Supplementary information

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Materials and methods

General informations

(R,R)-1,2-diaminocyclohexane·HCl and (S,S)-1,2-diaminocyclohexane·HCl were purchased from Arran Chemical Company LTD, 4-chlorobutyrophenone from Alfa Aesar, 4'-bromo-4-chlorobutyrophenone from Acros Organics and 4-bromophenyl isocyanate, 4-Chloro-1-(4-methylphenyl)-1-oxobutane and 5-chloro-1-(4-methylphenyl)-1-oxopentane from Fluorochem. All other reagents were purchased from Sigma-Aldrich 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. The water content in all solvents was monitored before use by titration on an Aquamax KF instrument.

Oxygen-free nitrogen was obtained from BOC gases and passed over dry molecular sieves 4Å. Flash column chromatography was performed on Davisil silica with particle size 40-63 μm. Thin layer chromatography was performed on Merck pre-coated Kieselgel 60F254 aluminium plates with UV realisation.

NMR spectra were recorded on Varian VNMRS 400 and 500 spectrometers at 25 °C. Assignments were based on standard 1H-1H and 1H-13C two-dimensional techniques. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for 1H and 13C NMR (1H-NMR: 7.26 ppm and 13C NMR: 77.16 ppm for CDCl3). 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 analysis was 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, 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-deg-dm⁻¹·cm⁻³·g⁻¹] and are uncorrected for enantiomeric excess.

HRMS were measured with a LCT mass spectrometer Micromass/Waters corp. USA and a Waters GC/MS GCT premier mass spectrometer. The tertiary alcohols were unstable under both ESI and EI ionization methods. However, although the derived THF and THP were unstable under ESI ionization, their HRMS could be obtained under EI (at 35 eV) on the GC/MS system, which in all cases showed only one peak.

Grignard reagent solutions (MeMgBr 3.0 M in Et₂O, MeMgl 3.0 M in Et₂O, EtMgBr 3.0 M in Et₂O, iBuMgBr 2.0 M in Et₂O) were purchased from Sigma-Aldrich except for phenethylmagnesium bromide 1.7 M in Et₂O which was prepared from (2-bromoethyl)benzene and magnesium turnings. Grignard reagents solutions were titrated before use with 1.0 M menthol solution, using 1,10-phenanthroline as indicator.¹ The solutions of ketones 0.5 M in dry toluene were stored in J Young flasks over 4Å molecular sieves.

Ligands L1 and L2 were prepared according to our reported procedure.²
Experimental procedures and characterizations

General procedure for the preparation of ketones 2/3

In a 50 mL flame-dried Schlenk flask under nitrogen was prepared a solution of acyl chloride (10.0 mmol) in the selected arene (35.0 mmol). The solution was cooled to 0 °C and aluminium trichloride (11.0 mmol) was added portionwise over 10 minutes. The mixture was stirred at 0 °C for the indicated time and then poured into ice (75 g) and extracted with Et₂O (3 x 40 mL). The combined organic layers 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 97:3 to obtain the pure ketone.

4'-methoxy-4-chlorobutyrophenone 2c

![Image of 2c]

Reaction conducted for 30 minutes at 0 °C. Off-white solid, 94% yield

$^1$H-NMR (400 MHz, CDCl₃): δ 7.97-7.94 (m, 2H), 6.95-6.92 (m, 2H), 3.87 (s, 3H), 3.68-3.65 (m, 2H), 3.14-3.10 (m, 2H), 2.25-2.18 (m, 2H); $^{13}$C-NMR (100.6 MHz, CDCl₃): δ 197.6, 163.7, 130.4, 130.0, 113.9, 55.6, 44.9, 35.0, 27.1. Analytical data in accordance with literature reported results.

5-chlorovalerophenone 3a

![Image of 3a]

Reaction conducted for 30 minutes at 0 °C. Off-white solid, 80% yield.

$^1$H-NMR (400 MHz, CDCl₃): δ 7.97-7.94 (m, 2H), 7.59-7.54 (m, 1H), 7.49-7.45 (m, 2H), 3.60-3.57 (m, 2H), 3.04-3.00 (m, 2H), 1.95-1.83 (m, 4H); $^{13}$C-NMR (100.6 MHz, CDCl₃): δ 199.8, 137.0, 133.2, 128.8, 128.1, 44.9, 37.7, 32.2, 21.7. Analytical data in accordance with literature reported results.

4'-bromo-5-chlorovalerophenone 3b

![Image of 3b]
Reaction conducted for 3 hours at room temperature. Off-white solid, 38% yield.

\[^{1}\text{H-}NMR\ (400\ \text{MHz, CDCl}_3): \delta 7.83-7.79\ (m, 2H), 7.61-7.58\ (m, 2H), 3.59-3.56\ (m, 2H), 2.99-2.96\ (m, 2H), 1.93-1.83\ (m, 4H);\ \[^{13}\text{C-}NMR\ (100.6\ \text{MHz, CDCl}_3): \delta 198.6, 135.7, 132.1, 129.7, 128.4, 44.8, 37.7, 32.1, 21.5.\ \]Analytical data in accordance with literature reported results.\(^4\)

**4'-methoxy-5-chlorovalerophenone 3c**

![Image of 4'-methoxy-5-chlorovalerophenone 3c](image)

Reaction conducted for 30 minutes at 0 °C. Off-white solid, 93% yield.

\[^{1}\text{H-}NMR\ (400\ \text{MHz, CDCl}_3): \delta 7.96-7.92\ (m, 2H), 6.95-6.91\ (m, 2H), 3.87\ (s, 3H), 3.59-3.56\ (m, 2H), 2.98-2.94\ (m, 2H), 1.93-1.82\ (m, 4H);\ \[^{13}\text{C-}NMR\ (100.6\ \text{MHz, CDCl}_3): \delta 198.3, 163.6, 130.4, 130.1, 113.9, 55.6, 44.9, 37.3, 32.3, 21.9.\ \]Analytical data in accordance with literature reported results.\(^4\)

**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 2a-c/3a-c (3.0 mmol) in dry toluene (10 mL). The solution was cooled to -78 °C and the Grignard reagent (4.5 mmol) was added dropwise. The mixture was stirred at -78 °C for 1 hour and then quenched with NH\(_4\)Cl sat. (3 mL) and H\(_2\)O (3 mL). The phases were separated and the aqueous phase was extracted with Et\(_2\)O (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\(_2\)O 95:5 to 80:20 to obtain the pure tertiary alcohol.

**General procedure for the preparation of chiral non-racemic tertiary alcohols**

To a 25 mL flame-dried Schlenk flask under nitrogen was added a 0.5 M solution of ketone 2a-c/3a-c in dry toluene (0.1 mmol, 0.200 mL) followed by dry toluene (1.3 mL). Ligand L1 (50 mg, 0.133 mmol) was added, the solution was stirred magnetically at 750 rpm for 5 minutes at room temperature and then cooled to -78 °C. The Grignard reagent in Et\(_2\)O (0.243 mmol) was diluted with dry toluene (400 μL) and was added dropwise over 15 minutes. The reaction mixture was stirred at -78 °C for 1 hour and then quenched at that temperature with a solution of IPA/H\(_2\)O 1:1 (0.3 mL), followed by NH\(_4\)Cl 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 phases were separated and the aqueous phase was extracted with heptane (3 x 10 mL). The combined organic phases were washed with AcOH 20% solution (2 x 10 mL), H\(_2\)O (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\(_2\)O 95:5 to
80:20 to obtain the pure scalemic tertiary alcohol 4/5. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

5-chloro-2-phenylpentan-2-ol 4aa

![Chemical structure of 4aa](image)

Colourless oil, 71% yield, 91% ee

HPLC analysis on chiral stationary phase: Column Chiralpak IB, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, $t_{el}$ = 29.8 min, $t_{m}$ = 32.6 min

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.45-7.42 (m, 2H), 7.37-7.33 (m, 2H), 7.27-7.23 (m, 1H), 2.01-1.88 (m, 2H), 1.85-1.74 (m, 2H), 1.72-1.61 (m, 2H), 1.59 (s, 3H)

$^{13}$C-NMR (100.6 MHz, CDCl$_3$): δ 147.4, 128.4, 126.9, 124.8, 74.5, 45.6, 41.5, 30.7, 27.6

Analytical data were in accordance with literature reported results. 5

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**Totals:** 3.84622e4  982.60999
(R)-6-chloro-3-phenylhexan-3-ol 4ab

\[
\text{HO} \quad \begin{array}{c}
\text{Cl} \\
\end{array}
\]

4ab

Colourless oil, 69% yield, 93% ee

HPLC analysis on chiral stationary phase: Column Chiralpak IB, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, \( t_M = 20.1 \text{ min} \), \( t_m = 21.6 \text{ min} \)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.39-7.32 (m, 4H), 7.26-7.22 (m, 1H), 3.52-3.43 (m, 2H), 2.02-1.75 (m, 5H), 1.66 (br s, 1H), 1.60-1.49 (m, 1H), 0.77 (t, \( J = 7.4 \) Hz, 3H)

\(^{13}\)C-NMR (100.6 MHz, CDCl\(_3\)): \( \delta \) 145.4, 128.3, 126.7, 125.4, 77.1, 45.8, 40.0, 35.9, 27.2, 7.8

Analytical data were in accordance with literature reported results.\(^5\)
1-chloro-6-methyl-4-phenylheptan-4-ol 4ac

![Chemical Structure](image)

Colourless oil, 63% yield, 96% ee

HPLC analysis on chiral stationary phase: Column Chiralpak IB, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, t_m= 14.8 min, t_M= 17.3 min

$^1$H-NMR (400 MHz, CDCl₃): $\delta$ 7.40-7.31 (m, 4H), 7.26-7.20 (m, 1H), 3.52-3.40 (m, 2H), 2.02-1.42 (m, 8H), 0.91 (d, $J = 6.6$ Hz, 3H), 0.69 (d, $J = 6.6$ Hz, 3H)

$^{13}$C-NMR (100.6 MHz, CDCl₃): $\delta$ 145.8, 128.3, 126.5, 125.4, 77.4, 52.2, 45.8, 41.6, 27.0, 24.6, 24.5, 24.2

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Totals: 1.78596e4 584.71337
6-chloro-1,3-diphenylhexan-3-ol 4ad

![Chemical Structure](image)

Colourless oil, 70% yield, 96% ee

HPLC analysis on chiral stationary phase: Column Chiralpak IA, Heptane/EtOH 95:5, flow 1 mL/min, 210 nm, 21 °C, t_m=12.7 min, t_M=14.9 min

$^1$H-NMR (400 MHz, CDCl₃): δ 7.45-7.36 (m, 4H), 7.31-7.09 (m, 6H), 3.53-3.42 (m, 2H), 2.67-2.57 (m, 1H), 2.43-2.33 (m, 1H), 2.26-1.92 (m, 4H), 1.89-1.75 (m, 1H), 1.72 (br s, 1H), 1.63-1.49 (m, 1H)

$^{13}$C-NMR (100.6 MHz, CDCl₃): δ 145.2, 142.2, 128.6, 128.5, 128.4, 126.9, 126.0, 125.3, 77.0, 45.6, 45.2, 40.7, 30.1, 27.1

### HPLC Data

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Totals: 7.22069e4 1924.27045

8
3-(4-bromophenyl)-6-chlorohexan-3-ol 4bb

![Chemical Structure](image)

Colourless oil, 83% yield, 88% ee

HPLC analysis on chiral stationary phase: Column Chiralpak AS-H, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, t_M= 29.5 min, t_m= 37.3 min

^1H-NMR (400 MHz, CDCl₃): δ 7.47-7.44 (m, 2H), 7.26-7.23 (m, 2H), 3.51-3.42 (m, 2H), 1.98-1.73 (m, 5H), 1.65 (br s, 1H), 1.56-1.43 (m, 1H), 0.75 (t, J = 7.4 Hz, 3H);

^13C-NMR (100.6 MHz, CDCl₃): δ 144.4, 131.4, 127.4, 120.6, 76.9, 45.6, 40.0, 35.9, 27.0, 7.7

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**Totals:** 1.83156e4 343.82177
6-chloro-3-(4-methoxyphenyl)hexan-3-ol 4cb

Colourless oil, 68% yield, 97% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 90:10, flow 1 mL/min, 210 nm, 21 °C, 
$t_M$ = 9.8 min, $t_m$ = 12.1 min

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.30-7.26 (m, 2H), 6.89-6.86 (m, 2H), 3.81 (s, 3H), 3.52-3.43 (m, 2H), 1.98-1.73 (m, 5H), 1.62-1.51 (m, 2H), 0.76 (t, $J$ = 7.4 Hz, 3H)

$^{13}$C-NMR (100.6 MHz, CDCl$_3$): δ 158.3, 137.5, 126.6, 113.6, 76.8, 55.4, 45.8, 40.0, 35.8, 27.2, 7.9

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Totals: 2.59300e4 1433.29884
(R)-6-chloro-2-phenylhexan-2-ol 5aa

Colourless oil, 69% yield, 95% ee

HPLC analysis on chiral stationary phase: Column (S,S)-Whelk-O 1, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, t<sub>m</sub>= 14.6 min, t<sub>M</sub>= 16.3 min

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.44-7.41 (m, 2H), 7.37-7.32 (m, 2H), 7.27-7.23 (m, 1H), 3.47 (t, J = 6.8 Hz, 2H), 1.88-1.69 (m, 5H), 1.58 (s, 3H), 1.49-1.38 (m, 1H), 1.35-1.23 (m, 1H)

<sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ 147.8, 128.4, 126.8, 124.9, 74.7, 45.0, 43.5, 33.0, 30.3, 21.6

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7-chloro-3-phenylheptan-3-ol 5ab

Colourless oil, 72% yield, 95% ee

HPLC analysis on chiral stationary phase: Column Chiralpak IB, Heptane/EtOH 99.9:0.1, flow 1 mL/min, 210 nm, 21 °C, t_M = 52.0 min, t_m = 54.9 min

^1H-NMR (400 MHz, CDCl₃): δ 7.39-7.32 (m, 4H), 7.26-7.21 (m, 1H), 3.50-3.41 (m, 2H), 1.94-1.66 (m, 7H), 1.51-1.39 (m, 1H), 1.26-1.14 (m, 1H), 0.76 (t, J = 7.4 Hz, 3H)

^13C-NMR (100.6 MHz, CDCl₃): δ 145.8, 128.2, 126.6, 125.4, 77.2, 44.9, 42.0, 35.5, 33.1, 21.2, 7.9

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Totals :  5.27971e4  873.30402
8-chloro-2-methyl-4-phenyloctan-4-ol 5ac

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\begin{align*}
&\text{Colourless oil, 65% yield, 95\% ee} \\
&\text{HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C,} \\
&t_M = 12.6 \text{ min, } t_m = 16.6 \text{ min} \\
&{^1}H-NMR (400 MHz, CDCl}_3): \delta 7.39-7.31 (m, 4H), 7.25-7.20 (m, 1H), 3.49-3.40 (m, 2H), 1.87-1.64 (m, 7H), 1.62-1.39 (m, 2H), 1.19-1.08 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.69 (d, J = 6.6 Hz, 3H) \\
&{^{13}}C-NMR (100.6 MHz, CDCl}_3): \delta 146.2, 128.2, 126.4, 125.4, 77.6, 51.9, 44.9, 43.6, 33.0, 24.7, 24.5, 24.2, 21.0
\end{align*}
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13
7-chloro-1,3-diphenylheptan-3-ol 5ad

![Structural formula of 5ad](image)

Colourless oil, 72% yield, 93% ee

HPLC analysis on chiral stationary phase: Column Chiralpak AS-H, Heptane/EtOH 95:5, flow 1 mL/min, 210 nm, 21 °C, 
t<sub>R</sub>= 16.0 min, t<sub>m</sub>= 19.3 min

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.44-7.37 (m, 4H), 7.30-7.24 (m, 3H), 7.19-7.14 (m, 1H), 7.12-7.10 (m, 2H), 3.49-3.43 (m, 2H), 2.62 (ddd, J = 13.6, 11.1, 6.3 Hz, 1H), 2.37 (ddd, J = 13.6, 11.2, 5.2 Hz, 1H), 2.22-2.09 (m, 2H), 1.93-1.80 (m, 2H), 1.79-1.64 (m, 3H), 1.53-1.42 (m, 1H), 1.27-1.16 (m, 1H)

<sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): δ 145.6, 142.3, 128.6, 128.5, 128.4, 126.8, 126.0, 125.3, 77.1, 44.9, 44.9, 42.7, 33.0, 30.1, 21.1

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3-(4-bromophenyl)-7-chloroheptan-3-ol 5bb

[Chemical structure image]

Colourless oil, 80% yield, 88% ee

HPLC analysis on chiral stationary phase: Column Chiralpak AS-H, Heptane/EtOH 95:5, flow 1 mL/min, 210 nm, 21 °C, t_M = 8.3 min, t_m = 10.2 min

^1^H-NMR (400 MHz, CDCl_3): δ 7.47-7.44 (m, 2H), 7.26-7.23 (m, 2H), 3.50-3.41 (m, 2H), 1.90-1.65 (m, 6H), 1.62 (br s, 1H), 1.50-1.40 (m, 1H), 1.22-1.11 (m, 1H), 0.75 (t, J = 7.4 Hz, 3H)

^13^C-NMR (100.6 MHz, CDCl_3): δ 144.8, 131.3, 127.4, 120.5, 77.0, 44.9, 42.0, 35.6, 32.9, 21.1, 7.8

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Totals: 2.92373e4
7-chloro-3-(4-methoxyphenyl)heptan-3-ol 5cb

![Chemical Structure](image)

Colourless oil, 64% yield, 97% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 95:5, flow 1 mL/min, 210 nm, 21 °C, t_M = 14.7 min, t_m = 20.7 min

\(^1\)H-NMR (400 MHz, CDCl₃): \(\delta\) 7.30-7.26 (m, 2H), 6.89-6.85 (m, 2H), 3.81 (s, 3H), 3.50-3.42 (m, 2H), 1.90-1.67 (m, 6H), 1.63 (br s, 1H), 1.48-1.37 (m, 1H), 1.27-1.15 (m, 1H), 0.76 (t, \(J = 7.4\) Hz, 3H)

\(^13\)C-NMR (100.6 MHz, CDCl₃): \(\delta\) 158.2, 137.9, 126.6, 113.5, 76.9, 55.3, 45.0, 41.9, 35.4, 33.1, 21.2, 7.9

---

General procedure for the NaH-promoted cyclization to tetrahydrofurans (Method A)

In a 10 mL flame-dried Schlenk flask under nitrogen was prepared a solution of the \(\gamma\)-chloro alcohol 4 (0.1 mmol) in dry THF (1 mL). The solution was cooled to 0 °C and NaH 95% (13 mg, 0.5 mmol) was added. The reaction mixture was stirred for 18 hours at room temperature. The reaction was cooled to 0 °C and carefully quenched by adding H₂O (1 mL) drop wise under vigorous stirring. The mixture was extracted with Et₂O (3 x 5 mL) and the combined organic
Phases were dried over sodium sulfate, filtered, and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel eluting with pentane/Et₂O 99:1 to obtain pure 2,2-disubstituted tetrahydrofurans 6. The enantiomeric excess was calculated by HPLC analysis on chiral stationary phase.

(R)-2-methyl-2-phenyltetrahydrofuran 6aa

![6aa](image)

Colourless oil, 93% yield, 91% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.8:0.2, flow 1 mL/min, 210 nm, 21 °C, tₐ = 9.3 min, tₘ = 11.8 min

$^1$H-NMR (400 MHz, CDCl₃): δ 7.42-7.39 (m, 2H), 7.35-7.30 (m, 2H), 7.24-7.20 (m, 1H), 4.05-4.00 (m, 1H), 3.95-3.89 (m, 1H), 2.25-2.18 (m, 1H), 2.06-1.97 (m, 2H), 1.87-1.76 (m, 1H), 1.54 (s, 3H)

$^{13}$C-NMR (100.6 MHz, CDCl₃): δ 148.3, 128.2, 126.4, 124.8, 84.4, 67.7, 39.6, 29.8, 25.9

$[α]_{D}^{25}$: + 4.7 (c. 0.8, CHCl₃); Lit. (for (S)-8aa) $[α]_{D}^{25}$: - 4.1 (c. 0.64, CH₂Cl₂)

Analytical data were in accordance with literature reported results.

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Totals: 5.65536e4 2043.33226
(R)-2-ethyl-2-phenyltetrahydrofuran 6ab

6ab

Colourless oil, 91% yield, 93% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.5:0.5, flow 1 mL/min, 210 nm, 21 °C, t_m= 8.1 min, t_M= 8.8 min

$^1$H-NMR (500 MHz, CDCl₃): δ 7.37-7.30 (m, 4H), 7.23-7.19 (m, 1H), 3.99-3.95 (m, 1H), 3.91-3.86 (m, 1H), 2.20-2.15 (m, 1H), 2.07-2.01 (m, 1H), 1.97-1.89 (m, 1H), 1.88-1.73 (m, 3H), 0.76 (t, $J = 7.4$ Hz, 3H)

$^{13}$C-NMR (125.7 MHz, CDCl₃): δ 146.8, 128.0, 126.3, 125.5, 87.3, 67.6, 37.9, 35.2, 25.8, 8.9

$[\alpha]_{D}^{20} = 9.0$ (c. 0.7, CHCl₃)

Analytical data were in accordance with literature reported results.⁵
2-isobutyl-2-phenyltetrahydrofuran 6ac

Colourless oil, 93% yield, 96% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, t_m= 4.8 min, t_M= 5.7 min

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.38-7.29 (m, 4H), 7.23-7.18 (m, 1H), 4.00-3.87 (m, 2H), 2.21-2.15 (m, 1H), 2.03-1.80 (m, 3H), 1.76-1.66 (m, 2H), 1.51-1.41 (m, 1H), 0.88 (d, $J = 6.6$ Hz, 3H), 0.69 (d, $J = 6.7$ Hz, 3H)

$^{13}$C-NMR (100.6 MHz, CDCl$_3$): δ 147.0, 128.0, 126.3, 125.5, 87.4, 67.4, 51.0, 39.8, 25.3, 24.9, 24.4, 24.1

[α]$_D^{20}$: -7.6 (c. 1.1, CHCl$_3$)

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Totals: 2.60847e4 2319.66006
2-phenethyl-2-phenyltetrahydrofuran 6ad

Colourless oil, 94% yield, 94% ee

HPLC analysis on chiral stationary phase: Column Chiralpak IC, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, \( t_{\text{m}} = 4.7 \text{ min}, t_{\text{m}} = 5.1 \text{ min} \)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta 7.44-7.41 \text{ (m, 2H)}, 7.38-7.34 \text{ (m, 2H)}, 7.27-7.22 \text{ (m, 3H)}, 7.16-7.10 \text{ (m, 3H)}, 4.07-3.94 \text{ (m, 2H)}, 2.71-2.63 \text{ (m, 1H)}, 2.36-2.29 \text{ (m, 1H)}, 2.25-2.05 \text{ (m, 4H)}, 2.02-1.93 \text{ (m, 1H)}, 1.87-1.77 \text{ (m, 1H)} \)

\(^{13}\)C-NMR (100.6 MHz, CDCl\(_3\)): \( \delta 146.6, 142.8, 128.4, 128.4, 128.2, 126.5, 125.7, 125.4, 86.7, 67.8, 44.6, 38.9, 31.0, 25.7 \)

HRMS: (El, 35 eV) Calculated for C\(_{18}\)H\(_{20}\)O 252.1514 ([M]+); found 252.1504

\([\alpha]_{D}^{20} + 12.3 \text{ (c. 1.0, CHCl\(_3\))} \)

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Totals: 1448.63014 113.82023
2-ethyl-2-(4-bromophenyl)tetrahydrofuran 6bb

\[
\text{Br} \rightarrow \text{O}
\]

6bb

Colourless oil, 95% yield, 87% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.5:0.5, flow 1 mL/min, 210 nm, 21°C, \(t_m = 5.4\) min, \(t_M = 5.6\) min

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta 7.45-7.41\) (m, 2H), 7.24-7.21 (m, 2H), 3.98-3.92 (m, 1H), 3.88-3.83 (m, 1H), 2.14-1.88 (m, 3H), 1.83-1.70 (m, 3H), 0.75 (t, \(J = 7.4\) Hz, 3H)

\(^13\)C-NMR (100.6 MHz, CDCl\(_3\)): \(\delta 145.9, 131.1, 127.5, 120.2, 87.0, 67.7, 38.0, 35.1, 25.7, 8.8\)

HRMS: (EI, 35 eV) Calculated for C\(_{12}\)H\(_{15}\)OBr 254.0306 ([M]+); found 254.0303

\([\alpha]^D_{20}\) : -3.1 (c. 1.0, CHCl\(_3\))
2-ethyl-2-(4-methoxyphenyl)tetrahydrofuran 6cb

\[ \begin{align*}
\text{MeO} & \quad \cdots \quad \text{O} \\
6cb
\end{align*} \]

Colourless oil, 91% yield, 96% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99:1, flow 1 mL/min, 254 nm, 21 °C, \( t_m = 10.7 \text{ min}, \ t_M = 12.3 \text{ min} \)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.29-7.25 (m, 2H), 6.87-6.84 (m, 2H), 3.97-3.92 (m, 1H), 3.89-3.83 (m, 1H), 3.80 (s, 3H), 2.18-2.12 (m, 1H), 2.03-1.87 (m, 2H), 1.84-1.72 (m, 3H), 0.76 (t, \( J = 7.4 \text{ Hz, 3H} \))

\(^13\)C-NMR (100.6 MHz, CDCl\(_3\)): \( \delta \) 158.2, 138.7, 126.6, 113.4, 87.0, 67.4, 55.4, 37.8, 35.3, 25.7, 9.0

HRMS: (El, 35 eV) Calculated for C\(_{13}\)H\(_{18}\)O\(_2\) 206.1307 ([M]\(^+\)); found 206.1309

\( [\alpha]_{D}^{20} = -9.1 \) (c. 1.0, CHCl\(_3\))

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Totals: 2692.61197 113.29172
Conditions screening for the base-promoted cyclization to tetrahydropyrans

Alcohol 5ad was chosen as model compound due to the lower volatility of the cyclized product 7ad compared to other THP derivatives. A screening of different non-nucleophilic bases showed KHMDS in THF being the reagent of choice for the transformation, furnishing 7ad in high yield after 1 hour (Table 1, entry 5).

Table 1 Optimization of conditions for base-promoted cyclization of δ-chloro tertiary alcohols to 2,2-disubstituted THPs.

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<sup>a</sup> Reactions were run on 0.1 mmol scale. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by HPLC analysis on chiral stationary phase.

General procedure for the KHMDS-promoted cyclization to tetrahydropyrans (Method B)

In a 10 mL flame-dried Schlenk flask under nitrogen was prepared a solution of the δ-chloro alcohol 5 (0.1 mmol) in dry THF (1 mL). The solution was cooled to 0 °C and KHMDS 1.0 M solution in THF (150 μL, 0.15 mmol) was added drop wise. The reaction mixture was allowed to warm up to room temperature, stirred for 1 hour and then quenched with NH₄Cl sat. (1 mL) and extracted with Et₂O (3 x 5 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel eluting with pentane/Et₂O 98:2 to obtain pure 2,2-disubstituted tetrahydropyrans 7. The enantiomeric excess was calculated by HPLC analysis on chiral stationary phase.
(R)-2-methyl-2-phenyltetrahydro-2H-pyran 7aa

![Chemical Structure](image)

**7aa**

Colourless oil, 90% yield, 93% ee

HPLC analysis on chiral stationary phase: Column Chiralpak AS-H, Heptane/EtOH 99.5:0.5, flow 1 mL/min, 210 nm, 21 °C, t_m= 9.8 min, t_M= 11.8 min

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.44-7.34 (m, 4H), 7.26-7.22 (m, 1H), 3.76-3.71 (m, 1H), 3.53-3.46 (m, 1H), 2.43-2.28 (m, 1H), 1.79-1.59 (m, 3H), 1.56-1.41 (m, 2H), 1.39 (s, 3H)

$^{13}$C-NMR (100.6 MHz, CDCl$_3$): δ 145.5, 128.6, 126.6, 126.1, 76.1, 62.9, 34.7, 32.9, 26.1, 20.2

HRMS: (EI, 35 eV) Calculated for C$_{12}$H$_{16}$O 176.1201 ([M]+); found 176.1208

[α]$_D^{25}$: -48.2 (c. 0.6, CHCl$_3$); Lit. (for (S)-9aa) [α]$_D^{25}$: +59.1 (c. 0.34, CH$_2$Cl$_2$)

**HPLC Data**

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2-ethyl-2-phenyltetrahydro-2H-pyran 7ab

Colourless oil, 88% yield, 95% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, tm= 6.7 min, tM= 10.0 min

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.38-7.33 (m, 4H), 7.27-7.22 (m, 1H), 3.73-3.68 (m, 1H), 3.53-3.47 (m, 1H), 2.32-2.26 (m, 1H), 1.80-1.58 (m, 5H), 1.53-1.38 (m, 2H), 0.66 (t, J = 7.5 Hz, 3H)

$^{13}$C-NMR (100.6 MHz, CDCl$_3$): δ 143.4, 128.3, 127.1, 126.5, 78.8, 62.7, 37.6, 32.7, 26.4, 20.0, 7.8

HRMS: (EI, 35 eV) Calculated for C$_{13}$H$_{18}$O 190.1358 ([M]$^+$); found 190.1360

[$\alpha$]$_D^{28}$ - 11.4 (c. 1.0, CHCl$_3$)

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Totals : 1.26394e4 566.04619
2-isobutyl-2-phenyltetrahydro-2H-pyran 7ac

Colourless oil, 90% yield, 95% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.9:0.1, flow 1 mL/min, 210 nm, 21 °C, \( t_m = 4.8 \text{ min} \), \( t_M = 5.2 \text{ min} \)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.40-7.33 (m, 4H), 7.25-7.21 (m, 1H), 3.73-3.68 (m, 1H), 3.54-3.48 (m, 1H), 2.29-2.24 (m, 1H), 1.79-1.58 (m, 4H), 1.54-1.38 (m, 4H), 0.73-0.70 (m, 6H)

\(^{13}\)C-NMR (100.6 MHz, CDCl\(_3\)): \( \delta \) 144.2, 128.3, 126.9, 126.4, 78.9, 62.5, 53.5, 34.1, 26.3, 24.8, 24.5, 23.7, 20.1

HRMS: (EI, 35 eV) Calculated for C\(_{15}\)H\(_{22}\)O 218.1671 ([M]+); found 218.1676

\( [\alpha]_D^{25} \) = -54.3 (c. 1.5, CHCl\(_3\))

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Totals: 1.88876e4 1127.27326
2-phenethyl-2-phenyltetrahydro-2H-pyran 7ad

Colourless oil, 89% yield, 93% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.5:0.5, flow 1 mL/min, 210 nm, 21 °C, t_m= 9.1 min, t_M= 16.1 min

1H-NMR (400 MHz, CDCl3): δ 7.46-7.38 (m, 4H), 7.30-7.20 (m, 3H), 7.15-7.11 (m, 1H), 7.08-7.06 (m, 2H), 3.81-3.76 (m, 1H), 2.53-2.45 (m, 1H), 2.42-2.28 (m, 2H), 2.14-2.06 (m, 1H), 1.96-1.88 (m, 1H), 1.85-1.78 (m, 1H), 1.75-1.62 (m, 2H), 1.57-1.45 (m, 2H)

13C-NMR (100.6 MHz, CDCl3): δ 143.6, 142.7, 128.4, 128.4, 128.3, 126.8, 126.6, 125.7, 78.2, 62.7, 46.0, 33.7, 29.8, 26.3, 20.0

HRMS: (EI, 35 eV) Calculated for C19H22O 266.1671 ([M]+); found 266.1677

[α]D20 + 4.0 (c. 1.0, CHCl3)

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Totals: 2.31883e4 560.18100
2-ethyl-2-(4-bromophenyl)tetrahydro-2H-pyran 7bb

Colourless oil, 89% yield, 87% ee

HPLC analysis on chiral stationary phase: Column Chiralpak AS-H, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, t_m = 4.6 min, t_M = 4.9 min

^1^H-NMR (400 MHz, CDCl$_3$): δ 7.49-7.45 (m, 2H), 7.25-7.21 (m, 2H), 3.72-3.68 (m, 1H), 3.48-3.42 (m, 1H), 2.23-2.18 (m, 1H), 1.78-1.56 (m, 5H), 1.49-1.37 (m, 2H), 0.65 (t, J = 7.5 Hz, 3H)

^13^C-NMR (100.6 MHz, CDCl$_3$): δ 142.7, 131.4, 128.9, 120.5, 78.5, 62.7, 37.1, 32.7, 26.3, 19.9, 7.7

[α]$_{D}^{20}$: -36.0 (c. 1.0, CHCl$_3$)

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Totals: 3.44450e4 2825.98148
2-ethyl-2-(4-methoxyphenyl)tetrahydro-2H-pyran 7cb

![Chemical Structure](image)

7 cb

Colourless oil, 90% yield, 96% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, t_m = 8.4 min, t_M = 10.5 min

$^1$H-NMR (400 MHz, CDCl₃): δ 7.28-7.25 (m, 2H), 6.91-6.88 (m, 2H), 3.82 (s, 3H), 3.69-3.66 (m, 1H), 3.51-3.44 (m, 1H), 2.29-2.23 (m, 1H), 1.76-1.56 (m, 5H), 1.52-1.38 (m, 2H), 0.66 (t, J = 7.5 Hz, 3H)

$^{13}$C-NMR (100.6 MHz, CDCl₃): δ 158.2, 135.2, 128.3, 113.6, 78.6, 62.6, 55.3, 37.8, 32.6, 26.4, 20.0, 7.9

HRMS: (EI, 35 eV) Calculated for C₁₄H₂₀O₂ 220.1463 ([M]⁺); found 220.1456

$\alpha_D^{28}$: -28.3 (c. 1.0, CHCl₃)

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![Graphs](image)
Asymmetric addition of ethylmagnesium bromide to butyrophenone.

\[
\begin{align*}
\text{HO}
\end{align*}
\]

Reaction of butyrophenone with EtMgBr in Et₂O, in the presence of ligand \((R,R)-\text{L1}\), followed the general procedure for the preparation of tertiary alcohols described above.

3-phenylhexan-3-ol

Colourless oil, 67% yield, 92% ee

HPLC analysis on chiral stationary phase: Column Chiralcel OJ-H, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, \(t_M = 10.6\) min, \(t_m = 12.9\) min

\(^1\text{H}-\text{NMR} (400\text{ MHz, CDCl}_3): \delta 7.37-7.30 (m, 4H), 7.23-7.19 (m, 1H), 1.91-1.70 (m, 4H), 1.66 (s, 1H), 1.35-1.22 (m, 1H), 1.12-1.01 (m, 1H), 0.84 (t, \(J = 7.3\) Hz, 3H), 0.74 (t, \(J = 7.4\) Hz, 3H)

\(^{13}\text{C}-\text{NMR} (100.6\text{ MHz, CDCl}_3): \delta 146.2, 128.1, 126.4, 125.5, 77.4, 45.1, 35.5, 16.9, 14.6, 7.9
Asymmetric addition of ethylmagnesium bromide to valerophenone.

\[
\text{EtMgBr (2.4 equiv.) } \quad \text{(R,R)-L1 (1.3 equiv.)}
\]

\[
\text{Toluene, 0.05 M} \quad -78 ^\circ \text{C, 1 h}
\]

Reaction of valerophenone with EtMgBr in Et₂O, in the presence of ligand (R,R)-L1, followed the general procedure for the preparation of tertiary alcohols described above.

3-Phenylheptan-3-ol

Colourless oil, 69% yield, 93% ee

HPLC analysis on chiral stationary phase: Column Chiralpak IA, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, tₘₙ = 9.1 min, tₘᵦ = 9.7 min

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

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

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Totals: 1.68965e4 1306.25208
Preparation of (S)-(−)-Gossonorol and (R)-(+) -Gossonorol

Preparation of 5-methyl-1-(4-methylphenyl)-1-oxo-hex-4-ene 1

Various bases and conditions were screened for the preparation of ketone 1 in one step by reaction of p-methylacetophenone with 3,3-dimethylallyl bromide (Table 2). Lithium bis(trimethylsilyl)amide (LiHMDS) showed the best selectivity between mono and bis alkylation, delivering the desired mono alkylate ketone 1 in high yield. On the other hand, the use of NaH or KHMDS yielded significant amounts of the bis alkylated ketone 1a.

Table 2 Screening of conditions for the preparation of ketone 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>15 (equiv.)</th>
<th>16 (equiv.)</th>
<th>T (°C)</th>
<th>Solvent</th>
<th>1/1a</th>
<th>Yield 1</th>
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<td>5:95</td>
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<tr>
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<td>27:73</td>
<td>-</td>
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<td>0 °C</td>
<td>THF</td>
<td>38:62</td>
<td>-</td>
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<tr>
<td>5</td>
<td>LiHMDS (1.0)</td>
<td>1.1</td>
<td>1.0</td>
<td>0 °C</td>
<td>THF</td>
<td>96:4</td>
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<tr>
<td>6</td>
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<td>1.0</td>
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<td>THF</td>
<td>95:5</td>
<td>86%</td>
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</table>

Reactions were run on 0.2 mmol scale. Ratio calculated by 1H-NMR analysis of the crude reaction mixture.

Procedure:

In a 25 mL flame-dried Schlenk flask under nitrogen was prepared a solution of p-methylacetophenone (0.139 mL, 0.987 mmol) in anhydrous THF (2 mL). The solution was cooled to 0 °C with an ice bath and LiHMDS 1.0 M solution in THF (0.987 mL, 0.987 mmol) was added dropwise. The yellow solution was stirred at 0 °C for 20 minutes, then 3,3-dimethylallyl bromide (0.057 mL, 0.493 mmol) was added dropwise and the mixture stirred at 0 °C for 2 hour. The reaction was quenched with NH₄Cl sat. solution (4 mL), the phases separated and the aqueous phase extracted with Et₂O (3 x 10 mL). The combined organic layers 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 98:2 to obtain pure ketone 1.
5-methyl-1-(4-methylphenyl)-1-oxo-hex-4-ene 1

\[
\text{O} \quad \begin{array}{c}
\text{Me} \\
\text{C} \\
\text{Me} \\
\end{array}
\quad \text{CH}_2
\]

Colourless oil, 86% yield

\[^1^H\text{-NMR}\ (500\text{ MHz, }\text{CDCl}_3): \delta 7.88-7.86 (m, 2H), 7.27-7.25 (m, 2H), 5.20-5.17 (m, 1H), 2.99-2.96 (m, 2H), 2.44-2.40 (m, 5H), 1.70 (s, 3H), 1.64 (s, 3H)\]

\[^{13}C\text{-NMR}\ (125.7\text{ MHz, }\text{CDCl}_3): \delta 199.9, 143.8, 134.7, 132.8, 129.4, 128.3, 123.2, 38.8, 25.8, 23.2, 21.8, 17.8\]

Analytical data were in accordance with literature reported results.\(^7\)

**Preparation of (S)-(−)-Gossonorol and (R)-(+)−Gossonorol**

(S)-(−)-Gossonorol was prepared by reaction of ketone 1 with MeMgBr in the presence of ligand (S,S)-L1, following the general procedure for the preparation of chiral non-racemic tertiary alcohols described above.

\[
\begin{array}{c}
\text{O} \\
\text{MeMgBr (2.4 equiv.)} \\
(S,S)-\text{L1 (1.3 equiv.)} \\
\text{Tol. 0.05 M} \\
-78 \text{ °C, 1 h}
\end{array}
\]

\[(S)-(−)-\text{Gossonorol}}
\]

Colourless oil, 66% yield, 93% ee

HPLC analysis on chiral stationary phase: Column Chiralpak IA, Heptane/EtOH 97:3, flow 1 mL/min, 210 nm, 21 °C, \( t_m = 9.2 \) min, \( t_{at} = 13.9 \) min

\[^1^H\text{-NMR}\ (500\text{ MHz, }\text{CDCl}_3): \delta 7.33-7.30 (m, 2H), 7.16-7.14 (m, 2H), 5.11-5.08 (m, 1H), 2.34 (s, 3H), 1.98-1.81 (m, 5H), 1.65 (s, 3H), 1.53 (s, 3H), 1.50 (s, 3H)\]

\[^{13}C\text{-NMR}\ (125.7\text{ MHz, }\text{CDCl}_3): \delta 145.1, 136.1, 132.3, 129.0, 124.8, 124.4, 75.0, 43.8, 30.7, 25.8, 23.1, 21.1, 17.8\]

\[\left[\alpha\right]^{20}_D = -11.9 \text{ (c. 1.0, CHCl}_3\text{)}; \text{Lit. (for (R)-Gossonorol) }\left[\alpha\right]^{20}_D = +15.0 \text{ (c. 1.0, CHCl}_3\text{)}\]

Analytical data were in accordance with literature reported results.\(^8\)
The opposite enantiomer \((R)-(+)-Gossonorol\) was obtained by switching the ligand to \((R,R)-L1\).

**(R)-(+)-Gossonorol**

Colourless oil, 64% yield, 93% ee

HPLC analysis on chiral stationary phase: Column Chiralpak IA, Heptane/EtOH 97:3, flow 1 mL/min, 210 nm, 21 °C, \(t_m=9.7\) min \(t_m=14.6\) min; \([\alpha]_D^{20}: +15.1 \text{ (c. 1.3, CHCl}_3\); Lit.: \([\alpha]_D^{20}: +15.0 \text{ (c. 1.0, CHCl}_3\)

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The opposite enantiomer \((R)-(+)-Gossonorol\) was obtained by switching the ligand to \((R,R)-L1\).

**(R)-(+)-Gossonorol**

Colourless oil, 64% yield, 93% ee

HPLC analysis on chiral stationary phase: Column Chiralpak IA, Heptane/EtOH 97:3, flow 1 mL/min, 210 nm, 21 °C, \(t_m=9.7\) min \(t_m=14.6\) min; \([\alpha]_D^{20}: +15.1 \text{ (c. 1.3, CHCl}_3\); Lit.: \([\alpha]_D^{20}: +15.0 \text{ (c. 1.0, CHCl}_3\)

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Carbamate Derivative for X-Ray analysis

**Preparation of (R)-6-chloro-2-phenylhexan-2-yl (4-bromophenyl)carbamate 8**

In a 15 mL flame-dried J Young flask, under nitrogen, tin(II) 2-ethylhexanoate (57 mg, 0.141 mmol) was dissolved in dry benzene (1 mL). To the solution was added 6-chloro-1,3-diphenylhexan-3-ol 5aa (30 mg, 0.141 mmol, 95% ee) followed by 4-bromophenyl isocyanate (28 mg, 0.141 mmol). The reaction mixture was stirred at 70 °C for 1 hour and then diluted with H₂O (2 mL) and Et₂O (1 mL). The phases were separated and the aqueous phase extracted with Et₂O (2 x 5 mL). The combined organic layers were washed with NaHCO₃ sat. (2 x 5 mL), H₂O (5 mL) and brine (5 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/EtOAc 95:5 to obtain the pure carbamate 8. Recrystallization from MeOH delivered suitable crystals for X-Ray analysis.

White solid, 72% yield, 96% ee

HPLC analysis on chiral stationary phase: Column (S,S)-Whelk-O 1, Heptane/EtOH 97:3, flow 1 mL/min, 254 nm, 21 °C, tₘᵣᵣᵣ= 18.3 min, tᵣᵣᵣᵣ= 22.2 min

¹H-NMR (400 MHz, CDCl₃): δ 7.38-7.35 (m, 6H), 7.29-7.23 (m, 3H), 6.69 (br s, 1H), 3.51-3.48 (m, 2H), 2.07-2.03 (m, 2H), 1.92 (s, 3H), 1.77-1.70 (m, 2H), 1.46-1.37 (m, 2H)

¹³C-NMR (100.6 MHz, CDCl₃): δ 151.8, 144.8, 137.3, 132.0, 128.5, 127.3, 124.6, 120.2, 115.8, 84.4, 44.9, 42.2, 32.7, 25.1, 21.4

HRMS: (ESI) Calculated for C₁₉H₂₁NO₂NaBrCl 432.0342 ([M+Na⁺]; found 432.0341

[α]ᵢ₀³ – 6.5 (c. 0.2, CHCl₃)
Preparation of (S)-γ-ethyl-γ-phenylbutyrolactone 9

(S)-γ-Ethyl-γ-phenylbutyrolactone 9 was prepared by oxidation of compound (S)-6ab, following the procedure reported by Capriati and co-workers.9

(S)-γ-Ethyl-γ-phenylbutyrolactone 9
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 95:5, flow 1 mL/min, 210 nm, 21 °C, $t_m=18.2$ min, $t_M=20.3$ min

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.39-7.27 (m, 5H), 2.65-2.53 (m, 1H), 2.51-2.41 (m, 3H), 2.00 (q, $J = 7.4$ Hz, 2H), 0.82 (t, $J = 7.4$ Hz, 3H)

$^{13}$C-NMR (100.6 MHz, CDCl$_3$): $\delta$ 176.8, 142.8, 128.6, 127.6, 124.9, 90.0, 35.4, 34.7, 28.9, 8.4

$[\alpha]_D^{20} = -62$ (c. 0.4 in CCl$_4$); Lit. (for (S)-11): $[\alpha]_D^{23} = -70$ (c. 0.56, CCl$_4$)

Analytical data were in accordance with previously reported results. $^9$

<table>
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<td>[min]</td>
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Totals: 2.06189e4 598.65419

Preparation of (S)-(-)-Boivinianin A

Preparation of (S)-2-methyl-2-(p-tolyl)tetrahydrofuran  10
(S)-2-methyl-2-(p-toly)tetrahydrofuran 10 was prepared in two steps from 4-chloro-1-(4-methylphenyl)-1-oxobutane 11 following the procedures described above for chiral non-racemic tertiary alcohols. The intermediate tertiary alcohol (S)-5-chloro-2-(p-toly)pentan-2-ol 11a was used immediately in the following cyclization (using Method A) due to racemization on standing.

(S)-5-chloro-2-(p-toly)pentan-2-ol 11a

Colourless oil, 50% yield, 96% ee (the rest of the material was remaining starting ketone 11 recovered)

HPLC analysis on chiral stationary phase: Column Chiralpak IA, Heptane/EtOH 95:5, flow 1 mL/min, 254 nm, 21 °C, t_M = 11.1 min, t_M' = 15.2 min

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.32-7.30 (m, 2H), 7.17-7.15 (m, 2H), 3.52-3.44 (m, 2H), 2.34 (s, 3H), 1.99-1.87 (m, 2H), 1.84-1.73 (m, 1H), 1.69-1.60 (m, 2H), 1.57 (s, 3H)

$^{13}$C-NMR (100.6 MHz, CDCl$_3$): δ 144.5, 136.5, 129.1, 124.8, 74.4, 45.6, 41.5, 30.8, 27.6, 21.1

$[\alpha]_{D}^{20}$: -8.3 (c. 1.0, CHCl$_3$)

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<th>Type</th>
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<th>Area [mAU*s]</th>
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<td>71.15291</td>
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</tbody>
</table>
(S)-2-methyl-2-(p-tolyl)tetrahydrofuran  

\[
\begin{align*}
&\text{Colourless oil, 88% yield, 96% ee} \\
&\text{HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 90:10, flow 1 mL/min, 254 nm, 21 °C,} \\
&t_m= 5.7 \text{ min, } t_M= 7.5 \text{ min} \\
&^1H-NMR (400 MHz, CDCl}_3): \delta 7.30-7.28 (m, 2H), 7.15-7.13 (m, 2H), 4.03-3.98 (m, 1H), 3.93-3.88 (m, 1H), 2.34 (s, 3H), \\
&2.23-2.16 (m, 1H), 2.03-1.92 (m, 2H), 1.87-1.75 (m, 1H), 1.52 (s, 3H) \\
&^{13}C-NMR (100.6 MHz, CDCl}_3): \delta 145.3, 136.0, 128.9, 124.8, 84.3, 67.6, 39.6, 29.9, 25.9, 21.1 \\
&[\alpha]_D^{19}: +7.8 (c. 0.4, CHCl}_3); \text{Lit.: } [\alpha]_D^{19}: +6.5 (c. 0.28, CH}_2Cl}_2)
\end{align*}
\]

Analytical data were in accordance with literature reported results. 

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<th>Peak</th>
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<th>Type</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
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Totals: 854.05178 78.90498
Oxidation of compound 10 to (S)-(-)-Boivinianin A

The oxidation of (S)-2-methyl-2-(p-tolyl)tetrahydrofuran 10 was performed applying the conditions reported by Sharpless and co-workers using RuO$_2$/NaIO$_4$ in CCl$_4$/H$_2$O/MeCN.$^{11}$

(S)-(-)-Boivinianin A

Colourless oil, 39% yield, 96% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 85:15, flow 0.5 mL/min, 254 nm, 21 °C, $t_m$= 17.4 min, $t_M$= 21.3 min

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.27-7.25 (m, 2H), 7.19-7.17 (m, 2H), 2.66-2.58 (m, 1H), 2.54-2.44 (m, 2H), 2.43-2.36 (m, 1H), 2.35 (s, 3H), 1.71 (s, 3H)

$^{13}$C-NMR (100.6 MHz, CDCl$_3$): δ 176.7, 141.5, 137.5, 129.4, 124.2, 87.2, 36.4, 29.6, 29.2, 21.1

$[^{25}]$$\alpha$D: -38.0 (c. 0.25, CHCl$_3$); Lit.: $[^{25}]$$\alpha$D: -40 (c. 0.25, CHCl$_3$)$^6$

Analytical data were in accordance with previously reported results.$^6$
(S)-2-methyl-2-(p-tolyl)tetrahydro-2H-pyran 14 was prepared in two steps from 5-chloro-1-(p-tolyl)-1-oxopentane 13 following the procedures described above for chiral non-racemic tertiary alcohols and cyclisation (Method B). The intermediate tertiary alcohol (S)-6-chloro-2-(p-tolyl)hexan-2-ol 13a was used immediately in the cyclization due to racemization on standing.

(S)-6-chloro-2-(p-tolyl)hexan-2-ol 13a

Colourless oil, 61% yield, 94% ee

HPLC analysis on chiral stationary phase: Column Chiralpak IC, Heptane/EtOH 99.5:0.5, flow 1 mL/min, 210 nm, 21 °C, $t_m$ = 17.3 min, $t_M$ = 17.9 min

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.32-7.30 (m, 2H), 7.17-7.15 (m, 2H), 3.47 (t, $J$ = 6.8 Hz, 2H), 2.34 (s, 3H), 1.86-1.68 (m, 5H), 1.56 (s, 3H), 1.46-1.26 (m, 2H)

$^{13}$C-NMR (100.6 MHz, CDCl$_3$): δ 144.9, 136.3, 129.0, 124.8, 74.6, 45.0, 43.5, 33.0, 30.3, 21.7, 21.1
(S)-2-methyl-2-(p-tolyl)tetrahydro-2H-pyran 14

Colourless oil, 83% yield, 94% ee

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.5:0.5, flow 0.5 mL/min, 210 nm, 21 °C, t_M= 19.6 min, t_m= 20.7 min

^1^H-NMR (400 MHz, CDCl₃): δ 7.31-7.29 (m, 2H), 7.19-7.17 (m, 2H), 3.74-3.69 (m, 1H), 3.52-3.45 (m, 1H), 2.35 (s, 3H), 2.32-2.27 (m, 1H), 1.76-1.39 (m, 5H), 1.37 (s, 3H)

^13^C-NMR (100.6 MHz, CDCl₃): δ 142.4, 136.1, 129.3, 126.1, 76.0, 62.9, 34.7, 33.1, 26.1, 21.1, 20.3

HRMS: (EI, 35 eV) Calculated for C₁₃H₁₈O 190.1358 ([M]⁺); found 190.1349

[α]D'^20^ +97.7 (c. 1.0, Acetone)
Oxidation of compound 14 to (S)-(-)-6-methyl-6-(p-tolyl)tetrahydro-2H-pyran-2-one 12

Various oxidation methods were tested for the preparation of compound 12 (Table 3). The RuO2/NaIO4 system in this case was not effective leading to degradation to mixtures of unidentified products. Methyltrioxorhenium/hydrogen peroxide12 as well as sodium bromate/potassium hydrogen sulfate13 showed no reactivity, with recovery of unreacted 14. On the other hand, oxidation with iron (III) chloride/potassium permanganate14 delivered the desired lactone 12.

**Table 3** Screening of conditions for the oxidation of tetrahydropyran 14 to lactone 12.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidative system (equiv.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield 12 (%)</th>
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<tbody>
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<td>RuO2 (0.03) NaIO4 (5.0)</td>
<td>CCl4/H2O</td>
<td>r.t.</td>
<td>18</td>
<td>-e</td>
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<tr>
<td>2</td>
<td>RuO2 (0.03) NaIO4 (5.0)</td>
<td>CCl4/H2O/MeCN</td>
<td>r.t.</td>
<td>18</td>
<td>-e</td>
</tr>
<tr>
<td>3</td>
<td>RuO2 (0.15) NaIO4 (5.0)</td>
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<td>r.t.</td>
<td>6</td>
<td>-e</td>
</tr>
<tr>
<td>4</td>
<td>MeReO3 (0.03) H2O2 (3.0)</td>
<td>MeOH</td>
<td>r.t.</td>
<td>24</td>
<td>-d</td>
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<tr>
<td>5</td>
<td>NaBrO3 (1.0) NaHSO4 (1.0)</td>
<td>Et2O/H2O</td>
<td>r.t.</td>
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<td>-d</td>
</tr>
<tr>
<td>6</td>
<td>FeCl3 (1.0) KMnO4 (3.0)</td>
<td>Acetone</td>
<td>-78 to r.t.</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>FeCl3 (3.0) KMnO4 (6.0)</td>
<td>Acetone</td>
<td>-78 to r.t.</td>
<td>18</td>
<td>49</td>
</tr>
</tbody>
</table>

Reactions were run on 0.2 mmol scale. Isolated yields. Degradation of compound 14. Recovery of compound 14.

**Procedure:**

A solution of (S)-2-methyl-2-(p-tolyl)tetrahydro-2H-pyran 14 (38 mg, 0.2 mmol, 94% ee) in acetone (2 mL) was cooled to -78 °C and KMnO4 (190 mg, 1.2 mmol) and FeCl3 (97 mg, 0.6 mmol) were added. The temperature was slowly raised
to r.t. over 2 hours and the mixture was stirred at r.t. for 18 hours. The mixture was then diluted with DCM 15 mL and H$_2$O (5 mL), the phases were separated and the aqueous phase extracted with DCM (5 x 15 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel eluting with pentane/EtOAc 80:20 to obtain compound 12 (49% yield, 91% ee)

$\text{(S)-(-)-6-methyl-6-(p-tolyl)tetrahydro-2H-pyran-2-one ~12}$

White solid, 49% yield, 91% ee

HPLC analysis on chiral stationary phase: Column Chiralpak AS-H, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, t$_{m}$= 27.5 min, t$_{M}$= 38.8 min

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.23-7.16 (m, 4H), 2.52-2.37 (m, 2H), 2.34 (s, 3H), 2.33-2.27 (m, 1H), 2.02-1.94 (m, 1H), 1.83-1.74 (m, 1H), 1.66 (s, 3H), 1.64-1.58 (m, 1H)

$^{13}$C-NMR (100.6 MHz, CDCl$_3$): $\delta$ 171.8, 141.7, 137.2, 129.5, 124.5, 85.5, 34.4, 31.6, 29.2, 21.1, 16.7

$[\alpha]_D^{20}$ : -32.5 (c. 0.2, MeOH); Lit: $[\alpha]_D^{20}$ : -38.0 (c. 0.17, MeOH)$^{15}$

Analytical data were in accordance with literature reported results.$^{15}$
X-Ray analysis of compound 8

Crystal 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. Anisotropic thermal displacement parameters were used for all non-hydrogen atoms. Crystals were selected at low temperature.

Crystallographic data for compound 8 have been deposited with the Cambridge Crystallographic Data Centre [CCDC 1883098]
Crystallographic data

Table 4. Crystal data and structure refinement for compound 8.

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NMR spectra

4'-methoxy-4-chlorobutyrophenone 2c
5-chlorovalerophenone 3a
4'-bromo-5-chlorovalerophenone 3b
4'-methoxy-5-chlorovalerophenone 3c
5-chloro-2-phenylpentan-2-ol  4aa
(R)-6-chloro-3-phenylhexan-3-ol 4ab
1-chloro-6-methyl-4-phenylheptan-4-ol 4ac
6-chloro-1,3-diphenylhexan-3-ol  4ad
3-(4-bromophenyl)-6-chlorohexan-3-ol 4bb
6-chloro-3-(4-methoxyphenyl)hexan-3-ol 4cb
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7-chloro-3-phenylheptan-3-ol 5ab
8-chloro-2-methyl-4-phenyloctan-4-ol 5ac
7-chloro-1,3-diphenylheptan-3-ol 5ad
3-(4-bromophenyl)-7-chloroheptan-3-ol 5bb
7-chloro-3-(4-methoxyphenyl)heptan-3-ol 5cb

![Chemical Structure of 7-chloro-3-(4-methoxyphenyl)heptan-3-ol 5cb](image-url)
(R)-2-methyl-2-phenyltetrahydrofuran 6aa
(R)-2-ethyl-2-phenyltetrahydrofuran 6ab

6ab
2-isobutyl-2-phenyltetrahydrofuran  6ac
2-phenethyl-2-phenyltetrahydrofuran 6ad
2-ethyl-2-(4-bromophenyl)tetrahydrofuran 6bb
2-ethyl-2-(4-methoxyphenyl)tetrahydrofuran 6cb

MeO

6 cb
(R)-2-methyl-2-phenyltetrahydro-2H-pyran 7aa
2-ethyl-2-phenyltetrahydro-2H-pyran 7ab
2-isobutyl-2-phenyltetrahydro-2H-pyran 7ac
2-phenethyl-2-phenyltetrahydro-2H-pyran  7ad
2-ethyl-2-(4-bromophenyl)tetrahydro-2H-pyran  7bb
2-ethyl-2-(4-methoxyphenyl)tetrahydro-2H-pyran 7cb
3-phenylhexan-3-ol
3-Phenylheptan-3-ol
5-methyl-1-(4-methylphenyl)-1-oxo-hex-4-ene 1
(S)-(-)-Gossonorol
(R)-6-chloro-2-phenylhexan-2-yl (4-bromophenyl)carbamate 8
(S)-\textit{\textgamma}-ethyl-\textit{\textgamma}-phenylbutyrolactone 9
(S)-5-chloro-2-(p-tolyl)pentan-2-ol  11a
(S)-2-methyl-2-(p-tolyl)tetrahydrofuran

10

[Chemical Structure Image]

[Chemical Spectra Image]
(S)-(-)-Boivinianin A
(S)-6-chloro-2-(p-tolyl)hexan-2-ol 13a
(S)-2-methyl-2-(p-tolyl)tetrahydro-2H-pyran  14
(S)-6-methyl-6-(p-tolyl)tetrahydro-2H-pyran-2-one 12
References