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 \((R,R)-4\text{HCl}\) and \((S,S)-1,2\)-diaminocyclohexane monohydrochloride \((S,S)-4\text{HCl}\) 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 \(\text{N}_2\). 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 \(\mu\text{m}\). 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 \(^\circ\text{C}\). Assignments were based on standard \(^1\text{H}-^1\text{H}\) and \(^1\text{H}-^{13}\text{C}\) two-dimensional techniques. Chemical shifts (\(\delta\)) are reported in ppm relative to residual solvent signals for \(^1\text{H}\) and \(^{13}\text{C}\) NMR (\(^1\text{H}\)-NMR: 7.26 ppm and \(^{13}\text{C}\) 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 \(\mu\text{m}\) 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 \([100\cdot\text{deg}\cdot\text{dm}^{-1}\cdot\text{cm}^{-1}\cdot\text{g}^{-1}]\) 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\(_2\)O, MeMgI 3.0 M in Et\(_2\)O, EtMgBr 3.0 M in Et\(_2\)O, PhMgBr 3.0 M in Et\(_2\)O, para-chlorophenylmagnesium bromide 1.0 M in Et\(_2\)O, para-fluorophenylmagnesium bromide 2.0 M in Et\(_2\)O, para-methoxyphenylmagnesium bromide 0.5 M in Et\(_2\)O, para-tolylmagnesium bromide 0.5 M in Et\(_2\)O) 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\(_2\)O, using 1,2-dibromoethane as activating agent, and stored in J Young flasks under \(\text{N}_2\). Grignard reagents solutions were titrated before use with a 1.0 M (-)-menthol solution in dry toluene, using 1,10-phenanthroline as indicator. 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 \(\text{N}_2\).

Ligand \((R,R)-\text{LO}'\) was prepared according to our previously reported procedure.
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

![Reaction Scheme]

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 Et₂O (3 x 100 mL). The combined organic layers were washed with H₂O (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 NaHCO₃ sat. (200 mL) and extracted with DCM (3 x 100 mL). The combined organic phases were washed with H₂O (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/H₂O 85:15.
2,4-Di-tert-butyl-6-(((1R,2R)-2-(dimethylamino)cyclohexyl)(methyl)amino)methyl)phenol, 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$_2$O.

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-(((1R,2R)-2-(dimethylamino)cyclohexyl)(methyl)amino)methyl)phenol, 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 – 2.51 (m, 1H), 2.56 – 2.52 (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$_2$O ([M+H]$^+$) 319.2754, found 319.2749.

Elemental analysis calculated for C$_{20}$H$_{34}$N$_2$O: 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-(((1R,2R)-2-(dimethylamino)cyclohexyl)(methyl)amino)methyl)-6-methylphenol, L2

White solid, 50% yield (over 2 steps).
Purification: recrystallization from MeOH.

\[ ^1H-NMR \ (400 \text{ MHz, CDCl}_3) \delta \ 7.03 \ (d, \ J = 2.2 \text{ Hz, 1H}), \ 6.81 \ (d, \ J = 2.2 \text{ Hz, 1H}), \ 3.91 \ (d, \ J = 12.8 \text{ Hz, 1H}), \ 3.14 \ (\text{br s, 1H}), \ 2.63 - 2.61 \ (m, \ 1H), \ 2.56 - 2.51 \ (m, \ 1H), \ 2.28 \ (s, \ 6H), \ \text{etc.} \]

\[ ^{13}C-NMR \ (101 \text{ MHz, CDCl}_3) \delta \ 153.7, \ 140.1, \ 126.7, \ 124.4, \ 124.3, \ 122.6, \ 64.5, \ 64.2, \ 39.6 \text{ br, 38.3 br, 33.8, 31.8, 25.9, 25.7, 23.6, 22.0, 16.6.} \]

HRMS (ESI) calculated for C\textsubscript{21}H\textsubscript{37}N\textsubscript{2}O ([M+H]+) 333.2892, found 333.2906.

m.p. = 72-73 °C.

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

White solid, 40% yield (over 2 steps).
Purification: recrystallization from MeOH.

\[ ^1H-NMR \ (400 \text{ MHz, CDCl}_3) \delta \ 7.02 \ (d, \ J = 7.3 \text{ Hz, 1H}), \ 6.82 \ (d, \ J = 7.3 \text{ Hz, 1H}), \ 6.63 \ (t, \ J = 7.4 \text{ Hz, 1H}), \ 3.91 \ (d, \ J = 12.8 \text{ Hz, 1H}), \ 3.15 \ (\text{br s, 1H}), \ 2.64 - 2.62 \ (m, \ 1H), \ 2.56 - 2.54 \ (m, \ 1H), \ 2.29 \ (s, \ 6H), \ 2.24 \ (s, \ 3H), \ 2.04 - 2.01 \ (m, \ 1H), \ 1.94 - 1.91 \ (m, \ 1H), \ 1.83 - 1.81 \ (m, \ 2H), \ 1.26 - 1.12 \ (m, \ 4H). \]

\[ ^{13}C-NMR \ (101 \text{ MHz, CDCl}_3) \delta \ 156.1, \ 129.9, \ 127.6, \ 125.3, \ 123.4, \ 117.6, \ 64.5, \ 64.2, \ 52.8 \text{ br, 39.6 br, 38.4 br, 25.9, 25.7, 23.5, 22.0, 16.3.} \]

HRMS (ESI) calculated for C\textsubscript{17}H\textsubscript{29}N\textsubscript{2}O ([M+H]+) 277.2268, found 277.2280.

Elemental analysis calculated for C\textsubscript{17}H\textsubscript{28}N\textsubscript{2}O: 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

![Chemical structure](image)

5e \(X = F\)  
5f \(X = Cl\)  
5g \(X = Br\)

**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 Et₂O (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 N₂ 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). The nature of the precipitate collected to obtain L4-L6. The crude products were purified via recrystallization from EtOH/H2O or MeOH to obtain pure ligands (R,R)-L4-L6 as crystalline solids.

2-(((1R,2R)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-6-fluorophenol, L4
White solid, 40% yield (over 3 steps).

Purification: recrystallization from EtOH/H$_2$O.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$) $\delta$ - 137.7 (dd, $J = 11.0$ Hz, 4.0 Hz).

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

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

Purification: recrystallization from MeOH.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 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, 1H), 1.88 – 1.77 (m, 2H), 1.23 – 1.13 (m, 4H).

$^{13}$C-NMR (101 MHz, CDCl$_3$) $\delta$ 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$_{23}$ClN$_2$: C, 64.75; H, 8.49; N, 9.44. Found C, 64.36; H, 8.51; N, 9.27.

2-Bromo-6-((((1R,2R)-2-(dimethylamino)cyclohexyl)(methyl)amino)methyl)phenol, L6
White solid, 38% yield (over 3 steps).

Purification: recrystallization from MeOH.

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.39 (dd, \(J = 7.9, 1.5\) Hz, 1H), 6.90 (dd, \(J = 7.4, 1.5\) Hz, 1H), 6.57 (t, \(J = 7.7, 1\)H), 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\(_3\)) \(\delta\) 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\(_2\)OBr ([M+H]+) 341.1221, found 341.1228.

Elemental analysis calculated for C\(_{16}\)H\(_{25}\)N\(_2\)O: 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\(_3\)PO\(_4\) 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\(_2\)O or MeOH.

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

![Diagram of the reaction](image-url)
### General procedure for the synthesis of ligands L7-L14 via Suzuki-Miyaura coupling

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 K₃PO₄ 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 Na₂SO₄ 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.

| Entry | Pd-Catalyst       | Base             | Solvent                        | T (°C) | Time (h) | L7 conv. (%)a | L7 yield (%)b |
|-------|-------------------|------------------|--------------------------------|--------|----------|---------------|---------------|
| 1     | Pd(OAc)₂          | i-Pr₂NH          | THF/H₂O                        | 50     | 48       | -             | -             |
| 2     | Pd(dppf)Cl₂       | K₂CO₃ aq. or K₂PO₄ aq. | Toluene/EtOH                | 100    | 48       | -             | -             |
| 3     | RuPhos Pd G3      | K₂PO₄ aq.        | THF                            | 50     | 24       | 50            | -             |
| 4     | RuPhos Pd G3      | K₂PO₄ aq.        | Toluene/EtOH                   | 100    | 12       | >95           | -             |
| 5c    | RuPhos Pd G3      | K₂PO₄ aq.        | Toluene/EtOH                   | 100    | 6        | >95           | 72            |

*a* Conversion determined by ¹H-NMR analysis of the crude reaction mixture; *b* Isolated yields; *c* RuPhos Pd G2 pre-catalyst showed similar performances.
3-(((1R,2R)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-[1,1'-biphenyl]-2-ol, L7

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

Further purification via recrystallization from MeOH.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$O ($[M+H]^+$) 339.2450, found 339.2436.

Elemental analysis calculated for C$_{22}$H$_{30}$N$_2$O: C, 78.06; H, 8.93; N, 8.28. Found C, 78.05; H, 8.99; N, 8.26.

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

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

Further purification via recrystallization from MeOH.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$O$_2$ ($[M+H]^+$) 369.2527, found 369.2542.
3-((((1R,2R)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-3',5'-dimethyl-[1,1'-biphenyl]-2-ol, L9

![L9](image)

White solid, 18% yield. Reaction time = 12 hours.
Purification: column chromatography on alumina, cyclohexane/Et$_3$N 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$_2$O ([M+H$^+$]) 367.2749, found 367.2749.

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

![L10](image)

White solid, 66% yield. Reaction time = 12 hours.
Purification: column chromatography on silica gel, DCM/acetone/Et$_3$N 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, 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$_2$O ([M+H$^+$]) 381.2913, found 381.2906.
3-(((1R,2R)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-4’-(trifluoromethyl)-[1,1’-biphenyl]-2-ol, L11

White solid, 76% yield. Reaction time = 12 hours.
Purification: column chromatography on silica gel, cyclohexane/Et₃N 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, 124.7 (q, J = 273 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$_2$OF$_3$ ([M+H]$^+$) 407.2307, found 407.2310.

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

Yellow solid, 68% yield. Reaction time = 3 hours.
Purification: recrystallisation from EtOH/H$_2$O.

$^{1}$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$_6$N$_2$O: 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-(((1R,2R)-2-(Dimethylamino)cyclohexyl)(methyl)amino)methyl)-6-(naphthalen-1-yl)phenol, L13

![L13](image)

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 and 124.0, 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$_2$O ([M+H]$^+$) 389.2575, found 389.2593.

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

![L14](image)

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

Purification: column chromatography on alumina, cyclohexane/Et$_3$N 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$_{36}$H$_{35}$N$_2$O ([M+H]$^+$) 439.2739, found 439.2749.
Preparation of N-pyrrolidyl analogue ligand L12’

i) Preparation of \((R,R)-N\text{-pyrrolidyl-1,2-DACH}\) 9

To a solution of \((R,R)-1,2\text{-diaminocyclohexane monohydrochloride}\) 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 Na₂SO₄, 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) \((R,R)-2-(2,5\text{-dimethylpyrrol-1-yl})\text{-cyclohexylamine}\) 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 NaHCO₃ 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 Na₂SO₄. 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 H₂O (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 NaHCO₃ 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 Na₂SO₄ 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-(((1R,2R)-2-(2,5-dimethyl-1H-pyrro-1-yl)cyclohexyl)(methyl)amino)methyl)phenol, 11

![Image of compound 11](image)

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

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

\(^1\)H-NMR (400 MHz, CDCl₃) 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, CDCl₃) 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 C₂₁H₂₇BrN₂O ([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

\((R,R)-11\) (3.50 g, 8.94 mmol), RuPhos Pd G2 (1 mol %) and 3,5-bis-(trifluoromethyl)benzeno-boronic 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 K₃PO₄ 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$_2$SO$_4$. 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-(((1R,2R)-2-(2,5-Dimethyl-1H-pyrrol-1-yl)cyclohexyl)(methyl)amino)methyl)-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-ol, L12’

![Chemical Structure](image)

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$_6$N$_2$O ([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$_2$O

The Grignard reagents which were not commercially available as Et$_2$O solutions, were prepared from the corresponding alkyl bromides or aryl bromides and magnesium turnings in dry Et$_2$O, 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$_2$O 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$_2$O, since the standard THF one showed generally poor performances).

\[
\begin{align*}
\text{R–Br} & \quad \text{Mg turnings (1.2 equiv.)} \\
& \quad \text{1,2-Dibromoethane (5 mol\%)} \\
& \quad \text{Et$_2$O 1.0 M} \\
& \quad 20 \, ^\circ\text{C to 35 \, ^\circ\text{C}, 1 h}} \\
\end{align*}
\]

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$_2$O (Note 1). The magnesium turnings were covered with the minimum volume of dry Et$_2$O (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$_2$O (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$_2$O. 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 Et₂O (10 mL). The solution was cooled to -82 °C and the Grignard reagent (4.5 mmol, solution in Et₂O or THF) was added dropwise. The mixture was stirred at -82 °C for 1 hour and then quenched with NH₄Cl sat. (3 mL) and H₂O (3 mL). The phases were separated and the aqueous phase was extracted with Et₂O (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/Et₂O 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 N₂ cold bath. The Grignard reagent in Et₂O (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/H₂O 1:1 (0.3 mL), followed by NH₄Cl 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 H₂O (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/Et₂O 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 H₂O (20% v/v, 2 x 10 mL). The work-up was then continued as described above for isolating the alcohol product, by washing with H₂O (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 Et₂O (3 x 10 mL) or DCM (3 x 10 mL). The combined organic phases were washed...
with H₂O (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/H₂O.

**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 N₂. 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 Et₂O 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 N₂ gas to a total volume of ca. 0.9 – 1.0 mL (withdrawn from the N₂ atmosphere above the Grignard solution. Specifically, after withdrawing the Grignard solution, the needle was raised out of the solution into the N₂ 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 N₂.

**Addition of alkyl Grignard reagents to ketones**

**2-Phenylbutan-2-ol, 2a**

\[
\text{(S)-2a} \quad \text{Acetophenone + EtMgBr} \\
\text{(R)-2a} \quad \text{Propiophenone + MeMgBr}
\]

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

¹H-NMR (400 MHz, CDCl₃) 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).

¹³C-NMR (101 MHz, CDCl₃) 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; \((R,R)-L12\)).

\[\text{Signal 2: DAD1 C, Sig=210,8 Ref=360,100}\]

\[
\begin{array}{c|c|c|c|c|c|c}
\text{Peak} & \text{RetTime} & \text{Type} & \text{Width} & \text{Area} & \text{Height} & \text{Area} \\
\text{#} & \text{[min]} & \text{[min]} & \text{[mAU*s]} & \text{[mAU]} & \% \\
\hline
1 & 11.055 & VB & 0.3048 & 2.04648e4 & 1071.84814 & 95.9643 \\
2 & 13.753 & MM & 0.2961 & 860.63348 & 48.43842 & 4.0357 \\
\end{array}
\]

Totals : \(2.13255e4\) 1120.20656

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

\[\text{Signal 2: DAD1 C, Sig=210,8 Ref=360,100}\]

\[
\begin{array}{c|c|c|c|c|c|c}
\text{Peak} & \text{RetTime} & \text{Type} & \text{Width} & \text{Area} & \text{Height} & \text{Area} \\
\text{#} & \text{[min]} & \text{[min]} & \text{[mAU*s]} & \text{[mAU]} & \% \\
\hline
1 & 11.753 & VB & 0.2264 & 1327.75342 & 88.83912 & 22.0544 \\
2 & 14.459 & BBA & 0.2839 & 4401.83490 & 244.49513 & 77.1456 \\
\end{array}
\]

Totals : \(5809.60840\) 333.33425

\(2\)-\((\text{o-Tolyl})\)butan-2-ol, \(2b\)

\[
\begin{align*}
\text{Colourless oil.} \\
67\% \text{ yield, } 95\% \text{ ee, } (R,R)-L12.
\end{align*}
\]

\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 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).

\(^{13}\text{C-NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 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.

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

Colourless liquid.

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

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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.
2-(4-Bromophenyl)butan-2-ol, 2d

Colourless oil.

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

**\(^1\)H-NMR** (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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.

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

![Structure of 2-(4-(Trifluoromethyl)phenyl)butan-2-ol, 2e]
Colourless oil.
87% yield, 60% ee, (R,R)-L12.

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta 7.70 - 7.46 \text{ (m, 4H)}, 1.90 - 1.87 \text{ (m, 2H)}, 1.56 \text{ (s, 3H)}, 0.80 \text{ (t, J = 7.4 Hz, 3H)}\).

\(^{13}\)C-NMR (101 MHz, CDCl\(_3\)) \(\delta 151.7, 125.3, 125.1, 125.0, 125.0, 120.2, 74.8, 36.6, 29.8, 8.1\).

\(^{19}\)F-NMR (376 MHz, CDCl\(_3\)) \(\delta -62.4\).

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: \(t_m = 10.91 \text{ min.}\) and \(t_M = 12.02 \text{ min.}\)

![HPLC graph]

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

| Peak | RetTime | Width | Area | Height | Area |
|------|---------|-------|------|--------|------|
| 1    | 10.912  | 0.2233| 2271.54004 | 154.72166 | 20.4248 |
| 2    | 12.021  | 0.2473| 8849.95605  | 543.36005  | 79.5752 |

Totals : 1.11215e4 700.08171

3-Phenylheptan-3-ol, 2f

![Chemical structure]

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

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta 7.40 - 7.32 \text{ (m, 4H)}, 7.25 - 7.21 \text{ (m, 1H)}, 1.91 - 1.74 \text{ (m, 4H)}, 1.70 \text{ (s, 1H)}, 1.30 - 1.22 \text{ (m, 3H)}, 1.06 - 1.02 \text{ (m, 1H)}, 0.84 \text{ (t, J = 7.2 Hz, 3H)}, 0.76 \text{ (t, J = 7.4 Hz, 3H)}\).

\(^{13}\)C-NMR (100.6 MHz, CDCl\(_3\)) \(\delta 146.3, 128.1, 126.3, 125.5, 77.3, 42.4, 35.5, 25.8, 23.2, 14.2, 7.9\).

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.

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

![Chemical structure image]

Colourless liquid.

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

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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.  

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

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

\[ \text{\textsuperscript{1}H-NMR} \text{ (400 MHz, CDCl}_3\text{)} \delta 7.45 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 1.90 - 1.71 (m, 4H), 1.60 (bs, 1H), 1.28 - 1.22 (m, 4H), 0.83 (t, J = 7.1 Hz, 3H), 0.74 (t, J = 7.4 Hz, 3H). \]

\[ \text{\textsuperscript{13}C-NMR} \text{ (101 MHz, CDCl}_3\text{)} \delta 145.3, 131.2, 127.5, 120.3, 77.2, 42.5, 35.6, 25.7, 23.2, 14.1, 7.8. \]

Analytical data was in accordance with literature reported results.\textsuperscript{6}

HPLC analysis on chiral stationary phase: Chiracel\textsuperscript{®} 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.

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\(_6\)H\(_4\)MgBr).

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\(_6\)H\(_4\)MgBr).

\(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.42 – 7.23 (m, 9H), 2.16 (s, 1H), 1.93 (s, 3H).

\(^13\)C-NMR (126 MHz, CDCl\(_3\)) \(\delta\) 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.\(^7\)

\([\alpha]_D^{23}\) -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\(^\circ\) 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\(_6\)H\(_4\)MgBr; \((R,R)\)-L12).

\(b\) \((R)\)-3a 82% ee, retention times: \(t_m = 29.72\) min. and \(t_m = 34.36\) min. (acetophenone + \(p\)-Cl-C\(_6\)H\(_4\)MgBr; \((R,R)\)-L12').
1-(3,4-Dichlorophenyl)-1-phenylethan-1-ol, 3b

Colourless oil.

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

\(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(^\oplus\) OJ-H column, 95/5 heptane/EtOH, 1 mL/min., 20 °C, 230 nm, retention times: \(t_\text{m} = 13.90\) min. and \(t_\text{M} = 16.37\) min.
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$_3$) $\delta$ 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$_3$) $\delta$ 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.  

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: \( t_m = 15.11 \text{ min} \) and \( t_M = 15.76 \text{ min} \) (with ligand \((R,R)-L12\))

\[
\begin{array}{cccc}
\text{Signal 2: DAD1 C, Sig=210,8 Ref=360,100} \\
\text{Peak} & \text{RetTime} & \text{Type} & \text{Width} & \text{Area} \\
\hline
1 & 15.113 & MF & 0.2774 & 687.27509 \\
2 & 15.758 & FM & 0.3027 & 8951.41504
\end{array}
\]


b) 79% ee, retention times: \( t_m = 12.65 \text{ min} \) and \( t_M = 13.89 \text{ min} \) (with ligand \((R,R)-L12'\))

\[
\begin{array}{cccc}
\text{Signal 2: DAD1 C, Sig=210,9 Ref=360,100} \\
\text{Peak} & \text{RetTime} & \text{Type} & \text{Width} & \text{Area} \\
\hline
1 & 12.647 & MM & 0.2377 & 1081.59301 \\
2 & 13.866 & MM & 0.2073 & 9117.67578
\end{array}
\]
1-(4-Methoxyphenyl)-1-phenylethan-1-ol, 3d

![Structure](image)

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-C₆H₅MgBr).

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

**1H-NMR** (400 MHz, CDCl₃) 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).

**13C-NMR** (101 MHz, CDCl₃) 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: tᵣ = 50.8 min. and tᵢ = 55.0 min. (4'-methoxyacetophenone + PhMgBr; (R,R)-L12').
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_6H_4MgBr; (R,R)-L12').

![Graph](image1)

Signal 1: DAD1 A, Sig=254.8 Ref=360,100

| Peak | RetTime | Type | Width | Area | Height | Area % |
|------|---------|------|-------|------|--------|-------|
| 1    | 19.435  | BB   | 0.846 | 3179.7060 | 51.65665 | 82.0070 |
| 2    | 33.260  | HM   | 0.940 | 697.65118 | 12.36160 | 17.9930 |

Totals: 5377.55748 64.00024

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

![Structure](image2)

Colourless oil.

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

\(^1\)H-NMR (400 MHz, CDCl_3) \( \delta \) 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) \( \delta \) 148.3, 145.3, 136.8, 129.0, 128.3, 127.0, 125.9 (2C), 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.
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-\(\text{Me-C}_6\text{H}_4\)MgBr).

\(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 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).

\(^{13}\text{C-NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 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.\(^7\)

\textbf{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: \(t_m = 10.09\) min. and \(t_m = 10.09\) min. (2′-methylacetophenone + PhMgBr; \((R,R)\)-L12).
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.
1-(4-Bromophenyl)-1-phenylethan-1-ol, 3h

![Chemical structure of 1-(4-Bromophenyl)-1-phenylethan-1-ol, 3h](image)

Colourless solid.

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

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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.\(^\text{10}\)

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

Yellow oil.

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

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(^\text{R}\) IA column, 97/3 heptane/EtOH, 1 mL/min., 20 °C, 254 nm, retention times: \(t_n = 10.70\) min and \(t_m = 12.02\) min.
1-(4-Bromophenyl)-1-phenylpentan-1-ol, 3l

Colourless oil.

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

$\text{H-NMR (400 MHz, CDCl}_3\text{)} \delta 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).

$\text{C-NMR (101 MHz, CDCl}_3\text{)} \delta 146.8, 146.3, 131.3, 128.4, 128.0, 127.2, 126.1, 120.8, 78.1, 41.7, 26.0, 23.2, 14.2.$

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

Colourless oil.

60% yield, 80% ee, (R,R)-L12’.

\(^1H\)-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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.
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).
**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.\(^1\) 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 (%) | 3a conv. (%) |
|-------|----|---------|----------|-----------|-------------|
| 1     | I  | (R,R)-L12 | 1        | 20        | 5           |
| 2     | Br | (R,R)-L12 | 1        | 20        | 5           |
| 3     | I  | (R,R)-L10 | 1        | 15        | -           |
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

\[
\begin{array}{cccc}
4 & l & (R,R)-L11 & 1 & 15 & - \\
5 & l & (R,R)-L0 & 1 & - & - \\
6 & l & (R,R)-L12 & 24 & 10 & 13 \\
\end{array}
\]

\( a \) ee determined by HPLC analysis on chiral stationary phase; 
\( b \) Conversion determined by \(^1\)H-NMR analysis of the crude reaction mixture.

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 \( p\)-C1PPhMgBr, 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).
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. 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.

![Synthetic strategy for the determination of the absolute configuration of benzylic chiral tertiary alcohols via X-Ray crystallographic analysis.](image-url)

Figure S1 ORTEP diagram of (R)-13 (thermal ellipsoids at 50% probability level).
Establishing the absolute configuration of the \textit{para}-bromophenyl substituted alcohol (\textit{R},\textit{R})-2h enabled, in turn, the determination of the configuration of the parent compound 2f, featuring an unsubstituted phenyl ring. Alcohol (\textit{R},\textit{R})-2h could undergo debromination of the \textit{para}-bromophenyl group, without affecting the benzylic chiral centre of the tertiary alcohol. A sample of enantioenriched \textit{(R),\textit{R}}-2h was converted into \textit{(R)-2f} via a lithium-bromide exchange/protonation sequence, by treatment of \textit{(R)-2h} with \textit{n}-butyllithium in THF at -82 °C, followed by protonation of the lithiated intermediate 14 with aqueous acid (Scheme S2).

Enantioconservative debromination of \textit{(R)-2h} to \textit{(R)-2f} via lithium-bromide exchange/protonation.

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

Opposite asymmetric induction observed in the preparation of 2h with (\textit{R},\textit{R})-L12 / (\textit{R},\textit{R})-L0.

The behavior observed by the exclusive ligand/ketone combination (\textit{R},\textit{R})-L12/\textit{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 (\textit{R},\textit{R})-lignads promote the addition of \textit{RMgBr} to the phenone \textit{si} face, independently by the type of Grignard and ketone. In line with the other ligands, (\textit{R},\textit{R})-L12 closely follows the general asymmetric induction trend over a range of structurally diverse ketones, made exception for \textit{para}-bromovalerophenone, showing preferential addition to the \textit{re} face. The exclusivity of the combination (\textit{R},\textit{R})-L12/1h was demonstrated by testing: i) 1h with ligands (\textit{R},\textit{R})-L0, L0’ and L12’; ii) ligand (\textit{R},\textit{R})-L12 with \textit{para}-halovalerophenone, with halogen = F, Cl, I; iii) ligand (\textit{R},\textit{R})-L12 with \textit{para}-bromophenones analogous to 1h, e.g. \textit{para}-bromoacetophenone and \textit{para}-bromopropiophenone, which all followed the general asymmetric induction trend (i.e. addition to \textit{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 (Et₂O), 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).

eme 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 Et₂O), in a dry NMR tube under N₂, 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: \(^1H\)-NMR and \(^1H\)-\(^1H\) COSY). On the contrary, \(^{13}C\)-NMR, HSQC and HMBC spectra featured extensive signal overlapping which hampered their use.
Figure S3 ¹H-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 ¹H-¹H 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-Kα (1.54184 Å). An analytical absorption correction based on the shape of the crystal was performed. The structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares on F² for all data using SHELXL-97. Anisotropic thermal displacement parameters were used for all non-hydrogen atoms. Crystals were selected at low temperature.

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.

| Property                                    | Value                      |
|---------------------------------------------|----------------------------|
| 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} \times 3 (C_{7}H_{8}) |
| Formula weight                              | 2430.09                    |
| Temperature                                 | 100(2) K                   |
| Wavelength                                  | 1.54184 Å                  |
| Crystal system                              | Monoclinic                 |
| Space group                                 | P2₁ (#4)                   |
| Unit cell dimensions                        | a = 19.2717(2) Å, \( \alpha = 90^\circ \). |
|                                           | b = 16.1154(2) Å, \( \alpha = 93.454(1)^\circ \). |
|                                           | c = 19.6920(3) Å, \( \alpha = 90^\circ \). |
| Volume                                      | 6104.66(14) Å³             |
| Z                                           | 2                          |
| Density (calculated)                        | 1.322 Mg/m³                |
| Absorption coefficient                      | 3.090 mm⁻¹                 |
| F(000)                                      | 2556                       |
| Crystal size                                | 0.126 x 0.049 x 0.017 mm³  |
| Theta range for data collection             | 3.12 to 76.92°             |
| Index ranges                                | \(-24 \leq h \leq 23, -20 \leq k \leq 20, -23 \leq l \leq 24\) |
| 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 \[I>2\sigma(I)\]           | 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
Table S3 Crystal data and structure refinement for compound (R)-13.

| Property                                      | Value                                      |
|-----------------------------------------------|--------------------------------------------|
| Identification code                           | gil118                                     |
| Empirical formula                             | C_{20}H_{23}N_{2}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, \( \alpha = 90^\circ \).
|                                              | b = 18.1183(2) Å, \( \beta = 109.2355(9)^\circ \).
|                                              | c = 15.8577(2) Å, \( \gamma = 90^\circ \). |
| Volume                                        | 4091.96(9) Å³                             |
| Z                                             | 8                                          |
| Density (calculated)                          | 1.523 Mg/m³                                 |
| Absorption coefficient                        | 5.121 mm⁻¹                                  |
| F(000)                                        | 1888                                       |
| Crystal size                                  | 0.169 x 0.092 x 0.018 mm³                  |
| Theta range for data collection               | 3.508 to 76.941°.                          |
| Index ranges                                  | -19\leq h \leq 18, -22\leq k \leq 22, -19\leq l \leq 19 |
| Reflections collected                         | 82455                                      |
| Independent reflections                       | 17120 [R(int) = 0.0494]                    |
| Completeness to theta                         | 100.0 %                                    |
| Absorption correction                         | Gaussian                                   |
| Max. and min. transmission                    | 0.915 and 0.575                            |
| Refinement method                             | Full–matrix least–squares on F²            |
| Data / restraints / parameters                 | 17120 / 1 / 909                            |
| Goodness–of–fit on F²                         | 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 $3 \times 10^{-4}$ 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) |
|-----------|------|---------|--------|
| ![Structure](image1.png) | 1 | Toluene | -4208.23249 |
| ![Structure](image2.png) | $S_1$ | Toluene | -4208.23445 |
NMR Spectra

\((R,R)-L0\) $^1$H-NMR (CDCl$_3$)

\((R,R)-L0\) $^{13}$C-NMR (CDCl$_3$)
(R,R)-L1 \textsuperscript{1}H-NMR (CDCl\textsubscript{3})

(R,R)-L1 \textsuperscript{13}C-NMR (CDCl\textsubscript{3})
(R,R)-L3 $^1$H-NMR (CDCl$_3$)

\[ \text{N} \quad \text{O} \quad \text{H} \quad \text{Me} \]

(R,R)-L3 $^{13}$C-NMR (CDCl$_3$)

\[ \text{N} \quad \text{O} \quad \text{H} \quad \text{Me} \]
(R,R)-L4 $^1$H-NMR (CDCl$_3$)

![NMR Spectrogram](Image)

(R,R)-L4 $^{13}$C-NMR (CDCl$_3$)

![NMR Spectrogram](Image)
(R,R)-L4  {superscript}19F-NMR (CDCl₃)
(R,R)-L5 $^1$H-NMR (CDCl$_3$)

(R,R)-L5 $^{13}$C-NMR (CDCl$_3$)
(R,R)-L7 $^1$H-NMR (CDCl$_3$)

(R,R)-L7 $^{13}$C-NMR (CDCl$_3$)
(R,R)-L8 \textsuperscript{1}H-NMR (CDCl\textsubscript{3})

(R,R)-L8 \textsuperscript{13}C-NMR (CDCl\textsubscript{3})
(R,R)-L9 $^1$H-NMR (CDCl$_3$)

(\text{structure})

(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 ¹H-NMR (CDCl₃)

(R,R)-L11 ¹³C-NMR (CDCl₃)
(R,R)-L11 $^{19}$F-NMR (CDCl$_3$)
$^{19}$F-NMR (CDCl$_3$)

$^{(R,R)}$-L12
(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 \textsuperscript{1}H-NMR (CDCl\textsubscript{3})

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{B} & \\
\text{Br} & \\
\end{align*}
\]

(R,R)-11 \textsuperscript{13}C-NMR (CDCl\textsubscript{3})
(R,R)-L12' $^1$H-NMR (CDCl$_3$)

(R,R)-L12' $^{13}$C-NMR (CDCl$_3$)
(R,R)-L12' $^{19}$F-NMR (CDCl$_3$)
3a $^1$H-NMR (CDCl$_3$)

3a $^{13}$C-NMR (CDCl$_3$)
3b \[^1\text{H-NMR} (\text{CDCl}_3)\]

![3b \[^1\text{H-NMR} (\text{CDCl}_3)\]](image)

3b \[^{13}\text{C-NMR} (\text{CDCl}_3)\]

![3b \[^{13}\text{C-NMR} (\text{CDCl}_3)\]](image)
$3c \ {^1}H\text{-NMR (CDCl}_3\text{)}$
3e $^1$H-NMR (CDCl$_3$)

$^1$H-NMR spectrum showing chemical shifts and splitting patterns.

3e $^{13}$C-NMR (CDCl$_3$)

$^{13}$C-NMR spectrum showing chemical shifts and peak assignments.
3f $^1$H-NMR (CDCl$_3$)

3f $^{13}$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$_3$)
3I $^1$H-NMR (CDCl$_3$)

3I $^{13}$C-NMR (CDCl$_3$)
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