9, 125.6, 75.7, 30.8.

HRMS (ESI) calculated for $C_{14}H_{11}Cl_2$ ([M-OH]$^+$) 249.0232, found 249.0238.

HPLC analysis on chiral stationary phase: Chiralcel® OJ-H column, 95/5 heptane/EtOH, 1 mL/min., 20 °C, 230 nm, retention times: t_m = 13.90 min. and t_M = 16.37 min.

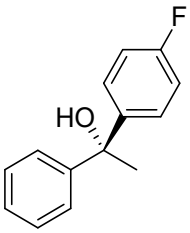




Signal 3: DAD1 D, Sig=230,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.930	VB	0.3232	4509.73633	211.17001	11.1811
2	16.366	VB	0.4770	3.58237e4	1190.78699	88.8189
Totals :				4.03334e4	1401.95700	

1-(4-Fluorophenyl)-1-phenylethan-1-ol, 3c



Colourless oil.

94% conversion, 86% *ee*, (*R*,*R*)-**L12**.

44% conversion, 79% *ee*, (*R*,*R*)-**L12'**.

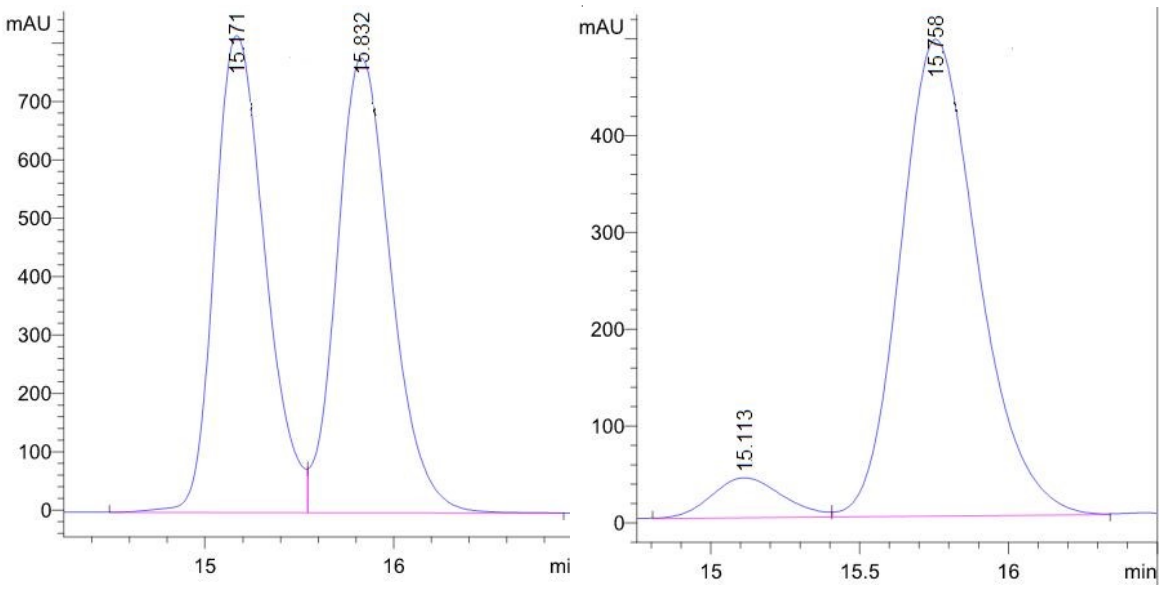
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 6H), 7.28 – 7.22 (m, 1H), 7.02 – 6.95 (m, 2H), 2.16 (s, 1H), 1.94 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 161.9 (d, *J* = 245.2 Hz), 147.9, 144.0 (d, *J* = 3.2 Hz), 128.4, 127.7, 127.3, 125.9, 115.0 (d, *J* = 21.2 Hz), 76.0, 31.2.

Analytical data were in accordance with literature reported results.[9]

HPLC analysis on chiral stationary phase: Chiralpak® IB column, 99/1 heptane/EtOH, 1 mL/min., 20 °C, 210 nm.

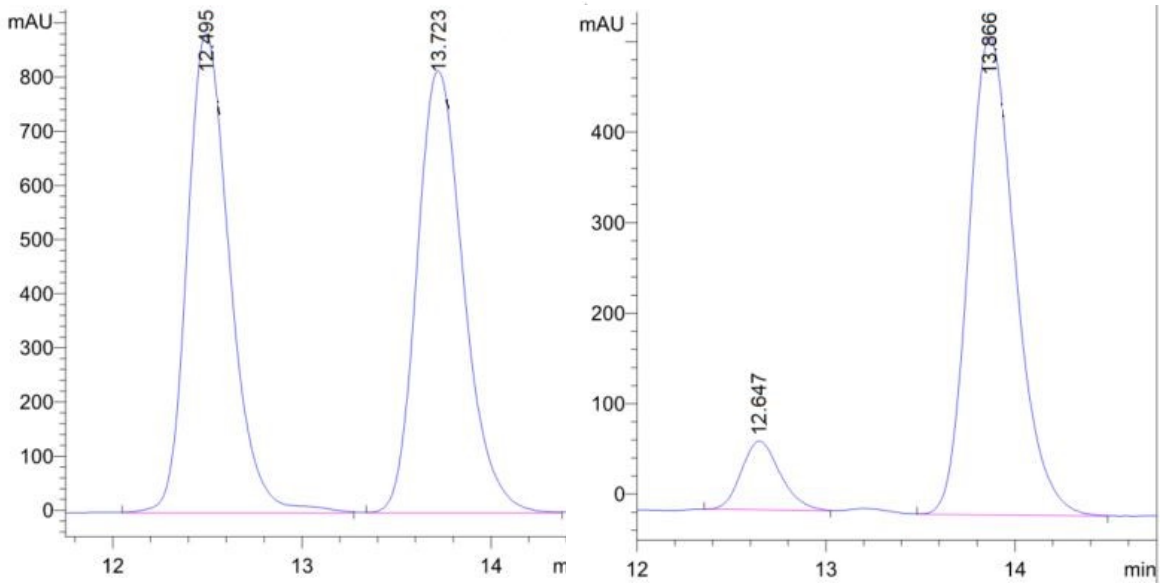
a) 86% *ee*, retention times: t_m = 15.11 min. and t_M = 15.76 min. (with ligand (*R*,*R*)-**L12**)



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.113	MF	0.2774	687.27509	41.29776	7.1304
2	15.758	FM	0.3027	8951.41504	492.88519	92.8696
Totals :				9638.69012	534.18296	

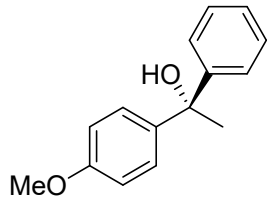
b) 79% *ee*, retention times: t_m = 12.65 min. and t_M = 13.89 min. (with ligand (*R*,*R*)-**L12'**)



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.647	MM	0.2377	1081.58301	75.84336	10.6045
2	13.866	MM	0.2873	9117.67578	528.97742	89.3955
Totals :				1.01993e4	604.82078	

1-(4-Methoxyphenyl)-1-phenylethan-1-ol, 3d



Colourless oil.

45% yield, 77% *ee*, (*S*)-**3d**, (*R*,*R*)-**L12'** (4'-methoxyacetophenone + PhMgBr).

44% yield, 65% *ee*, (*R*)-**3d**, (*R*,*R*)-**L12** (acetophenone + *p*-OMe-C_4H_6MgBr).

53% yield, 70% *ee*, (*S*)-**3d**, (*R*,*R*)-**L12** (4'-methoxyacetophenone + PhMgBr).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.35 – 7.27 (m, 4H), 7.26 – 7.20 (m, 1H), 6.87 – 6.81 (m, 2H), 3.79 (s, 3H), 2.14 (s, 1H), 1.93 (s, 3H).

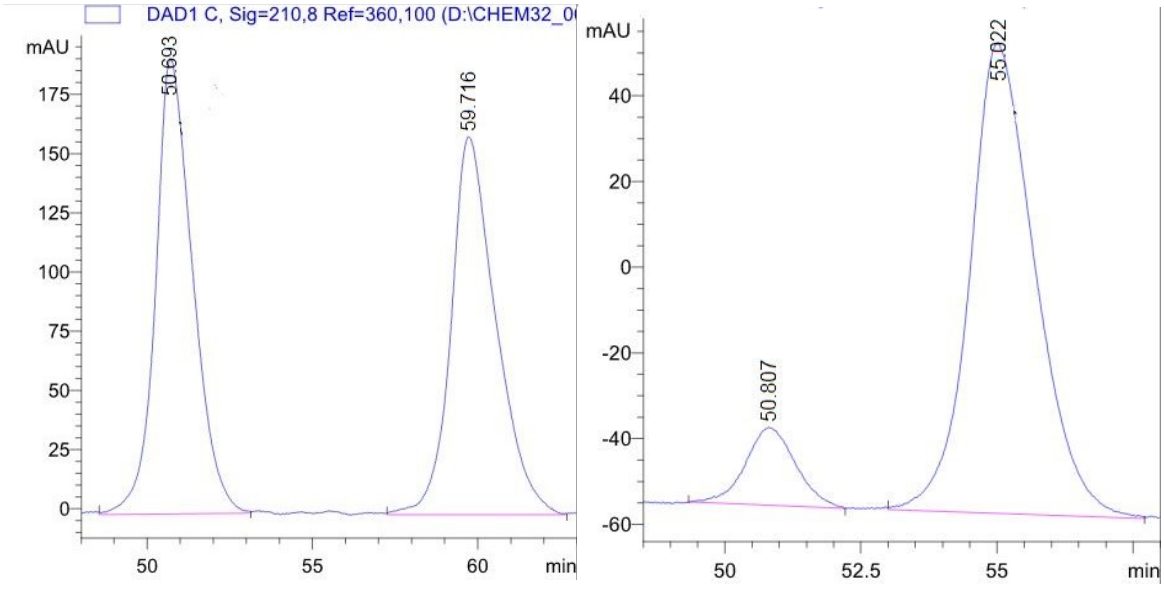
^{13}C-NMR (101 MHz, $CDCl_3$) δ 158.6, 148.4, 140.5, 128.3, 127.3, 127.0, 125.9, 113.6, 76.1, 55.4, 31.2.

Analytical data were in accordance with literature reported results.[7]

HPLC analysis on chiral stationary phase:

a) Chiralpak® IA column, 99/1 heptane/EtOH, 1 mL/min., 20 °C, 210 nm.

(*S*)-**3d** 77% *ee*, retention times: t_m = 50.8 min. and t_M = 55.0 min. (4'-methoxyacetophenone + PhMgBr; (*R*,*R*)-**L12'**).



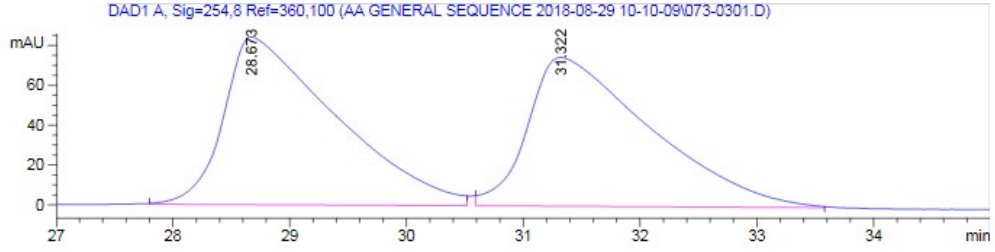

```
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

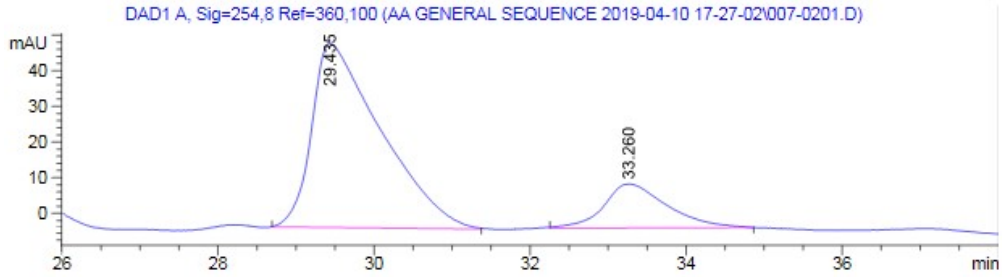
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  50.807 MM    1.0662 1161.32898   18.15326  11.2517
   2  55.022 MM    1.3893 9160.01660  109.89131  88.7483

Totals :                 1.03213e4   128.04457
```

b) Chiralpak® IA column, 98/2 heptane/EtOH, 1 mL/min., 20 °C, 254 nm.

(*R*)-**3d** 64% *ee*, retention times: t_M = 29.4 min. and t_m = 33.3 min. (acetophenone + *p*-OMe-C_4H_6MgBr; (*R*,*R*)-**L12'**).

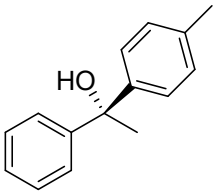




Signal 1: DAD1 A, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.435	BB	0.8484	3179.70630	51.63865	82.0070
2	33.260	MM	0.9406	697.65118	12.36160	17.9930
Totals :				3877.35748	64.00024	

1-Phenyl-1-(*p*-tolyl)ethan-1-ol, 3e



Colourless oil.

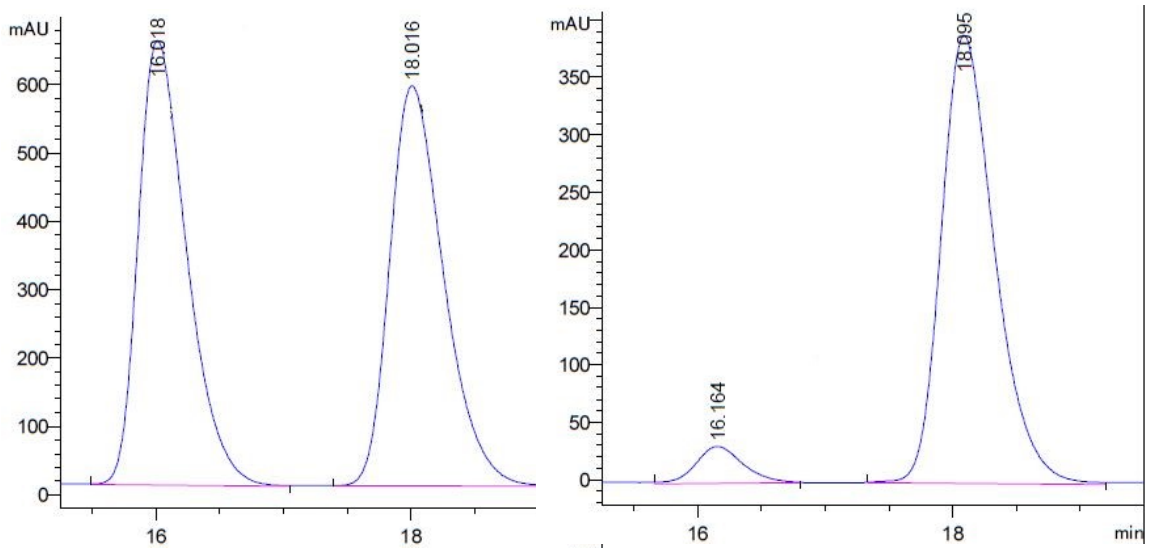
43% conversion, 86% *ee*, (*R*,*R*)-**L12'**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.35 – 7.27 (m, 4H), 7.26 – 7.20 (m, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 2.33 (s, 3H), 2.14 (s, 1H), 1.94 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 148.3, 145.3, 136.8, 129.0, 128.3, 127.0, 125.9 (2*C*), 76.3, 31.0, 21.1.

Analytical data were in accordance with literature reported results.[7]

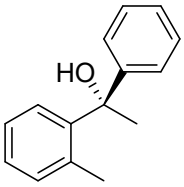
HPLC analysis on chiral stationary phase: Chiralcel® OJ-H column, 90/10 heptane/EtOH, 1 mL/min., 20 °C, 210 nm, retention times: t_m = 16.16 min. and t_M = 18.10 min.



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.164	MM	0.4348	839.86371	32.19463	6.8564
2	18.095	MM	0.4875	1.14096e4	390.04379	93.1436
Totals :				1.22494e4	422.23842	

1-Phenyl-1-(*o*-tolyl)ethan-1-ol, 3f



Colourless oil.

60% yield, 84% *ee*, (*R*,*R*)-**L12** (2'-methylacetophenone and PhMgBr).

44% NMR conversion, 40% *ee*, (*R*,*R*)-**L12** (acetophenone and *o*-Me-C_6H_4MgBr).

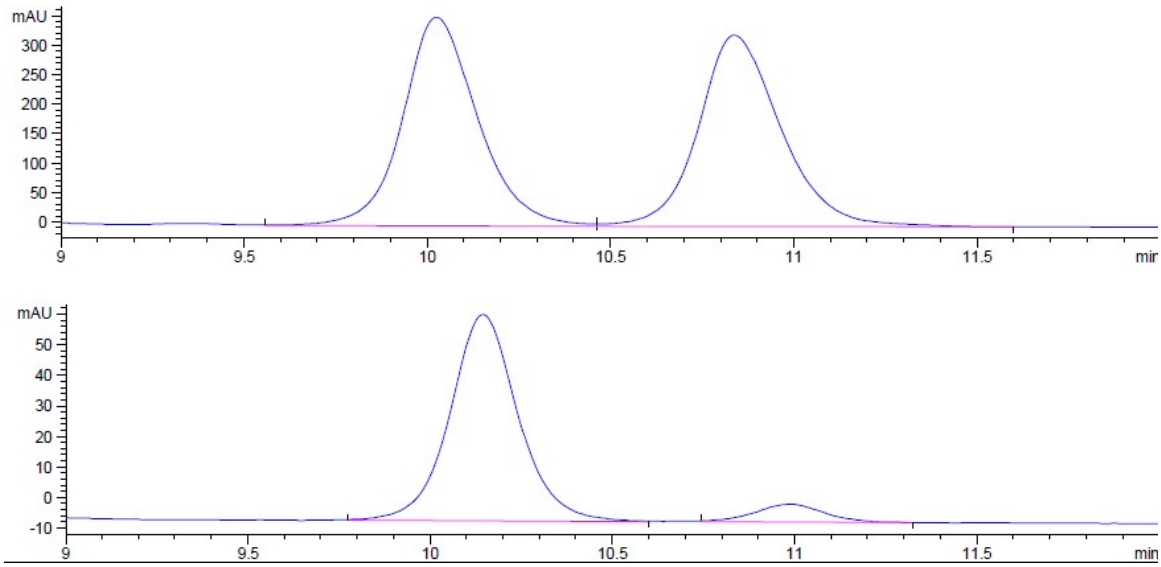
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.68 (m, 1H), 7.32 – 7.19 (m, 7H), 7.12 – 7.09 (m, 1H), 2.11 (s, 1H), 1.98 (s, 3H), 1.93 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 148.1, 144.7, 137.3, 132.6, 128.3, 127.8, 126.7, 126.1, 125.5, 125.4, 76.9, 32.3, 21.5.

Analytical data were in accordance with literature reported results.[7]

HPLC analysis on chiral stationary phase: Chiralcel® OJ-H column, 98/2 heptane/EtOH, 1 mL/min, 20 °C, 230 nm.

84% *ee*, retention times: t_M = 10.15 min. and t_m = 10.99 min. (2'-methylacetophenone + PhMgBr; (*R*,*R*)-**L12**).

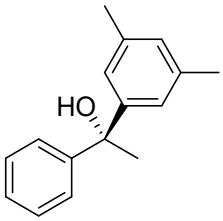



```
Signal 3: DAD1 D, Sig=230,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.145 BB    0.1983  882.52576   67.59531  91.9440
   2  10.988 BB    0.1928   77.32582    5.82843   8.0560

Totals :                  959.85158   73.42374
```

1-(3,5-Dimethylphenyl)-1-phenylethan-1-ol, 3g



Colourless oil.

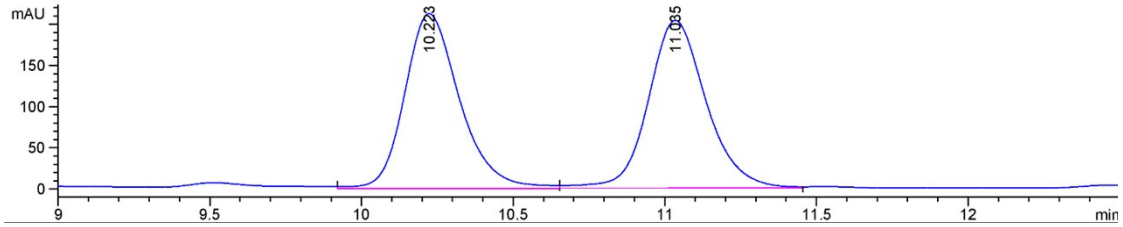
80% yield, 70% *ee*, (*R*,*R*)-**L12**.

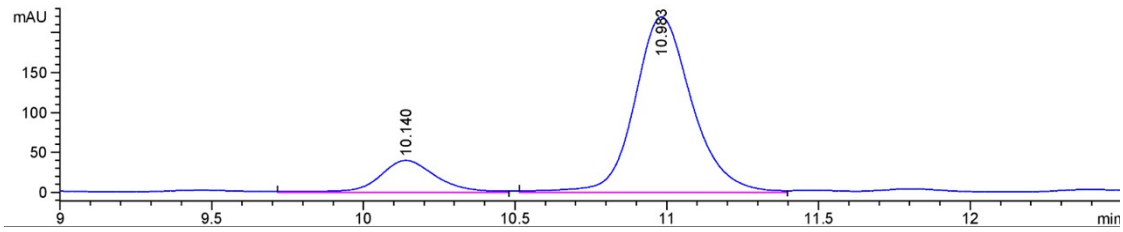
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.41 (m, 2H), 7.34 – 7.30 (m, 2H), 7.26 – 7.22 (m, 1H), 7.03 (br s, 2H), 6.89 (br s, 1H), 2.29 (s, 6H), 1.93 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 148.3, 148.1, 137.8, 128.8, 128.3, 127.0, 125.9, 123.8, 76.3, 31.1, 21.6.

HRMS (ESI) calculated for $C_{16}H_{18}ONa$ ([M+Na]$^{+}$) 249.1267, found 249.1255.

HPLC analysis on chiral stationary phase: Chiralpak® IB column, 99/1 heptane/EtOH, 1 mL/min., 20 °C, 230 nm, retention times: t_m = 10.14 min and t_M = 10.98 min.

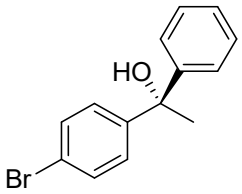




Signal 3: DAD1 D, Sig=230,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.140	VB	0.1953	507.53931	39.66140	15.0003
2	10.983	BV	0.1989	2875.98047	219.40410	84.9997
Totals :				3383.51978	259.06549	

1-(4-Bromophenyl)-1-phenylethan-1-ol, 3h



Colourless solid.

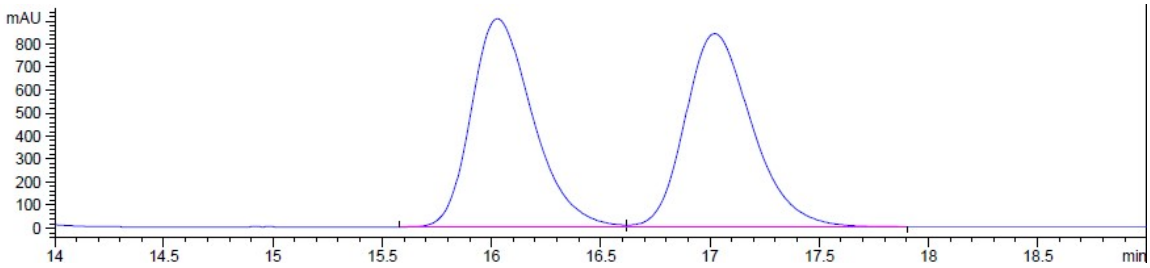
69% yield, 75% *ee*, (*R*,*R*)-**L12**.

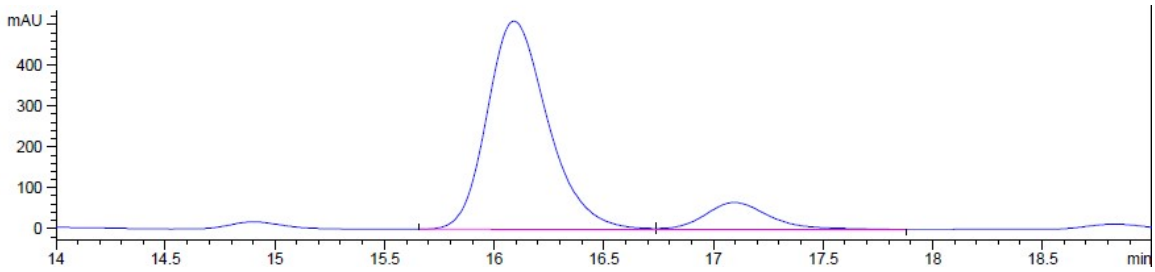
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 4H), 7.34 – 7.22 (m, 5H), 2.23 (s, 1H), 1.91 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 147.5, 147.3, 131.3, 128.5, 127.8, 127.4, 125.9, 121.1, 76.1, 30.9.

Analytical data were in accordance with literature reported results.[10]

HPLC analysis on chiral stationary phase: Chiralpak® IB column, 99/1 heptane/EtOH, 1 mL/min., 20 °C, 210 nm, retention times: t_M = 16.09 min. and t_m = 17.10 min.

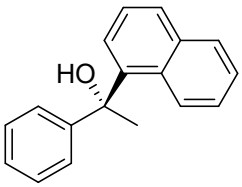




Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.091	BV	0.2953	9845.67285	509.80463	87.6857
2	17.096	VB	0.3155	1382.68958	66.25545	12.3143
Totals :				1.12284e4	576.06007	

1-(Naphthalen-1-yl)-1-phenylethanol, 3i



Yellow oil.

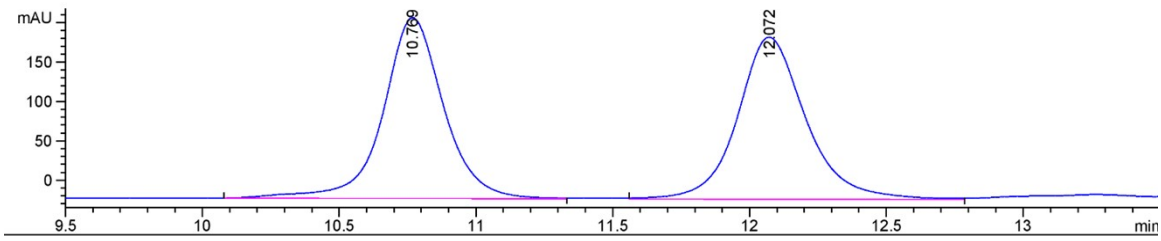
>95% NMR conversion, 38% *ee*, (*R*,*R*)-**L12**.

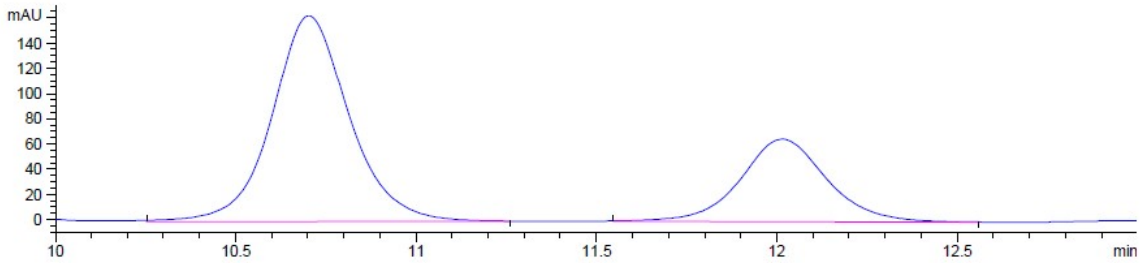
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 4H), 7.51 – 7.48 (m, 2H), 7.39 – 7.33 (m, 3H), 7.27 – 7.18 (m, 4H), 2.42 (s, 1H), 2.07 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 148.7, 142.2, 135.0, 130.8, 129.2, 128.9, 128.4, 127.4, 126.9, 125.5, 125.4, 125.3, 124.8, 124.2, 77.3, 33.0.

Analytical data were in accordance with literature reported results.[3]

HPLC analysis on chiral stationary phase: Chiralpak® IA column, 97/3 heptane/EtOH, 1 mL/min., 20 °C, 254 nm, retention times: t_M = 10.70 min and t_m = 12.02 min.

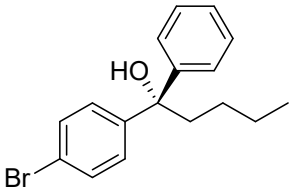




Signal 1: DAD1 A, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.702	BB	0.2223	2437.05273	163.10019	69.0876
2	12.015	BB	0.2505	1090.43042	65.42350	30.9124
Totals :				3527.48315	228.52369	

1-(4-Bromophenyl)-1-phenylpentan-1-ol, 3l



Colourless oil.

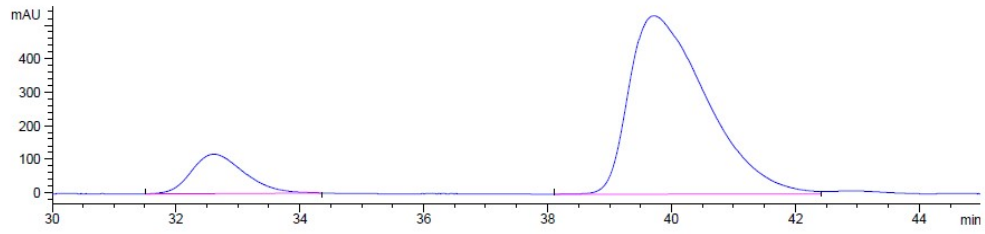
60% yield, 74% *ee*, (*R*,*R*)-**L12**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 4H), 7.34 – 7.28 (m, 4H), 7.26 – 7.22 (m, 1), 2.29 – 2.22 (m, 2H), 2.13 (br s, 1H), 1.41 – 1.18 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 146.8, 146.3, 131.3, 128.4, 128.0, 127.2, 126.1, 120.8, 78.1, 41.7, 26.0, 23.2, 14.2.

HRMS (ESI) calculated for $C_{17}H_{18}Br$ ([M-OH]$^+$) 301.0582, found 301.0592.

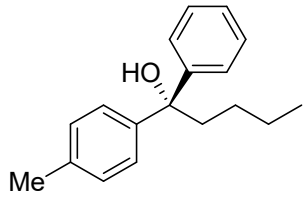
HPLC analysis on chiral stationary phase: Chiralcel® OJ-H column, 99.5/0.5 heptane/EtOH, 1 mL/min., 20 °C, 210 nm, retention times: t_m = 32.62 min. and t_M = 39.72 min.



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.618	BB	0.8119	7013.32764	117.57596	13.1610
2	39.719	BB	1.1522	4.62755e4	532.32025	86.8390
Totals :				5.32888e4	649.89621	

1-Phenyl-1-(*p*-tolyl)pentan-1-ol, 3m



Colourless oil.

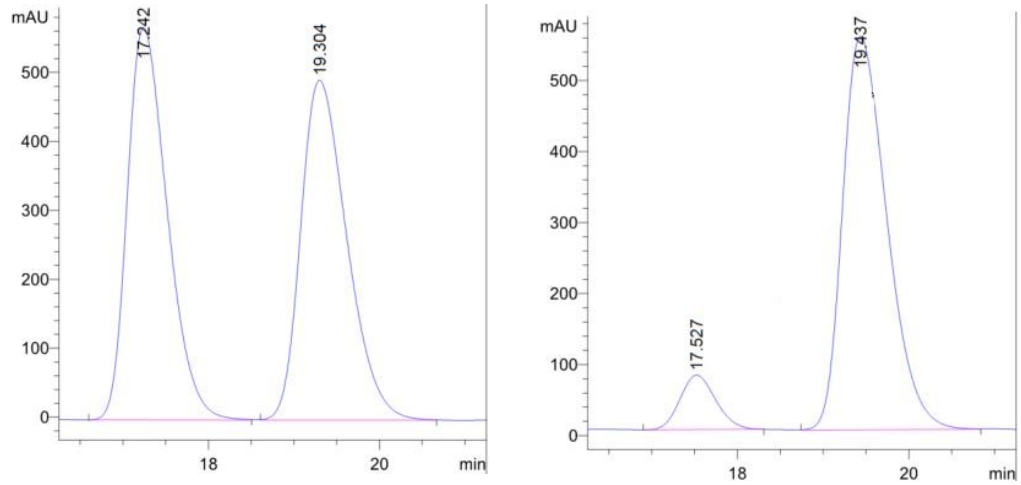
60% yield, 80% *ee*, (*R*,*R*)-**L12'**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.34 – 7.27 (m, 4H), 7.24 – 7.17 (m, 1H), 7.12 – 7.10 (m, 2H), 2.32 (s, 3H), 2.29 – 2.21 (m, 2H), 2.06 (s, 1H), 1.38 – 1.22 (m, 4H), 0.87 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 147.5, 144.5, 136.5, 129.0, 128.2, 126.8, 126.12, 126.11, 78.3, 41.9, 26.1, 23.3, 21.1, 14.2.

IR (film) 3466, 2954, 2869, 1511, 1446, 975, 815, 608 cm^{-1}.

HPLC analysis on chiral stationary phase: Chiralcel® OJ-H column, 99/1 heptane/EtOH, 1 mL/min., 20 °C, 210 nm, retention times: t_m = 17.53 min. and t_M = 19.44 min.

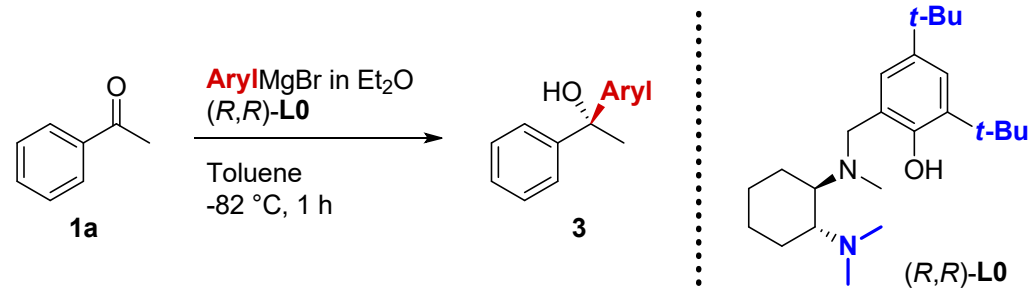


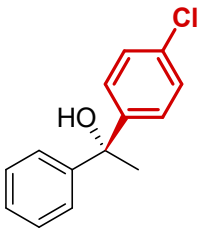
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.527	MM	0.4835	2225.39233	76.71674	10.0429
2	19.437	MM	0.5996	1.99334e4	554.03467	89.9571
Totals :				2.21588e4	630.75140	

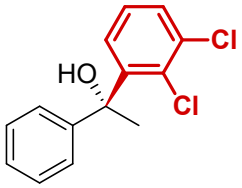
Previously attempted addition of aryl Grignard reagents to ketones with (*R*,*R*)-L0

Previous attempts of the addition of aryl Grignard reagents to acetophenone **1a** in the presence of ligand (*R*,*R*)-**L0** proved poorly effective, providing the chiral tertiary alcohols **3** in low to modest *ee* (20% to 55% *ee*), except for 1-naphthylmagnesium bromide, which showed higher enantioselectivity (75% *ee*).

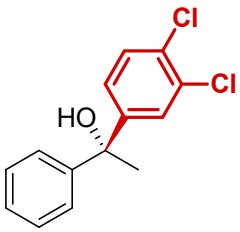




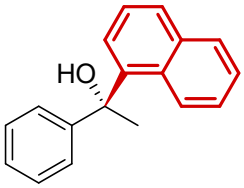
68%, 21% *ee*



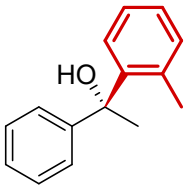
71%, 20% *ee*



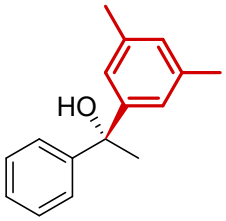
75%, 51% *ee*



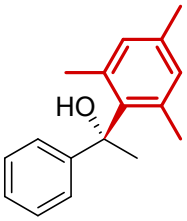
64%, 75% *ee*



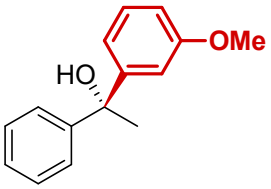
64%, 33% *ee*



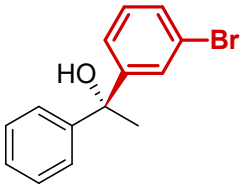
73%, 51% *ee*



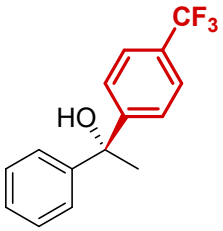
35%, 45% *ee*



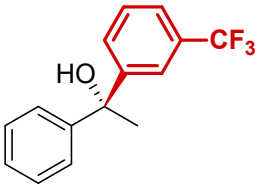
67%, 44% *ee*



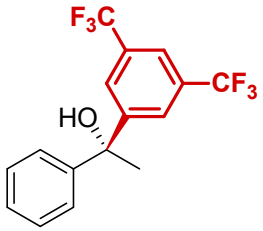
71%, 47% *ee*



76%, 55% *ee*



69%, 55% *ee*

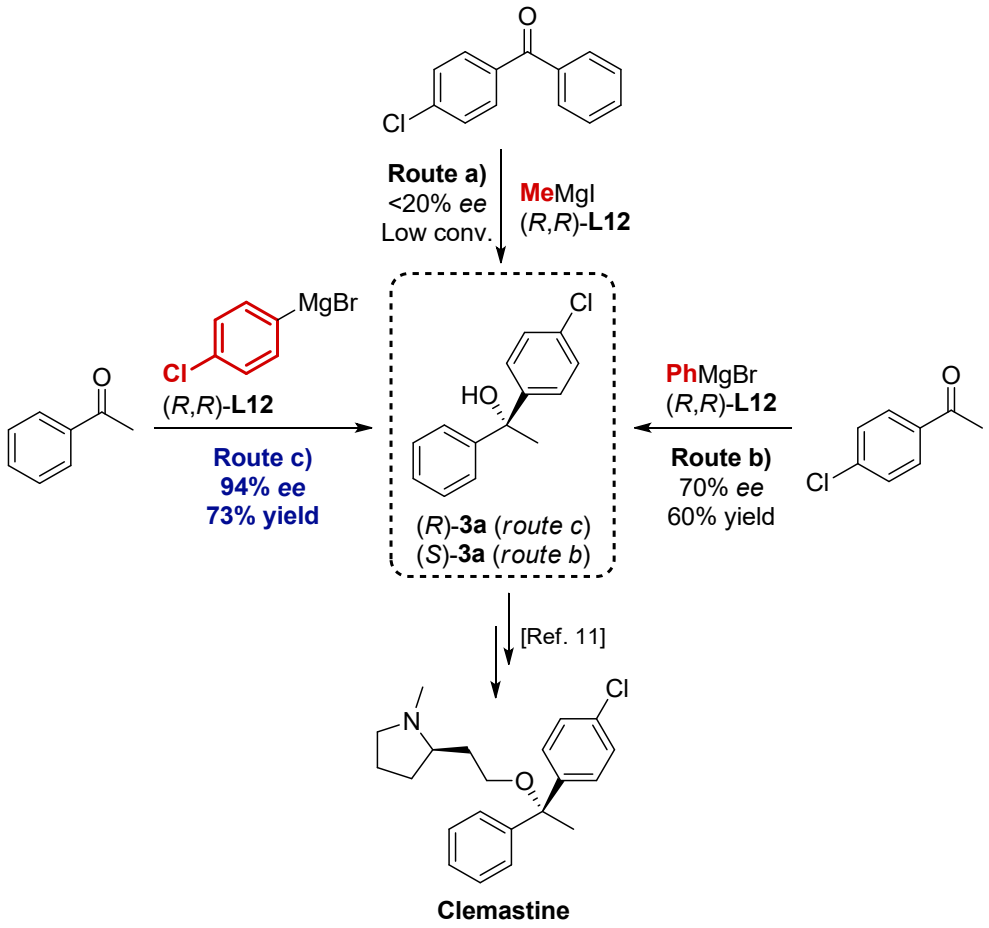


82%, 9% *ee*

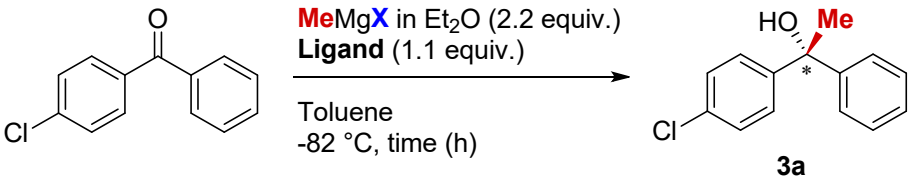
Formal synthesis of clemastine API

The efficiency and flexibility of the asymmetric Grignard methodology was demonstrated by the implementation of the 3-disconnections approach for the preparation of the alcohol (*R*)-**3a**, key intermediate in the preparation of the antihistamine API clemastine.[11] Optimization of the three synthetic disconnections offered by the Grignard method leading to (*R*)-**3a** resulted in the development of a new effective formal synthesis of clemastine.

Optimization of the 3 synthetic routes towards (*R*)-3a via asymmetric Grignard synthesis



Route a): screening of MeMgX and ligands



Entry	X	Ligand	Time (h)	3a *ee* (%) [a]	3a conv. (%) [b]
1	I	(*R*,*R*)-**L12**	1	20	5
2	Br	(*R*,*R*)-**L12**	1	20	5
3	I	(*R*,*R*)-**L10**	1	15	-

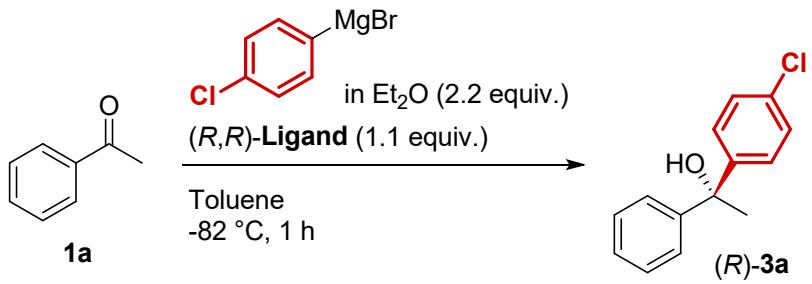
4	I	(*R*,*R*)-**L11**	1	15	-
5	I	(*R*,*R*)-**L0**	1	-	-
6	I	(*R*,*R*)-**L12**	24	10	13

[a] *ee* determined by HPLC analysis on chiral stationary phase;
[b] Conversion determined by ^{1}H-NMR analysis of the crude reaction mixture.

Route c): ligands screening and order of addition optimization

Having established the superior efficiency provided by route c), i.e. using *p*-ClPhMgBr as Grignard reagent, compared to the use of MeMgX (route a) and PhMgBr (route b), we focused on the optimization of route c) by screening the following factors: i) ligand structure and ii) ligand deprotonation and order of addition.

i) Ligands screening



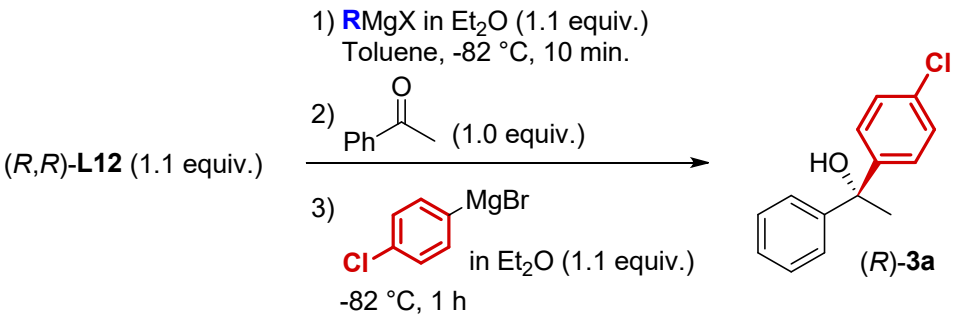
Entry	(*R*,*R*)-Ligand	(*R*)-3a *ee* (%) [a]	(*R*)-3a yield (%) [b]
1	**L12**	89	78
2	**L12'**	82	44
3	**L0**	21	51
4	**L7**	39	46
5	**L14**	14	n.d.

[a] *ee* determined by HPLC analysis on chiral stationary phase; [b] Isolated yields.

ii) Order of addition optimization: two-stage addition of Grignard reagent for sequential ligand deprotonation/1,2-addition

Next, the standard procedure was modified into a sequential process involving the preliminary formation of the ligand-magnesium active complex, followed by the enantioselective 1,2-addition to the ketone substrate, by studying the order of addition of the reagents and the role of the Grignard reagent (RMgX) in the initial ligand deprotonation step.

Unlike the standard procedure, involving the addition of 2.0 equivalents of Grignard reagent to a mixture of ketone and ligand, the preliminary preparation of the ligand-magnesium active complex via ligand deprotonation by 1.0 equivalent of *p*-ClPhMgBr, followed by the addition of the ketone substrate and a second equivalent of Grignard reagent, enabled a more effective control of the enantioselectivity furnishing the alcohol (*R*)-**3a** in 94% *ee* (vs 89% *ee* of the standard procedure).

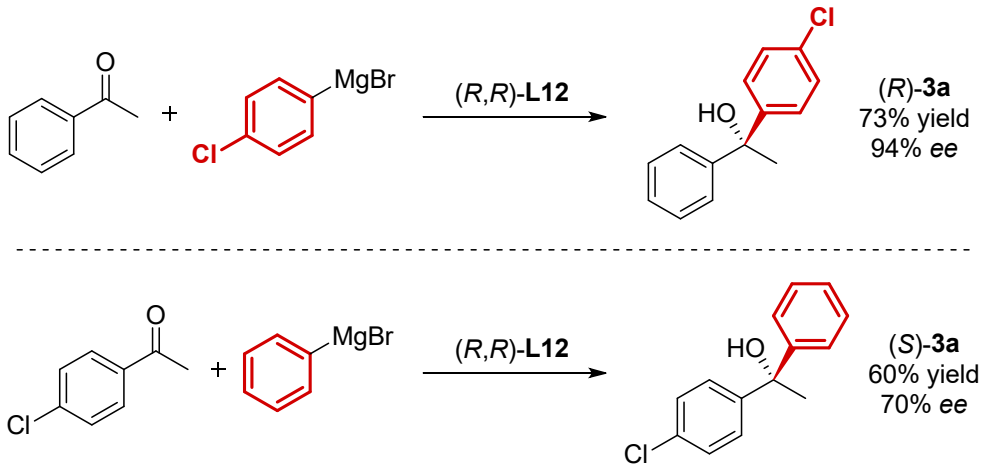


Entry	RMgX	(*R*)-**3a** *ee* (%) [a]	(*R*)-**3a** yield (%) [b]
1	MeMgI	78	n.d.
2	*i*-PrMgCl	86	n.d.
3	*p*-ClPhMgBr	94	73

[a] Enantiomeric excess determined by HPLC analysis on chiral stationary phase; [b] Isolated yields.

Access to both enantiomers (*R*)-3a and (*S*)-3a

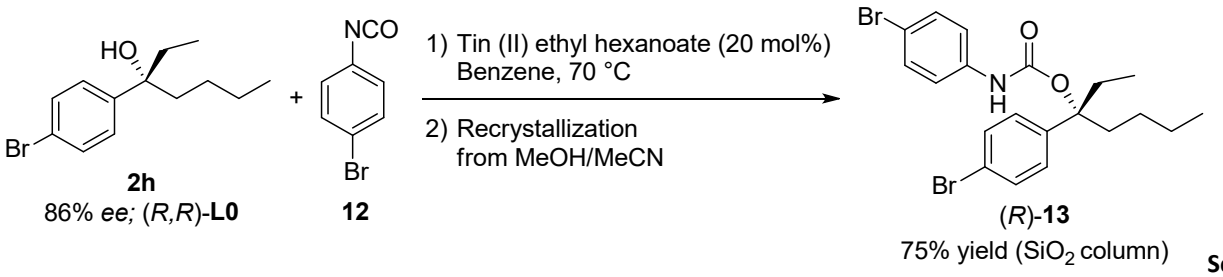
At last, it is worth noting that the use of ligand (*R*,*R*)-**L12** provided access to both enantiomers of the clemastine precursor, (*R*)-**3a** and (*S*)-**3a**, by simply changing the synthetic disconnection, without the need for inverting the configuration of the source of chirality as generally required in asymmetric synthesis.



Absolute configuration of chiral tertiary alcohols via O-derivatization as carbamates

The determination of the absolute configuration of chiral tertiary alcohols such as products **2a-h** and **3a-m** (Table 2 and 4, main article), still poses substantial challenges due to the poor chemical and stereochemical stability, and the ease of degradation and racemization of the benzylic tetrasubstituted stereocentres. In this context, we recently developed a general *O*-derivatization strategy for the determination of the absolute configuration of chiral tertiary alcohols via X-Ray crystallographic analysis of their solid *para*-bromophenyl carbamate derivatives.[12] The method was successfully applied to the study of the absolute configuration of product **2h** (Scheme S1), which in turn enabled to establish the configuration of **2f** (Scheme S2).

First, alcohol **2h** (86% *ee*, prepared via asymmetric addition of EtMgBr to *para*-bromophenyl valerophenone with ligand (*R,R*)-**L0**) was derivatized as solid carbamate by reaction with 4-bromophenyl isocyanate catalyzed by tin (II) ethyl hexanoate, in benzene at 70 °C (Scheme S1). Recrystallization of carbamate **13** from MeOH/MeCN delivered single crystals suitable for X-Ray analysis, which established the absolute configuration to be (*R*)-**13** (Figure S1), and in turn the alcohol to be (*R*)-**2h**.



Scheme S1 Synthetic strategy for the determination of the absolute configuration of benzylic chiral tertiary alcohols via X-Ray crystallographic analysis.

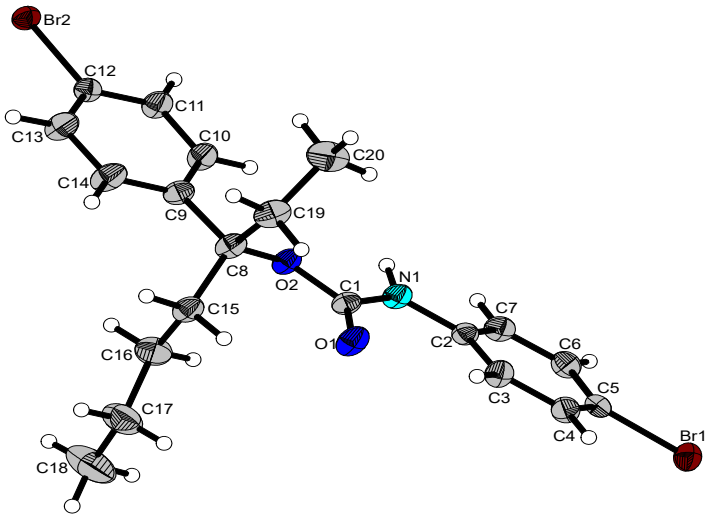
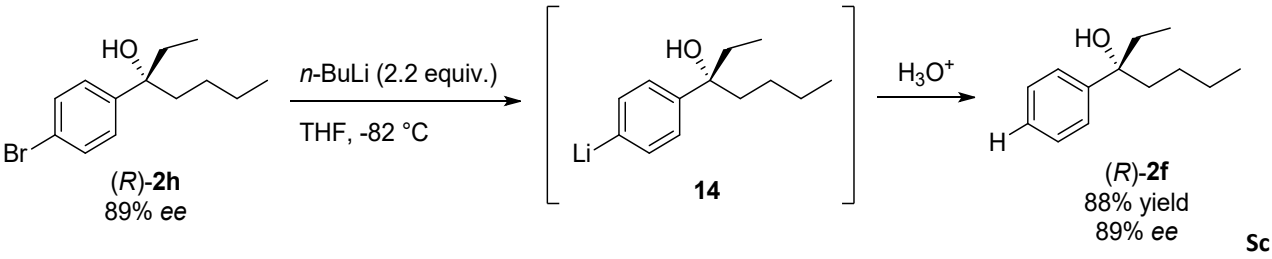


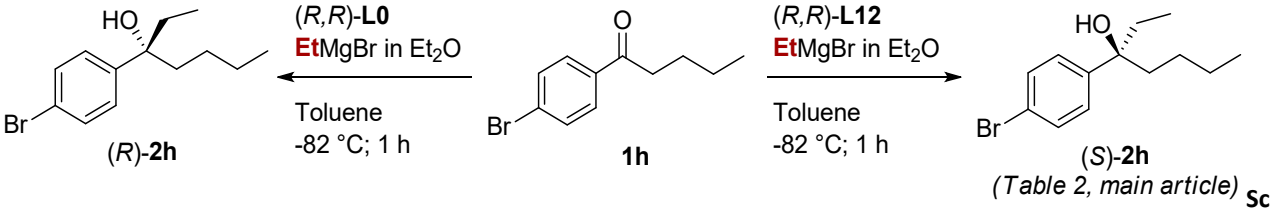
Figure S1 ORTEP diagram of (*R*)-**13** (thermal ellipsoids at 50% probability level).

Establishing the absolute configuration of the *para*-bromophenyl substituted alcohol (*R*)-**2h** enabled, in turn, the determination of the configuration of the parent compound **2f**, featuring an unsubstituted phenyl ring. Alcohol (*R*)-**2h** could undergo debromination of the *para*-bromophenyl group, without affecting the benzylic chiral centre of the tertiary alcohol. A sample of enantioenriched (*R*)-**2h** was converted into (*R*)-**2f** via a lithium-bromide exchange/protonation sequence, by treatment of (*R*)-**2h** with *n*-butyllithium in THF at -82 °C, followed by protonation of the lithiated intermediate **14** with aqueous acid (Scheme S2).



Scheme S2 Enantioconservative debromination of (*R*)-**2h** to (*R*)-**2f** via lithium-bromide exchange/protonation.

Surprisingly, after having established the absolute configuration of the alcohol (*R*)-**2h** obtained with ligand (*R,R*)-**L0**, we observed that the use of ligand (*R,R*)-**L12** (as shown in Table 2, Main Article) resulted in the formation of the opposite enantiomer (*S*)-**2h** (Scheme S3), as demonstrated by comparison of the HPLC traces of the products.



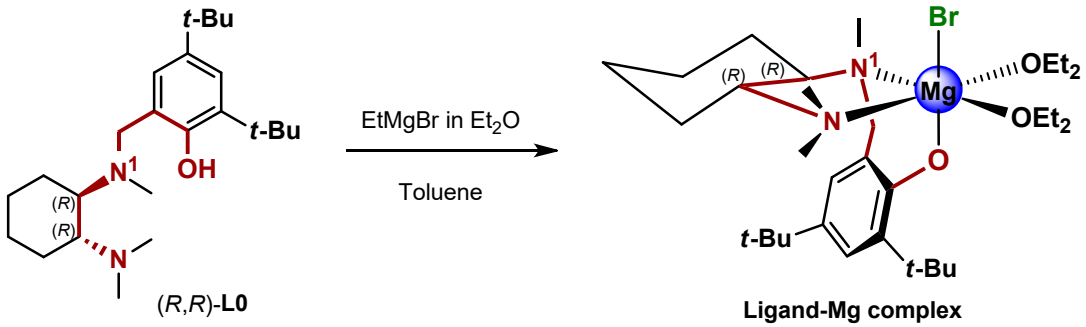
Scheme S3 Opposite asymmetric induction observed in the preparation of **2h** with (*R,R*)-**L12** / (*R,R*)-**L0**.

The behavior observed by the exclusive ligand/ketone combination (*R,R*)-**L12**/*para*-bromovalerophenone **1h**, represents an exception to the general asymmetric induction observed in the asymmetric Grignard method. Specifically, multiple evidence showed the asymmetric induction to be consistent among the class of DACH-derived ligands investigated so far, establishing that (*R,R*)-ligands promote the addition of RMgBr to the phenone *si* face, independently by the type of Grignard and ketone. In line with the other ligands, (*R,R*)-**L12** closely follows the general asymmetric induction trend over a range of structurally diverse ketones, made exception for *para*-bromovalerophenone, showing preferential addition to the *re* face. The exclusivity of the combination (*R,R*)-**L12**/**1h** was demonstrated by testing: i) **1h** with ligands (*R,R*)-**L0**, **L0'** and **L12'**; ii) ligand (*R,R*)-**L12** with *para*-halovalerophenone, with halogen = F, Cl, I; iii) ligand (*R,R*)-**L12** with *para*-bromophenones analogous to **1h**, e.g. *para*-bromoacetophenone and *para*-bromopropiophenone, which all followed the general asymmetric induction trend (i.e. addition to *si* face).

Additional absolute configurations for the products **2c** and **3d** (Table 2 and 4, Main Article) were determined by comparison with analytical data previously reported in the literature, which further confirmed the established asymmetric induction characterizing our Grignard methodology (please refer to the revised version of the manuscript for details).

Mechanistic studies

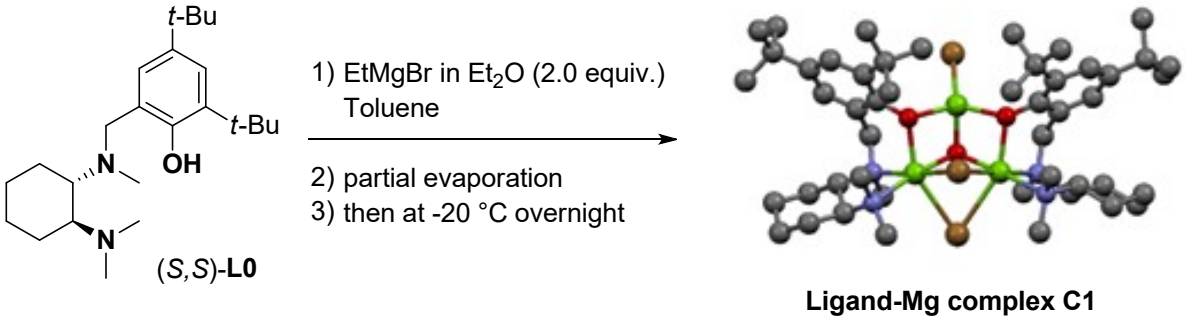
The study of the structure and role of the active species taking part in the asymmetric Grignard synthesis involved the combination of different techniques, such as X-ray crystallography, NMR analyses and further computational studies via DFT calculations. Taking into consideration the coordination sphere of magnesium and the tridentate nature of the DACH-derived ligands, together with the experimental observation indicating the need for a preliminary ligand deprotonation step with Grignard reagent, we hypothesized the presence of an equilibrium in solution involving multiple ligand-Mg species, potentially existing as mononuclear or dinuclear entity in solution, featuring a hexacoordinated Mg center with the participation of the N,N,O-tridentate ligand, halide, ethereal solvent and the ketone substrate (Scheme S4).



Scheme S4 Proposed mononuclear ligand-Mg complex generated in solution by deprotonation of (*R,R*)-**L0** with 1.0 equivalent of EtMgBr. The hexacoordinated magnesium center features: i) N,N,O-tridentate ligand; ii) halide (Br) and iii) ethereal solvent molecules (Et_2O), undergoing subsequent exchange with the ketone substrate.

X-Ray crystallographic analysis of the ligand-Mg species

An early X-ray crystallographic analysis of a ligand-Mg entity resulting from deprotonation of (*S,S*)-**L0** with 2.0 equivalents of EtMgBr in toluene, followed by slow evaporation of the toluene and standing overnight at -20 °C (Scheme S5), providing a crystalline sample suitable for X-ray analysis (Figure S2).



Scheme S5 Formation of the ligand-Mg complex **C1** via deprotonation of (*S,S*)-**L0** with EtMgBr.

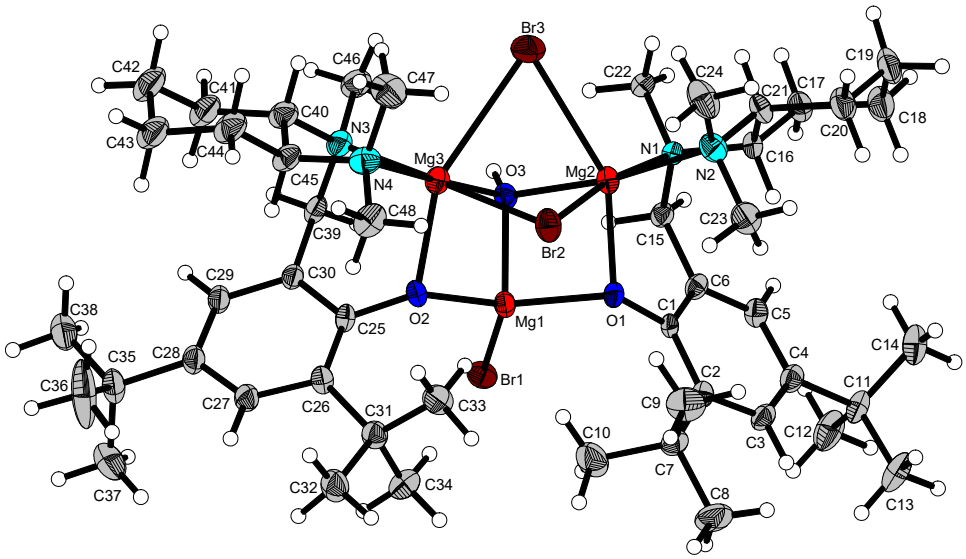
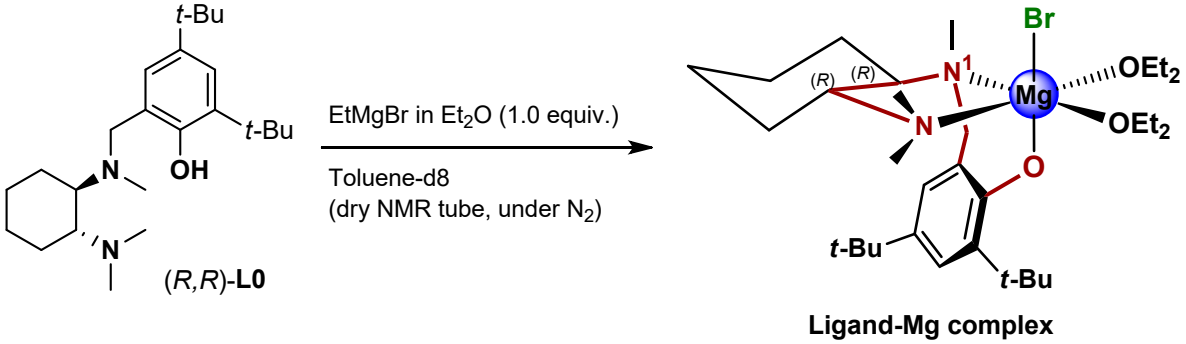


Figure S2 ORTEP diagram of the ligand-Mg complex **C1** (thermal ellipsoids at 50% probability level).

NMR analysis of the ligand-Mg species in solution



Scheme S6 Generation of the ligand-Mg complex in toluene-d8 by deprotonation of (*R,R*)-**L0** with EtMgBr.

The sample preparation involved the deprotonation of (*R,R*)-**L0** with 1.0 equivalent of EtMgBr (3.0 M solution in Et_2O), in a dry NMR tube under N_2, using dry toluene-d8 as solvent. The mixture was immediately analyzed via mono- and bi-dimensional NMR (Figure S3 and S4 show two relevant spectra: ^{1}H-NMR and ^{1}H-^{1}H COSY). On the contrary, ^{13}C-NMR, HSQC and HMBC spectra featured extensive signal overlapping which hampered their use.

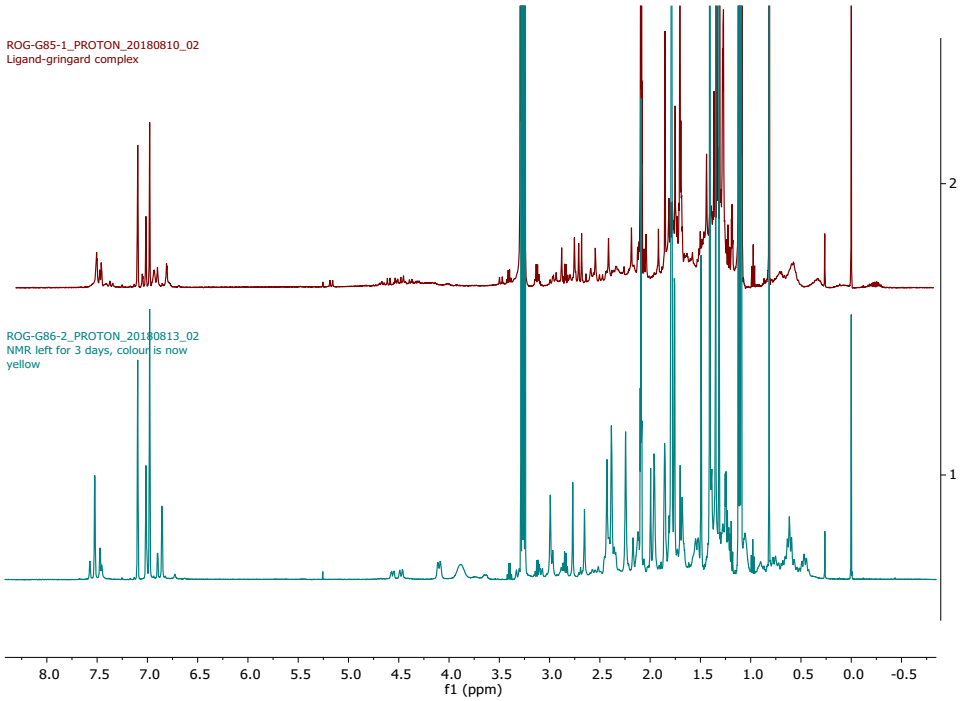


Figure S3 ^{1}H-NMR analysis of the ligand-Mg complex derived from deprotonation of (*R,R*)-**L0** with 1.0 equivalent of EtMgBr in toluene-d8: a) immediately after preparation (top) and b) after three days (bottom).

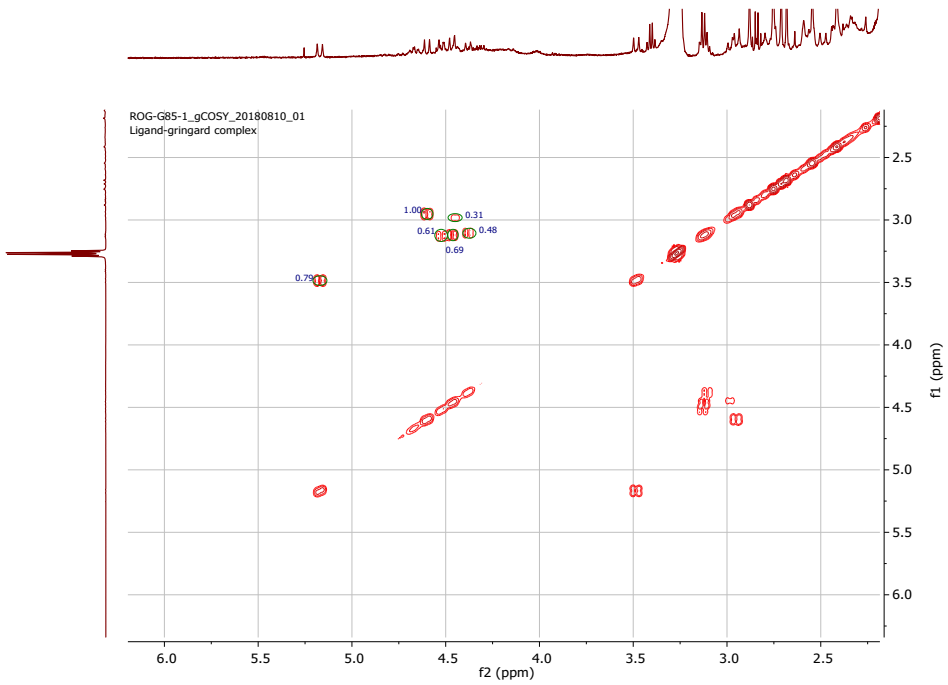


Figure S4 ^{1}H-^{1}H COSY of the ligand-Mg complex derived from deprotonation of (*R,R*)-**L0** with 1.0 equivalent of EtMgBr in toluene-d8. The benzylic signals indicate the presence of at least 5 species in solution.

X-Ray crystallographic analysis

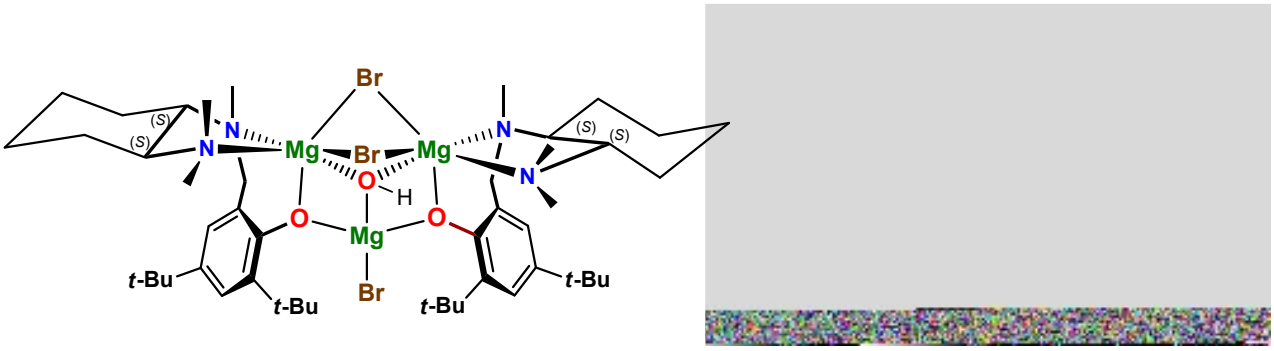
Crystallographic data were collected using a Rigaku Oxford Diffraction (former Agilent Technologies, former Oxford Diffraction) SuperNova A diffractometer, using Cu-K_α (1.54184 Å). An analytical absorption correction based on the shape of the crystal was performed.[13] The structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares on F^2 for all data using SHELXL-97.[14] Anisotropic thermal displacement parameters were used for all non-hydrogen atoms. Crystals were selected at low temperature.[15]

Crystallographic data for **C1** and (*R*)-**13** have been deposited with the Cambridge Crystallographic Data Centre.

C1 [CCDC 2158472]

(*R*)-**13** [CCDC 2158994]

Crystallographic data for compound C1



Ligand-Mg complex **C1**

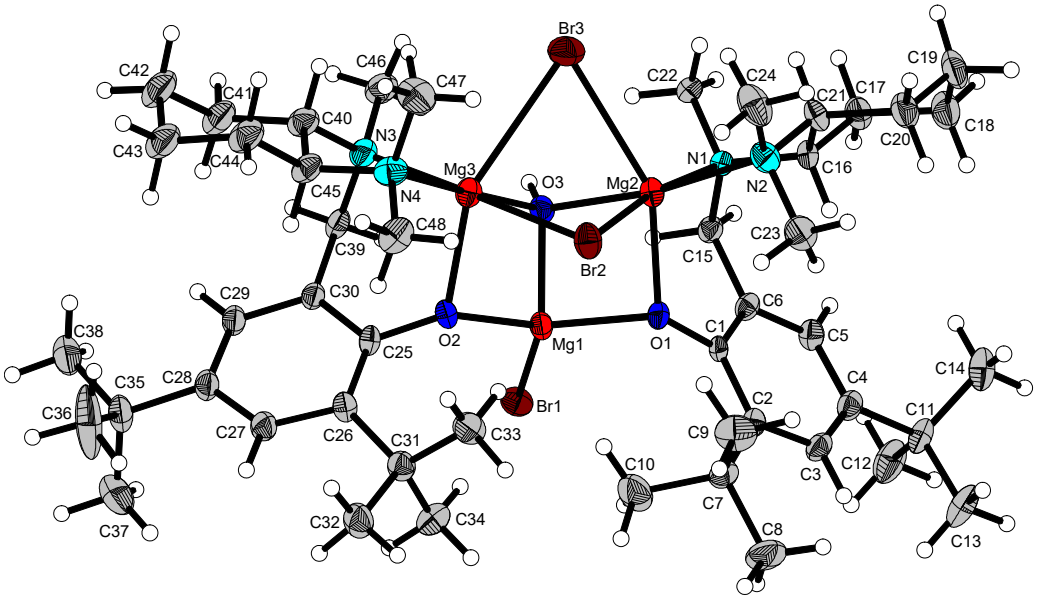
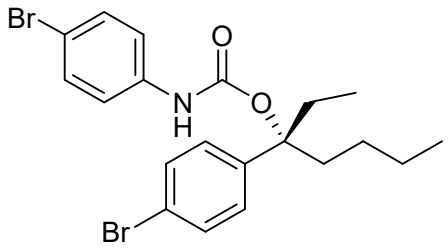


Table S2 Crystal data and structure refinement for compound **C1**.

Identification code	gil92
Empirical formula	$C_{117}\ H_{190}\ N_8\ O_6\ Mg_6\ Br_6$
Molecular formula	$(C_{48}\ H_{83}\ N_4\ O_3\ Mg_3\ Br_3)_2$ x 3 $(C_7\ H_8)$
Formula weight	2430.09
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	$P2_1$ (#4)
Unit cell dimensions	a = 19.2717(2) Å □= 90°.
	b = 16.1154(2) Å □= 93.454(1)°.
	c = 19.6920(3) Å □ = 90°.
Volume	6104.66(14) $Å^3$
Z	2
Density (calculated)	1.322 Mg/m^3
Absorption coefficient	3.090 mm^{-1}
F(000)	2556
Crystal size	0.126 x 0.049 x 0.017 mm^3
Theta range for data collection	3.12 to 76.92°.
Index ranges	–24<=h<=23, –20<=k<=20, –23<=l<=24
Reflections collected	79195
Independent reflections	24793 [R(int) = 0.0620]
Completeness to theta = 76.92°	99.0 %
Absorption correction	Gaussian
Max. and min. transmission	0.952 and 0.783
Refinement method	Full–matrix least–squares on F^2
Data / restraints / parameters	24793 / 1 / 1328
Goodness–of–fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0432, wR2 = 0.0991
R indices (all data)	R1 = 0.0576, wR2 = 0.1078
Absolute structure parameter	–0.019(11)
Largest diff. peak and hole	1.256 and –0.817 $e.Å^{-3}$

Crystallographic data for compound (*R*)-13



Carbamate (*R*)-**13**

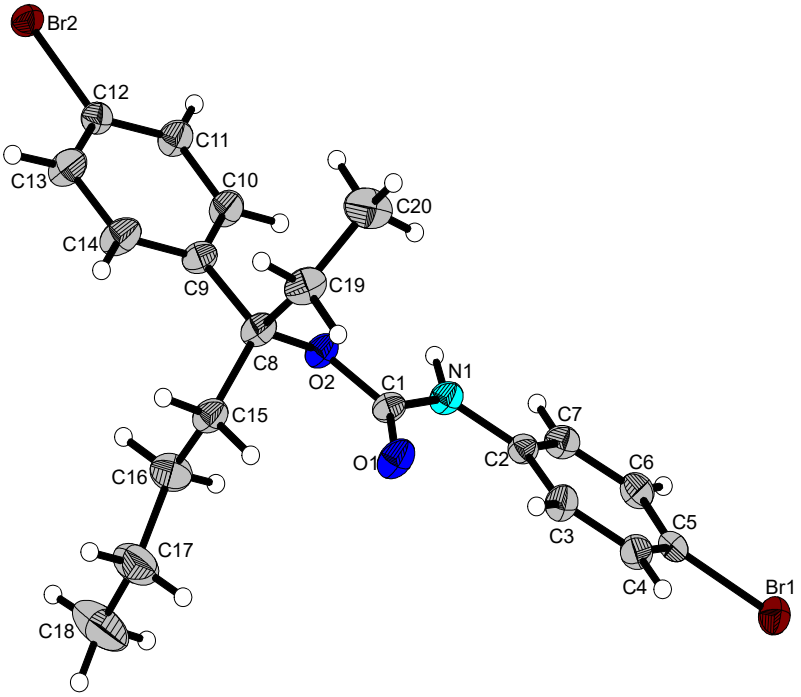
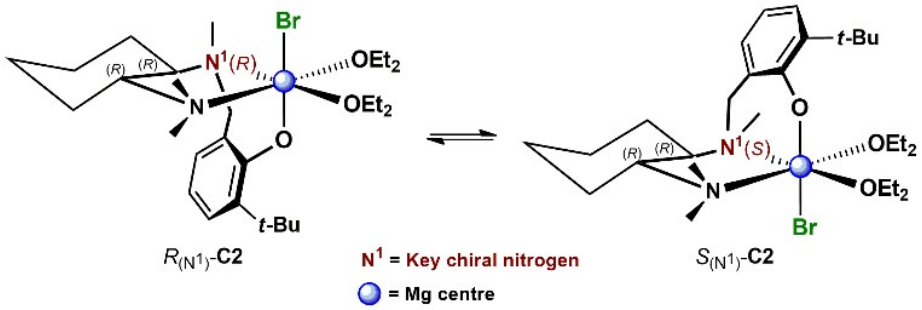


Table S3 Crystal data and structure refinement for compound (*R*)-**13**.

Identification code	gil118
Empirical formula	$C_{20}\ H_{23}\ N\ O_2\ Br_2$
Formula weight	469.21
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	$P2_1$ (#4)
Unit cell dimensions	a = 15.0842(2) Å, α = 90°.
	b = 18.1183(2) Å, β= 109.2355(9)°.
	c = 15.8577(2) Å, γ = 90°.
Volume	4091.96(9) $Å^3$
Z	8
Density (calculated)	1.523 Mg/m^3
Absorption coefficient	5.121 mm^{-1}
F(000)	1888
Crystal size	0.169 x 0.092 x 0.018 mm^3
Theta range for data collection	3.508 to 76.941°.
Index ranges	–19<=h<=18, –22<=k<=22, –19<=l<=19
Reflections collected	82455
Independent reflections	17120 [R(int) = 0.0494]
Completeness to theta = 67.684°	100.0 %
Absorption correction	Gaussian
Max. and min. transmission	0.915 and 0.575
Refinement method	Full–matrix least–squares on F^2
Data / restraints / parameters	17120 / 1 / 909
Goodness–of–fit on F^2	1.024
Final R indices [I>2sigma(I)]	R1 = 0.0276, wR2 = 0.0669
R indices (all data)	R1 = 0.0302, wR2 = 0.0686
Absolute structure parameter	–0.043(7)
Extinction coefficient	n/a
Largest diff. peak and hole	0.880 and –0.679 $e.Å^{-3}$

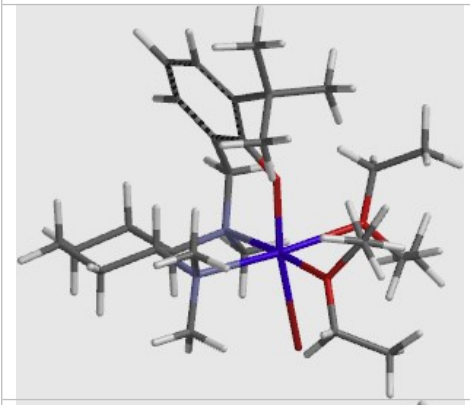
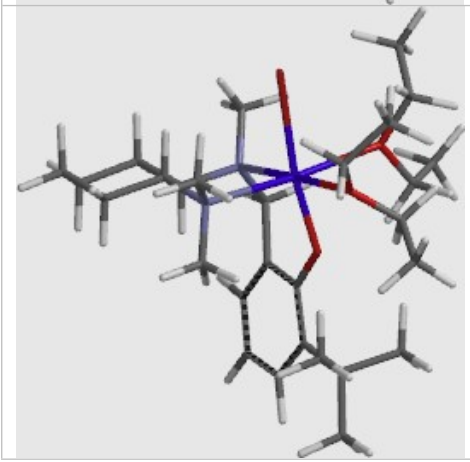
DFT Calculation data

Conformational search on the hexacoordinate diastereomeric complexes *R*- and *S-fac*-**C2** was performed at the MMFF level by using systematic algorithm for all four rotatable C-O bonds (diethyl ether fragments).



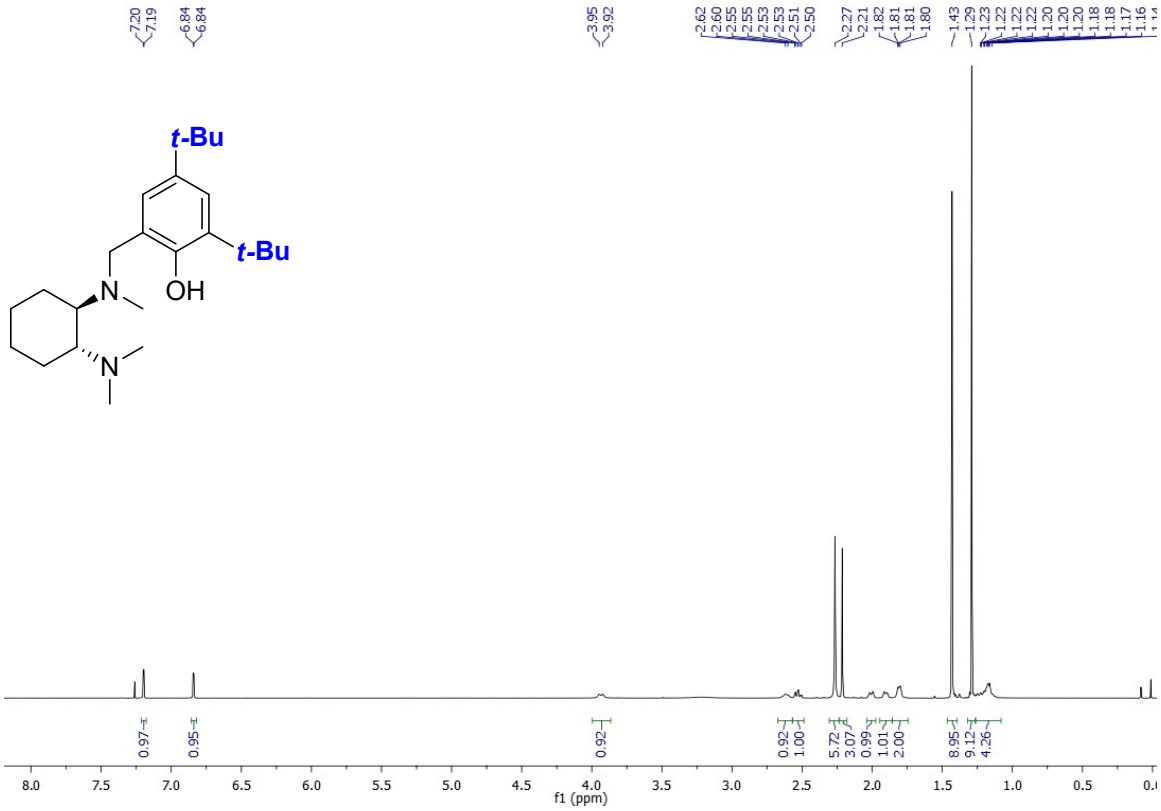
The diastereomeric conformer libraries were then processed by DFT energy calculations at the B3LYP/6-31G* level (SPARTAN 10 suite of programs) using default convergence criterion 3 x 10^{-4} hartrees/bohr. Solvent (toluene) corrections were introduced by using a PCM model. The lowest conformer energies for each diastereomeric library are listed below in Table S4.

Table S4 Total energies of minimised diastereomeric ligand-Mg complexes **C2**.

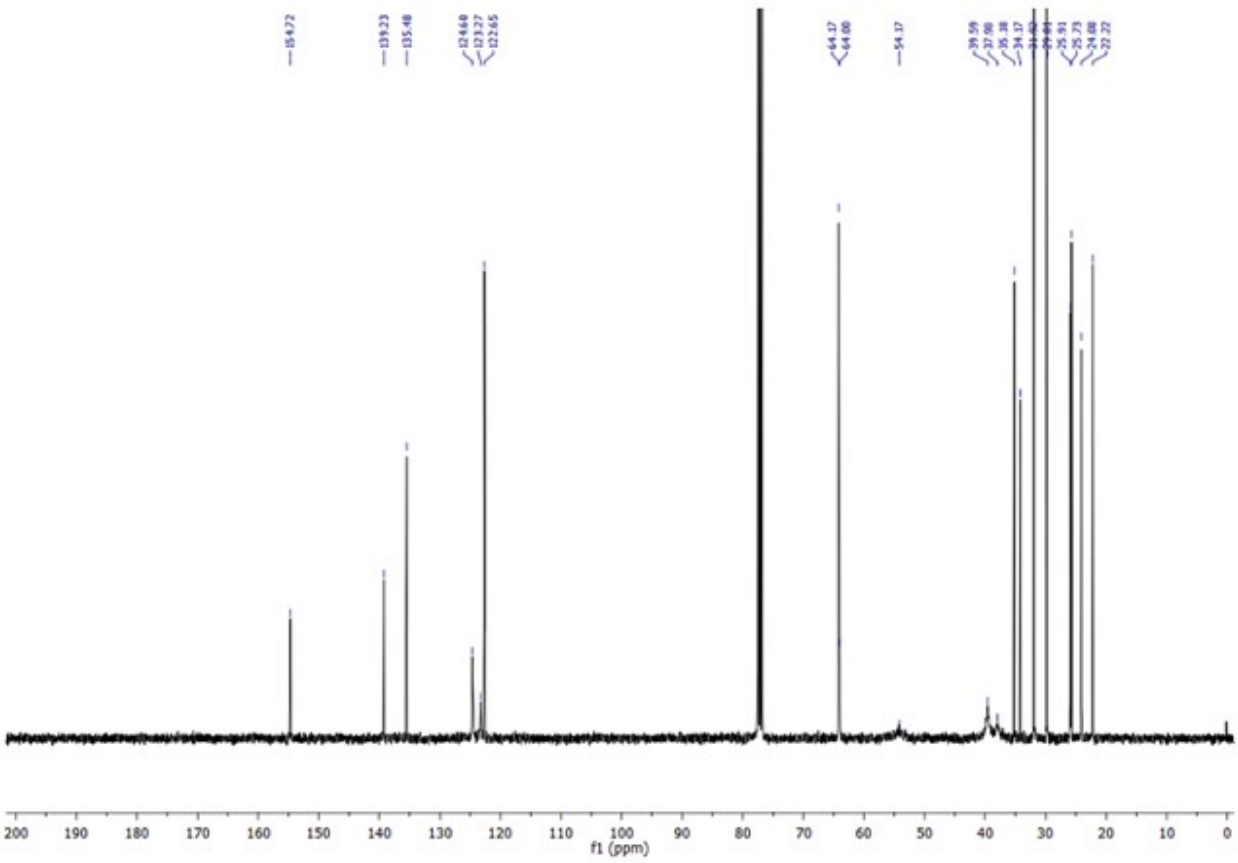
Structure	Code	Solvent	E (Ht)
	1	Toluene	-4208.23249
	*S*1	Toluene	-4208.23445

NMR Spectra

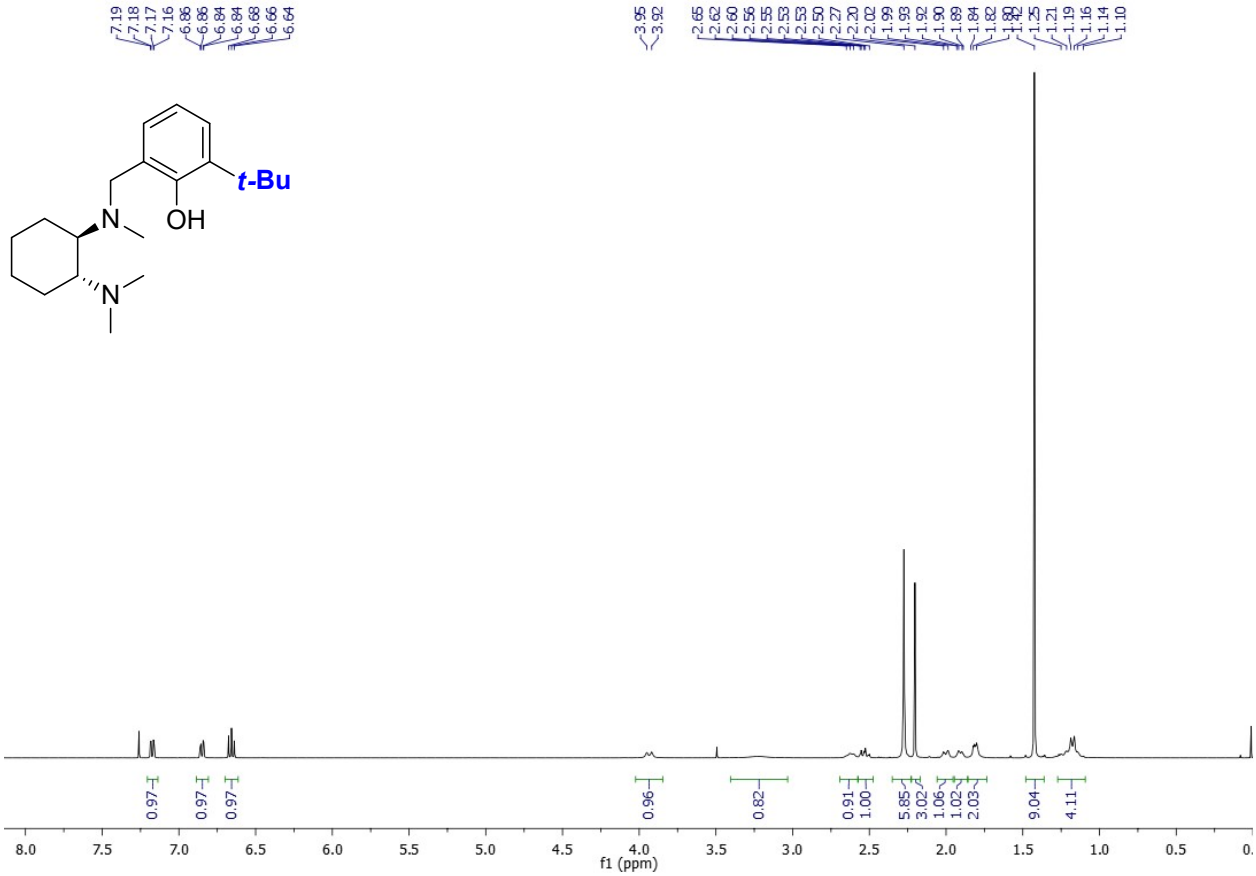
(*R*,*R*)-**L0** ^{1}**H-NMR** ($CDCl_3$)



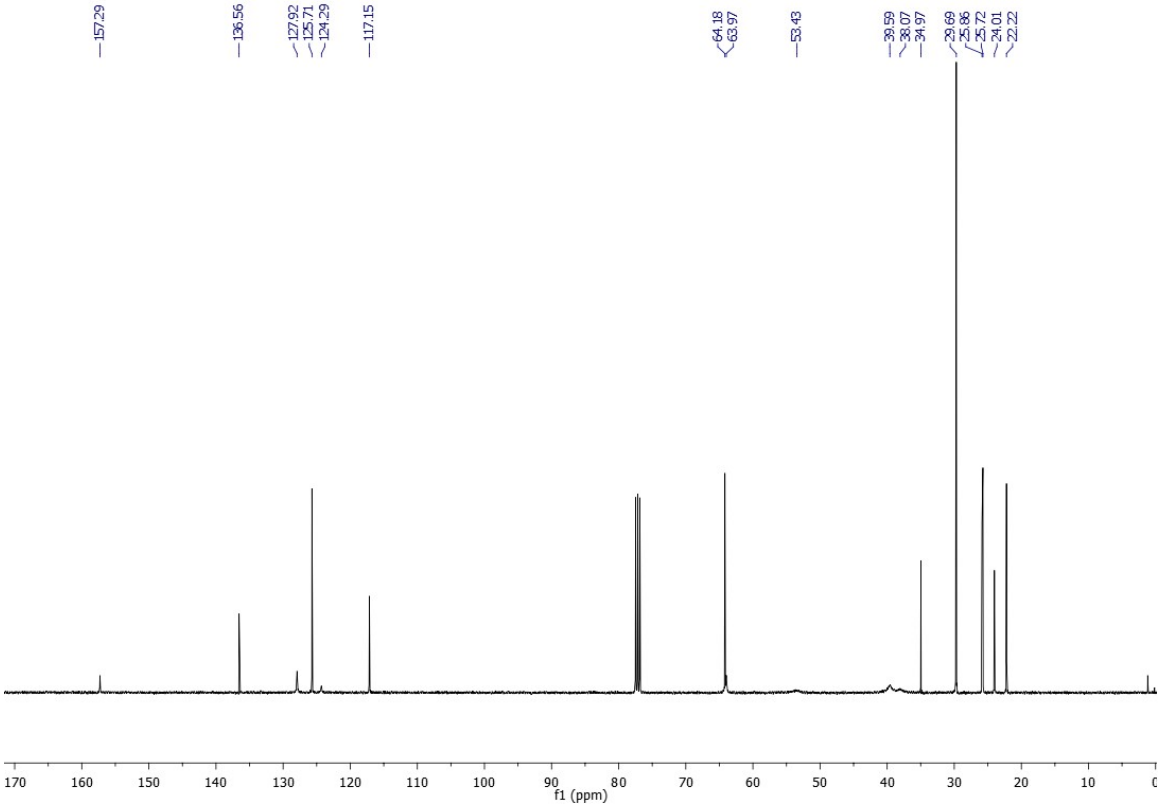
(*R*,*R*)-**L0** ^{13}**C-NMR** ($CDCl_3$)



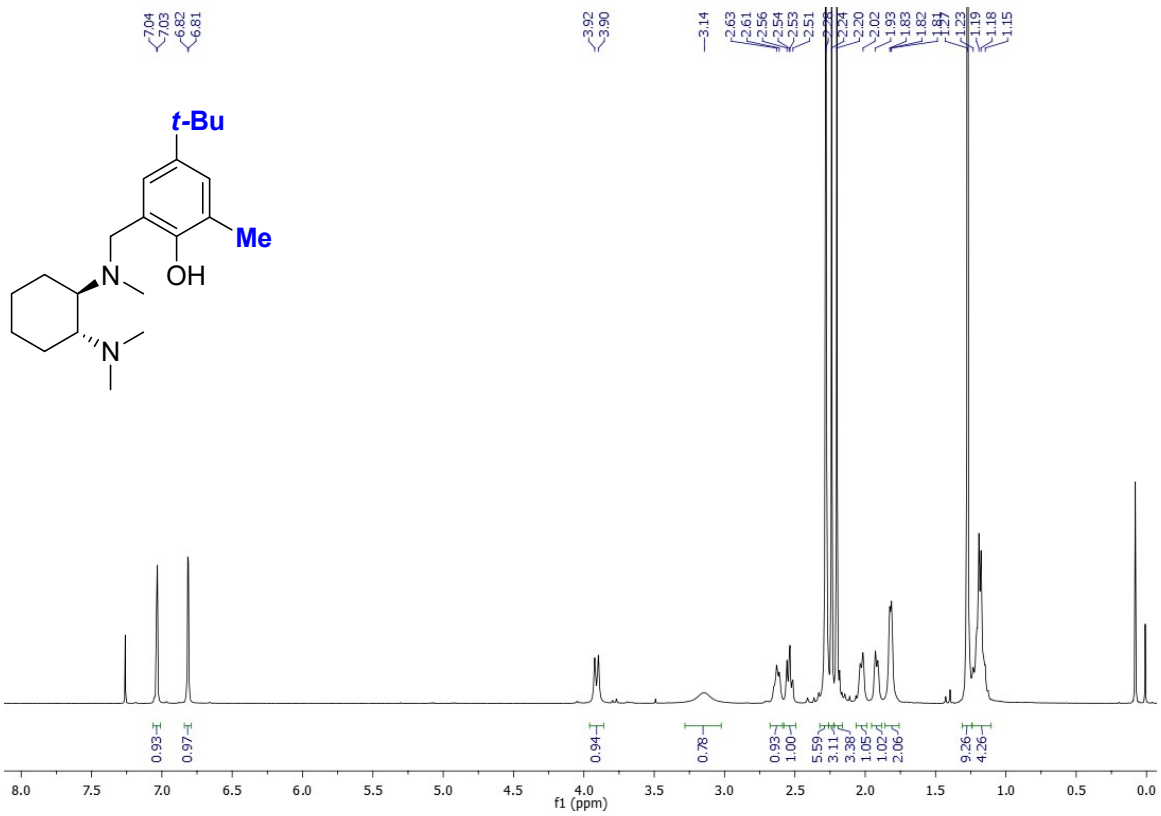
(*R*,*R*)-**L1** ^{1}**H-NMR** ($CDCl_3$)



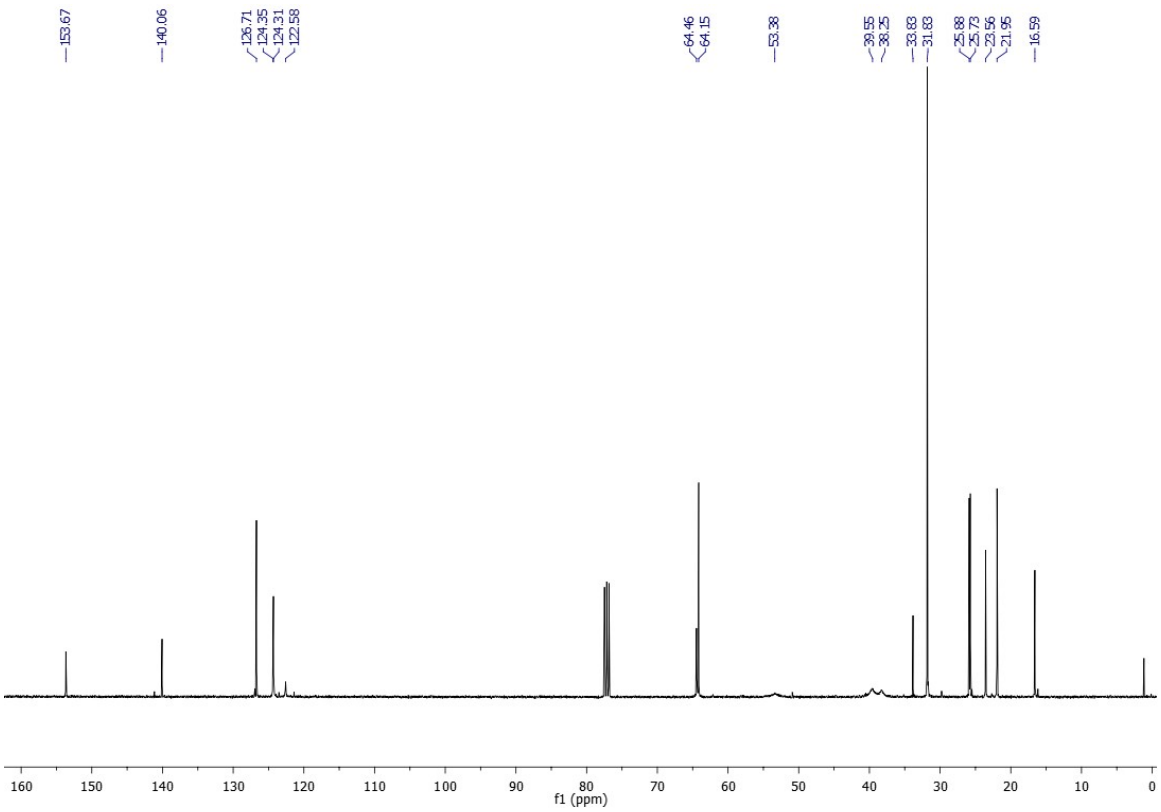
(*R*,*R*)-**L1** ^{13}**C-NMR** ($CDCl_3$)



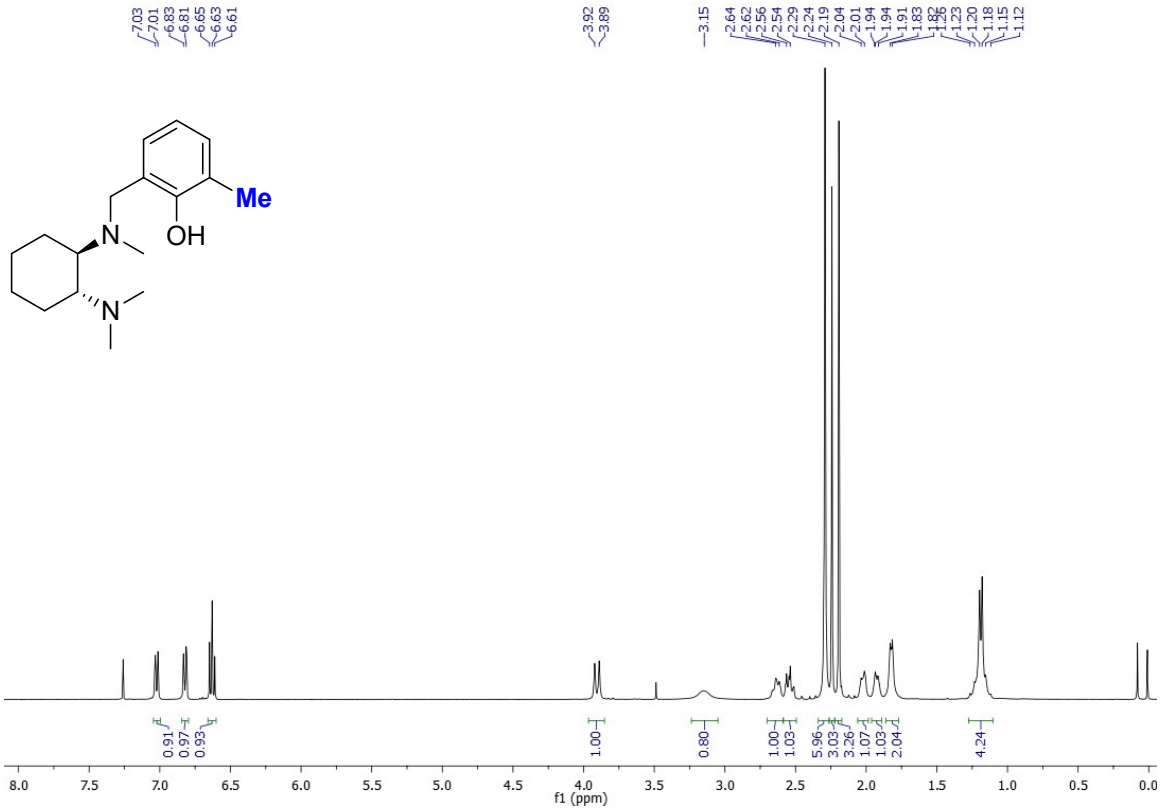
(*R*,*R*)-**L2** ^{1}**H-NMR** ($CDCl_3$)



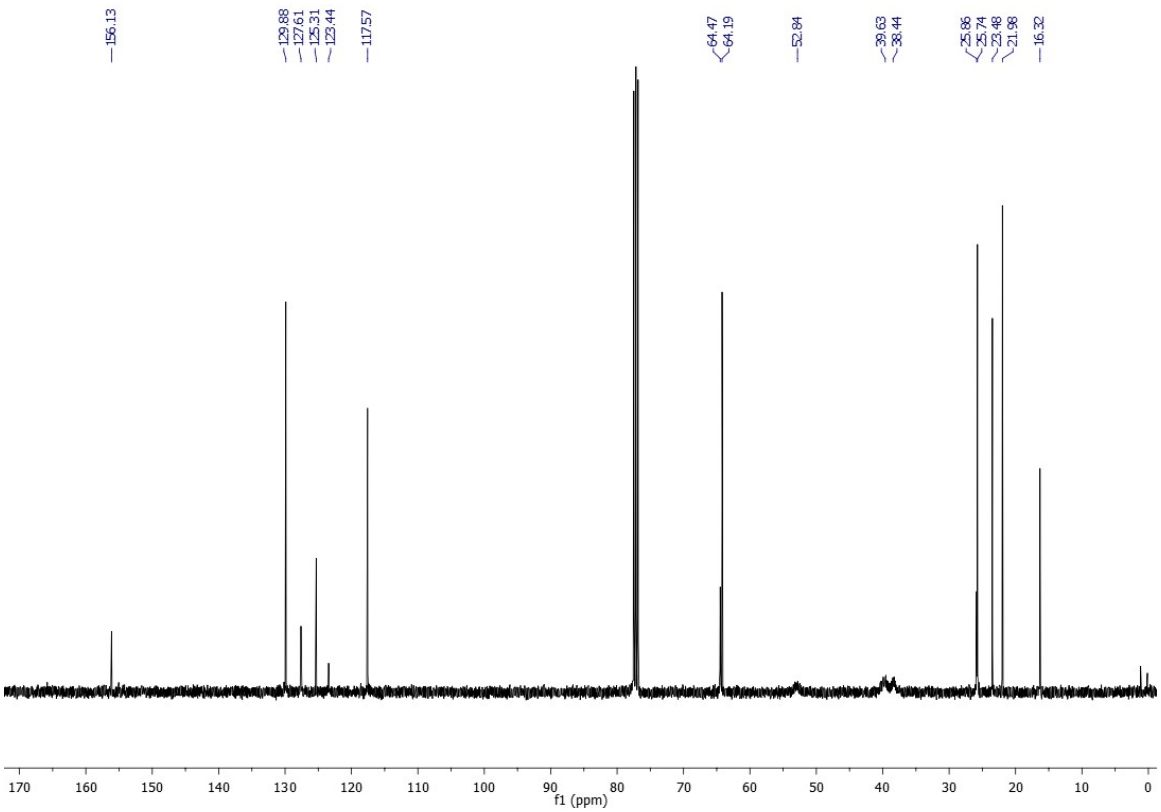
(*R*,*R*)-**L2** ^{13}**C-NMR** ($CDCl_3$)



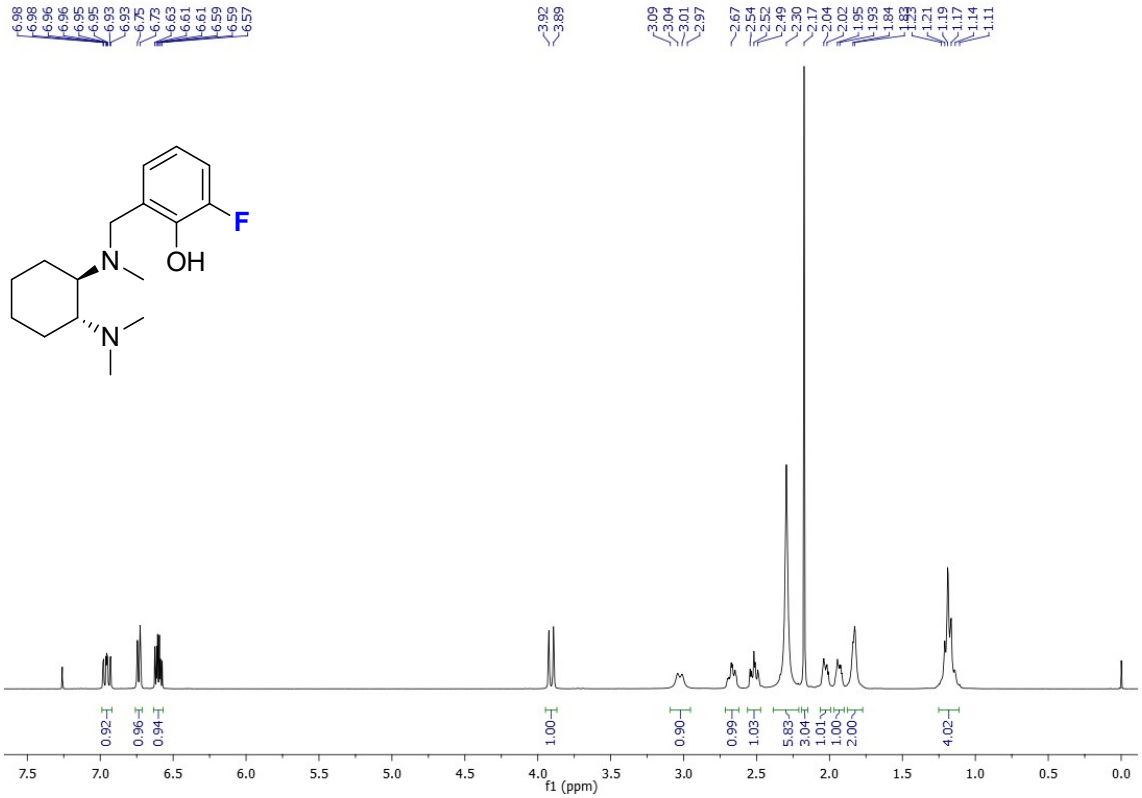
(*R*,*R*)-**L3** **^{1}H-NMR** ($CDCl_3$)



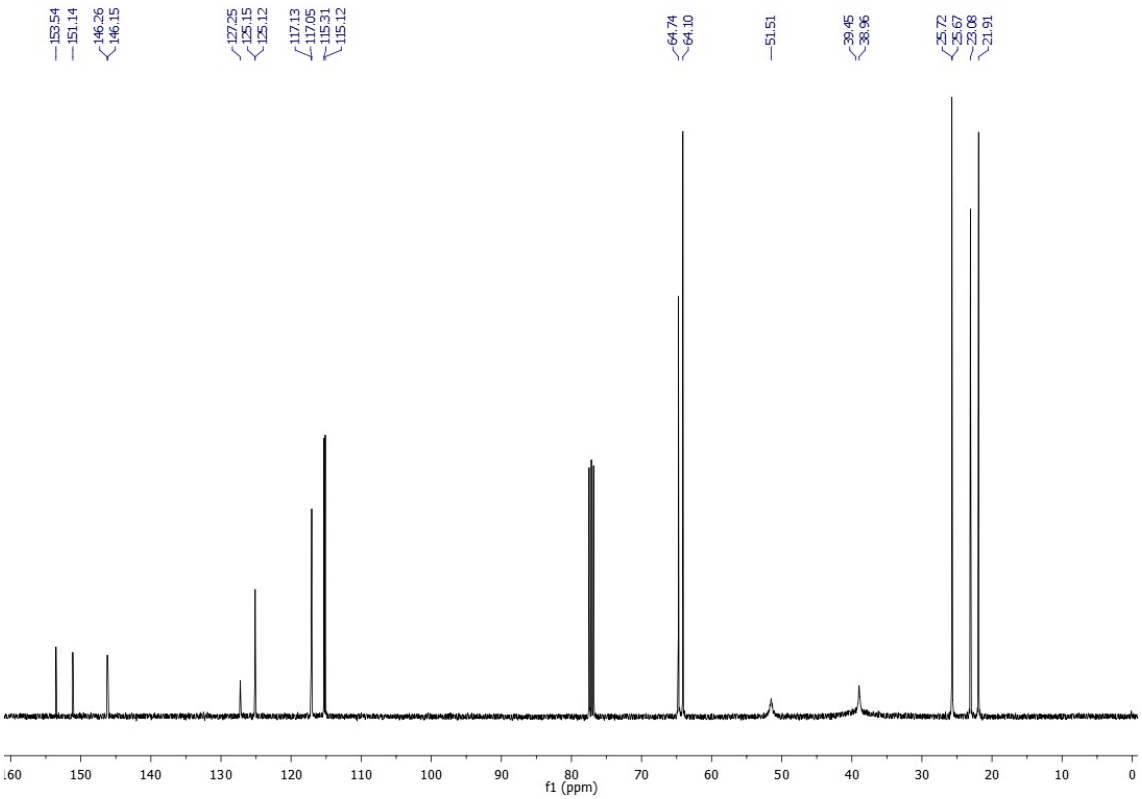
(*R*,*R*)-**L3** **^{13}C-NMR** ($CDCl_3$)



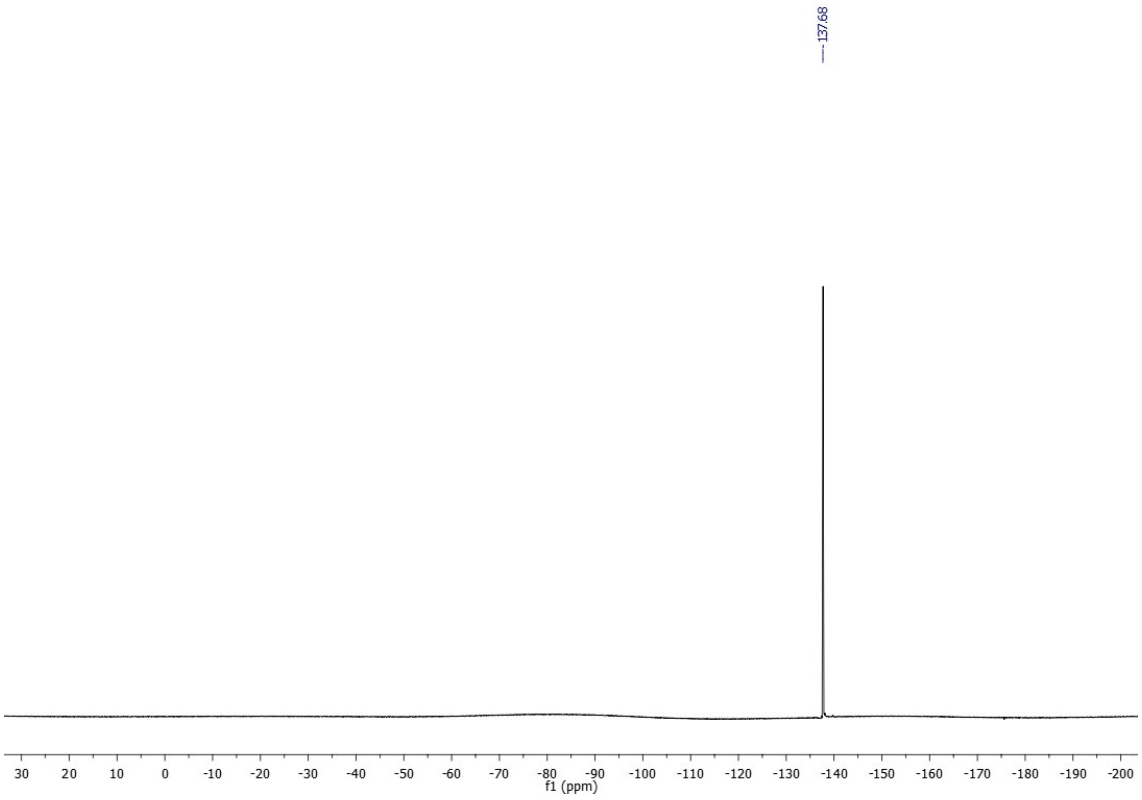
(*R*,*R*)-**L4** **^{1}H-NMR** ($CDCl_3$)



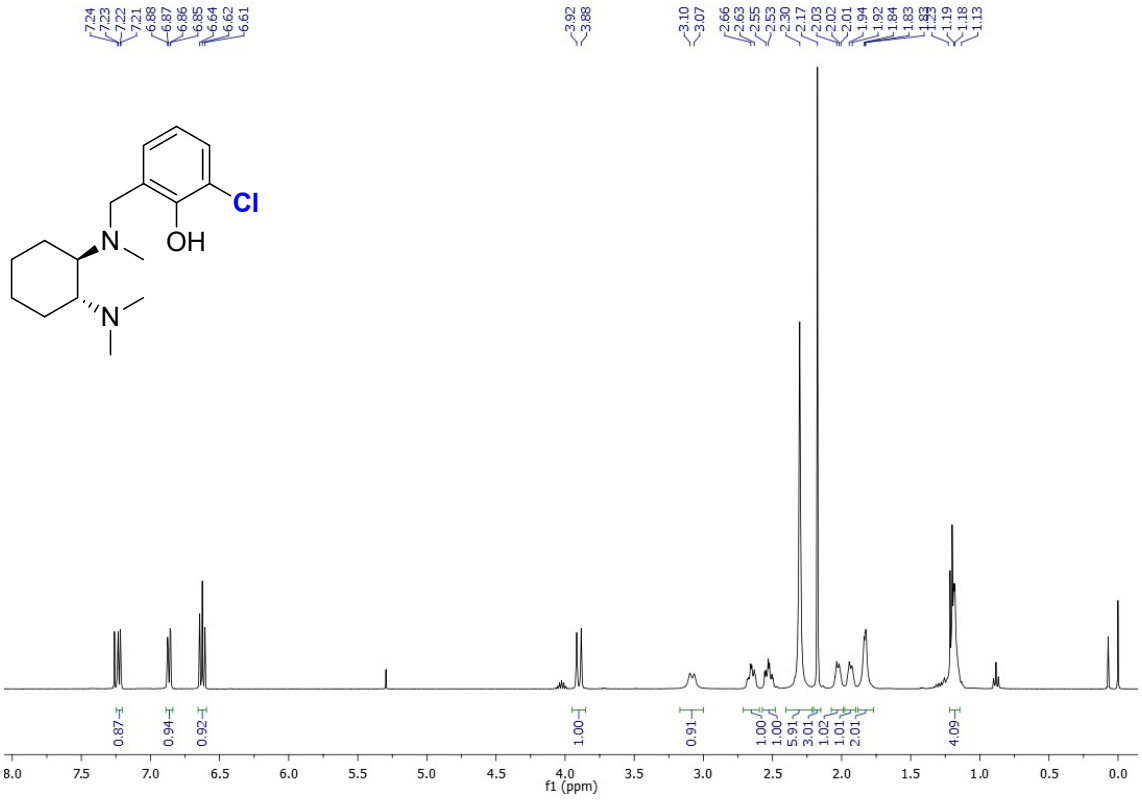
(*R*,*R*)-**L4** **^{13}C-NMR** ($CDCl_3$)



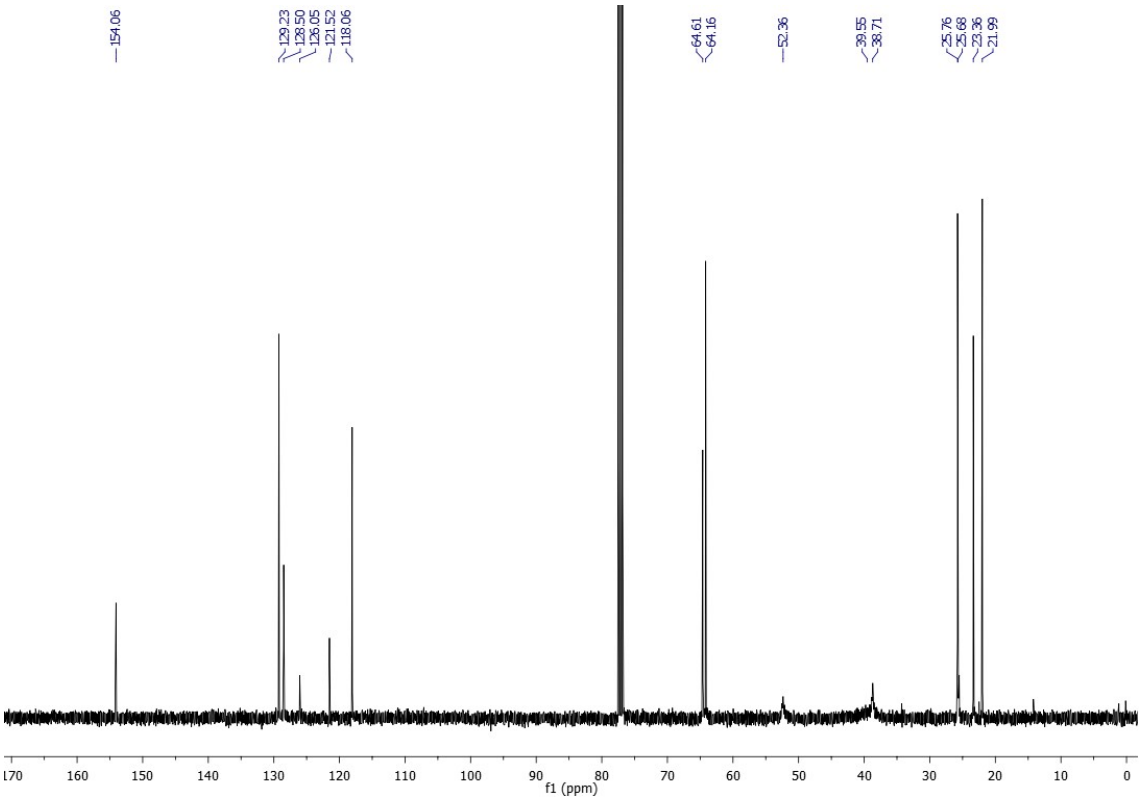
(*R*,*R*)-**L4** **^{19}F-NMR** ($CDCl_3$)



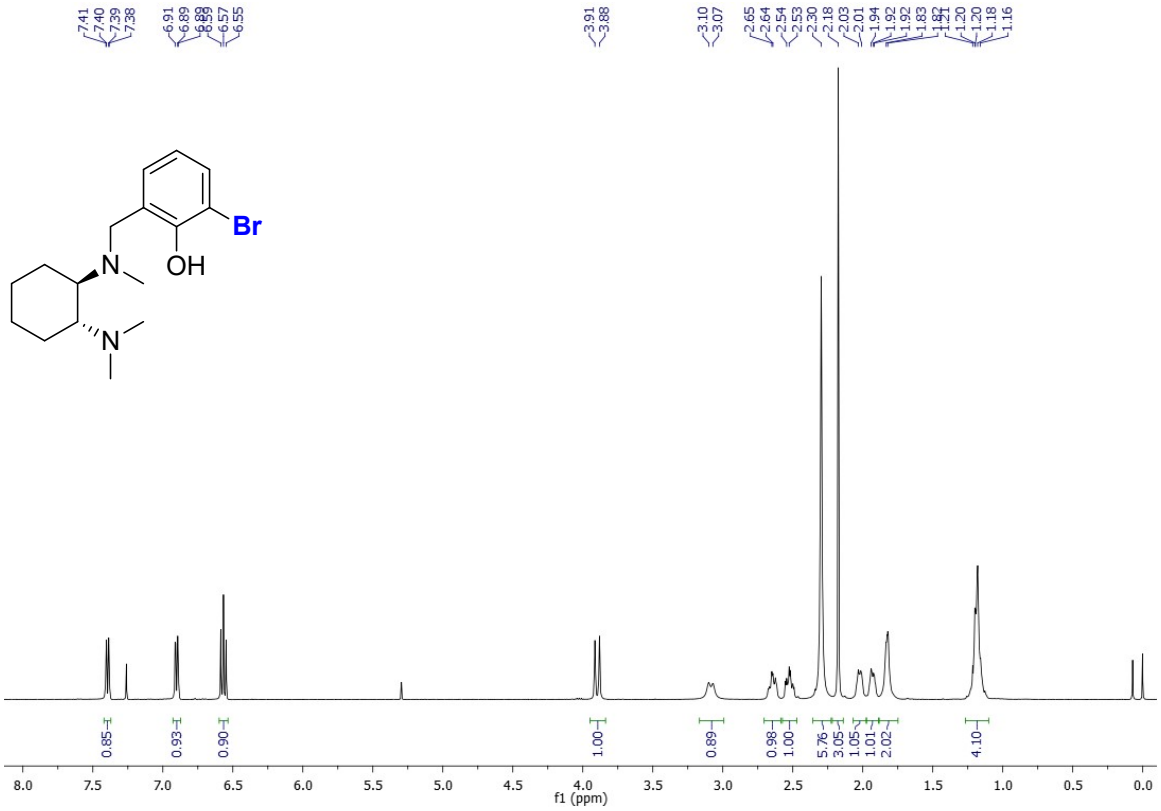
(*R*,*R*)-**L5** ^{1}**H-NMR** ($CDCl_3$)



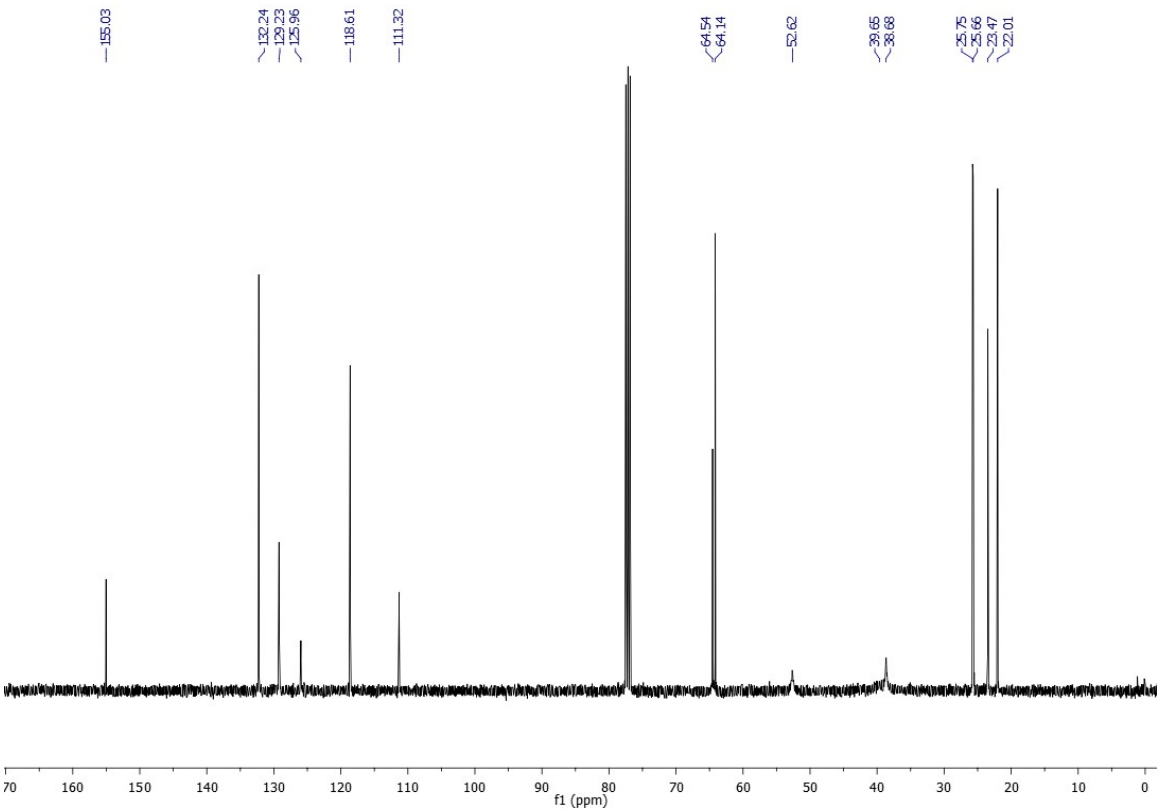
(*R*,*R*)-**L5** ^{13}**C-NMR** ($CDCl_3$)



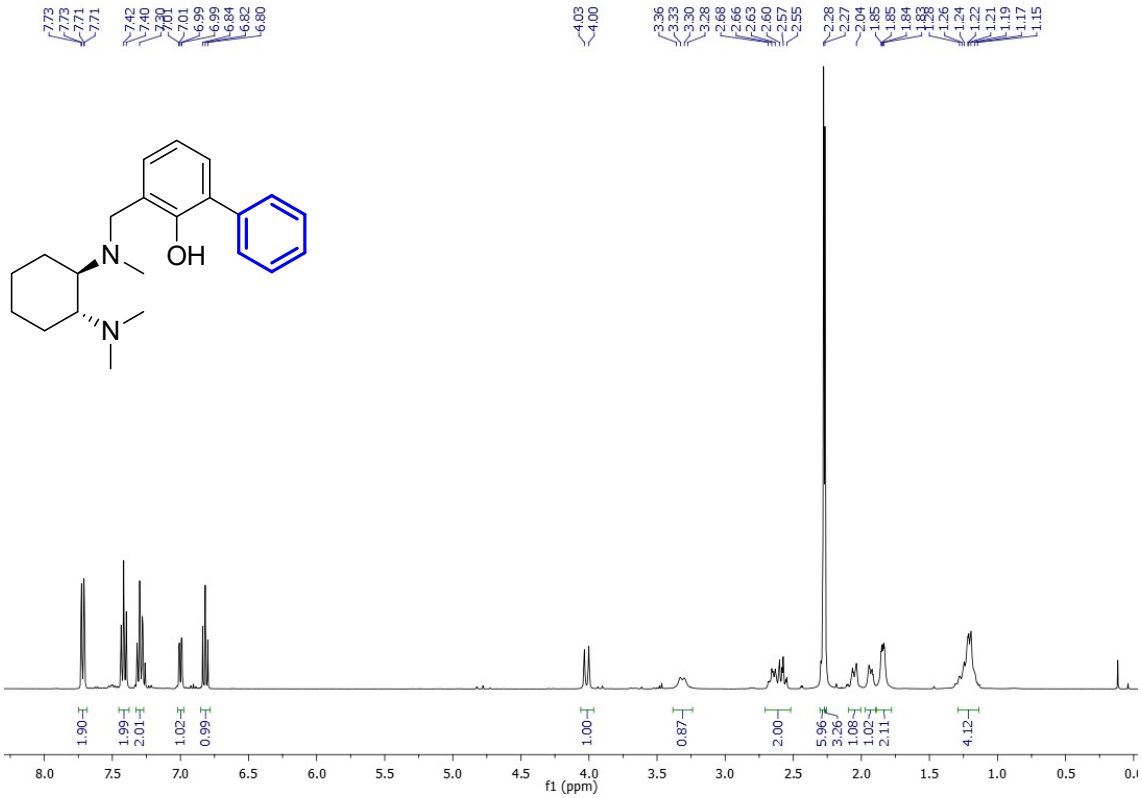
(*R*,*R*)-**L6** ^{1}**H-NMR** ($CDCl_3$)



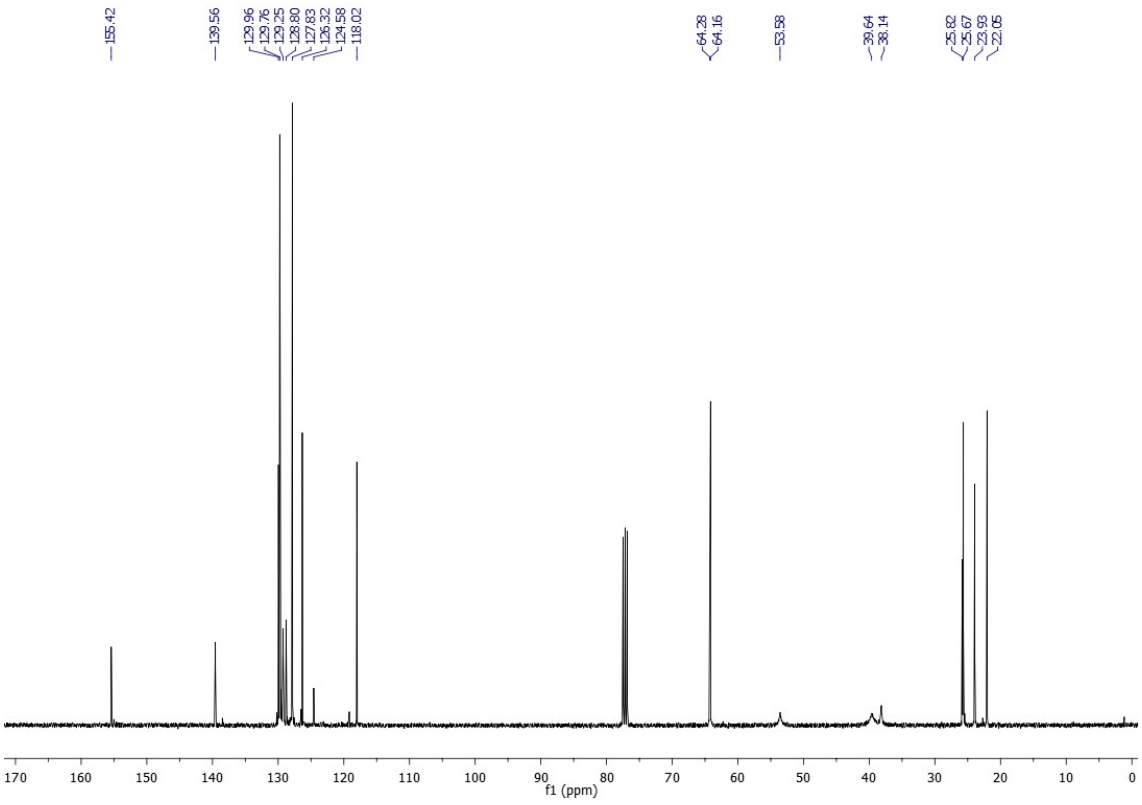
(*R*,*R*)-**L6** ^{13}**C-NMR** ($CDCl_3$)



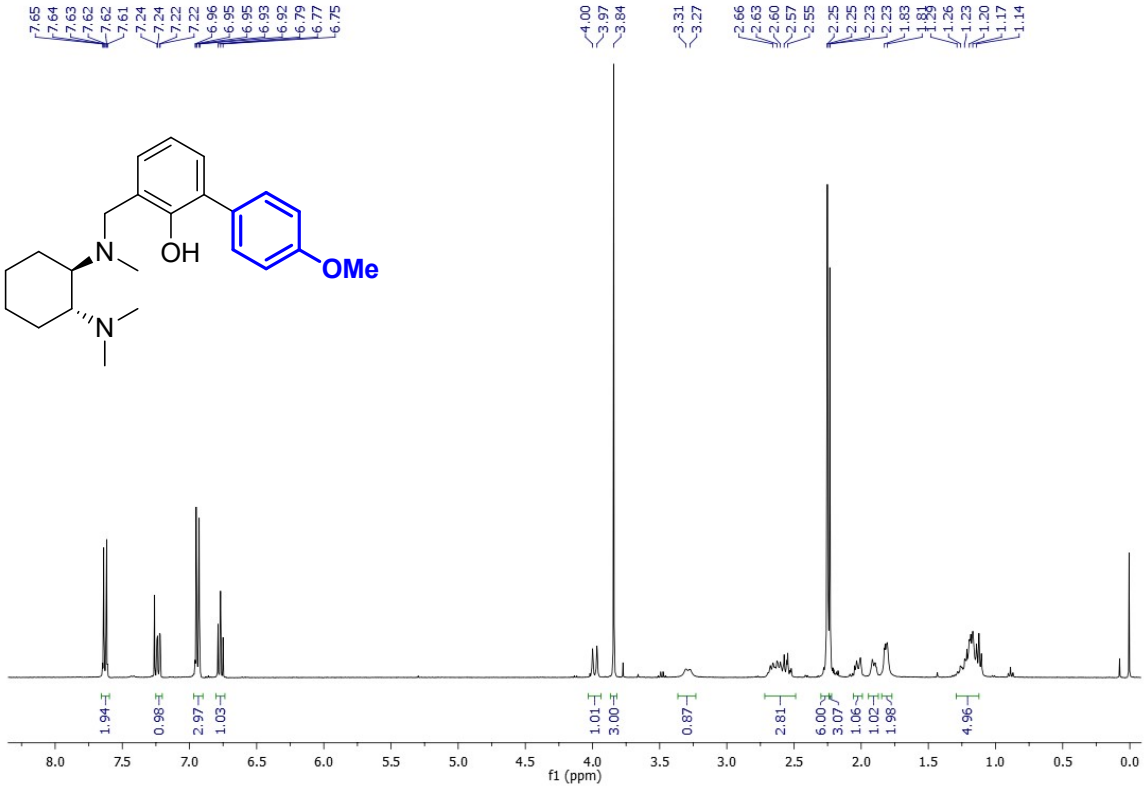
(*R*,*R*)-**L7** **^{1}H-NMR** ($CDCl_3$)



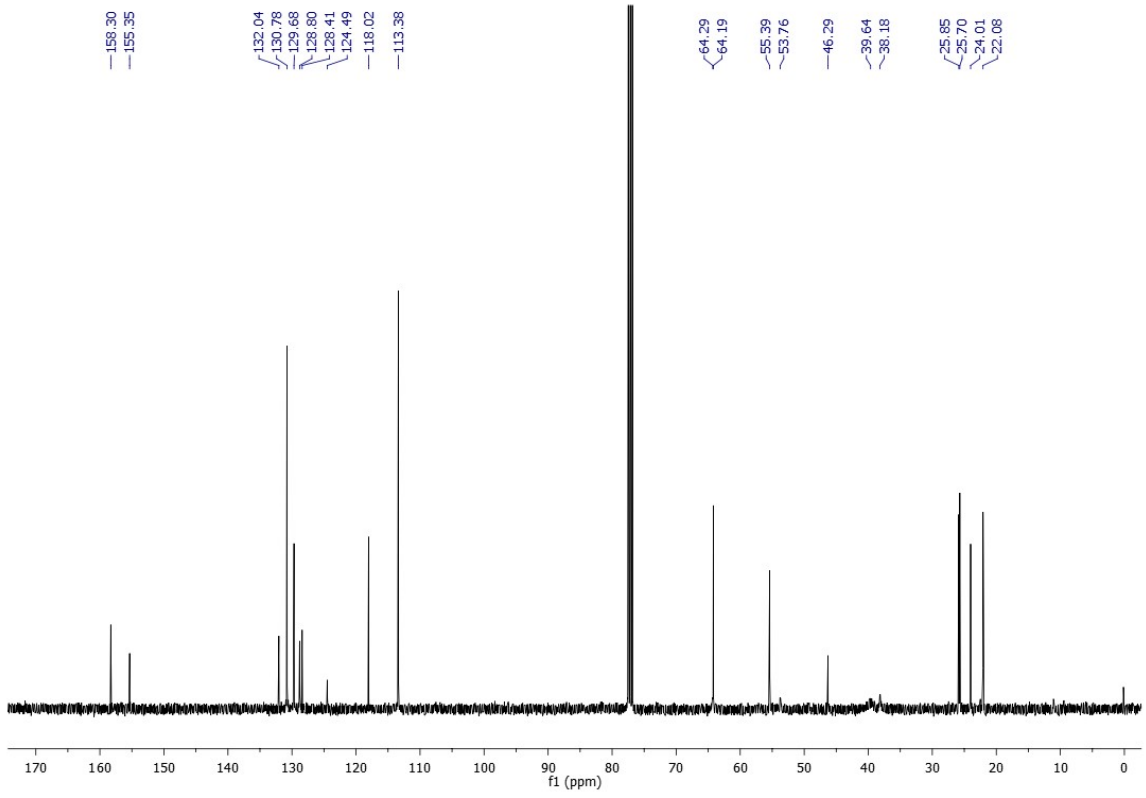
(*R*,*R*)-**L7** **^{13}C-NMR** ($CDCl_3$)



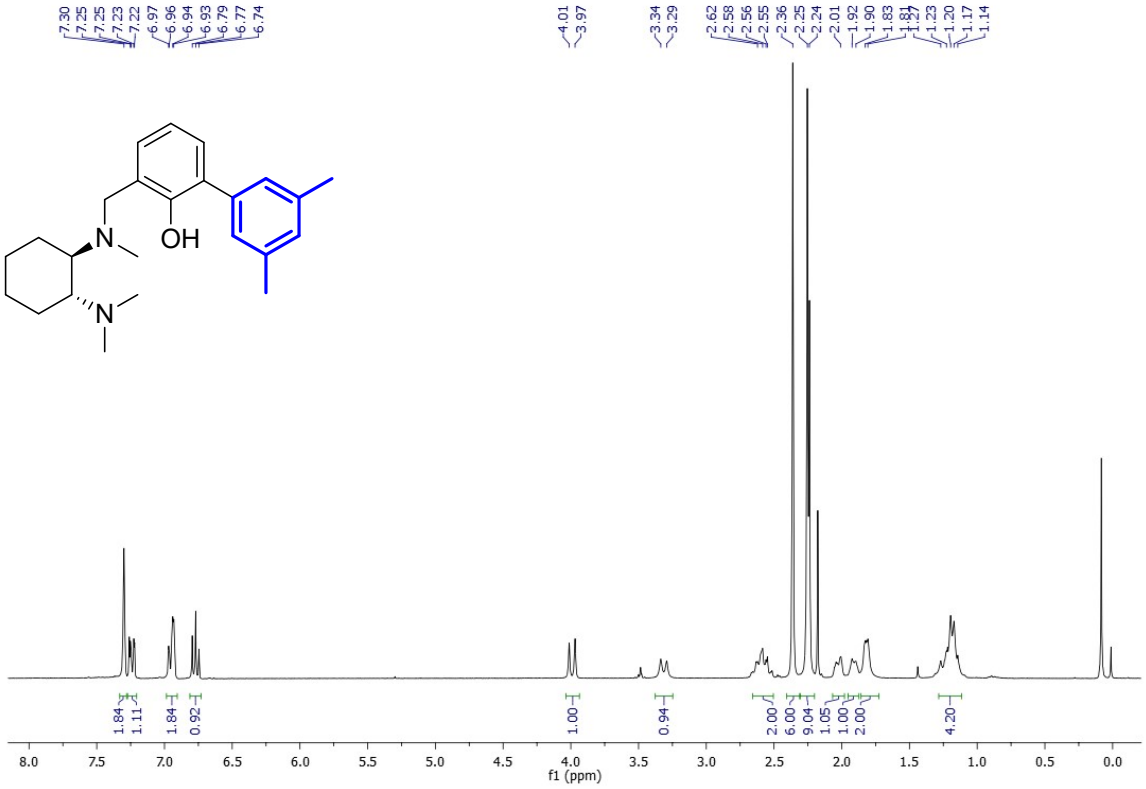
(*R*,*R*)-**L8** **^{1}H-NMR** ($CDCl_3$)



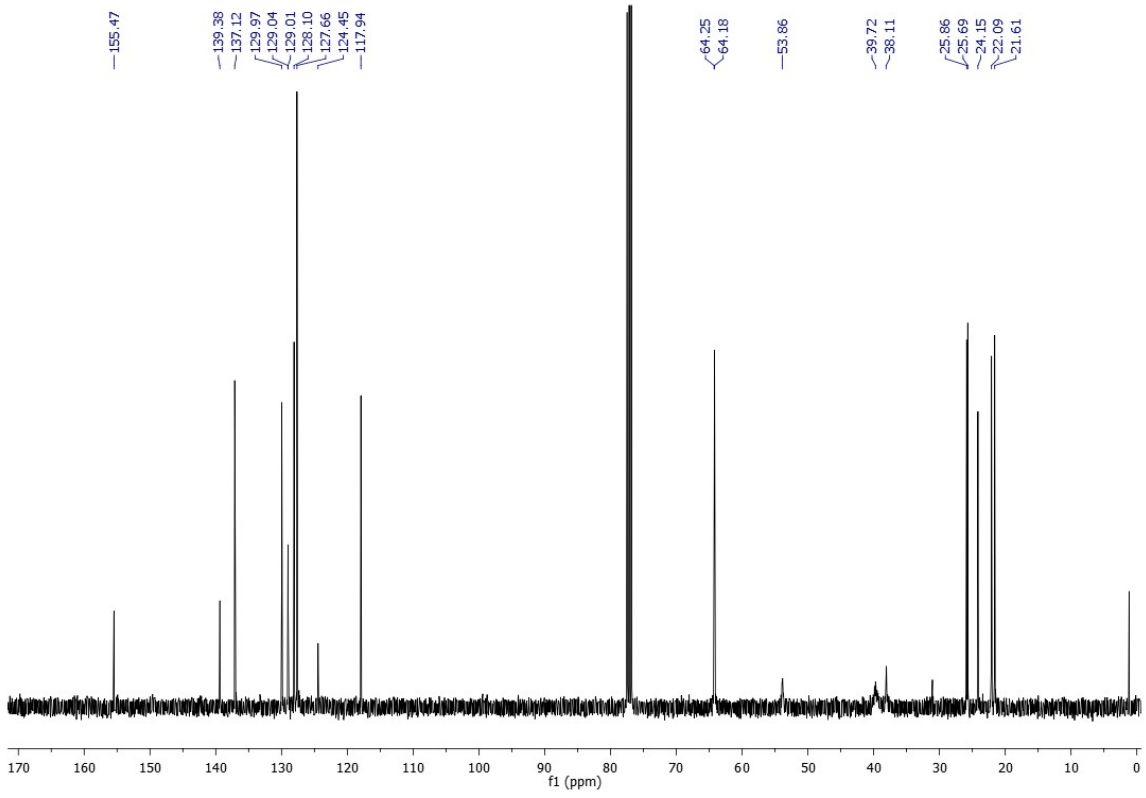
(*R*,*R*)-**L8** **^{13}C-NMR** ($CDCl_3$)



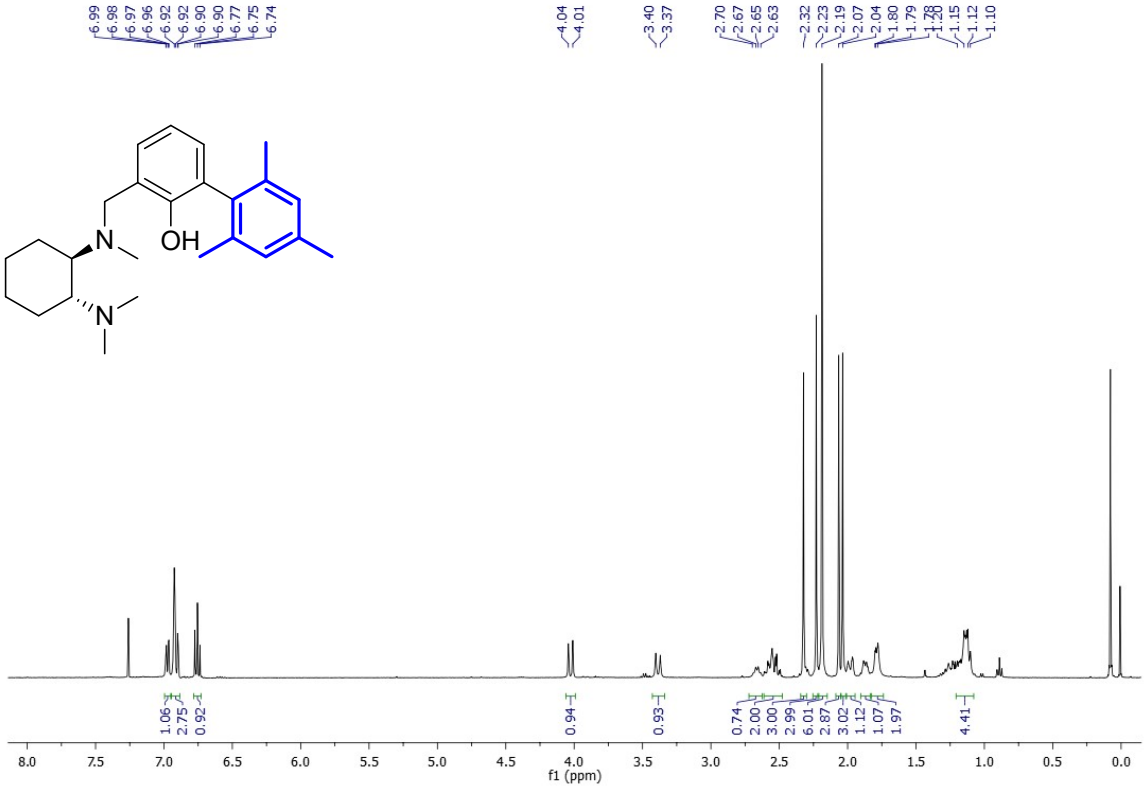
(*R*,*R*)-**L9** **^{1}H-NMR** ($CDCl_3$)



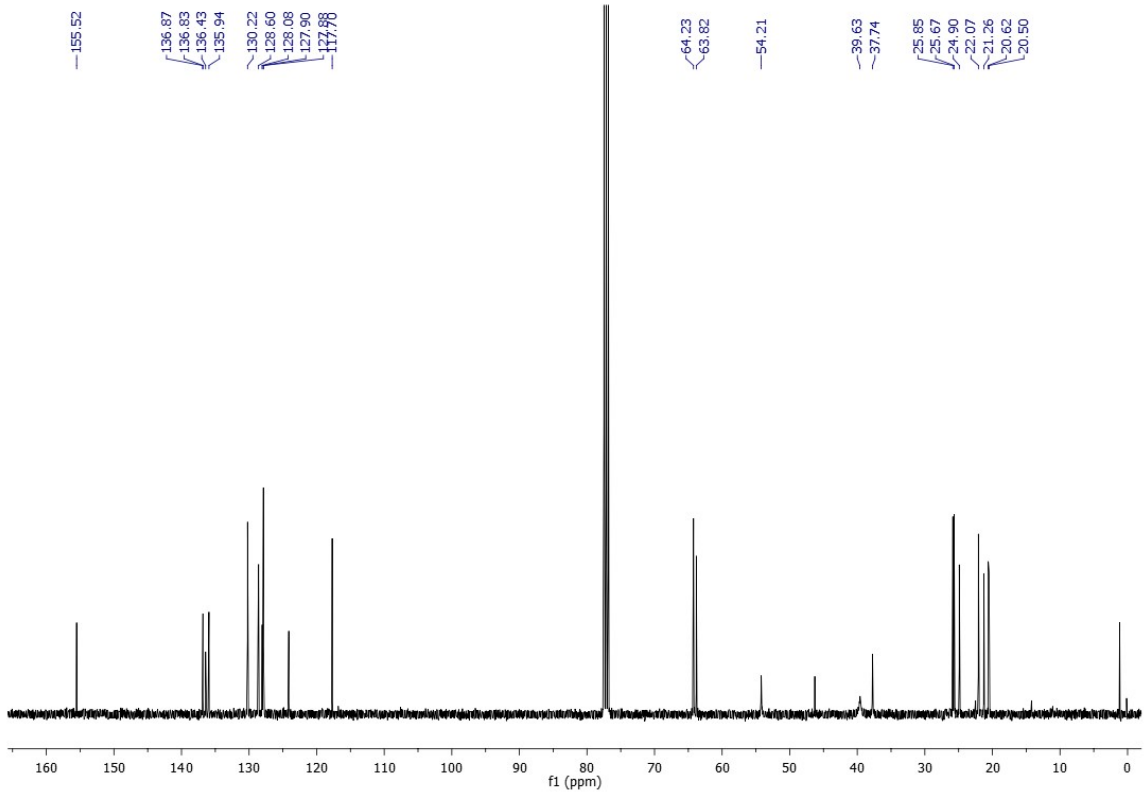
(*R*,*R*)-**L9** **^{13}C-NMR** ($CDCl_3$)



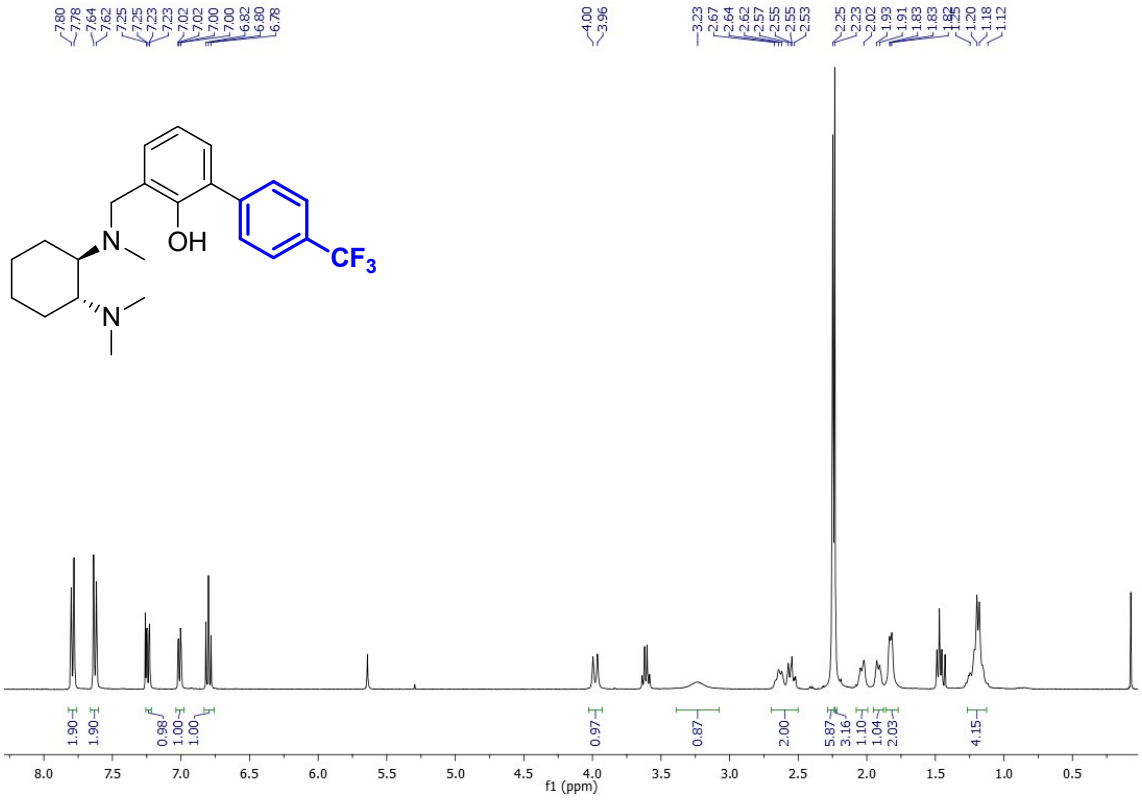
(*R*,*R*)-**L10** ^{1}**H-NMR** ($CDCl_3$)



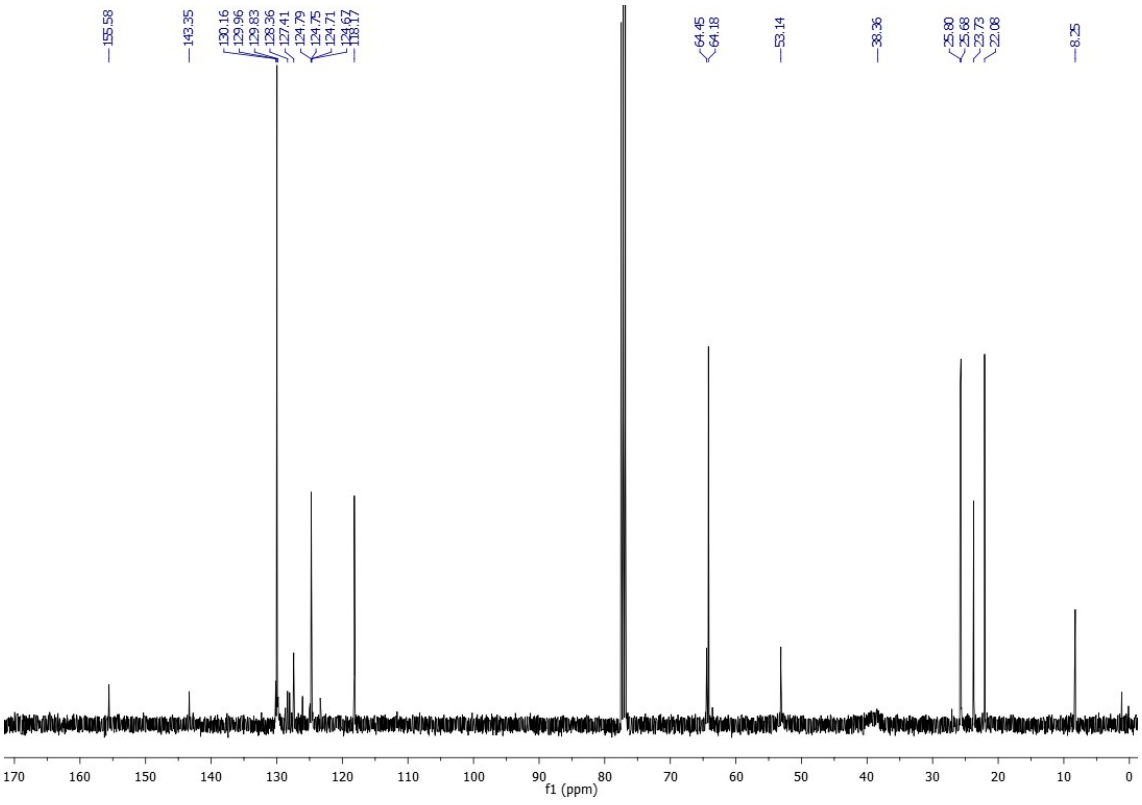
(*R*,*R*)-**L10** ^{13}**C-NMR** ($CDCl_3$)



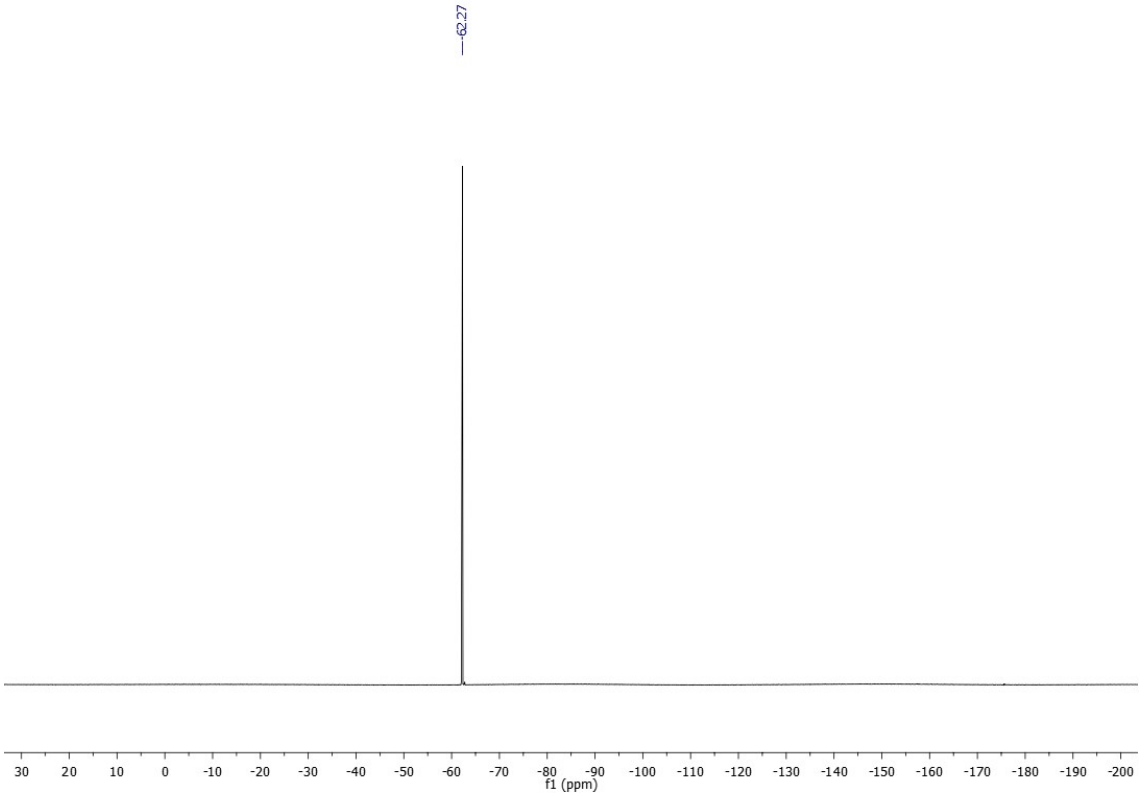
(*R*,*R*)-**L11** **^{1}H-NMR** ($CDCl_3$)



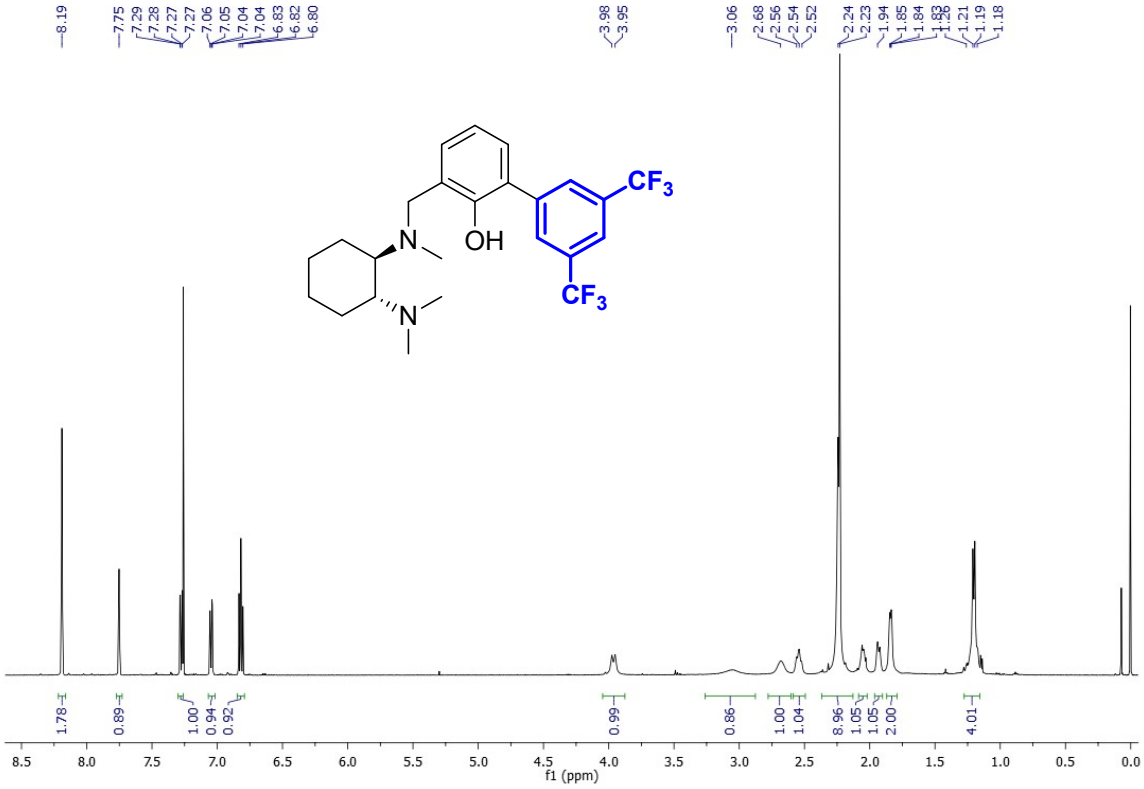
(*R*,*R*)-**L11** **^{13}C-NMR** ($CDCl_3$)



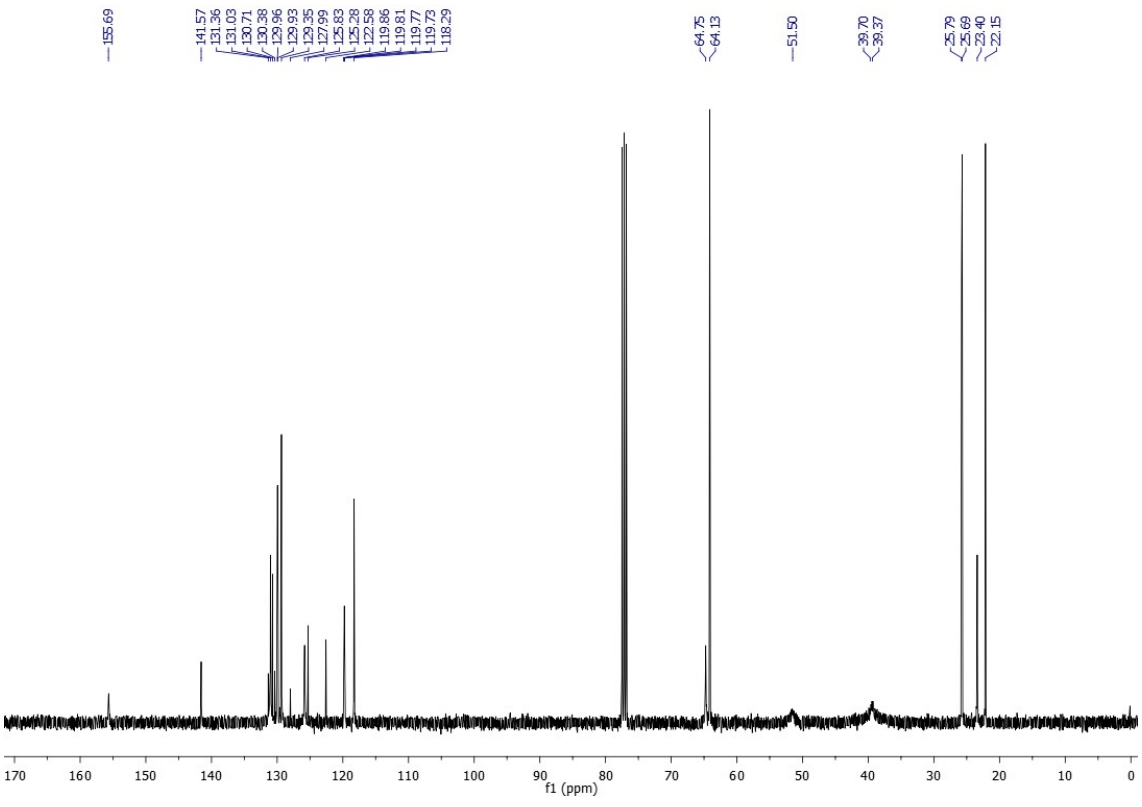
(*R*,*R*)-**L11** **^{19}F-NMR** ($CDCl_3$)



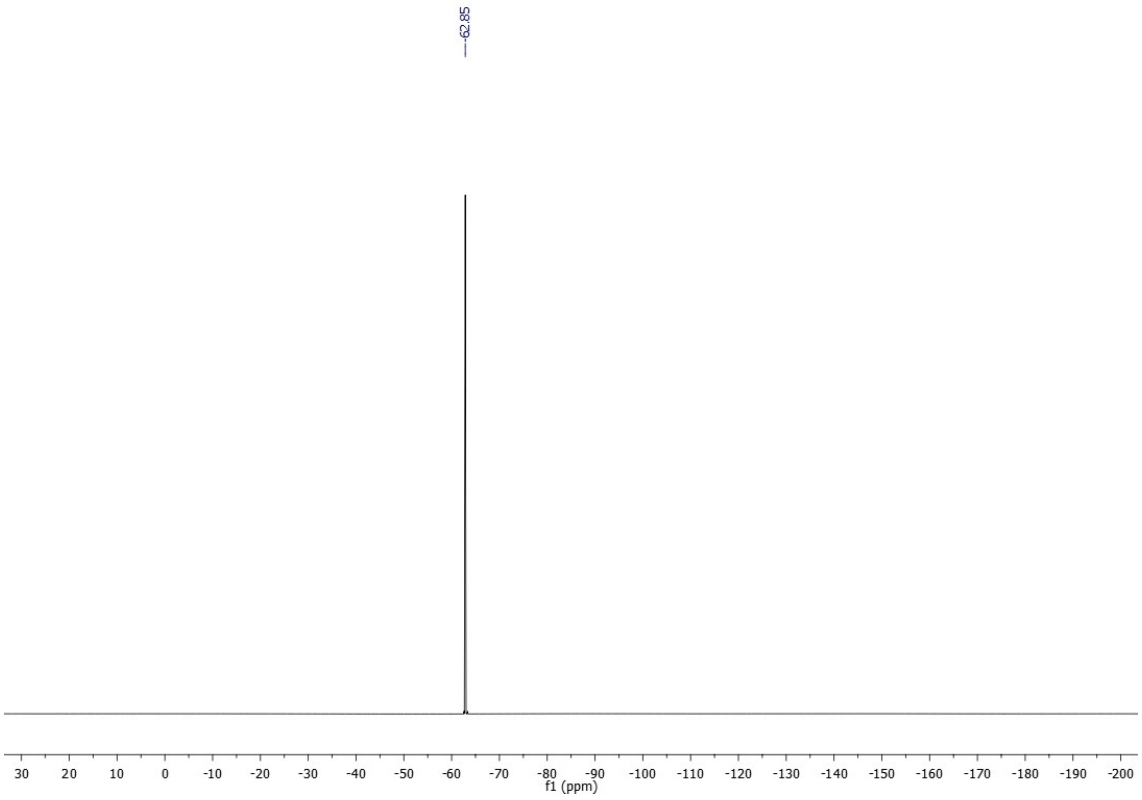
(*R*,*R*)-**L12** ^{1}**H-NMR** ($CDCl_3$)



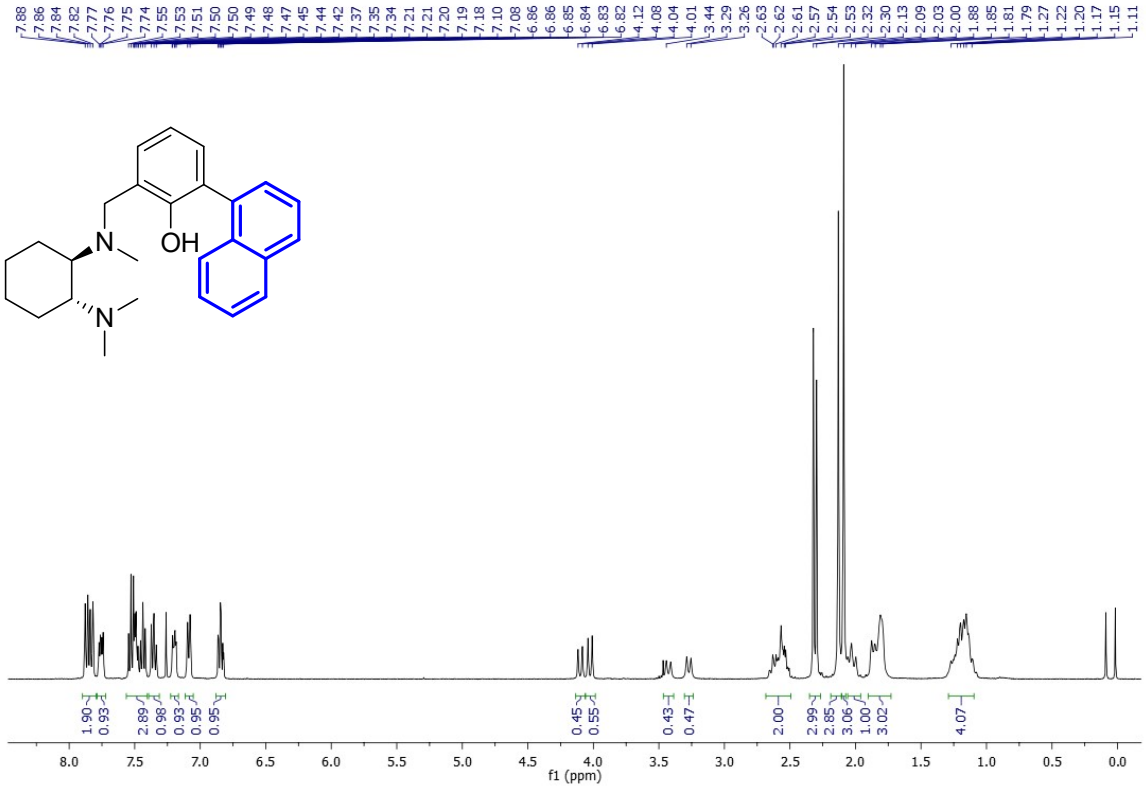
(*R*,*R*)-**L12** ^{13}**C -NMR** ($CDCl_3$)



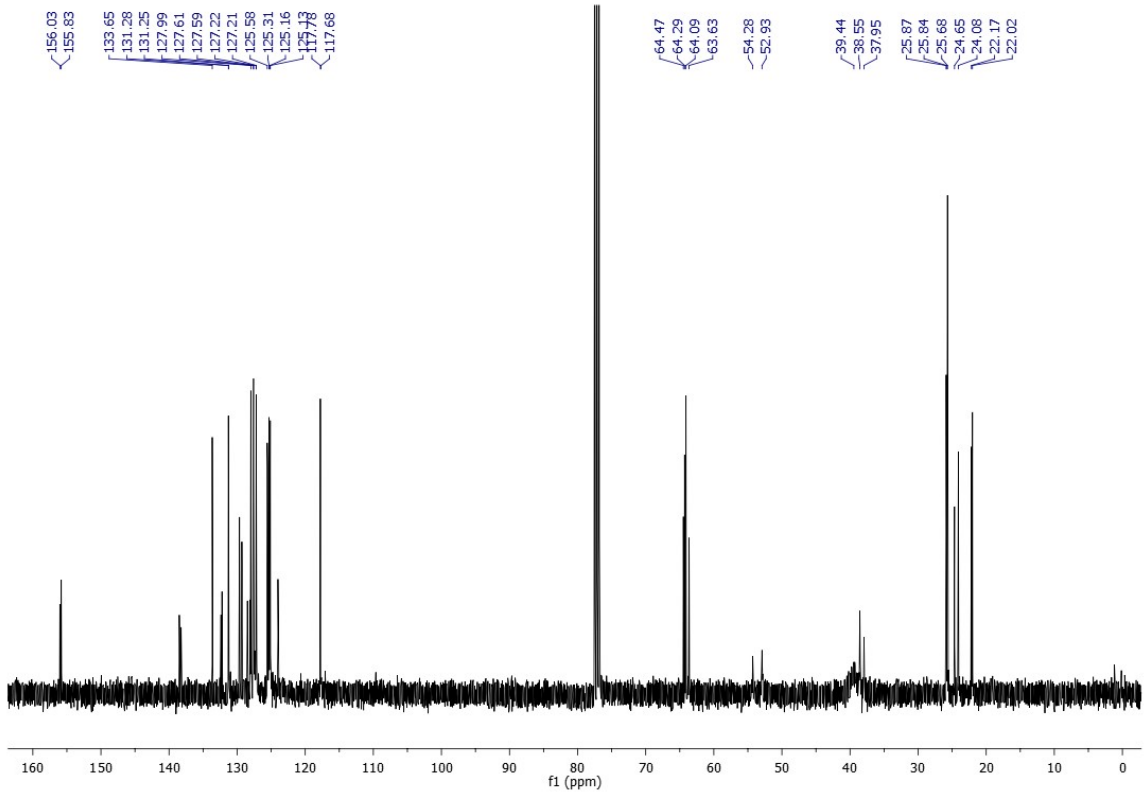
(*R*,*R*)-**L12** **^{19}F -NMR** ($CDCl_3$)



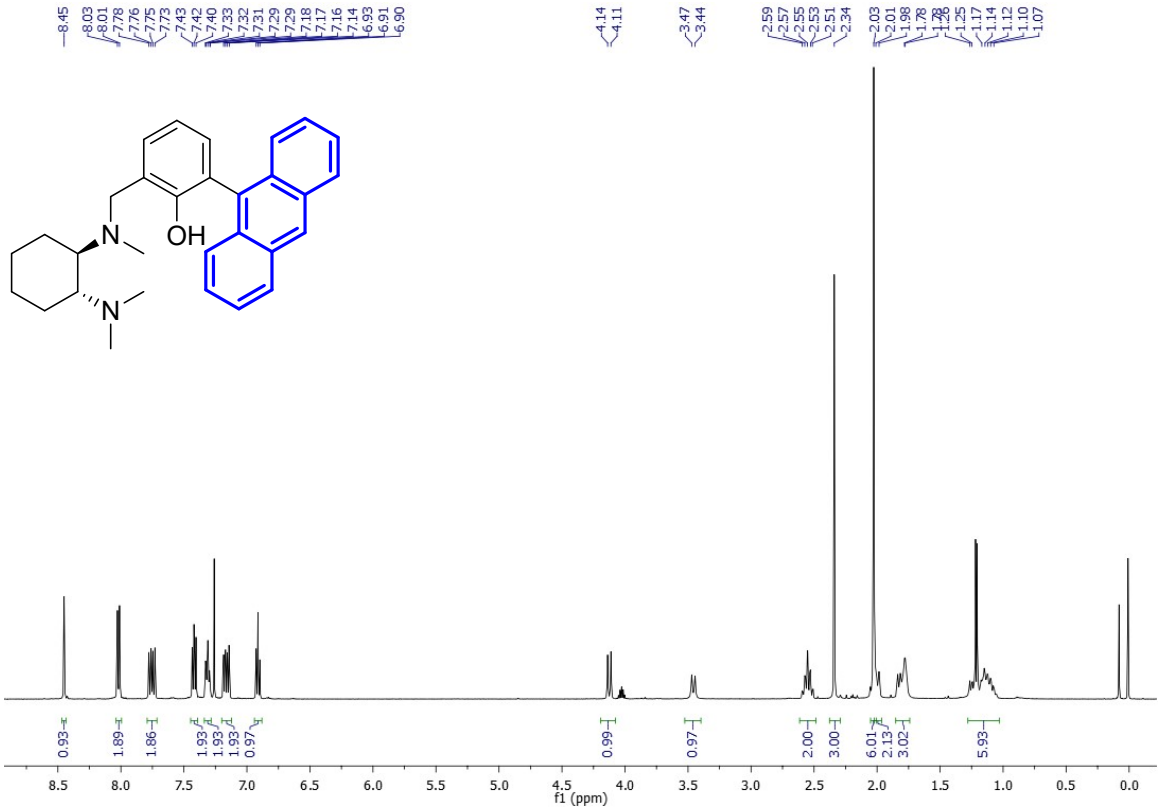
(*R*,*R*)-**L13** ^{1}**H-NMR** ($CDCl_3$)



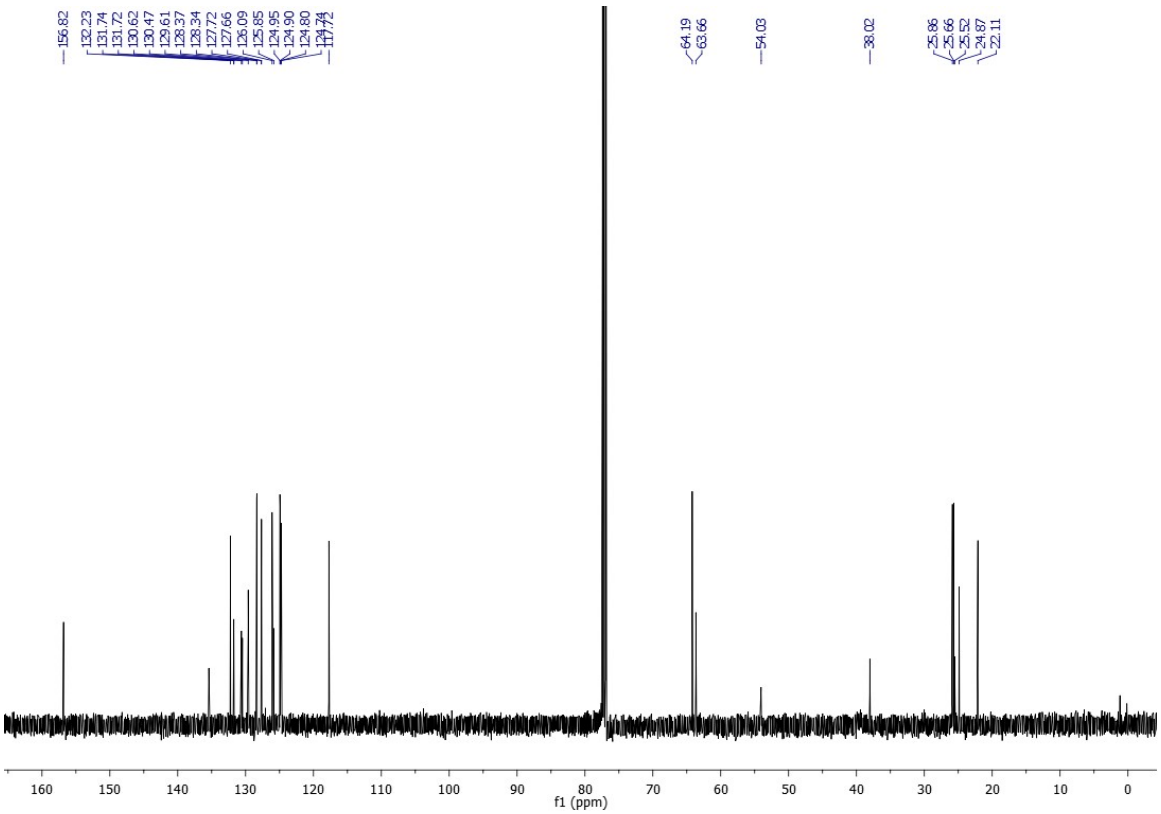
(*R*,*R*)-**L13** ^{13}**C-NMR** ($CDCl_3$)



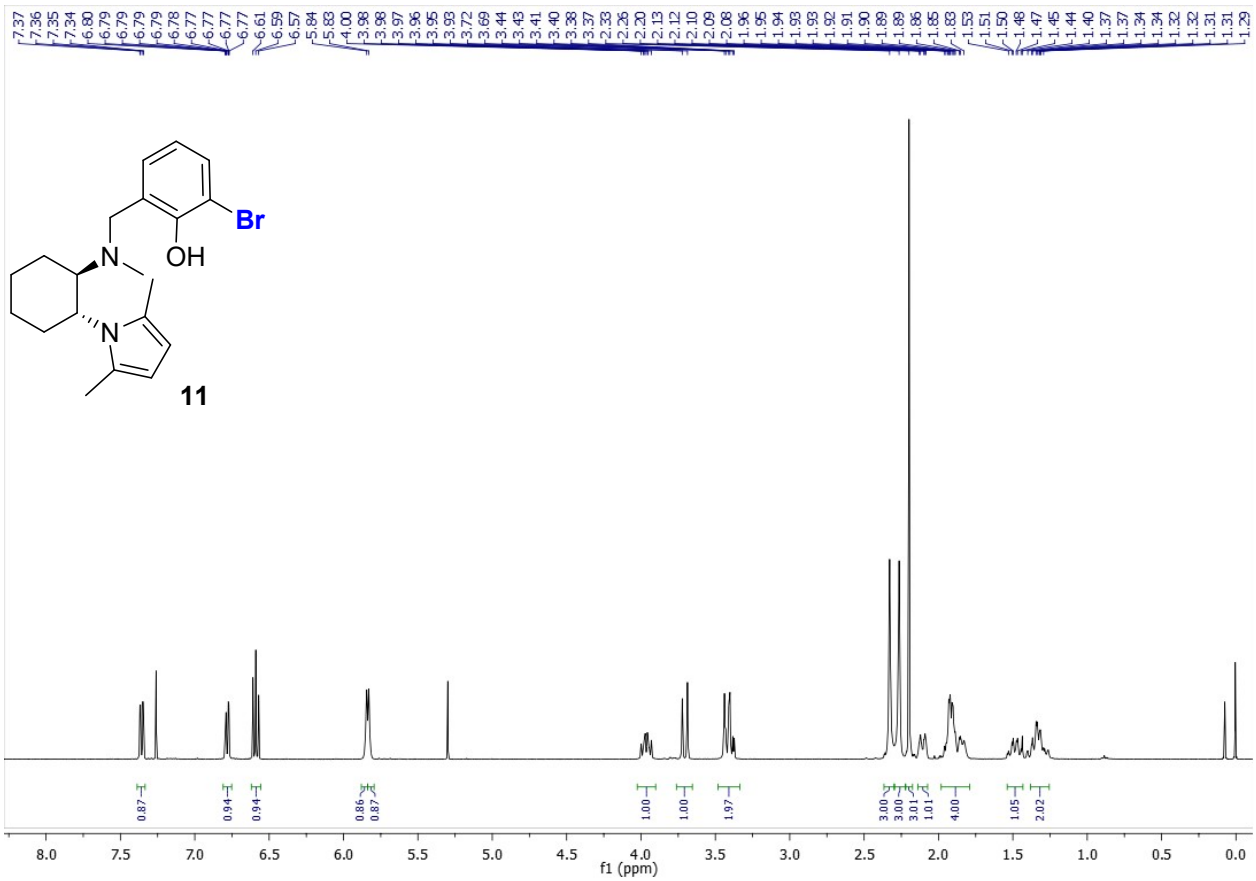
(*R*,*R*)-**L14** ^{1}**H-NMR** ($CDCl_3$)



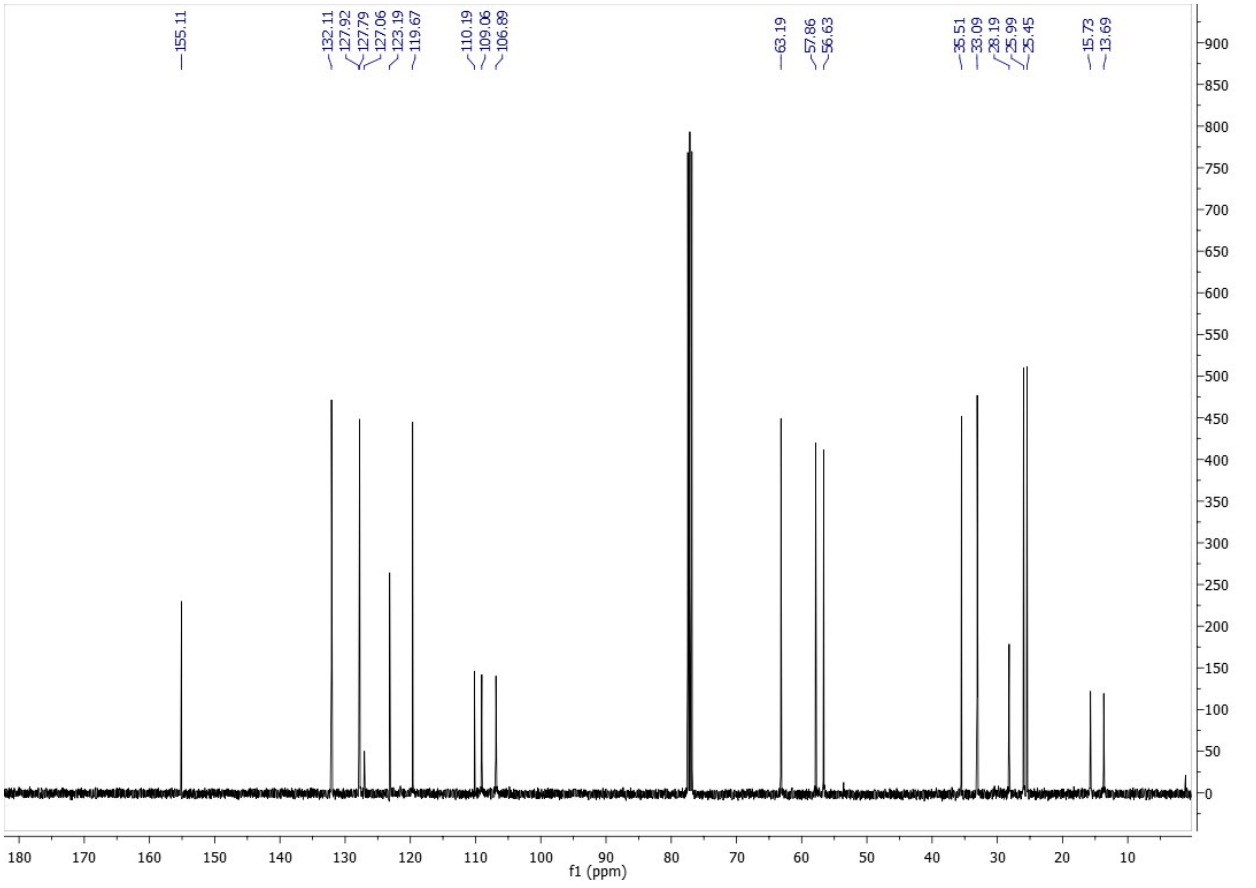
(*R*,*R*)-**L14** ^{13}**C-NMR** ($CDCl_3$)



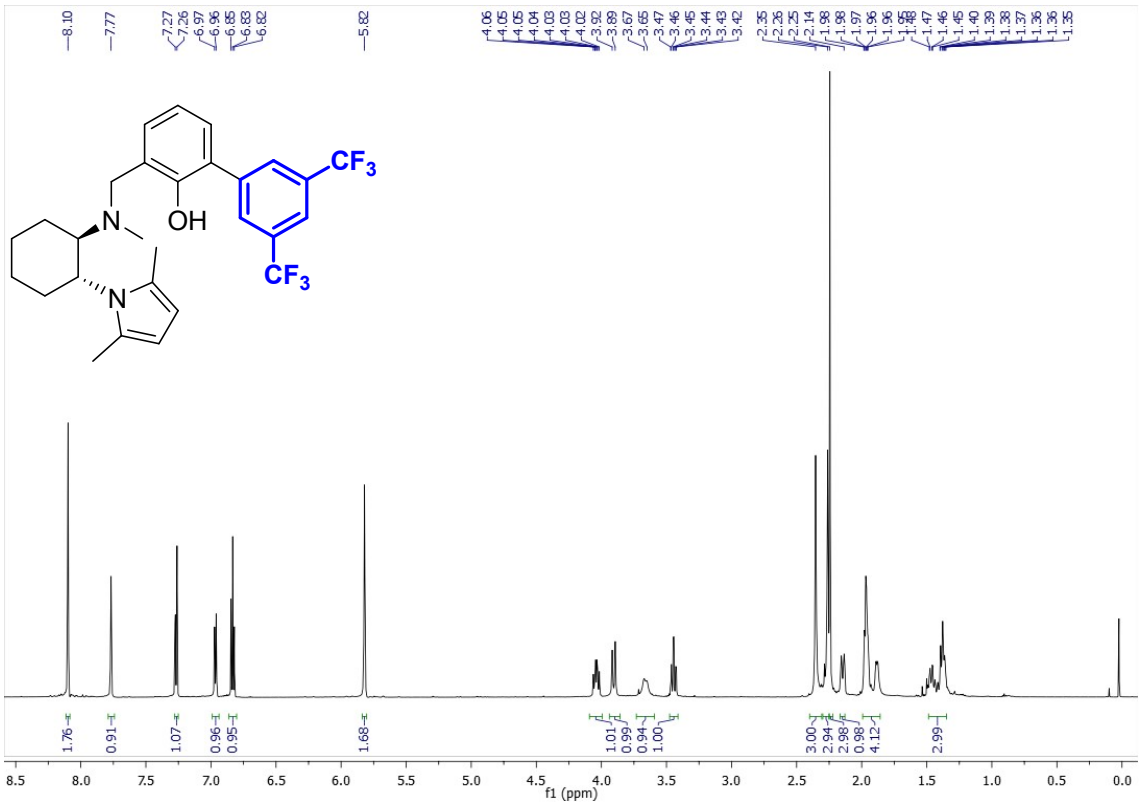
(*R*,*R*)-**11** ^{1}**H-NMR** ($CDCl_3$)



(*R*,*R*)-**11** ^{13}**C-NMR** ($CDCl_3$)



(*R*,*R*)-**L12' ^{1}H-NMR** ($CDCl_3$)



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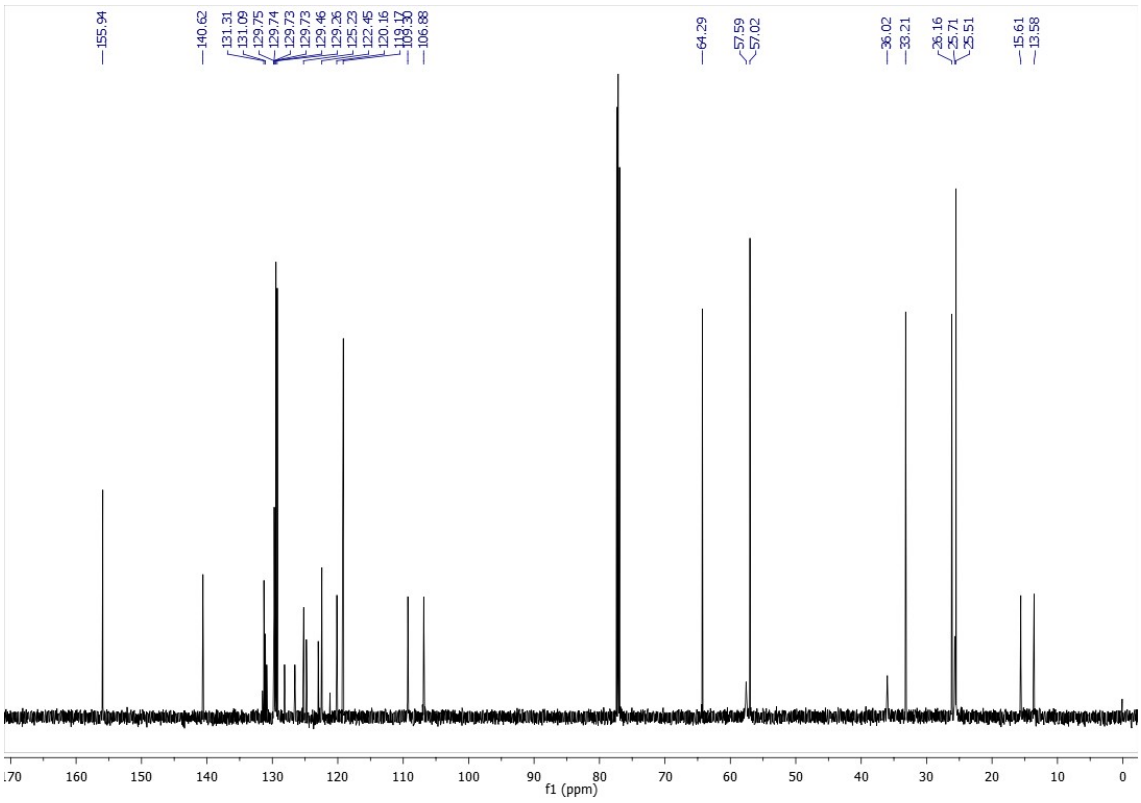
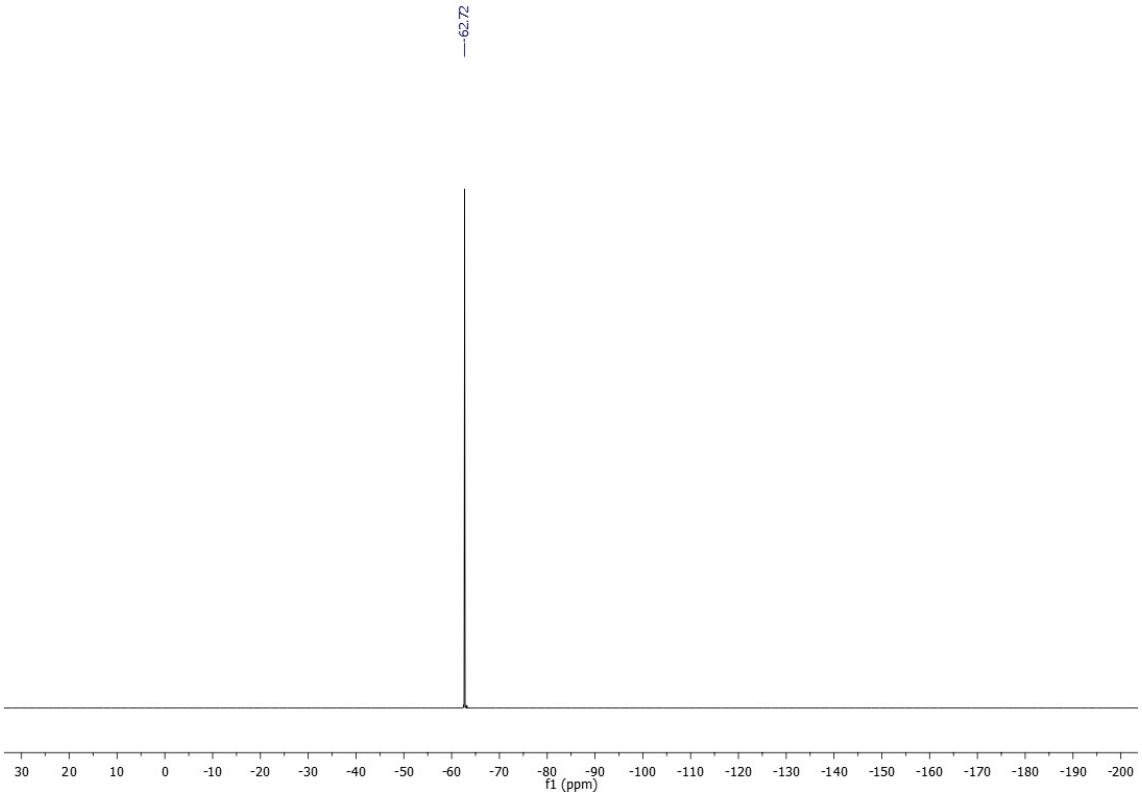
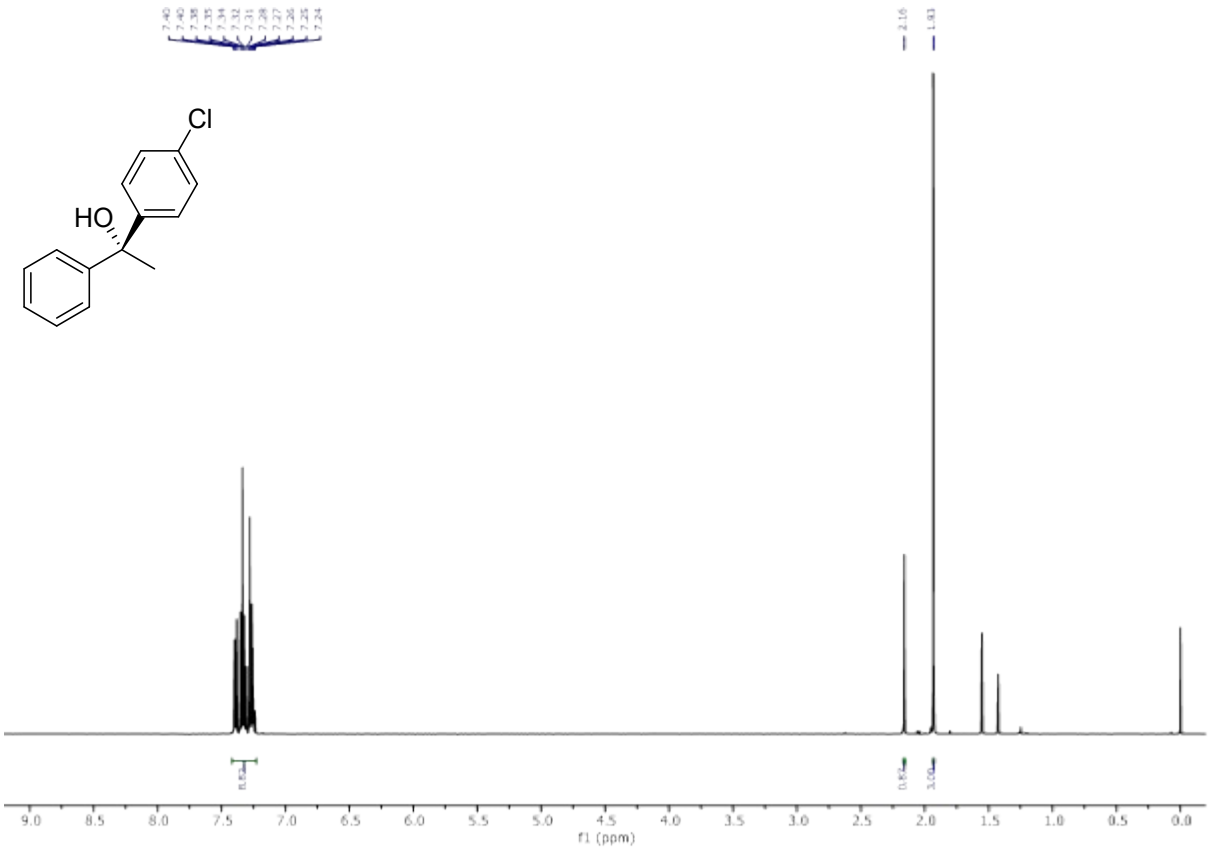


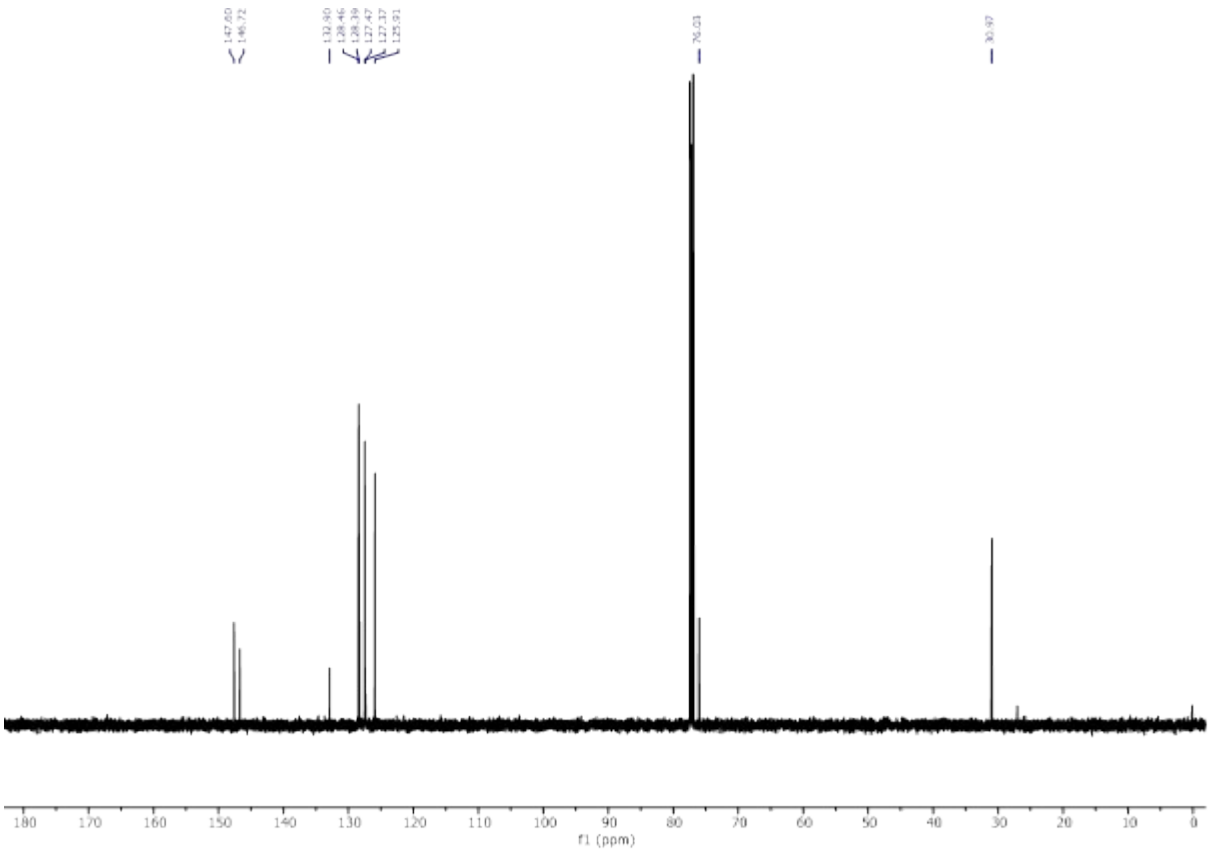
(*R*,*R*)-**L12' ^{19}F-NMR** ($CDCl_3$)



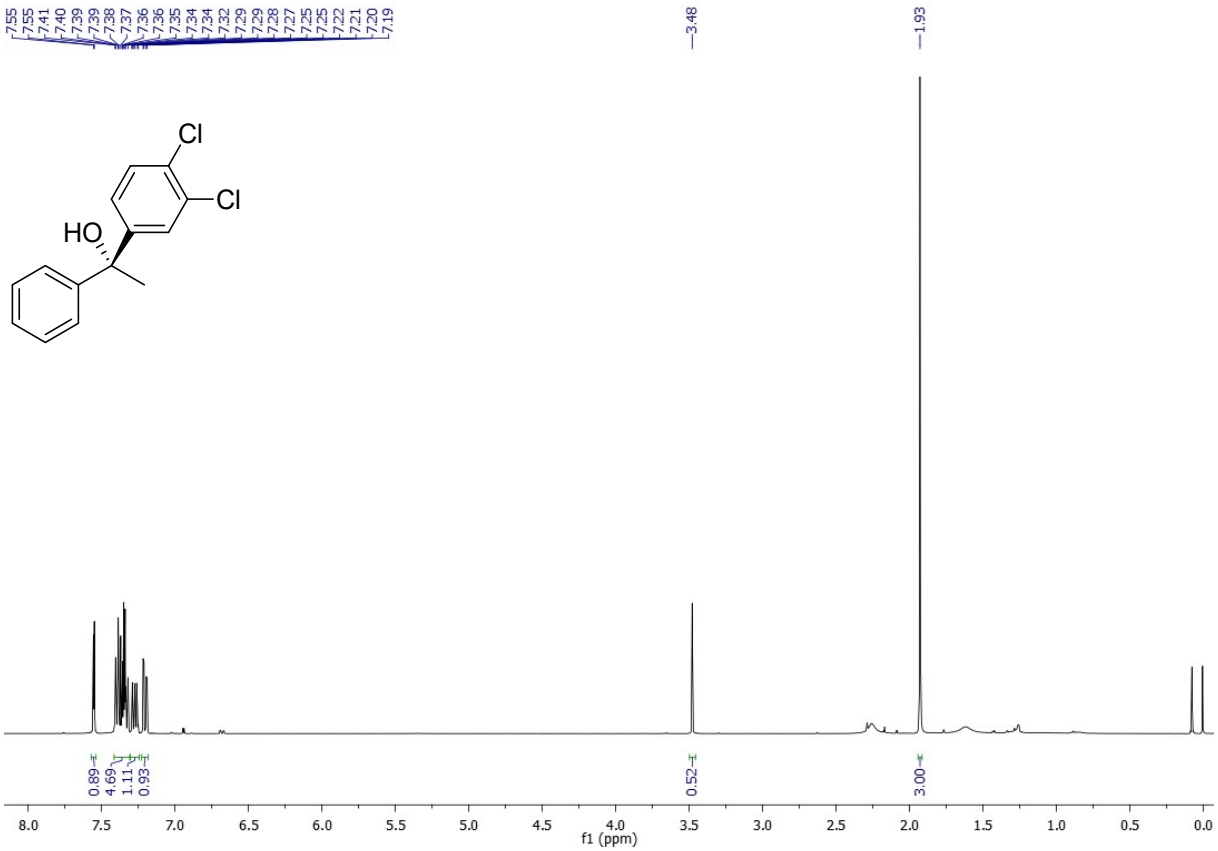
3a ^{1}H-NMR ($CDCl_3$)



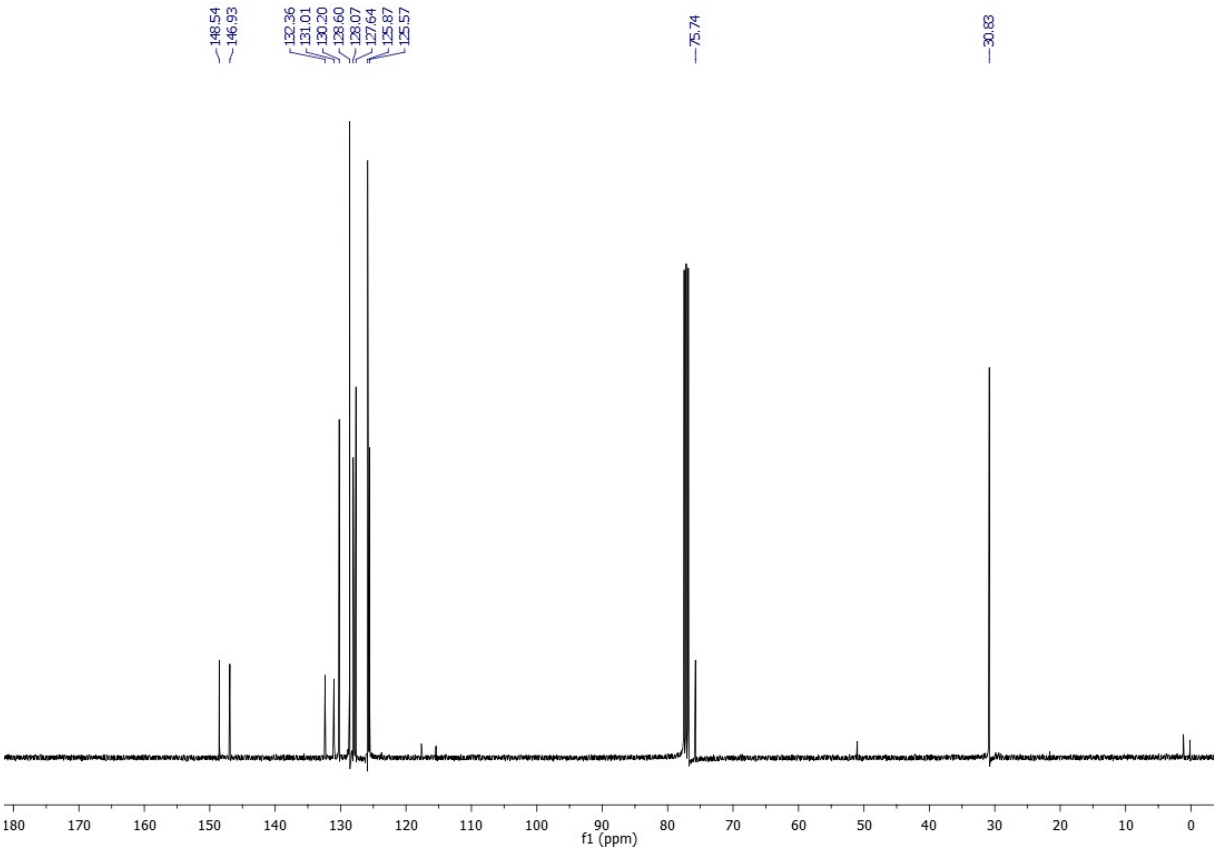
3a ^{13}C-NMR ($CDCl_3$)



3b ^{1}H-NMR ($CDCl_3$)



3b ^{13}C-NMR ($CDCl_3$)



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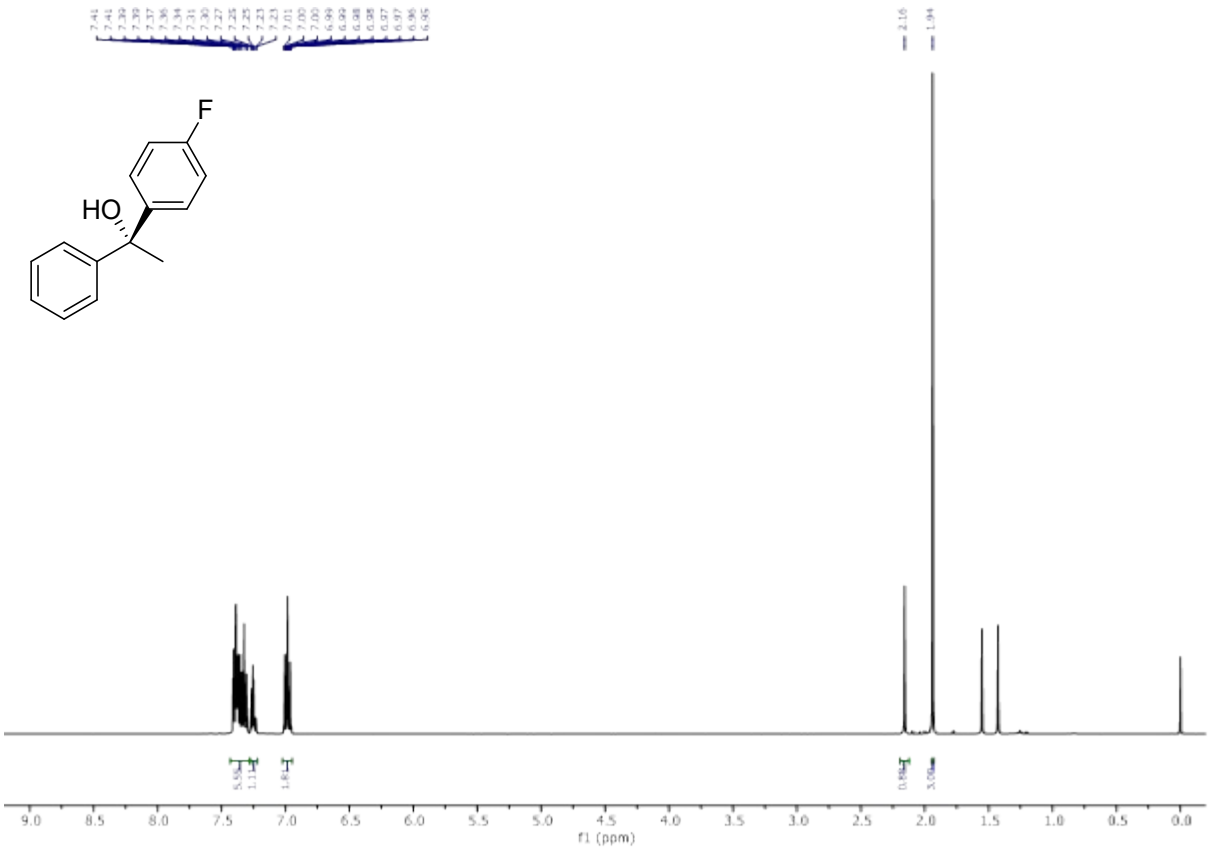
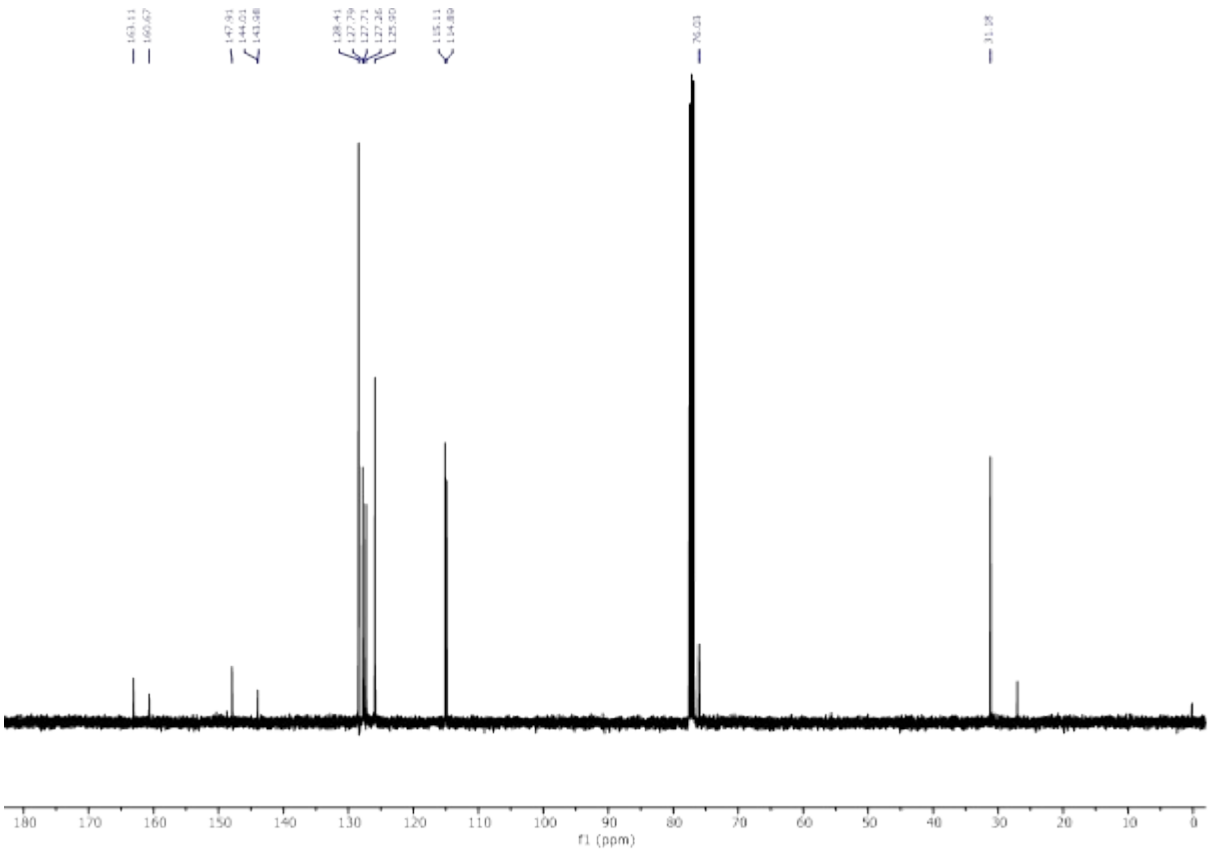
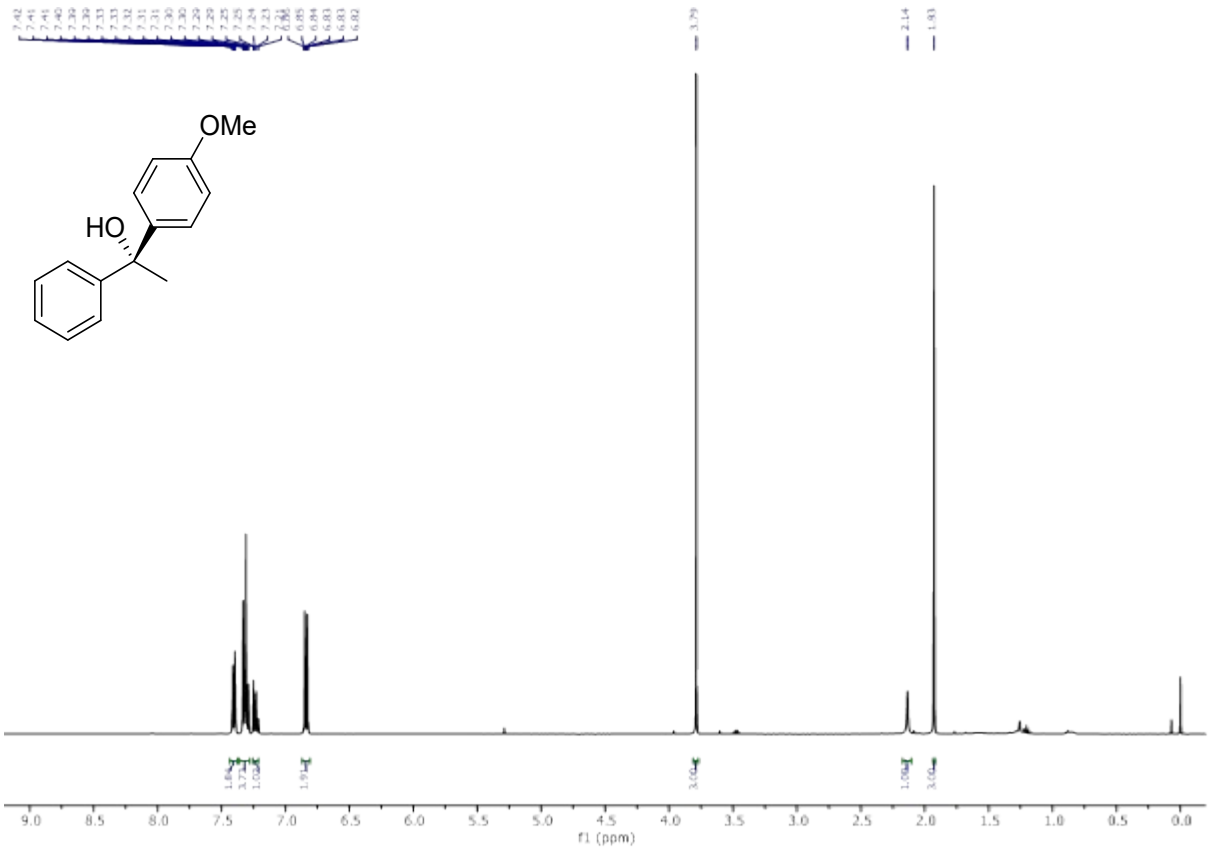


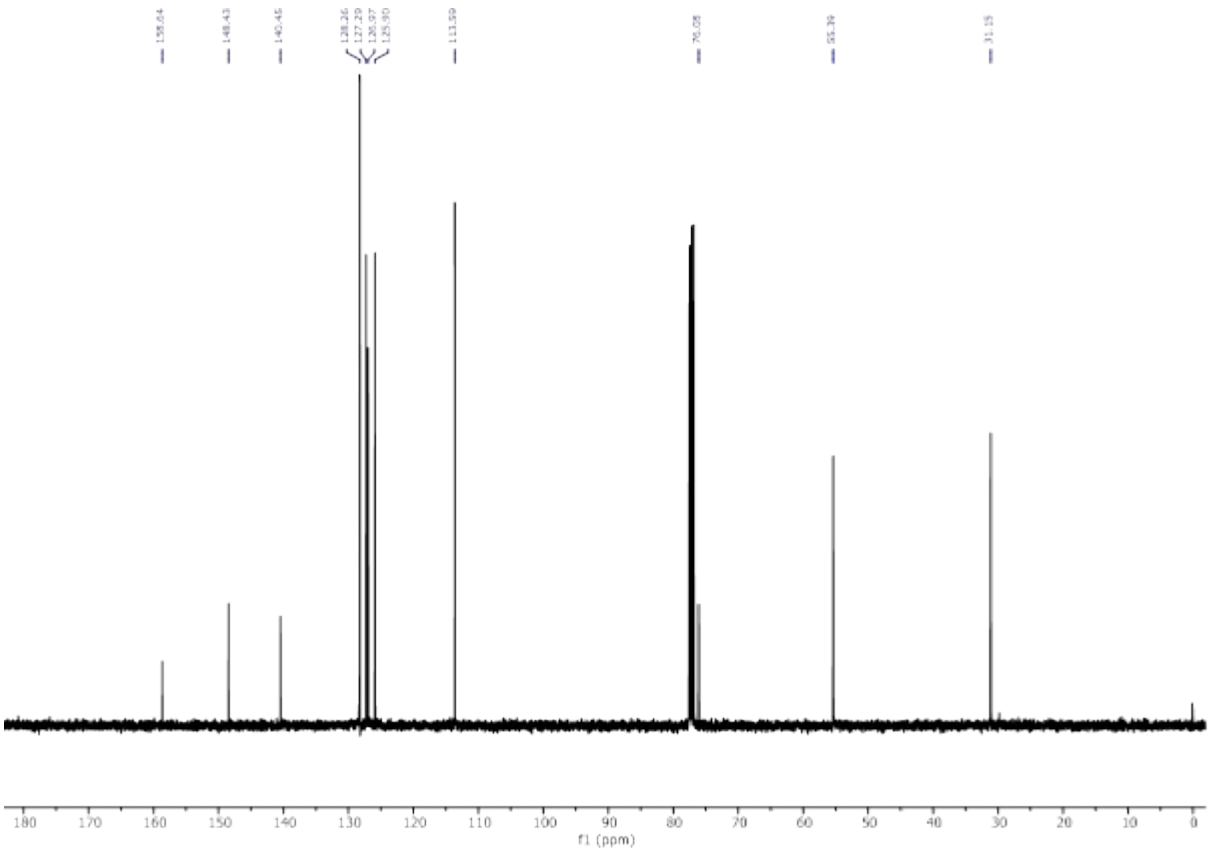
3c ^{13}C-NMR ($CDCl_3$)



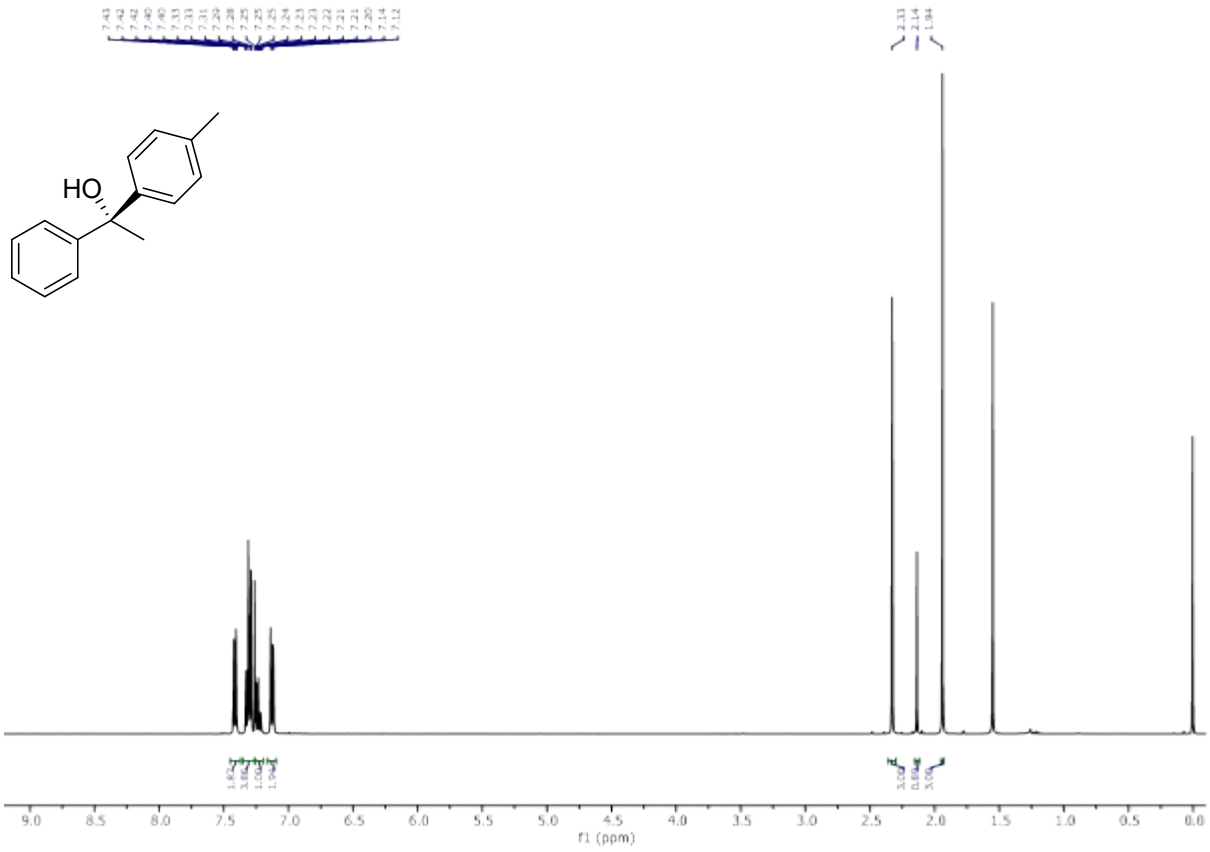
3d ^{1}H-NMR ($CDCl_3$)



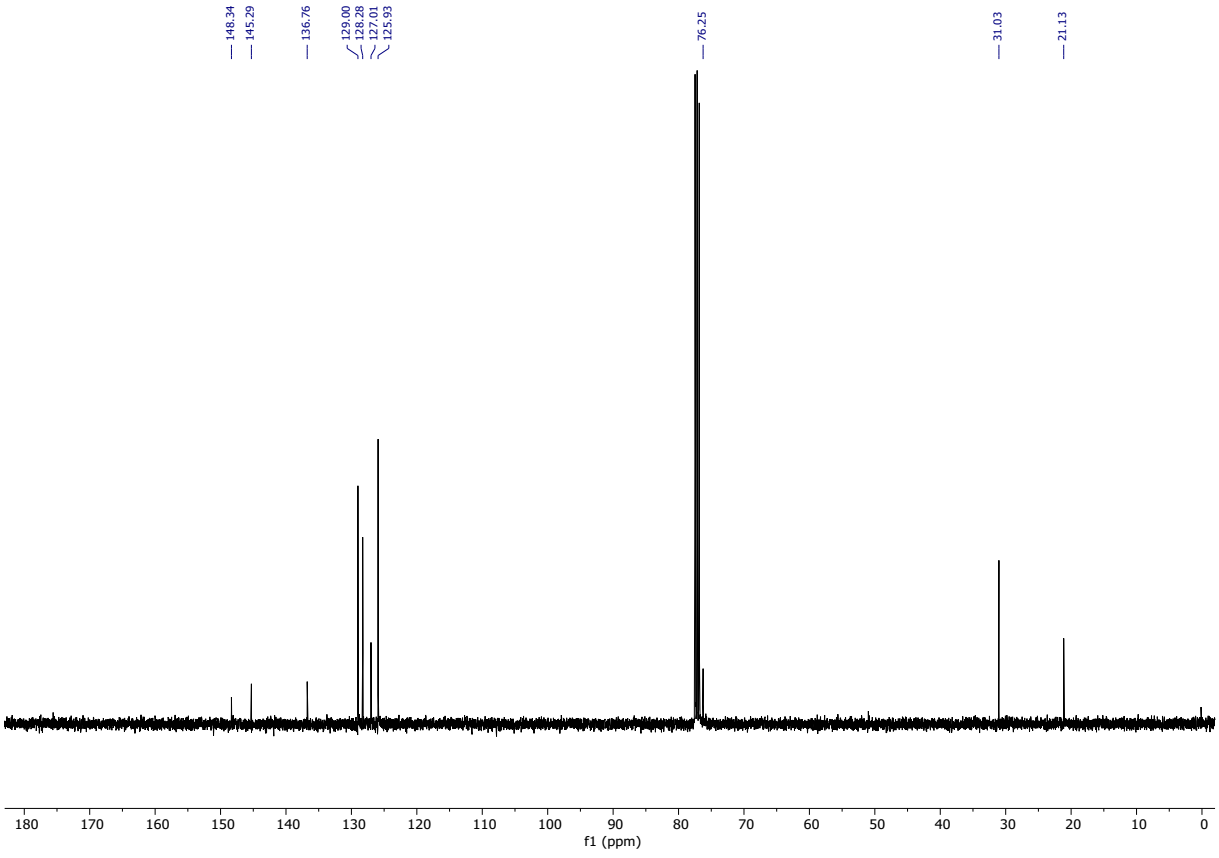
3d ^{13}C-NMR ($CDCl_3$)



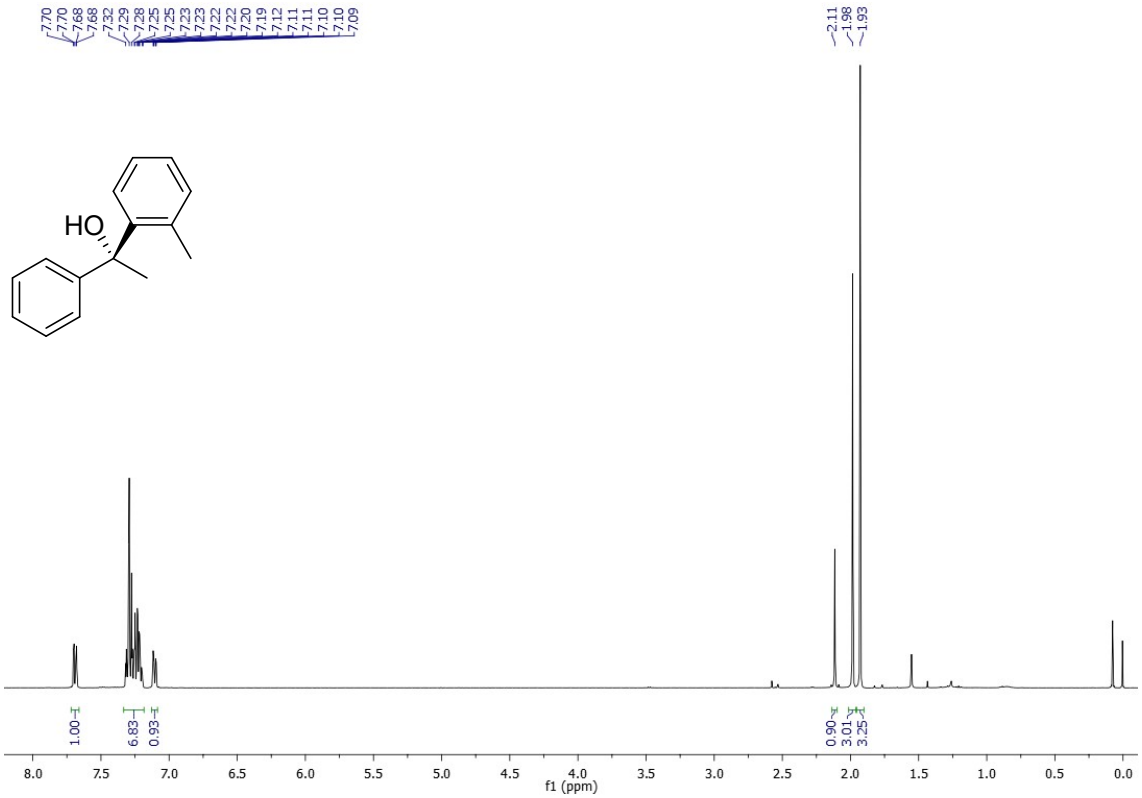
3e ^{1}H-NMR ($CDCl_3$)



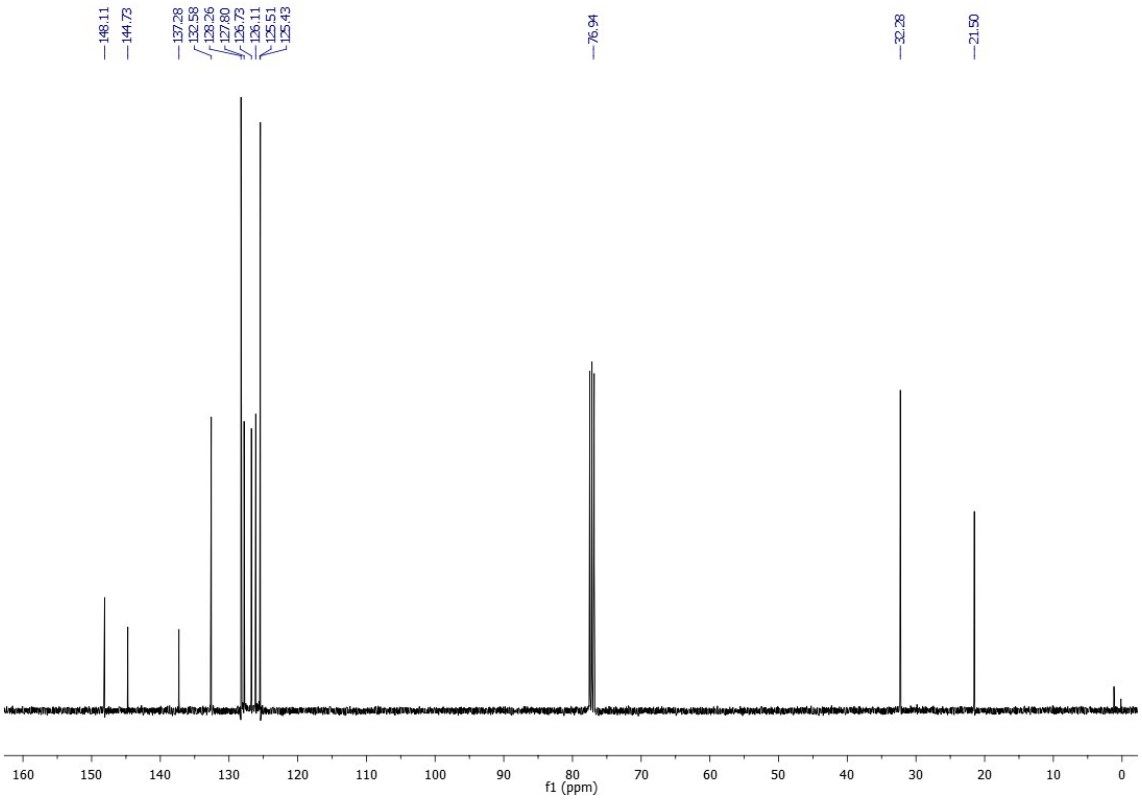
3e ^{13}C-NMR ($CDCl_3$)



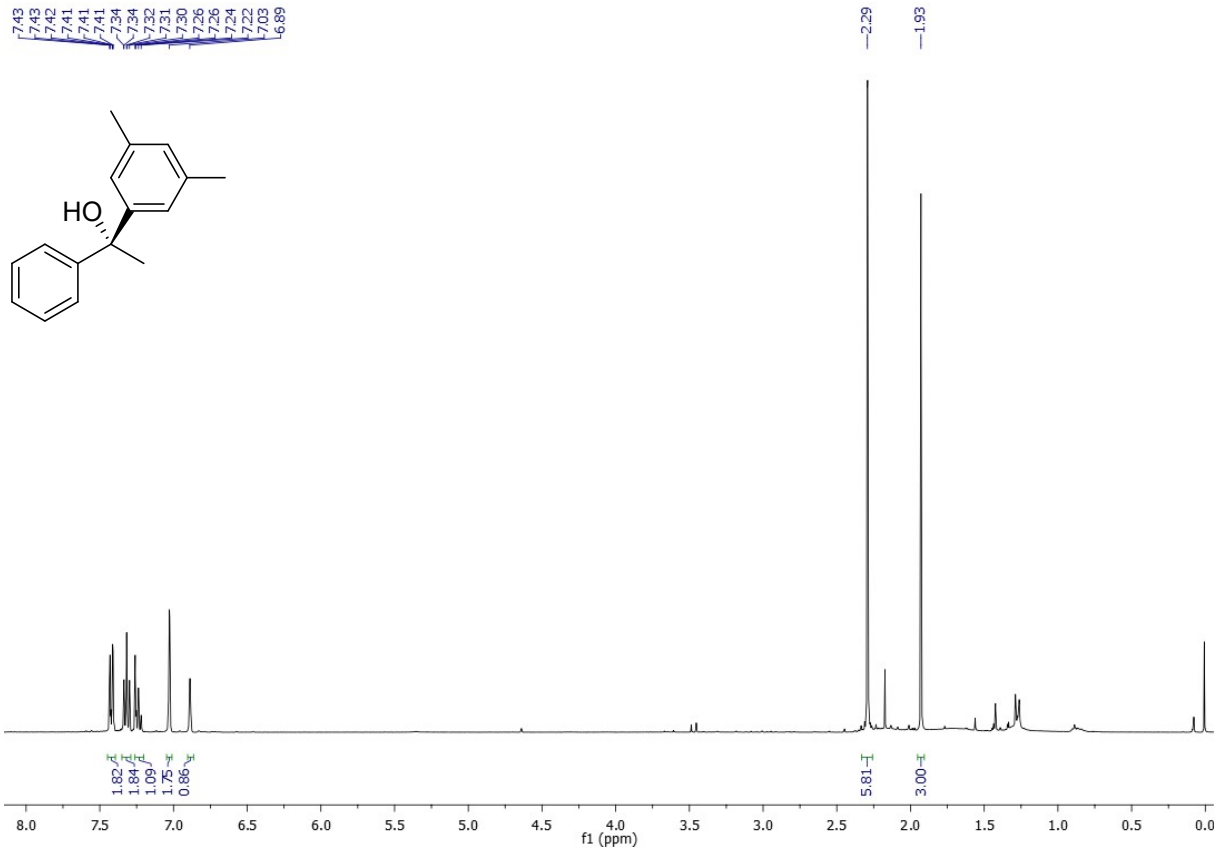
3f ^{1}H-NMR ($CDCl_3$)



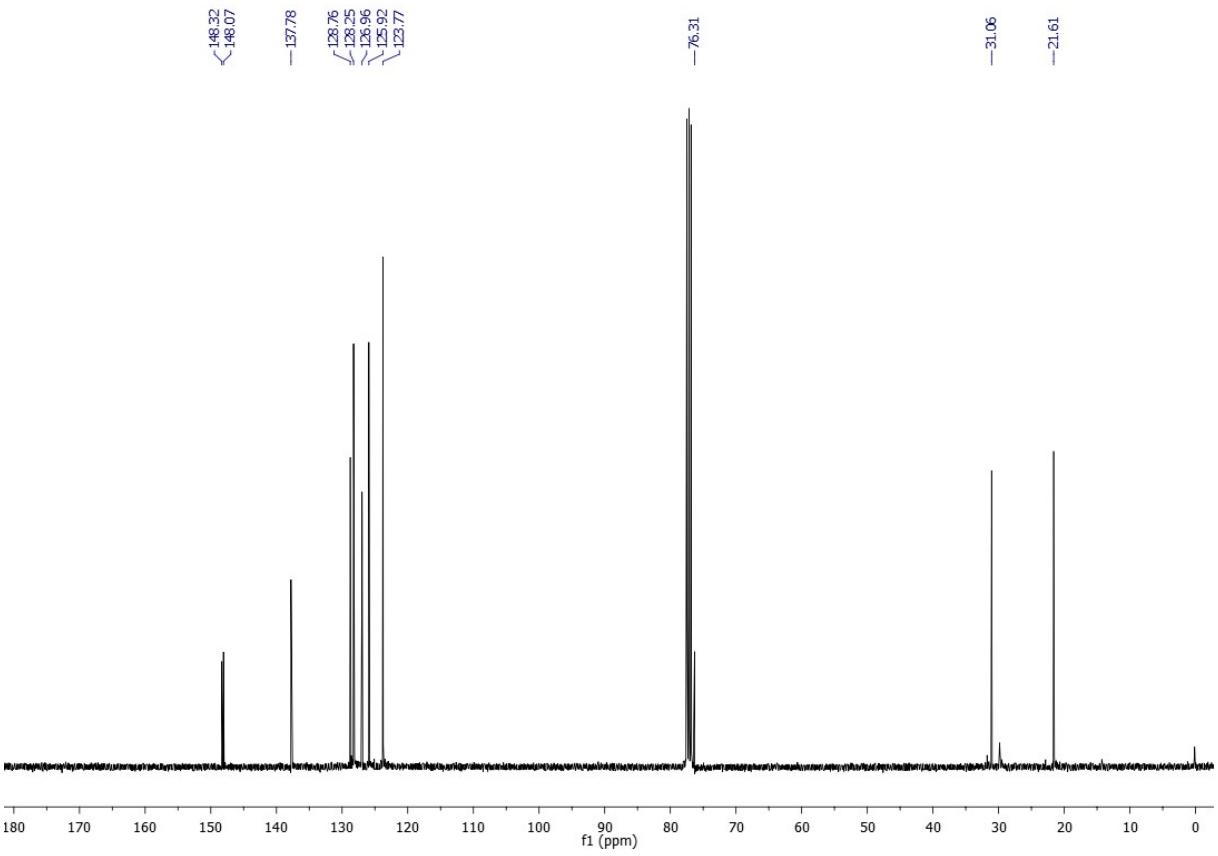
3f ^{13}C-NMR ($CDCl_3$)



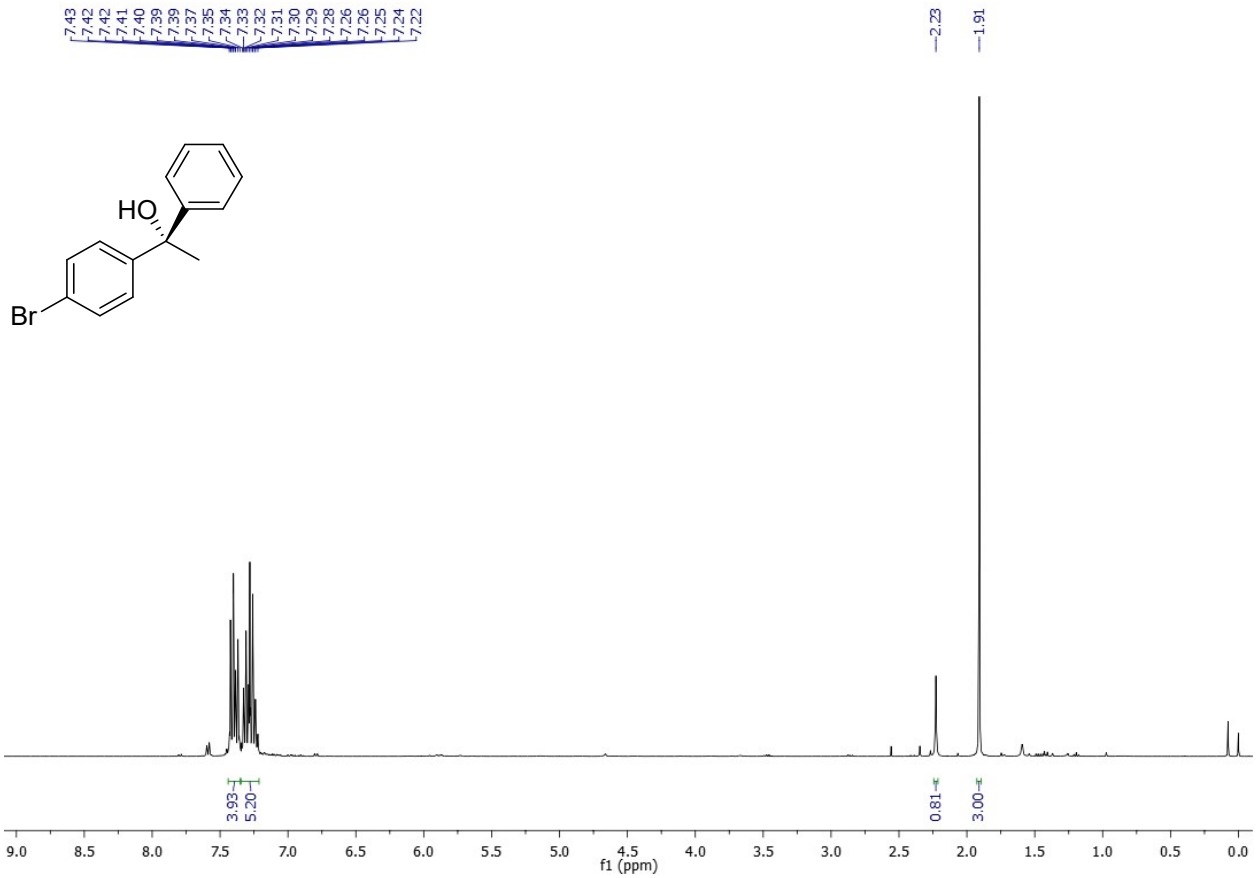
3g ^{1}H-NMR ($CDCl_3$)



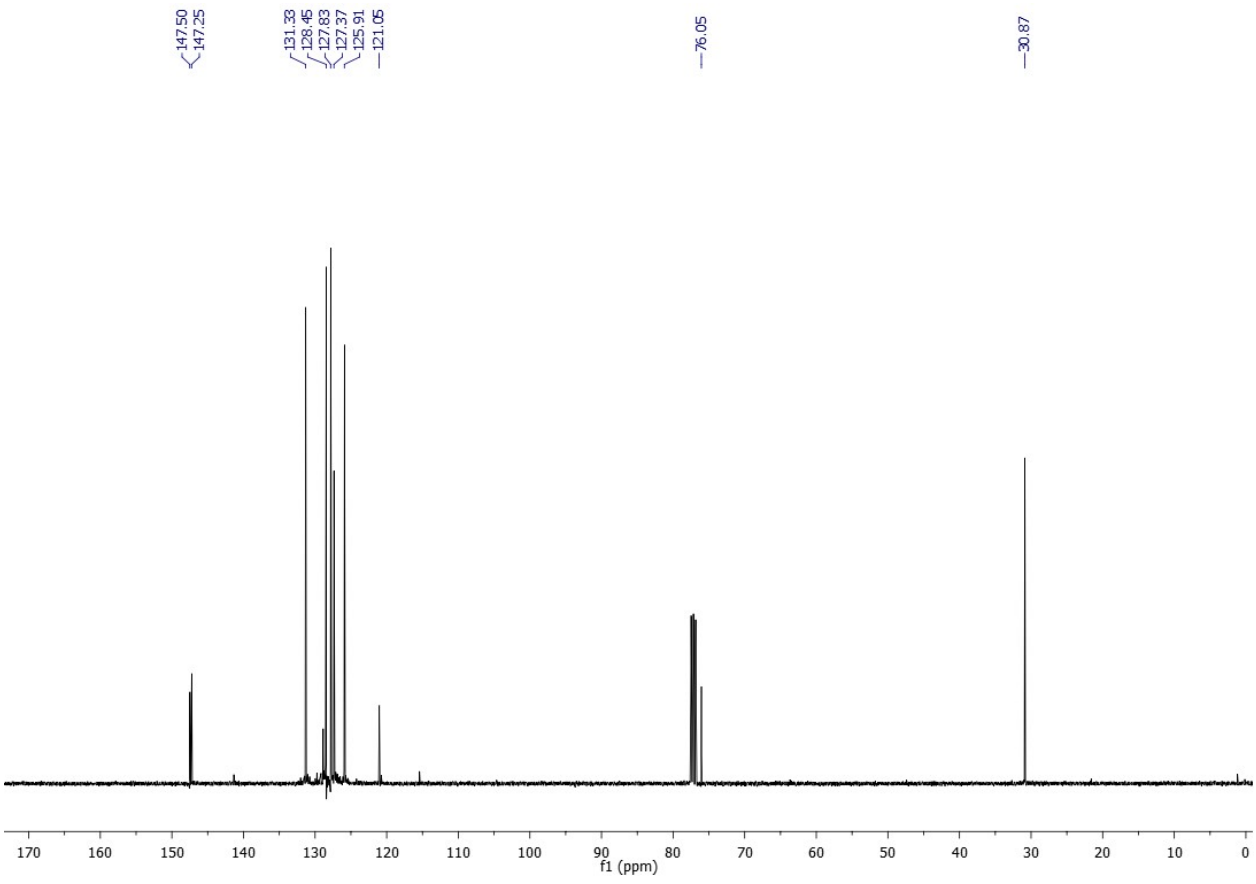
3g ^{13}C-NMR ($CDCl_3$)



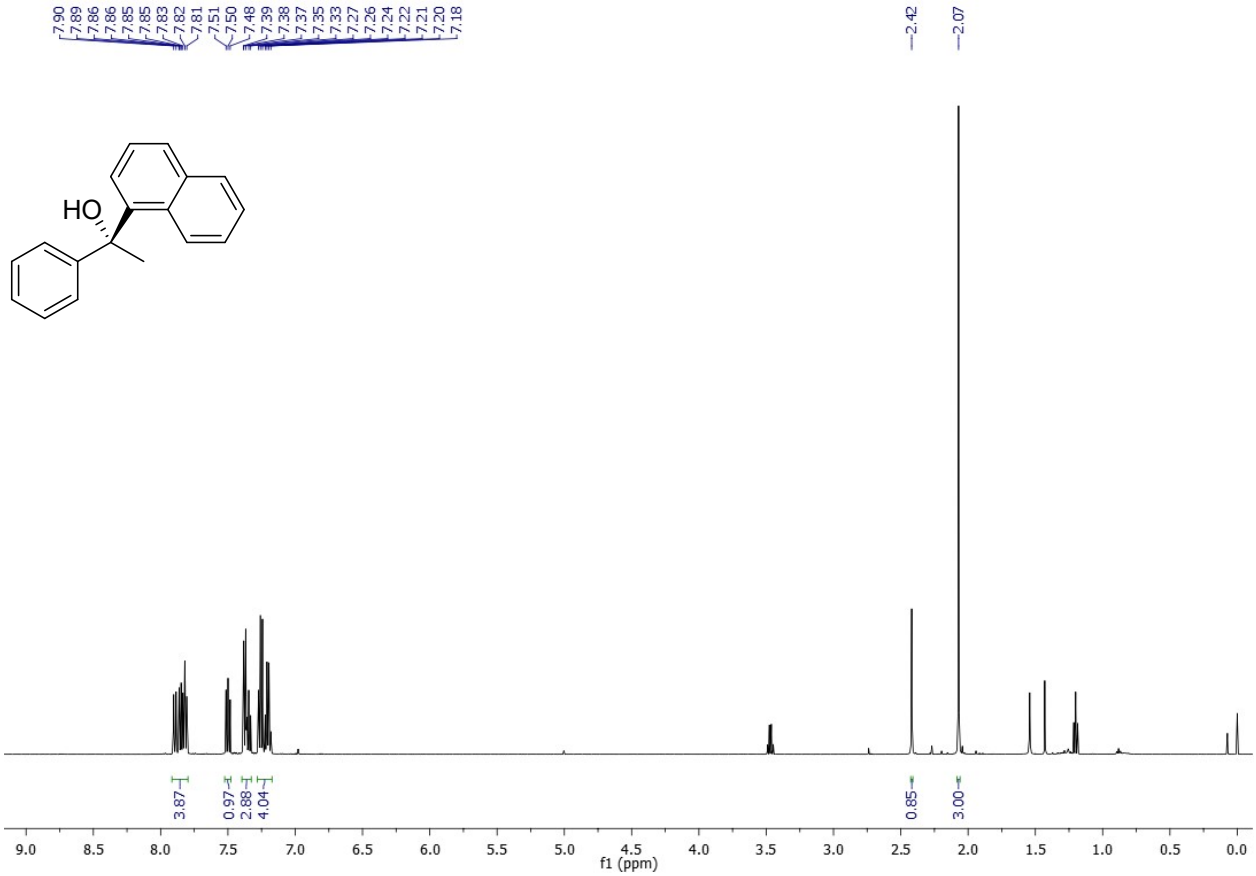
3h ^{1}H-NMR ($CDCl_3$)



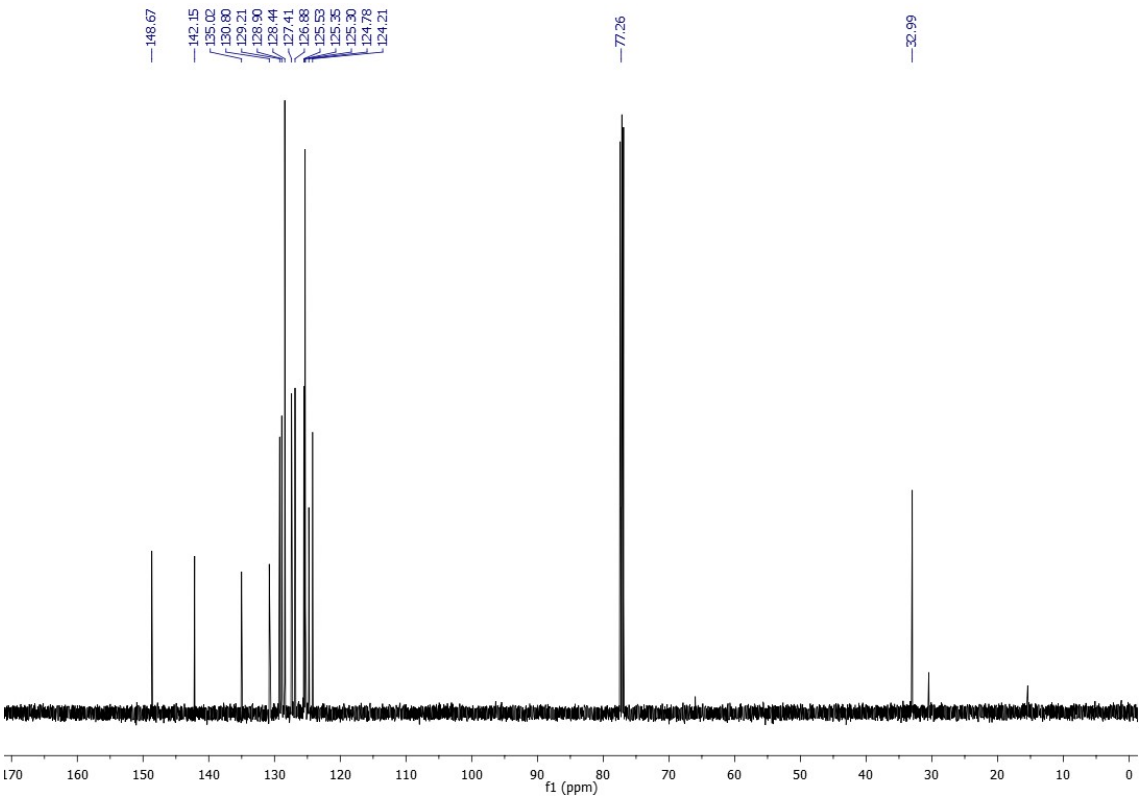
3h ^{13}C-NMR ($CDCl_3$)



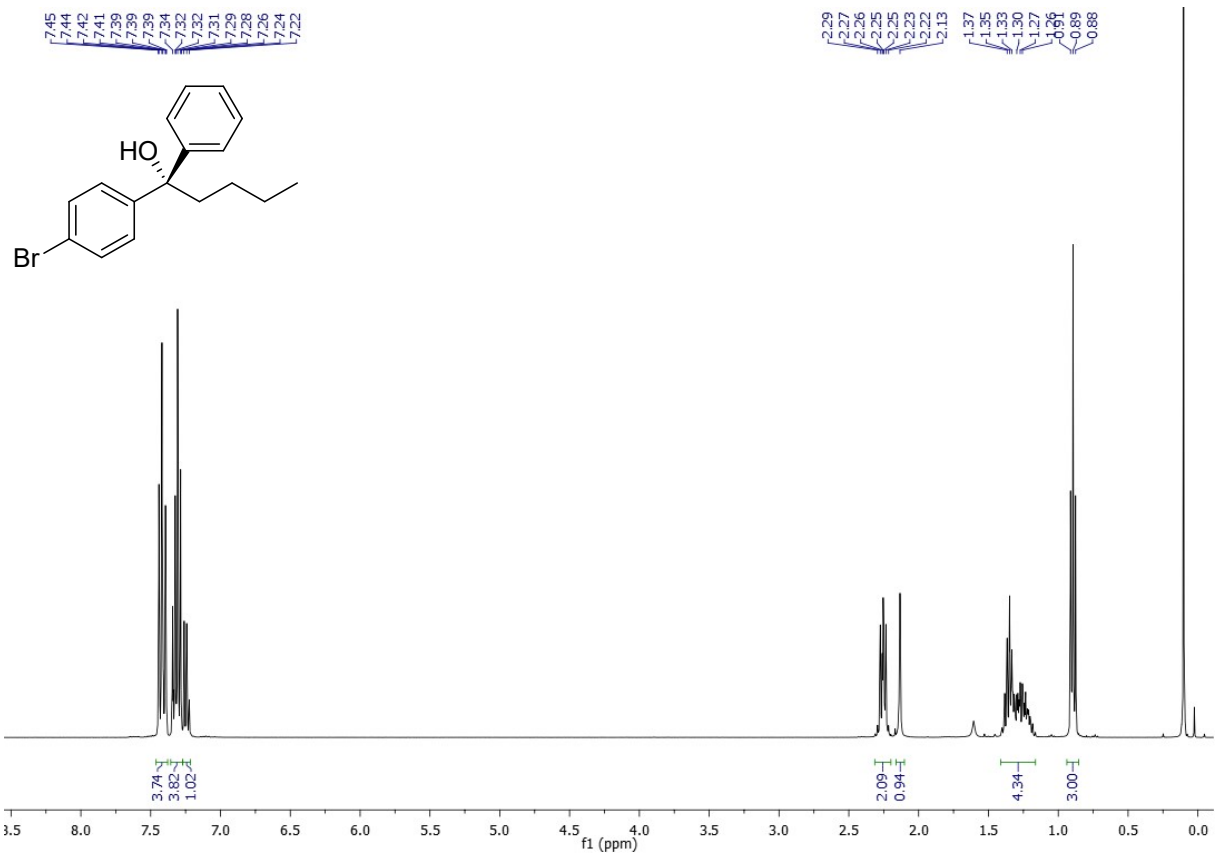
3i ^{1}H-NMR ($CDCl_3$)



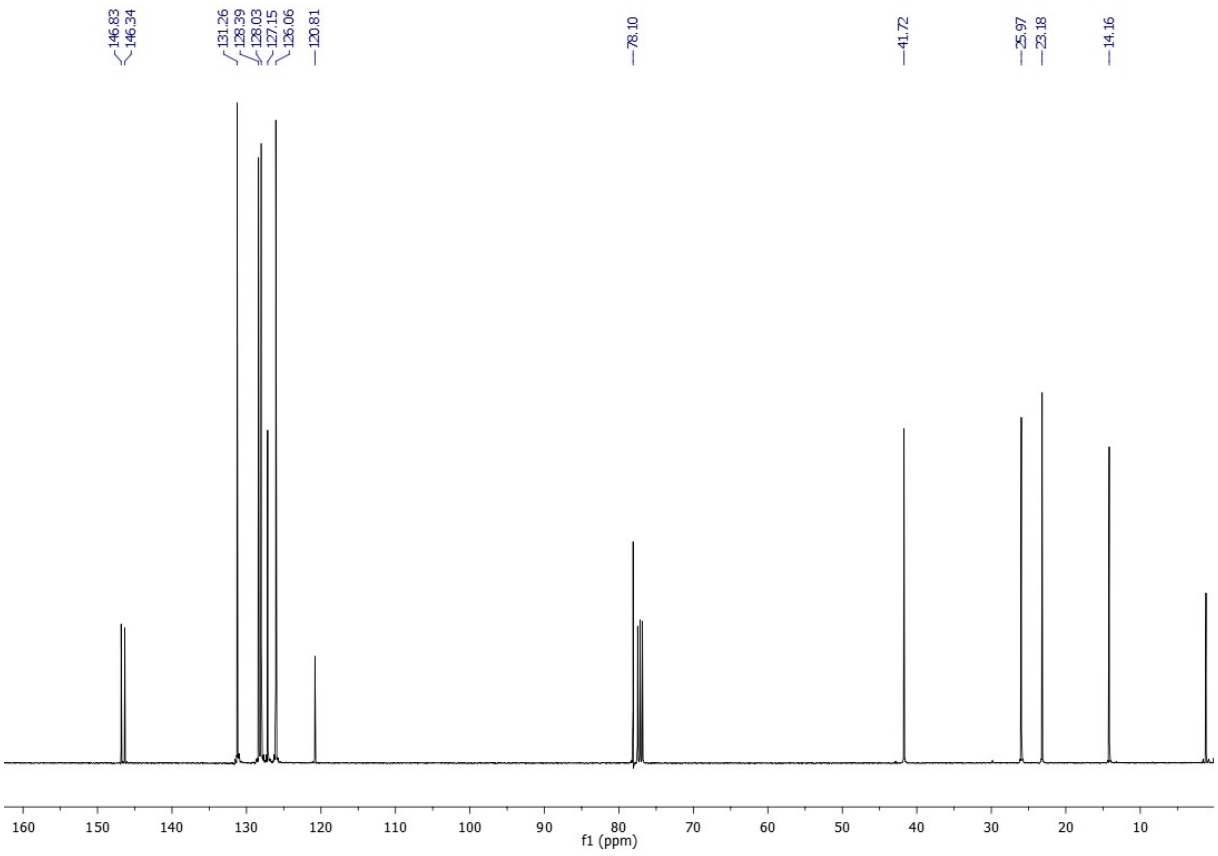
3i ^{13}C-NMR ($CDCl_3$)



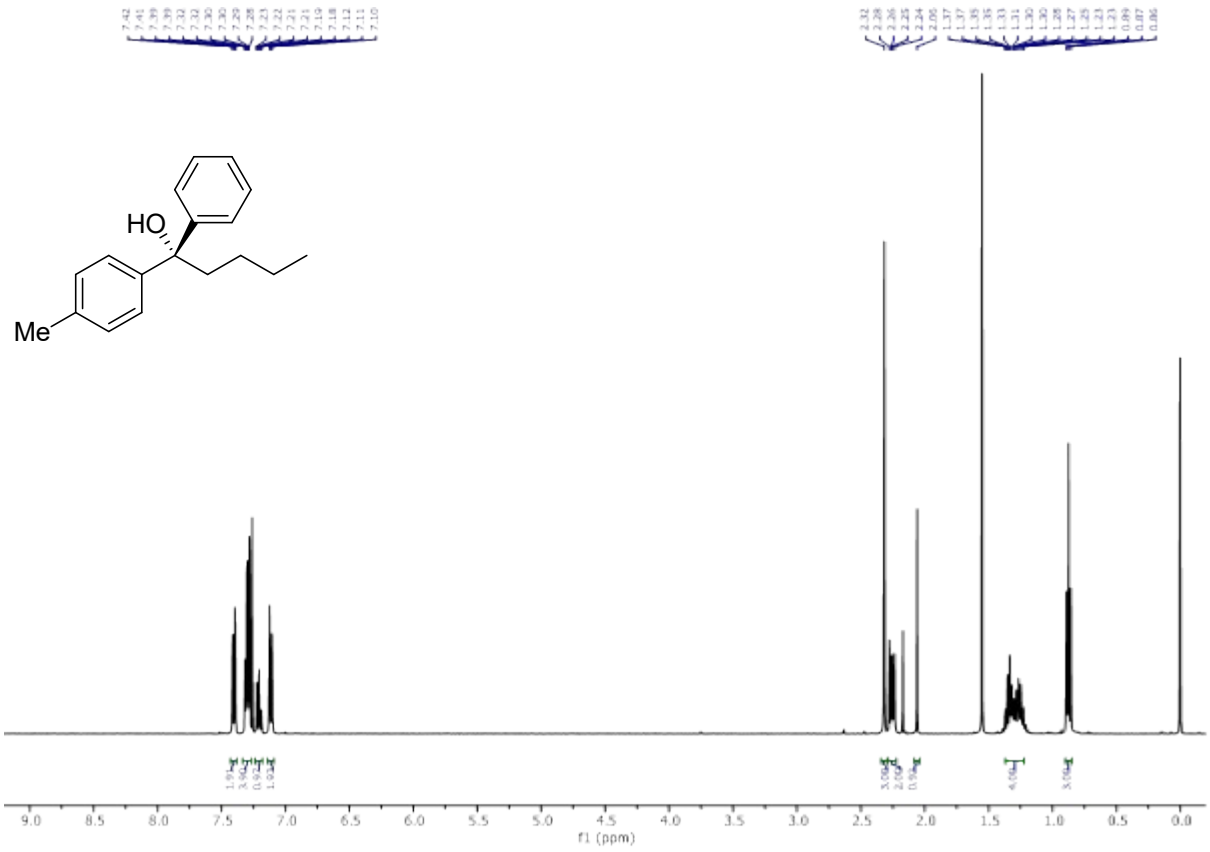
3l ^{1}H-NMR ($CDCl_3$)



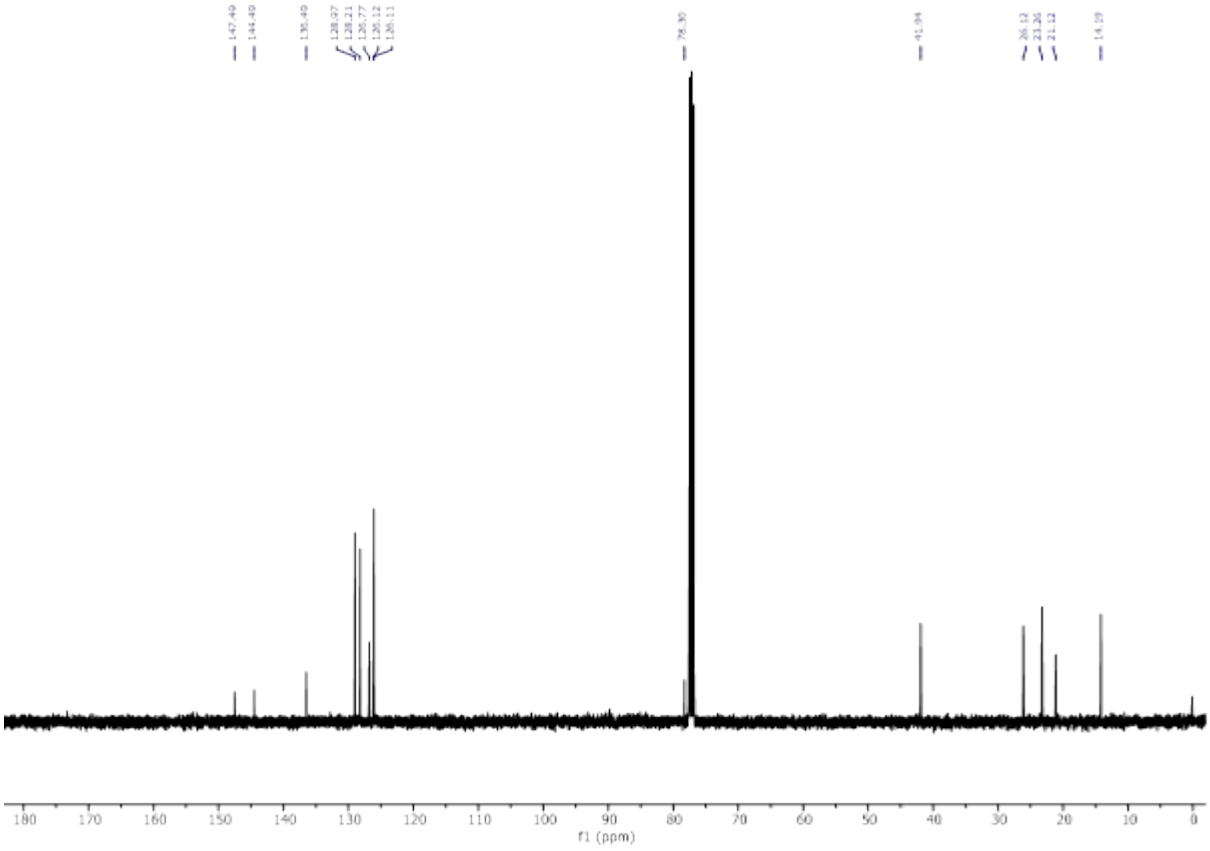
3l ^{13}C-NMR ($CDCl_3$)



3m ^{1}H-NMR ($CDCl_3$)



3m ^{13}C-NMR ($CDCl_3$)



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2) S. Kavanagh, D. G. Gilheany, *Org. Lett.* 2020, **22**, 8198.
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