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Tandem Metal- and Organocatalysis in Sequential Hydroformylation and Enantioselective Aldol Reactions

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Abstract: Metal-catalysed hydroformylation is successfully combined with organocatalysed stereoselective aldol addition into a tandem reaction sequence. This novel type of "tandem catalysis" allows access to complex molecular systems with high levels of enantioselectivity, using simple starting materials and an amino acid as the chiral catalyst.

Keywords: aldol reaction; hydroformylation; organocatalysis; tandem catalysis

Introduction

Control of stereochemistry during aldol addition reactions has attracted considerable interest over the last decades, as the aldol reaction is one of the most powerful and versatile methods in modern carbonyl chemistry.[1] Simple chiral organic molecules have been found to catalyse the direct aldol addition of unmodified ketones to aldehydes with high chemical and stereochemical efficiency.[2] On the other hand, hydroformylation of olefins, one of the largest industrially applied homogeneously catalysed processes, provides the synthetically useful aldehyde function for further transformations, e.g., aldol addition. Following a general trend in organic chemistry to combine several individual reaction steps to a single synthetic procedure,[3] we have developed hydroformylation/aldol reaction sequences[4] and here now report an enantioselective version with chiral organocatalysts.

Results and Discussion

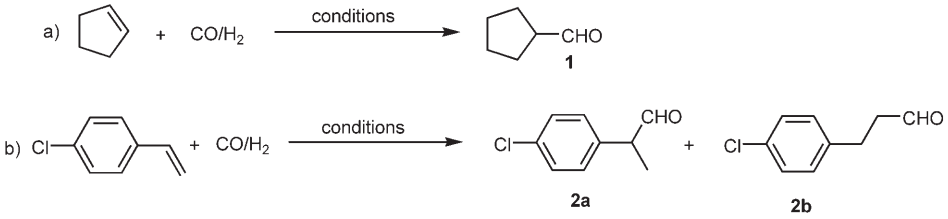
The conversion of cyclopentene and acetone to an aldol product under hydroformylation conditions in the presence of Rh catalyst and L-proline was selected as a first model reaction in order to avoid the regioselectivity problems of hydroformylation and aldol reactions. As an additional advantage the hydroformylation of this alkene can be performed under mild conditions.[5] The active catalyst for the hydroformylation was prepared *in situ* from $[Rh(acac)(CO)_2]$ and an excess of phosphorus ligand. L-Proline was employed as the organocatalyst since, according to previous investigations,[6] it exhibits excellent catalytic activity in enantioselective aldol reactions. Based on earlier findings that high pressure efficiently promotes L-proline-catalysed asymmetric aldol reactions in low-boiling solvents,[7] acetone was chosen both as a ketone component and a solvent.

In control experiments possible negative interactions between Rh catalyst and organocatalyst were tested in he hydroformylation of cyclopentene and 4-chlorostyrene in the presence of L-proline (Table 1).

As shown in Table 1, hydroformylation of olefins with triphenyl phosphite-modified rhodium catalyst both in the presence and in the absence of L-proline takes place with excellent conversions and yields (> 99%), no self-aldolisation of the aldehydes **1** and **2a, b** is observed (Table 1, entries 3, 4, 7 and 8). The unmodified Rh catalyst under the same conditions gives full conversion of cyclopentene but incomplete conversion of 4-chlorostyrene (Table 1, entries 1, 2, 5, and 6). According to GC and ^{1}H NMR analyses of crude mixtures during the hydroformylation reaction only aldehydes are formed. Under the conditions given in Table 1, aldehyde **2a** is generated with excellent regioselectivities (up to 99:1 branched/linear ratio), but shows no optical activity, thus L-proline does not influence the stereochemistry of the hydroformylation step.

Next we investigated whether rhodium catalysts are compatible with organocatalysed enantioselective aldol reactions, and performed test aldol reactions with preformed aldehyde **1** both under atmospheric

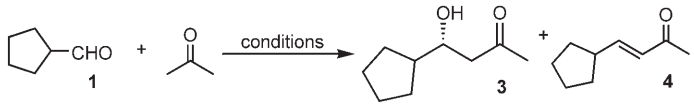
Table 1. Hydroformylation reactions both in the presence and in the absence of L-proline.



Entry	Conditions[a]	Substrate	Conversion [%][b]	Aldehyde yield [%][b]	b:l ratio[b]
1	$Rh(acac)(CO)_2$, acetone	cyclopentene	>99	>99	-
2	$Rh(acac)(CO)_2$, acetone	4-chlorostyrene	49	49	97:3
3	$Rh(acac)(CO)_2$, $P(OPh)_3$, acetone	cyclopentene	>99	>99	-
4	$Rh(acac)(CO)_2$, $P(OPh)_3$, acetone	4-chlorostyrene	>99	>99	98:2
5	$Rh(acac)(CO)_2$, L-proline, CH_2Cl_2	cyclopentene	>99	>99	-
6	$Rh(acac)(CO)_2$, L-proline, CH_2Cl_2	4-chlorostyrene	75	75	97:3
7	$Rh(acac)(CO)_2$, $P(OPh)_3$, L-proline, CH_2Cl_2	cyclopentene	>99	>99	-
8	$Rh(acac)(CO)_2$, $P(OPh)_3$, L-proline, CH_2Cl_2	4-chlorostyrene	>99	>99	99:1

[a] 20/20 bar CO/H_2, 40 °C, 72 h.
[b] Determined by GC using an internal standard.

Table 2. Aldol reactions in the presence of Rh catalysts both under atmospheric pressure and under hydroformylation conditions.



Entry	Conditions[a]	Temperature [°C]	Time [h]	Aldehyde conversion (%)[b]	Yield [%][c] **3**	**4**	*ee* [%][d] of **3**
1	L-proline, acetone	25	24	87	30	5	80
2	$Rh(acac)(CO)_2$, L-proline, acetone	25	24	93	27	3	71
3	$Rh(acac)(CO)_2$, $P(OPh)_3$, L-proline, acetone	25	24	88	38	12	78
4	20/20 bar CO/H_2, $Rh(acac)(CO)_2$, $P(OPh)_3$, L-proline, acetone	25	24	41	19	<1	81
5	20/20 bar CO/H_2, $Rh(acac)(CO)_2$, $P(OPh)_3$, L-proline, acetone	40	24	88	62	<1	81
6	20/20 bar CO/H_2, $Rh(acac)(CO)_2$, $P(OPh)_3$, L-proline, acetone	40	48	96	65	<1	79
7	20/20 bar CO/H_2, $Rh(acac)(CO)_2$, $P(OPh)_3$, L-proline, acetone	40	72	97	63	<1	78

[a] 20/20 bar CO/H_2, 40 °C, 72 h.
[b] Based on isolated unreacted aldehyde.
[c] Based on isolated product.
[d] Determined by chiral HPLC.

pressure and under hydroformylation conditions (Table 2). For the determination of results direct GC analysis was impossible. After injection of a crude reaction mixture aldol product **3** partially self-decomposed with generation of aldehyde **1**, therefore determination of the aldehyde conversion was based on isolated unreacted aldehyde.

As shown in Table 2, under atmospheric pressure at room temperature the presence of rhodium complexes only marginally affects the conversion of aldehyde **1** (Table 2, entries 2 and 3). In contrast, at room temperature under hydroformylation conditions, a decrease of aldehyde conversion and suppression of the elimination to product **4** are observed (Table 2, entry 4). Under hydroformylation conditions at 40 °C aldehyde **1** is almost fully converted to aldol product **3** within 48 h (Table 2, entry 6). Enantioselectivity is not affected by the pressure and presence of rhodium

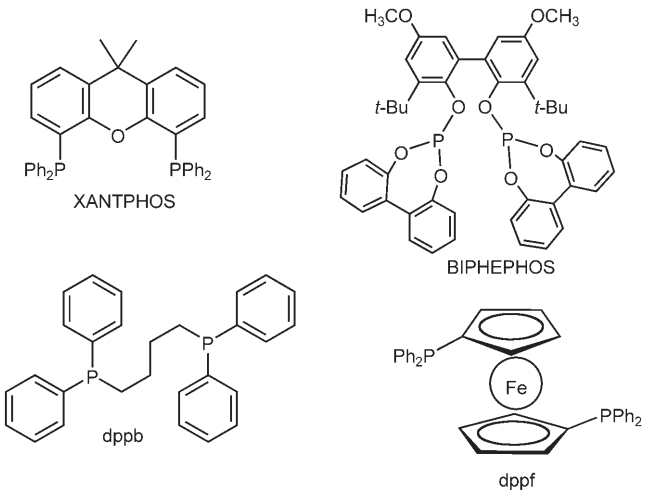


Figure 1. Phosphorus ligands tested.

catalysts. The absolute stereochemistry of the β-hydroxy group of the aldol adduct **3** being (*R*) was determined by Mosher's method.[8]

For effective tandem catalysis a range of phosphorus ligands (Figure 1) was tested for sequential hydroformylation and enantioselective aldol reactions of cyclopentene and acetone. The results are summarised in Table 3.

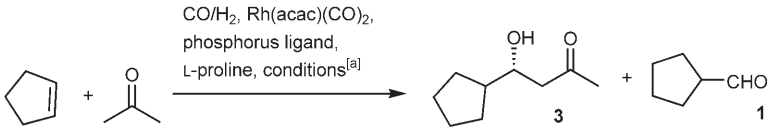
Surprisingly, the catalytic system with unmodified rhodium catalyst gave no conversion of the olefin (Table 3, entry 1). The steric and electronic properties of ligands drastically influence the rate of the hydroformylation reaction sequence. Rh catalyst modified with non-bulky PPh_3 ligand gave good conversion (89%) of the olefin after three days of reaction (Table 3, entry 2). Diphosphine ligands lowered the activity of the corresponding Rh catalysts. As a result the olefin is not converted with XANTPHOS, and poor conversion is observed with dppb and dppf ligands under the given conditions (*vide supra*), although good stereoselectivities (65–72% *ee*) of the aldol product **3** were obtained (Table 3, entries 3, 4 and 5).

Triphenyl phosphite and BIPHEPHOS show a significant advantage over all other phosphorus ligands tested. After 72 h the olefin is fully converted under hydroformylation conditions and the aldol product **3** is formed with good enantioselectivities (Table 3, entries 6 and 7). Usually phosphites give more active catalysts than phosphines. This is mainly based on electronic factors. The phosphite ligands as a stronger electron π-acceptor induce faster replacement of a carbonyl ligand by the alkene substrate, resulting in higher reaction rates.[5a,9]

As hydroformylation and aldol reactions are extremely sensitive to the reaction conditions, various CO and H_2 partial pressures were studied to ascertain pressure effects on tandem hydroformylation/enantioselective aldol reactions. The reactions of cyclopentene and acetone were performed at 10/10, 20/20, 30/30, 40/40 and 70/10 bar pressures of CO/H_2 (Table 4).

Reactions at 10/10, 20/20, 30/30 and 40/40 bar gas pressures provided medium to good yields (48–76%) of the desired compound **3** (Table 4, entries 1, 2, 3 and 4). In contrast with **6a, b** (*vide infra*), at 70/10 bar CO/H_2, a drastic decrease in yields of the aldol product **3** (23%) was observed. Noteworthy, varying the total pressure from 20 to 80 bar has only small effects on the enantioselectivities (73–81% *ee*).

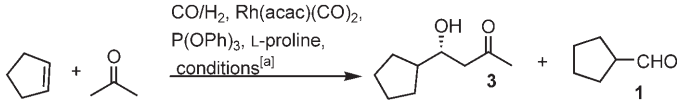
Table 3. Phosphorus ligand screening for the sequential hydroformylation/enantioselective aldol reactions.



Entry	Ligand	Reaction time [h]	Alkene conversion [%][b]	Isolated yield [%][c] **3**	**1**	*ee* (%)[d] of **3**
1	none	72	none	-	-	-
2	PPh_3	72	89	46	8	74
3	XANTPHOS	72	none	-	-	-
4	dppb	72	10	3	nd	65
5	dppf	72	17	7	3	72
6	BIPHEPHOS	72	>99	72	7	82
7	$P(OPh)_3$	72	>99	76	6	75
8	$P(OPh)_3$	48	95	70	8	81
9	$P(OPh)_3$	24	54	18	15	80

[a] 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% phosphorus ligand, 30 mol% L-proline, 20/20 bar CO/H_2, 40 °C, acetone.
[b] Determined by GC using an internal standard.
[c] Based on isolated product.
[d] Determined by chiral HPLC; nd = not determined.

Table 4. Influence of CO and H_2 partial pressures on sequential hydroformylation/enantioselective aldol reactions.



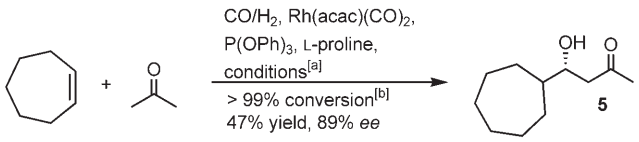
Entry	P_{CO} [bar]	P_{H_2} [bar]	Alkene conversion [%][b]	Isolated yield [%] **3**	**1**	*ee* [%][c] of **3**
1	10	10	>99	51	8	74
2	20	20	>99	76	6	75
3	30	30	>99	70	9	73
4	40	40	>99	48	3	81
5	70	10	>99	23	5	78

[a] 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40 °C, 72 h, acetone.
[b] Determined by GC using an internal standard.
[c] Determined by chiral HPLC.

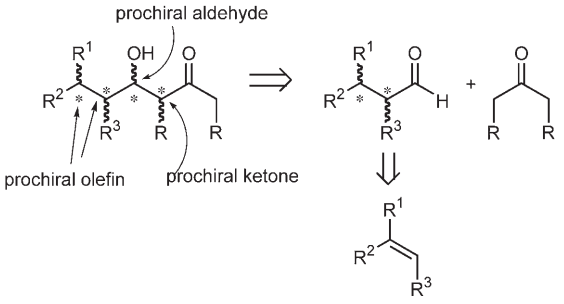
Using similar conditions cycloheptene on conversion by sequential hydroformylation and enantioselective aldol reactions, gives the aldol product **5** in 47% yield with 89% *ee* (Scheme 1). The absolute configuration of compound **5** was assigned by analogy with compound **3**.

Up to now, olefins and ketones explored in the sequential hydroformylation and enantioselective aldol reactions were not prochiral. For further studies prochiral olefins and/or prochiral ketones were considered since additional stereogenic centres are formed (Scheme 2).

At first, for the reaction between prochiral 4-chlorostyrene and acetone, pressure experiments were performed using 40 and 80 bar total gas pressures (Table 5). The absolute stereochemistry of the β-hydroxy group of the aldol adduct **6a** was determined by Mosher's method.[8] The relative configurations of compunds **6a, b** were assigned by analogy with the known racemic compounds **7a, b**[10] (*vide infra*).



Scheme 1. Sequential hydroformylation/enantioselective aldol reactions of cycloheptene and acetone. [a] 20/20 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40 °C, 72 h, acetone. [b] Determined by GC using an internal standard.



Scheme 2. Origin of stereogenic centres in sequential hydroformylation/enantioselective aldol reactions.

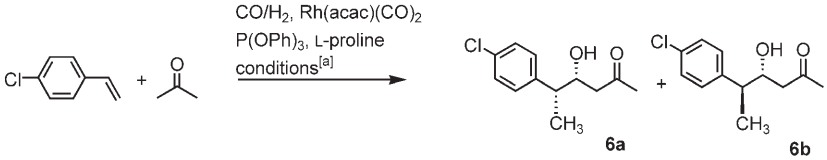
As shown in Table 5, here, no significant influence of pressure on yields, enantio- and diastereoselectivities was observed. The two major stereoisomers obtained have the same configuration at the carbon bonded to the hydroxy group and opposite configurations at the carbons bearing the methyl group. Here diastereoselectivities are not expected to be high since the hydroformylation step gives a racemate even in the presence of L-proline (see Table 1, entries 6 and 8), whereas the organocatalyst stereoselectively catalyses the aldol step towards the same configuration at the β-hydroxy group of both diastereoisomers.

Despite the findings that the best enantioselectivities were obtained at 80 bar total pressure, 20/20 bar CO/H_2 was selected as the milder reaction conditions for all further studies with styrene and 2,5-dihydrofuran as prochiral olefins, and cyclopentanone as a prochiral ketone (Table 6).

Styrene, as another prochiral olefin, gave identical results as compared to 4-chlorostyrene. In the reaction of prochiral 2,5-dihydrofuran acetone enantioselectivities of 71% were observed, but no diastereoselectivity. On the other hand, with non-prochiral cyclic alkenes and prochiral cyclopentanone very good yields and enantioselectivities, but again only low diastereoselectivities were obtained (Table 6, entries 3 and 4).

In order to determine the relative and absolute configurations of compounds **9a, b** and **10a, b** a control room temperature experiment was performed with cyclohexanecarbaldehyde and cyclopentanone in the presence of L-proline. (Scheme 3). The assignment

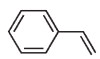
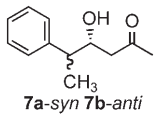
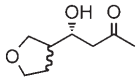
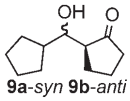
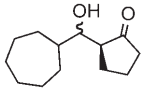
Table 5. Influence of CO and H_2 partial pressures on sequential hydroformylation/enantioselective aldol reactions.



Entry	P_{CO} [bar]	P_{H_2} [bar]	Alkene conversion [%][b]	Yield [%][c] **6a+6b**	*dr*[d] (*syn:anti*)	*ee* [%][e] **6a**	**6b**
1	20	20	>99	89	1.5 : 1	72	>99
2	40	40	>99	85	1.5 : 1	76	>99
3	70	10	>99	89	1.5 : 1	77	>99

[a] 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40 °C, 72 h, acetone.
[b] Determined by GC using an internal standard.
[c] Based on isolated product.
[d] Determined by ^1H NMR analyses.
[e] Determined by chiral HPLC.

Table 6. Sequential hydroformylation/enantioselective aldol reactions of alkenes with $P(OPh)_3$ modified rhodium catalyst.[a]

Entry	Substrate	Ketone = solvent	Product	Olefin conversion [%][b]	Yield [%][c]	*syn:anti*[d]	*ee* [%][e]
1			 **7a**-*syn* **7b**-*anti*	>99	83	1.5 : 1	72 (for *syn*); >99 (for *anti*)
2			 **8a**-*syn* **8b**-*anti*	>99	71	1 : 1	71 (for *syn*); 71 (for *anti*)
3			 **9a**-*syn* **9b**-*anti*	>99	59	1 : 2.7	95[f] (for *syn*); 96 (for *anti*)
4			 **10a**-*syn* **10b**-*anti*	>99	76	1 : 1.9	83 (for *syn*); 85 (for *anti*)

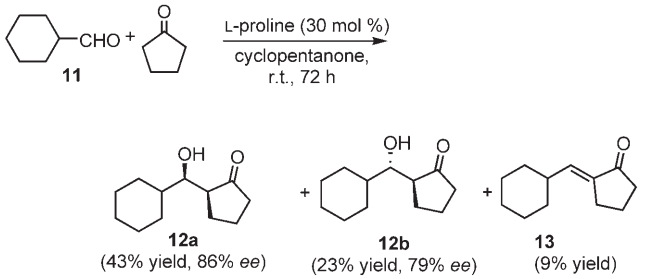
[a] 0.5 mol% $Rh(acac)(CO)_2$, 20/20 bar CO/H_2, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40 °C, 72 h.
[b] Determined by GC using an internal standard.
[c] Based on isolated product.
[d] Determined by ^1H NMR analyses.
[e] Determined by chiral HPLC.
[f] Determined by Mosher's method.

was based on the comparison of spectral data known for racemic compounds **12a, b**[11] and the results obtained in the reaction of cyclohexanone with benzaldehyde.[12]

In all cases the absolute configuration at the β-hydroxy group is not identical for the *syn/anti* diastereomers (Table 6, entries 3 and 4, and Scheme 3). Noteworthy, with cyclohexanecarbaldehyde (Scheme 3) the *syn:anti* ratio is reversed as compared to the tandem reactions with cyclic olefins and cyclopentanone described above (Table 6, entries 3 and 4). This shows a surprising sensitivity of the diastereoselectivity towards substrate structure and reaction conditions. Thus, for further investigations of *syn:anti* diastereoselectivities various parameters have to be explored.

Conclusions

In conclusion, we successfully combined a metal-catalysed (hydroformylation) reaction with an organocatalysed (stereoselective aldol) reaction in a tandem re-



Scheme 3. L-Proline-catalysed asymmetric aldol reaction of cyclohexanecarbaldehyde and cyclopentanone

action sequence. It could be demonstrated that organocatalysis of aldol reactions even under hydroformylation conditions occur with high enantioselectivities, although the usually observed[11] diastereoselectivities are still to be optimised. This novel type of "tandem catalysis"[13] is expected to be applicable to a variety of olefins and ketones, affording complex molecular systems with high levels of enantioselectivity, using simple starting materials and an amino acid as the chiral catalyst. We are currently investigating a combination of enantioselective hydroformylation and enantioselective aldol reactions in a tandem reaction sequence, with more complex starting materials, including combinations of both prochiral olefins and prochiral ketones.

Experimental Section

General Remarks

Hydroformylation experiments were carried out in a Berghof HR-200 high pressure reactor with magnetic stirring and electrical heating. The inside part of the cover was made from Teflon® to protect the solution from direct contact with the stainless steel. All reactions were carried out in freshly distilled solvents. Dichloromethane and triethylamine were distilled from calcium hydride. All phosphorus ligands, except BIPHEPHOS, are commercially available. BIPHEPHOS was synthesised according to the literature procedure.[14] Commercial reagents were used as received. Organic solutions were concentrated under reduced pressure on a rotary evaporator. Column chromatography was carried out using MN Kieselgel 60 (0.063–0.2 mm/70–230 mesh). TLC was performed on Merck Silica gel 60 F_{254} plates. Visualisation of the developed chromatograms was performed by ultraviolet irradiation (254 nm) or by anisaldehyde stain. Melting points were performed on a Büchi® melting point apparatus, and are uncorrected. For gas chromatographic analyses, a Carlo Erba HRGC Mega2 Series MFC 800 chromatograph with a Carlo Erba EL 580 flame-ionisation detector (FID) was used. Separations were performed on the column CHROMPACK DB-1701 (25 m × 0.32 mm × 1.0 μm). ^{1}H NMR spectra were recorded on Bruker 400 and Bruker 500 spectrometers, with residual proton signal of the deuterated solvent as the internal reference ($\delta_H = 7.26$ ppm for $CDCl_3$ and $\delta_H = 7.15$ ppm for C_6D_6). ^{13}C NMR spectra were recorded on the same spectrometers and referenced to solvent signals ($\delta_C = 77$ ppm for $CDCl_3$ and $\delta_C = 128.02$ ppm for C_6D_6). Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). The proton spectra are reported as follows δ/ppm (multiplicity, number of protons, coupling constant *J*/Hz). DEPT135 and two dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used where appropriate, to aid the assignment of signals in the ^{1}H and ^{13}C NMR spectra. IR spectra were recorded on an Impact 400 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the University of Dortmund Mass Spectral facility. Elemental analyses were carried out in the Laboratory of Elemental Analyses at the University of Dortmund. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Semi-preparative HPLC was performed using a SUPELCOSIL™ LC-SI 5 μm (25 cm × 21.2 mm) column. Analytical HPLC was performed on a Hewlett–Packard 1050 Series chromatographs using a CHIRALCEL OD (250 × 4.6 mm), CHIRALCEL OJ (250 × 4.6 mm) and CHRALPAK AD (250 × 4.6 mm) columns as noted.

Hydroformylation Reactions in the Presence of L-Proline (Table 1, entries 7 and 8)

To a solution of $Rh(acac)(CO)_2$ (5 mg, 0.019 mmol, 0.005 equivs.) in 5 mL of CH_2Cl_2 in a vial, was added $P(OPh)_3$ (24 mg, 0.078 mmol, 0.02 equivs.). The solution was stirred with a magnetic stirrer for 5 min and then charged with olefin (3.9 mmol, 1 equiv.), dodecane (199 mg, 1.17 mmol, 0.3 equivs.) and L-proline (135 mg, 1.17 mmol, 0.3 equivs.). The vial was transferred to the autoclave, pressurised to 20/20 bar CO/H_2 and heated to 40 °C. After the reaction was completed, the autoclave was cooled down to room temperature, depressurised, flushed with argon and opened to obtain a sample for GC analysis. Cyclopentene products: carrier gas 40 kPa He, temperature program of 30 °C for 10 min, then 15 °C/min to 260 °C; retention times: 4.57 min for cyclopentene, 17.60 min for cyclopentanecarbaldehyde, 21.23 min for dodecane. 4-Chlorostyrene products: carrier gas 65 kPa He, temperature program of 35 °C for 10 min, then 10 °C/min to 260 °C; retention times: 21.63 min for 4-chlorostyrene, 22.27 min for dodecane, 26.47 min for aldehyde **2a** (branched regioisomer), 27.86 min for aldehyde **2b** (linear regioisomer).

Aldol Reaction in the Presence of Rh Catalyst under Atmospheric Pressure (Table 2, entry 3)

To a solution of $Rh(acac)(CO)_2$ (5 mg, 0.019 mmol, 0.005 equivs.) in 5 mL of acetone in a flask, was added $P(OPh)_3$ (24 mg, 0.076 mmol, 0.02 equivs.). The solution was stirred with a magnetic stirrer for 5 min and then charged with cyclopentanecarbaldehyde (373 mg, 3.8 mmol, 1 equiv.) and L-proline (131 mg, 1.14 mmol, 0.3 equivs.). The resulting mixture was stirred at room temperature for 24 h. Then, the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated under vacuum (compounds **1** and **4** are volatile, it is not recom-

mended to use pressure less than 200 mbar at 40 °C) and the crude product was purified by column chromatography (MTBE/cyclohexane, 1:4) to give unreacted cyclopentanecarbaldehyde (yield: 36 mg, 12 %), (*Z*)-4-cyclopentylbut-3-en-2-one **4** (R_f = 0.68) as a pale yellow oil (yield: 51 mg, 12 %) and (*R*)-4-cyclopentyl-4-hydroxybutan-2-one **3** (R_f = 0.34) as a pale yellow oil (yield: 178 mg, 38 %). HPLC: CHIRALPAK AD, *n*-heptane/*i*-PrOH, 98.2:1.8, 1.0 mL min^{-1}, 280 nm, *ee* = 78 %: t_R (major) = 19.0 min; t_R (minor) = 20.5 min.

Aldol Reaction in the Presence of Rh-catalyst under Hydroformylation Conditions (Table 2, entry 6)

To a solution of $Rh(acac)(CO)_2$ (5 mg, 0.019 mmol, 0.005 equivs.) in 5 mL of acetone in a vial, was added $P(OPh)_3$ (24 mg, 0.076 mmol, 0.02 equivs.). The solution was stirred with a magnetic stirrer for 5 min and then charged with cyclopentanecarbaldehyde (373 mg, 3.8 mmol, 1 equiv.) and L-proline (131 mg, 1.14 mmol, 0.3 equivs.). The vial was transferred to the autoclave, pressurised to 20/20 bar CO/H_2 and heated to 40 °C. After the reaction was completed, the autoclave was cooled down to room temperature, depressurised, flushed with argon and opened. The reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated under vacuum (compounds **1** and **4** are volatile, it is not recommended to use pressure less than 200 mbar at 40 °C) and the crude product was purified by column chromatography (MTBE/cyclohexane, 1:4) to give unreacted cyclopentanecarbaldehyde (yield: 12 mg, 4 %) and (*R*)-4-cyclopentyl-4-hydroxybutan-2-one **3** (R_f = 0.34) as a pale yellow oil (yield: 396 mg, 65 %). HPLC: CHIRALPAK AD, *n*-heptane/*i*-PrOH, 98.2:1.8, 1.0 mL min^{-1}, 280 nm, *ee* = 79 %: t_R (major) = 19.0 min; t_R (minor) = 20.5 min.

Sequential Hydroformylation and Enantioselective Aldol Reactions

To a solution of $Rh(acac)(CO)_2$ (5 mg, 0.019 mmol, 0.005 equivs.) in 5 mL of ketone in a vial, was added a phosphorus ligand (0.076 mmol, 0.02 equivs.). The solution was stirred with a magnetic stirrer for 5 min and then charged with alkene (3.8 mmol, 1 equiv.) and L-proline (131 mg, 1.14 mmol, 0.3 equivs.). The vial was transferred to the autoclave, pressurised and heated to 40 °C. After the reaction was completed, the autoclave was cooled down to room temperature, depressurised, flushed with argon and opened to obtained a sample for GC analysis. Then the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated under vacuum and the crude product was purified by column chromatography.

Preparation of MTPA Derivatives (Mosher's Method)

The reaction was carried out in a dry Schlenk tube fitted with a rubber septum. The reagents were injected *via* syringe into the tube in the following order: Et_3N (300 μL, 220 mg), DMAP (1 mg, 0.01 mmol), *S*-(+)-MTPA-Cl (MTPA = α-methoxy-α-trifluoromethylphenylacetic acid) (35 mg, 26 μL, 0.14 mmol), CH_2Cl_2 (300 μL) and the substrate aldol (0.10 mmol). After 24 h of stirring, the mixture was diluted with diethyl ether, washed (cold dilute HCl, cold saturated $NaHCO_3$ and brine), dried ($MgSO_4$) and concentrated under reduced pressure to afford a colourless oil, which was further purified by column chromatography.

L-Proline-Catalysed Asymmetric Aldol Reaction of Cyclohexanecarbaldehyde and Cyclopentanone (Scheme 3)

To a stirred suspension of L-proline (126 mg, 1 mmol, 0.3 equivs.) in 5 mL of cyclopentanone was added cyclohexanecarbaldehyde (300 mg, 3.65 mmol, 1 equiv.). The resulting mixture was stirred at room temperature for 72 h. Then, the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated under vacuum and the crude product was purified by column chromatography (EtOAc/cyclohexane, 1:4) to afford compounds **13**,[15] **12a**[15] and **12b**.

(*E*)-2-(Cyclohexylmethylene)cyclopentanone (13): R_f = 0.50 (yield: 43 mg, 9 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (td, 1H, *J* = 6.0, 2.5 Hz), 2.58 (dt, 2H, *J* = 7.2, 2.5 Hz), 2.30 (t, 2H, *J* = 7.8 Hz), 2.19–2.10 (m, 1H), 1.94–1.89 (m, 2H), 1.75–1.61 (m, 5H), 1.32–1.10 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8, 25.4, 25.7, 26.5, 31.6, 38.5, 38.7, 135.2, 140.9, 207.9, in accord with the literature data.[15]

(*S*)-2-[(*R*)-Cyclohexyl(hydroxy)methyl]cyclopentanone (12a): R_f = 0.31 (yield: 225 mg, 43 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.98 (br. s, 1H), 3.51 (dd, 1H, *J* = 9.0, 1.9 Hz), 2.40–1.10 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6, 25.0, 26.4, 26.6, 30.0, 38.4, 40.9, 51.3, 76.0, 224.9, in accord with the literature data.[15] ^{1}H NMR (400 MHz, C_6D_6): δ = 4.29 (br. s, 1H), 3.37 (dd, 1H, *J* = 9.1, 2.5 Hz), 1.88–0.80 (m, 18H); ^{13}C NMR (100 MHz, C_6D_6): δ = 20.5, 25.2, 26.3, 26.8, 26.9, 27.1, 30.5, 38.1, 41.3, 51.1, 76.1, 223.6; $[\alpha]_D^{20}$: −112.8 (*c* 1.00, *n*-heptane); HPLC: CHIRALPAK AD, *n*-heptane/*i*-PrOH, 95:5, 1.0 mL min^{-1}, 280 nm, *ee* = 86 %: t_R (major) = 11.1 min; t_R (minor) = 9.7 min.

(*S*)-2-[(*S*)-Cyclohexyl(hydroxy)methyl]cyclopentanone (12b): R_f = 0.13 (yield: 120 mg, 23 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79 (dd, 1H, *J* = 9.0, 2.4 Hz), 2.33–0.82 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6, 22.4, 25.7, 26.0, 26.2, 29.0, 29.5, 39.0, 41.2, 52.1, 73.9, 222.3; ^{1}H NMR (400 MHz, C_6D_6): δ = 3.80 (dd, 1H, *J* = 8.8, 1.8 Hz), 2.06–0.66 (m, 18H); ^{13}C NMR (100 MHz, C_6D_6): δ = 20.8, 22.6, 26.2, 26.4, 26.7, 29.3, 29.7, 38.9, 41.8, 52.0, 74.0, 220.2; $[\alpha]_D^{20}$: +115.5 (*c* 1.00, *n*-heptane); HPLC: CHIRALCEL OD-H, *n*-heptane/*i*-PrOH, 98:2, 1.0 mL min^{-1}, 280 nm, *ee* = 79 %: t_R (major) = 12.3 min; t_R (minor) = 9.6 min.

(*R*)-4-Cyclopentyl-4-hydroxybutan-2-one (3) (Table 4, entry 4): Purified using column chromatography (EtOAc/cyclohexane, 1:4) to afford the title compound as a colourless oil (yield: 293 mg, 48 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84–3.79 (m, 1H), 2.96 (d, 1H, *J* = 3.2 Hz), 2.64 (dd, 1H, *J* = 17.6, 2.0 Hz), 2.52 (dd, 1H, *J* = 17.6, 9.6 Hz), 2.17 (s, 3H), 1.90–1.75 (m, 2H), 1.67–1.49 (m, 5H), 1.42–1.34 (m, 1H), 1.19–1.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 25.6, 28.7, 28.9, 30.7, 45.2, 49.0, 71.5, 210.2; HR-MS (FAB+): exact mass calculated for $[M+H]^+$ ($C_9H_{17}O_2$) requires *m*/*z* = 157.1229, found: *m*/*z* = 157.1155; elemental analysis (%),

calculated for $C_9H_{16}O_2$: C 69.19, H 10.32; found: C 68.96, H 10.60. IR (filM): $\nu_{max}=3435$, 2952, 2868, 1709, 1360 cm^{-1}; $[\alpha]_D^{20}$: +45.7 (*c* 1.00, *n*-heptane); HPLC: CHIRALPAK AD, *n*-heptane/*i*-PrOH, 98.2:1.8, 1.0 mL min^{-1}, 280 nm, *ee* = 81 %: t_R (major) = 19.1 min; t_R (minor) = 20.7 min.

(*Z*)-4-Cyclopentylbut-3-en-2-one (4): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (dd, 1H, *J* = 16.0, 8.0 Hz), 6.03 (d, 1H, *J* = 16.0 Hz), 2.61–2.54 (m, 1H), 2.30 (s, 3H), 1.89–1.21 (m, 8H), in accord with the literature data.[16]

(*R*)-4-Cycloheptyl-4-hydroxybutan-2-one (5): Purified using column chromatography (EtOAc/cyclohexane, 1:4) to afford the title compound as a colourless oil (yield: 337 mg, 47 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91–3.87 (m, 1H), 2.92 (d, 1H, *J* = 2.8 Hz), 2.60–2.48 (m, 2H), 2.16 (s, 3H), 1.86–1.17 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 26.9, 28.2, 29.2, 29.8, 30.8, 44.1, 46.6, 71.8, 210.5; HR-MS (FAB+): exact mass calculated for $[M+H]^+$ ($C_{11}H_{21}O_2$) requires *m*/*z* = 185.1542, found: *m*/*z* = 185.1565; elemental analysis (%), calculated for $C_{11}H_{20}O_2$: C 71.70, H 10.94; found: C 71.46, H 11.10; IR (film) $\nu_{max}=3435$, 2921, 2854, 1709, 1358 cm^{-1}; $[\alpha]_D^{20}$: +50.8 (*c* 1.00, *n*-heptane); HPLC: CHIRALPAK AD, *n*-heptane/*i*-PrOH, 98:2, 1.0 mL min^{-1}, 280 nm, *ee* = 89 %: t_R (major) = 15.7 min; t_R (minor) = 18.9 min.

5-(4-Chlorophenyl)-4-hydroxyhexan-2-one (6a, b) (Table 5, entry 1): Purified using column chromatography (EtOAc/cyclohexane, 1:4) to afford the mixture of *syn*/*anti* diastereomers (1.5:1) of the title compound as a colourless oil (yield: 0.786 g, 89 %). The diastereomers were separated on a semi-preparative HPLC column (EtOAc/cyclohexane, 1:6).

(4R,5R)-5-(4-Chlorophenyl)-4-hydroxyhexan-2-one (**6a**): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.26 (m, 2H), 7.21–7.11 (m, 2H), 4.06 (dddd, 1H, *J* = 7.8, 5.8, 5.8, 3.8 Hz), 3.13 (d, 1H, *J* = 3.8 Hz), 2.73 (qd, 1H, *J* = 7.8, 7.0 Hz), 2.41–2.39 (m, 2H), 2.08 (s, 3H), 1.33 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3, 30.8, 44.3, 47.4, 71.4, 128.4, 129.5, 132.3, 141.4, 209.4; HR-MS (FAB+): exact mass calculated for $[M+H]^+$ ($C_{12}H_{16}ClO_2$) requires *m*/*z* = 227.0839, found: *m*/*z* = 227.0822; elemental analysis (%), calculated for $C_{12}H_{15}ClO_2$: C 63.58, H 6.67; found: C 63.39, H 6.90; IR (film): $\nu_{max}=3464$, 2964, 2927, 1711, 1492, 1411, 1360, 1091, 1012, 828 cm^{-1}; $[\alpha]_D^{20}$: +17.8 (*c* 1.60, *n*-heptane); HPLC: CHIRALPAK AD, *n*-heptane/*i*-PrOH, 98:2, 1.0 mL min^{-1}, 230 nm, *ee* = 72 %: t_R (major) = 16.0 min; t_R (minor) = 17.3 min.

(4R,5S)-5-(4-Chlorophenyl)-4-hydroxyhexan-2-one (**6b**): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2H), 7.21–7.18 (m, 2H), 4.17 (ddd, 1H, *J* = 9.2, 6.00, 2.8 Hz), 2.78 (qd, 1H, *J* = 7.2, 6.0 Hz), 2.58 (dd, 1H, *J* = 17.3, 2.8 Hz), 2.43 (dd, 1H, *J* = 17.3, 9.2 Hz), 2.14 (s, 3H), 1.29 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.3, 30.8, 44.3, 47.4, 71.4, 128.4, 129.5, 132.3, 141.4, 209.4; HR-MS (FAB+): exact mass calculated for $[M+H]^+$ ($C_{12}H_{16}ClO_2$) requires *m*/*z* = 227.0839, found: *m*/*z* = 227.0822; elemental analysis (%), calculated for $C_{12}H_{15}ClO_2$: C 63.58, H 6.67; found: C 63.45, H 6.90; IR (film): $\nu_{max}=3464$, 2964, 2927, 1711, 1492, 1411, 1360, 1091, 1012, 828 cm^{-1}; $[\alpha]_D^{20}$: +45.4 (*c* 1.00, *n*-heptane); HPLC: CHIRALCEL OJ, *n*-heptane/*i*-PrOH, 97:3, 0.5 mL min^{-1}, 230 nm, *ee* > 99 %: t_R = 16.0 min.

4-Hydroxy-5-phenylhexan-2-one (7a,b): Purified using column chromatography (EtOAc/cyclohexane, 1:4) to afford the mixture of *syn*/*anti* diastereomers (1.5:1) of the title compound as a colourless oil (yield: 615 mg, 83 %). Diastereomers were separated on a semi-preparative HPLC column (EtOAc/cyclohexane, 1:6).

(4R,5R)-4-Hydroxy-5-phenylhexan-2-one (**7a**): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.29 (m, 2H), 7.24–7.16 (m, 3H), 4.09 (ddd, 1H, *J* = 7.9, 5.8, 5.8 Hz), 2.74 (qd, 1H, *J* = 7.9, 7.0 Hz), 2.42–2.40 (m, 2H), 2.07 (s, 3H), 1.36 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 30.7, 45.4, 47.9, 72.1, 126.6, 127.6, 128.6, 143.8, 210.1, in accord with the literature data;[17] HR-MS (FAB+): exact mass calculated for $[M+H]^+$ ($C_{12}H_{17}O_2$) requires *m*/*z* = 193.1229, found: *m*/*z* = 193.1236; elemental analysis (%), calculated for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.48, H 8.50; IR (film): $\nu_{max}=3461$, 2965, 1708, 1493, 1452, 1361, 1164, 702 cm^{-1}; $[\alpha]_D^{20}$: +13.8 (*c* 1.23, *n*-heptane); HPLC: CHIRALPAK AD, *n*-heptane/*i*-PrOH, 98:2, 1.0 mL min^{-1}, 254 nm, *ee* = 72 %: t_R (major) = 14.9 min; t_R (minor) = 15.8 min.

(4R,5S)-4-Hydroxy-5-phenylhexan-2-one (**7b**): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.31 (m, 2H), 7.26–7.22 (m, 3H), 4.20 (ddd, 1H, *J* = 9.3, 6.1, 2.6 Hz), 2.82 (qd, *J* = 7.0, 6.1 Hz), 2.58 (dd, 1H, *J* = 17.2, 2.6 Hz), 2.47 (dd, 1H, *J* = 17.2, 9.3 Hz), 2.14 (s, 3H), 1.31 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.0, 30.8, 45.0, 47.3, 71.7, 126.6, 128.1, 128.4, 142.8, 209.4, in accord with the literature data;[17] HR-MS (FAB+): exact mass calculated for $[M+H]^+$ ($C_{12}H_{17}O_2$) requires *m*/*z* = 193.1229, found: *m*/*z* = 193.1236; elemental analysis (%), calculated for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.62, H 8.60; IR (film): $\nu_{max}=3461$, 2965, 1708, 1493, 1452, 1361, 1164, 702 cm^{-1}; $[\alpha]_D^{20}$: +32.7 (*c* 1.97, *n*-heptane); HPLC: CHIRALCEL OJ, *n*-heptane/*i*-PrOH, 90:10, 1.0 mL min^{-1}, 254 nm, *ee* > 99 %: t_R = 13.4 min.

(*syn*+*anti*)-4-Hydroxy-4-(tetrahydrofuran-3-yl)butan-2-one (1:1 mixture, 8a,b): Purified using column chromatography (EtOAc) to afford a mixture of inseparable *syn*/*anti* diastereomers (1:1) of the title compound as a colourless oil (yield: 432 mg, 71 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.97–3.67 (m, 9H), 3.51–3.48 (m, 1H), 2.67 (dd, 1H, *J* = 17.5, 2.0 Hz), 2.56–2.50 (m, 3H), 2.30–2.24 (m, 2H), 2.174 (s, 3H), 2.170 (s, 3H), 2.03–1.97 (m, 1H), 1.94–1.87 (m, 1H), 1.87–1.79 (m, 1H), 1.57–1.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.1, 28.7, 30.7, 44.4, 48.4, 48.5, 68.0, 68.2, 68.8, 69.6, 70.5, 209.4, 209.5; HR-MS (FAB+): exact mass calculated for $[M+H]^+$ ($C_8H_{15}O_3$) requires *m*/*z* = 159.1021, found: *m*/*z* = 159.1014; elemental analysis (%), calculated for $C_8H_{14}O_3$: C 60.74, H 8.92; found: C 60.38, H 9.10; IR (film): $\nu_{max}=3411$, 2936, 2873, 1709, 1361, 1066 cm^{-1}; HPLC: CHIRALPAK AD, *n*-heptane/*i*-PrOH, 97:3, 1.0 mL min^{-1}, 280 nm, *ee* = 71 % (for I diastereomer), *ee* = 71 % (for II diastereomer): t_R (major I) = 32.1 min; t_R (major II) = 34.3 min; t_R (minor I) = 36.6 min; t_R (minor II) = 41.6 min.

(*S*)-2-[(*R*)-Cyclopentyl(hydroxy)methyl]cyclopentanone (9a): Purified using column chromatography (EtOAc/cyclohexane, 1:4, R_f = 0.48) to afford the title compound as a colourless oil (yield: 112 mg, 16 %). ^{1}H NMR (400 MHz, C_6D_6): δ = 4.15 (dd, 1H, *J* = 1.8, 1.0 Hz), 3.49 (ddd, 1H, *J* = 8.4, 3.4, 1.8 Hz), 1.85–1.44 (m, 13H), 1.36–1.30 (m, 1H), 1.10–0.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 25.7, 25.8, 26.0, 27.1, 28.8, 38.7, 43.5, 53.3, 74.3, 224.2; HR-MS (FAB+): exact mass calculated for $[M+H]^+$ ($C_{11}H_{19}O_2$) requires *m*/*z* = 183.1385, found: *m*/*z* = 183.1374, elemental analysis (%), calculated for $C_{11}H_{18}O_2$: C 72.49, H 9.95; found: C 72.28, H

10.10; IR (film): ν_{max} = 3496, 2952, 2867, 1720, 1405, 1159 cm^{-1}; $[\alpha]_D^{20}$: −119.0 (*c* 1.00, *n*-heptane).

(*S*)-2-[(*S*)-Cyclopentyl(hydroxy)methyl]cyclopentanone (9b): Purified using column chromatography (EtOAc/cyclohexane, 1:4, R_f = 0.25) to afford the title compound as a colourless oil (yield: 302 mg, 43%). ^{1}H NMR (400 MHz, C_6D_6): δ = 3.88 (dd, 1H, *J* = 9.2, 2.0 Hz), 2.02–0.86 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6, 22.4, 25.4, 29.1, 29.9, 39.0, 44.2, 53.7, 74.0, 221.6; HR-MS (FAB+): exact mass calculated for $[M+H]^+$ ($C_{11}H_{19}O_2$) requires *m*/*z* = 183.1385, found: *m*/*z* = 183.1351; elemental analysis (%), calculated for $C_{11}H_{18}O_2$: C 72.49, H 9.95; found: C 72.21, H 10.20; IR (film): ν_{max} = 3451, 2953, 2869, 1732, 1156 cm^{-1}; $[\alpha]_D^{20}$: +152.0 (*c* 1.00, *n*-heptane); HPLC: CHIRALCEL OD, *n*-heptane/*i*-PrOH, 90:10, 1.0 mL min^{-1}, 280 nm, *ee* = 96%: t_R (major) = 5.4 min; t_R (minor) = 4.7 min.

(*S*)-2-[(*R*)-Cycloheptyl(hydroxy)methyl]cyclopentanone (10a): Purified using column chromatography (EtOAc/cyclohexane, 1:4, R_f = 0.62) to afford the title compound as a colourless oil (yield: 211 mg, 26%). ^{1}H NMR (400 MHz, C_6D_6): δ = 3.45 (dd, 1H, *J* = 9.2, 2.0 Hz), 1.90–1.10 (m, 18H), 1.10–0.97 (m, 1H), 0.90–0.79 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ = 20.4, 26.4, 26.6, 27.4, 27.9, 28.9, 32.9, 38.0, 42.8, 51.6, 77.7, 223.6; HR-MS (FAB+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{23}O_2$) requires *m*/*z* = 211.1698, found: *m*/*z* = 211.1675; elemental analysis (%), calculated for $C_{13}H_{22}O_2$: C 74.24, H 10.54; found: C 73.96, H 10.80; IR (film): ν_{max} = 3498, 2923, 1712 cm^{-1}; $[\alpha]_D^{20}$: −90.3 (*c* 1.00, *n*-heptane); HPLC: CHIRALCEL OJ, *n*-heptane, 0.5 mL min^{-1}, 280 nm, *ee* = 83%: t_R (major) = 19.4 min; t_R (minor) = 21.1 min.

(*S*)-2-[(*S*)-Cycloheptyl(hydroxy)methyl]cyclopentanone (10b): Purified using column chromatography (EtOAc/cyclohexane, 1:4, R_f = 0.40) to afford the title compound as colourless crystals (yield: 406 mg, 50%); mp 72–74 °C. ^{1}H NMR (400 MHz, C_6D_6): δ = 3.87 (dd, 1H, *J* = 8.2, 1.8 Hz), 2.01–1.15 (m, 19H), 0.98–0.89 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ = 20.8, 22.9, 26.6, 26.8, 28.8, 29.3, 29.6, 30.7, 38.8, 43.4, 52.3, 73.3, 219.8; HR-MS (FAB+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{23}O_2$) requires *m*/*z* = 211.1698, found: *m*/*z* = 211.1724; elemental analysis (%), calculated for $C_{13}H_{22}O_2$: C 74.24, H 10.54; found: C 74.05, H 10.70; IR (KBr): ν_{max} = 3441, 2912, 1724 cm^{-1}; $[\alpha]_D^{20}$: +157.4 (*c* 1.00, *n*-heptane); HPLC: CHIRALPAK AD, *n*-heptane/*i*-PrOH, 98:2, 1.0 mL min^{-1}, 280 nm, *ee* = 85%: t_R (major) = 28.5 min; t_R (minor) = 26.8 min.

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