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L-Proline catalysed asymmetric aldol reactions in PEG-400 as recyclable medium and transfer aldol reactions

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Abstract—L-Proline-catalysed direct asymmetric aldol reaction of acetone with various aldehydes in PEG-400 is described. Recycling of the catalyst and solvent (PEG) was possible up to ten runs without loss of catalyst activity. L-Proline was also found to be an efficient catalyst for the asymmetric transfer aldol reaction between various aldehydes and diacetone alcohol for the first time. Good yields and enantioselectivities were observed with both methods.

1. Introduction

In general, most of the methodologies, which are available for the asymmetric aldol[1,2] reactions fall into one of the following categories: (a) the chiral auxiliary assisted aldol reactions based on the use of stoichiometric quantities of chiral appendage;[3] (b) chiral Lewis acid-catalysed Mukaiyama type and chiral Lewis-base catalysed aldol reactions;[4] (c) heterobimetallic bifunctional Lewis acid/Bronsted base-catalysed direct aldol reactions[5]; and (d) aldol reactions catalysed by aldolase enzymes and antibodies.[6] A significant characteristic of the later two methodologies is the employment of unmodified carbonyl compounds as aldol donor substrates, whereas the first two methodologies require some degree of preactivation of the substrates involved.

Asymmetric versions of the aldol reaction rely upon the use of chiral auxiliaries, however, it must be noted that there has been some success of using asymmetric catalysts, although they normally rely on a Mukaiyama type process.

The development of catalytic and enantioselective C– bond forming reactions is currently among the prime objectives in organic synthesis. Direct catalytic and enantioselective aldol reactions of unmodified ketones or aldehydes were reported by the research groups of Shibasaki,[7] Trost,[8] Jorgensen,[9] MacMillan,[10] List,[11] Barbas III[12] and Cordova[13] using organometallic or purely organic catalysts. Recent work has been attempted by using a recyclable ionic liquid as the solvent,[14] buffered aqueous media,[15] Zn-proline complexes in aqueous media or aqueous micelles.[16]

Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound, which does not contain a metal atom. The application of enantiomerically pure 'small' organic molecules represents a promising alternative catalytic concept in addition to other frequently used syntheses based on metal containing catalysts.[17] Some new direct asymmetric intermolecular reactions such as Mannich,[18] Michael[19] and other analogous reactions have been reported by Barbas III,[20] and others using proline as catalyst.[21]

2. Results and discussion

It is always economical if the catalytic reaction is performed in an ecofriendly solvent, which allows both solvent and catalyst to recycle. Poly(ethylene glycol) (PEG) is non-toxic and used as a rapid and recyclable reaction medium for the Heck reaction,[22] asymmetric dihydroxylation[23] and Baylis–Hillman reactions.[24] In continuation of this work, an efficient synthesis of chiral β-hydroxy ketones from various aldehydes and acetone in poly (ethylene glycol)-400 catalysed by L-proline has been developed (Scheme 1).[25]

Several groups studied the mechanism of L-proline catalysed direct asymmetric aldol reaction and proposed

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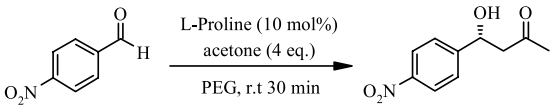


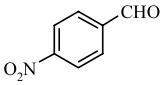
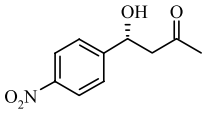
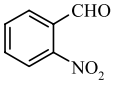
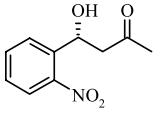
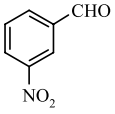
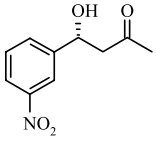
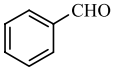
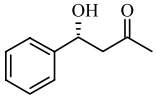
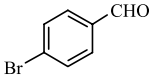
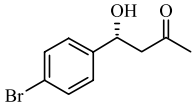
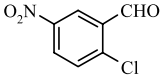
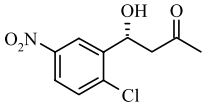
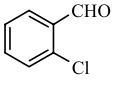
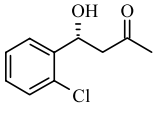
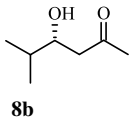
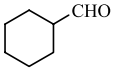
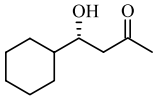
Scheme 1.

an enamine mechanism based on the Hajos–Parrish–Eder–Sauer–Wiechert reaction mechanism.[26]

We were particularly interested in developing an eco-friendly approach for the direct aldol reaction using PEG as a solvent for the following reasons.

(a) PEG is biologically compatible.[27]

Table 1. L-Proline catalysed asymmetric aldol reactions in PEG-400

Entry	Substrate	Time (min)	Product	Yield (%)[a]	ee (%)
1	 **1a**	30	 **1b**	94	67[b]
2	 **2a**	30	 **2b**	90	64[b]
3	 **3a**	30	 **3b**	88	70[b]
4	 **4a**	30	 **4b**	58	58[b]
5	 **5a**	30	 **5b**	85	65[b]
6	 **6a**	30	 **6b**	90	61[b]
7	 **7a**	30	 **7b**	88	60[c]
8	 **8a**	120	 **8b**	90	84[c]
9	 **9a**	180	 **9b**	65	71[c]

[a] Isolated yields after column chromatography; the products were characterised by spectral data.
[b] ee% by chiral HPLC.
[c] ee% by optical rotation.

(b) The polymer is available at a very low affordable price [ionic liquid cost 1200 – 2400 USD/kg, as against PEG-400, which cost 43 USD/kg].
(c) Requires only a low concentration of catalyst.
(d) Highly practical and a simple work-up procedure.

First we initiated our study by using 4-nitrobezaldehyde (entry 1, Table 1), acetone and L-proline (10 mol %) in PEG-400. The reaction was completed in 30 min and yielded 94% of product **1b** with 67% ee. Enantiomeric excess was determined using chiralcel OB-H column. After workup (extraction with ether) mother liquor (PEG+ proline) was kept aside for further runs. The transformation in conventional solvent (DMSO) took 4 h for completion of the reaction.

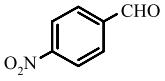
2-Nitrobenzaldehyde and 3-nitrobenzaldehydes (entries 2 and 3, Table 1) were reacted with acetone to give the aldol products **2b** and **3b** in good yields and enantioselectivities. Aldol reaction between simple benzaldehyde (entry 4, Table 1) and acetone afforded the product **4b** in 58% yield and 58% ee. The 4-bromobenzaldehyde, 2-chloro-5-nitrobenzaldehyde and 2-chlorobenzaldehyde (entries 5, 6 and 7, Table 1) underwent the aldol reaction smoothly giving the products **5b**, **6b** and **7b** in 85, 90 and 88% yields with 65, 61 and 60% ee's, respectively.

The aliphatic aldehydes, isobutyraldehyde and cyclohexane carboxaldehyde (entries 8 and 9, Table 1) have also proved to be efficient by producing the products **8b** and **9b** in 90 and 65% yields, respectively. The optical purity of the products was determined by their optical rotation (compared with the literature value). High enantioselectivity of 84% ee was obtained for the reaction of isobutyraldehyde with acetone in PEG.

We found L-proline to be an efficient catalyst for the direct asymmetric aldol reaction of acetone with aromatic and aliphatic aldehydes in PEG. Enantioselectivities depend on the aldehyde component and are typically in the seventies with aromatic aldehydes and in the eighties with aliphatic α-branched aldehydes.

We have studied the reusability of the catalyst as well as the solvent. A second run was performed without any modification. The simple addition of 4-nitrobenzaldehyde (entry 1, Table 2) and acetone to the mother liquor with stirring for 30 min resulted in the formation of the aldol product **1b** in 93% yield with similar enantioselectivity. Except for the third run, which showed a slight increase in enantioselectivity (71%), all the runs were similar in product yields and enantioselectivities. The efficient recycling was then proved by additional experiments until the tenth run (Table 2).

Table 2. L-Proline catalysed asymmetric aldol reactions in PEG

Entry	Substrate	Time (min)	Yield (%)[a]	ee (%)[b]
1		30	94	67
2	2nd run	30	93	68
3	3rd run	30	90	71
4	4th run	30	89	67
5	5th run	30	90	66
6	6th run	30	88	64
7	7th run	30	87	67
8	8th run	30	88	65
9	9th run	30	86	67
10	10th run	30	84	66

[a] Isolated yields after chromatography.
[b] ee% by chiral HPLC.

2.1. L-Proline catalysed asymmetric transfer aldol reaction

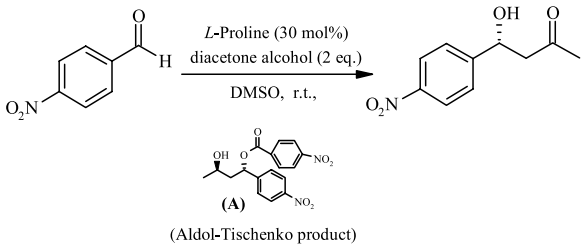
To further expand the scope of the L-proline catalysed C–bond forming reaction, we sought to apply this amine catalysed enamine generation to asymmetric transfer aldol reaction. The addition of nucleophiles to carbonyl compounds has been under investigation for decades. Examples include the addition of enolates to aldehydes and the Meerwein–Ponndorf–Verley reduction of ketones (hydride as a nucleophile). Recent achievements in this area are: alkynyl transfer reactions,[28] allyl transfer reaction[29] (as proposed to occur by a stepwise ionic mechanism) and cyanide transfer reactions.[30]

This concept of transfer aldol reaction has originated from above mentioned reactions. Aldol and retro aldol reactions are catalysed by either acid or base. The reversibility of the aldol reaction, that is, equilibrium between aldol and carbonyl compounds is one of the most important characteristics of the aldol reaction.[31] The retro aldol reaction has been recently found to have several new applications, for instance antibodies and enzymes have been found to catalyse retro aldol reactions allowing efficient kinetic resolution of racemic aldols. The retro aldol reaction has been utilised for the synthesis of bicyclo-[2.2.1]-heptane and cyclopentane derivatives, which in turn have been employed in the synthesis of a variety of diterpenoids, sesquiterpenes, biaryl compounds and bicyclo-[4.3.0]-nonane derivatives.[32]

Transfer aldol reaction involving diacetone alcohol as a source of ketone (acetone) is studied with several alkoxides, in these reactions Aldol–Tischenko reaction is competitive to get mono protected 1,3-diols and in few cases normal aldol products were observed.[33]

We initiated this study to explore L-proline as a mild organocatalyst for asymmetric transfer aldol reaction[34] between diacetone alcohol and various aldehydes. Interestingly the present procedure not only allowed to achieve condensation with good selectivity but also was mild enough to avoid Tischenko–Aldol product A (Scheme 2) in Lewis acid catalysed transfer aldol reactions.

First we examined the transfer aldol reaction between 4-nitrobenzaldehyde (entry 1, Table 3) and diacetone alcohol in the presence of L-proline (30 mol%) in DMSO to afford the corresponding β-hydroxy ketone **1b** in 86% yield and 71% ee. Even after increasing the catalyst concentration (100 mol%), there was no difference in yields and ee's (entry 2, Table 3). This reaction was also attempted in PEG-400 as solvent, however,



Scheme 2.

product yield and ee were lower compared to the standard solvent.

There is no direct evidence for the mechanism by which the reaction proceeds. However, we believe a cyclic transition state (re-facial attack of aldehyde to proline derivative) where a retro aldol and aldol reactions are initiated by the same catalyst (Scheme 3).

Similarly various other aldehydes such as 3-nitrobenzaldehyde, 4-bromobenzaldehyde, 2-chloro-5-nitrobenzaldehyde and 2-chlorobenzaldehyde (entries 3, 5, 6 and 7, Table 3) were subjected to this transformation and observed the yields of aldol products up to 88% and ee's up to 71%.

Transfer aldol reaction between simple benzaldehyde (entry 4, Table 3) and diacetone alcohol gave the product **4b** in 50% yield and 57% ee. In the case of anisaldehyde (entry 10, Table 3)(electron rich benzaldehyde) the aldol product **10b** was observed only after 5 days stirring at room temperature with 48% ee and 40% yield along with the dehydrated aldol condensation product.

Aliphatic aldehydes (entries 8 and 9, Table 3) were also good substrates for this reaction, wherein isobutyraldehyde provided aldol product **8b** in 80% yield and 84% ee and cyclohexane carboxaldehyde furnished **9b** in 91% yield with 86% ee.

Since, in principle aldol reactions are reversible, another question to be addressed in this context is whether the optical purity varies as a function of time. This is an important feature to be determined and we found that the ee of the aldol product in our model reaction (entry 1) does not vary significantly (ee = 71%) when monitored at different intervals (4, 8, 12 and 24 h), however, the formation of dehydrated aldol condensation product was observed after 8 h. In the case of aliphatic aldehydes having α-hydrogens (phenyl propanol), we have observed that the self-aldolisation of aldehyde was competitive.

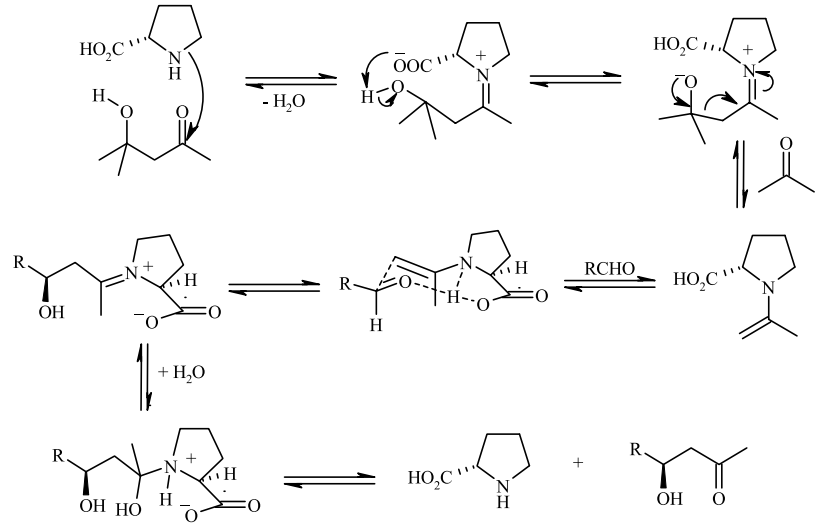
3. Conclusion

In summary, poly(ethylene glycol) (PEG) has been shown to be a rapid and reusable reaction medium for L-proline- catalysed asymmetric aldol reaction. The reusability of this solvent was studied over ten runs without loss of activity of either the catalyst or the solvent and we have also developed the first asymmetric transfer aldol reaction catalysed by L-proline. In this reaction no Aldol–Tischenko product was observed in contrast to other reported methods.

4. Experimental

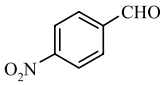
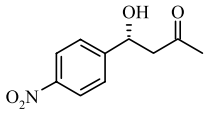
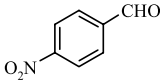
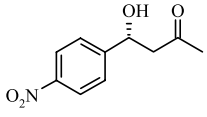
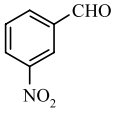
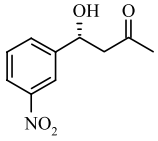
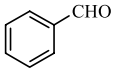
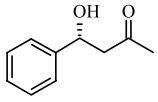
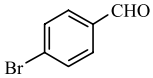
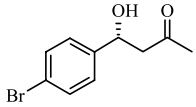
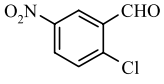
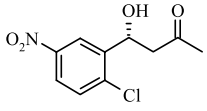
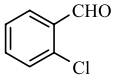
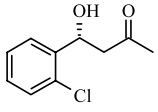
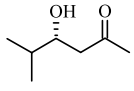
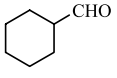
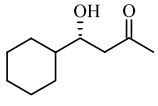
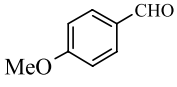
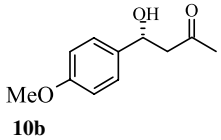
4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 meshes. IR spectra were recorded on Perkin-Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a Varian Gemini 200, Bruker 300 or Varian Unity 400 NMR spectrometers. Chemical shifts were reported in ppm with respect to internal TMS.



Scheme 3.

Table 3. L-Proline catalysed asymmetric transfer aldol reaction

Entry	Substrate	Time (min)	Product	Yield[a] (%)	ee (%)
1	 **1a**	4	 **1b**	86	71[b]
2	 **1a**	4	 **1b**	85	72[b,c]
3	 **3a**	6	 **3b**	88	70[b]
4	 **4a**	12	 **4b**	50	57[b]
5	 **5a**	12	 **5b**	65	71[d]
6	 **6a**	6	 **6b**	82	60[b]
7	 **7a**	8	 **7b**	70	60[d]
8	 **8a**	12	 **8b**	80	84[d]
9	 **9a**	12	 **9b**	91	86[d]
10	 **10a**	120	 **10b**	40	48[b]

[a] Isolated yields after column chromatography; the products were characterised by spectral data.
[b] ee% by chiral HPLC.
[c] L-Proline used 100 mol%.
[d] ee% by optical rotation.

Coupling constants (J) are quoted in Hz. Mass spectra were obtained on Finnegan MAT 1020B or micro mass VG 70-70H spectrometer operating at 70 eV using direct inlet system. HPLC was recorded on SHIMADZU HPLC using chiralcel OB-H column, hexane and isopropyl alcohol as eluents.

4.2. General procedure for the aldol reaction: procedure A

To a stirred solution of L-proline (10 mol%) in PEG (2 mL) was added acetone (4 mmol) at room temperature under inert atmosphere. After being stirred this mixture for 5 min, aldehyde (1 mmol) was added and allowed to stir for 30 min. The reaction medium was diluted with anhydrous ether (5 mL), stirred for 5 min, allowed to separate out and the ether layer was decanted. This process was repeated twice to obtain the product in ether where as the mother liquor (PEG + proline) was kept aside for further runs. This process was repeated up to ten runs without loss of the activity of the catalyst. Solvent was removed under vacuo and purified by silica gel column chromatography to give the pure product.

4.3. General procedure for transfer aldol reaction: procedure B

To a stirred solution of L-proline (30 mol%) in DMSO was added diacetone alcohol (4 mmol) at room temperature under inert atmosphere. After being stirred for 5 min aldehyde (2 mmol) was added, and allowed to stir for 4 h. After completion of the reaction (monitored by TLC), water was added and extracted with ethyl acetate twice (2× 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate. Solvent was removed under vacuo and purified by silica gel column chromatography to afford the pure product.

4.3.1. (4*R*)-Hydroxy-4-(4′-nitrophenyl)-butan-2-one (1b).[21] Pale brown viscous oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, J=7.0 Hz, 2H, Ar-*H*), 7.52 (d, J=7.0 Hz, 2H, Ar-*H*), 5.30–5.20 (m, 1H, –C*H*OH), 3.56 (br s, 1H, –O*H*), 2.85–2.80 (m, 2H, –CH_2CO), 2.21 (s, 3H, -COCH_3); Mass (EI): m/z 209 (M^+), 43; IR (neat): 3419, 2930, 1716, 1514, 1480, 1370 cm^{-1}; $[\alpha]_D^{25}$ +44.3 (c 1, $CHCl_3$) for 67% ee. Enantiomeric excess: 67% by procedure A and 71% by procedure B, which was determined by HPLC analysis using chiralcel OB-H column (isopropyl alcohol/hexane 15:85) UV 262 nm, flow rate 1.0 mL/min; major isomer, t_R 28.49 min and minor isomer, t_R 34.20 min.

4.3.2. (4*R*)-Hydroxy-4-(2′-nitrophenyl)-butan-2-one (2b).[14] Pale brown viscous oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (dd, J=1.2, 8.1 Hz, 1H, Ar-*H*), 7.91 (dd, J=1.2, 8.1 Hz, 1H, Ar-*H*), 7.71 (dt, J=1.2, 8.1 Hz, 1H, Ar-*H*), 7.44 (dt, J=1.2, 8.1 Hz, 1H, Ar-*H*), 5.70 (d, J=9.3 Hz, 1H, –C*H*OH), 3.76–3.70 (m, 1H, –O*H*), 3.15 (dd, J=2.1, 17.7 Hz, 1H, CH_2CO), 2.70 (dd, J=9.6, 18 Hz, 1H, –CH_2CO), 2.24 (s, 3H, –COCH_3); Mass (EI): m/z 209 (M^+), 43; IR (neat): 3416, 2934, 1719, 1512, 1376 cm^{-1}; $[\alpha]_D^{25}$ −109.2 (c 1, $CHCl_3$) for 64% ee. Enantiomeric excess: 64% by procedure A, which was determined by HPLC analysis using chiralcel OB-H column (isopropyl alcohol/hexane 15:85) UV 262 nm, flow rate 1.0 mL/min; major isomer, t_R 12.72 min and minor isomer, t_R 11.82 min.

4.3.3. (4*R*)-Hydroxy-4-(3′-nitrophenyl)-butan-2-one (3b).[21] Yellow viscous oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (s, 1H. Ar-*H*), 8.13 (d, J=8.6 Hz, 1H, Ar-*H*), 7.71 (d, J=7.5 Hz, 1H, Ar-*H*), 7.53 (t, J=7.5 Hz, 1H, Ar-*H*), 5.27–5.15 (m, 1H, –C*H*OH), 3.50 (br s, 1H, –O*H*), 2.82 (d, J=12.0 Hz, 2H, –CH_2CO), 2.23 (s, 3H, –COCH_3); Mass (EI): m/z 209 (M^+), 43; IR (neat): 3414, 2931, 1715, 1519, 1370 cm^{-1}; $[\alpha]_D^{25}$ +49.9 (c 1.2, $CHCl_3$) for 70% ee. Enantiomeric excess: 70% by procedure A and B, which was determined by HPLC analysis using chiralcel OB-H column (isopropyl alcohol/hexane 15:85) UV 262 nm, flow rate 1.0 mL/min; major isomer, t_R 31.55 min and minor isomer, t_R 36.58 min.

4.3.4. (4*R*)-Hydroxy-4-phenyl-butan-2-one (4b).[35,21] Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33–7.17 (m, 5H, Ar-*H*), 5.15–5.04 (m, 1H, –C*H*OH), 3.17 (br s, 1H, –O*H*), 2.80–2.75 (m, 2H, –CH_2CO), 2.17 (s, 3H, –COCH_3); Mass (EI): m/z 164 (M^+), 43; IR (neat): 3413, 2932, 1718, 1450, 890 cm^{-1}; $[\alpha]_D^{25}$ +60.0 (c 1, $CHCl_3$) for 83% ee [lit. value]. Enantiomeric excess: 58% by procedure A and 57% by procedure B, which was determined by optical rotation (compared with the literature value).

4.3.5. (4*R*)-Hydroxy-4-(4′-bromophenyl)-butan-2-one (5b).[21] Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J=8.4 Hz, 2H, Ar-*H*), 7.22 (d, J=8.4 Hz, 2H, Ar-*H*), 5.08 (dd, J=5.6, 7.8 Hz, 1H, –C*H*OH), 3.38 (br s, 1H, –O*H*), 2.80–2.70 (m, 2H, –CH_2CO), 2.20 (s, 3H, –COCH_3); Mass (EI): m/z 243 (M^+), 43; IR (neat): 3418, 2934, 1713, 1489, 1369, 1077, 538 cm^{-1}; $[\alpha]_D^{25}$ +53.3 (c 1, $CHCl_3$) for 90% ee [lit. value]. Enantiomeric excess: 65% by procedure A and 71% by procedure B, which was determined by optical rotation (compared with the literature value).

4.3.6. (4*R*)-Hydroxy-4-(2′-chloro-5′-nitrophenyl)-butan-2-one (6b). Colourless viscous oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.66 (s, 1H, Ar-*H*), 8.10 (dd, J=1.7, 8.8 Hz, 1H, Ar-*H*), 7.44 (d, J=9.6 Hz, 1H, Ar-*H*), 5.43 (d, J=12.0 Hz, 1H, –C*H*OH), 3.65 (s, 1H, –O*H*), 3.02 (dd, J=4.1, 12.5 Hz, 1H, –CH_2CO), 2.61 (dd, J=8.3, 16.6 Hz, 1H, –CH_2CO), 2.24 (s, 3H, –COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 208.3, 147.1, 142.3, 137.6, 130.2, 123.2, 122.7, 66.1, 49.3, 30.4; Mass (EI): m/z 243 (M^+), 183, 43; HRMS calcd for $C_{10}H_{10}ClNO_4$ (M^+) 243.0928, found 243.0898; IR (KBr): 3414, 2932, 1718, 1517, 1373, 1167, 1069 cm^{-1}; $[\alpha]_D^{25}$ + 84.45 (c 0.5, $CHCl_3$) for 64% ee. Enantiomeric excess: 64% by procedure A and 60% by procedure B, which was determined by HPLC analysis using chiralcel OB-H column (isopropyl alcohol/hexane 15:85) UV 262 nm, flow rate 1.0 mL/min; major isomer, t_R 12.72 min and minor isomer, t_R 11.82 min.

4.3.7. (4*R*)-Hydroxy-4-(2′-chlorophenyl)-butan-2-one (7b).[21] Colourless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J=8.6 Hz, 1H, Ar-*H*), 7.34–7.14 (m, 3H, Ar-*H*), 5.46 (d, J=10.4 Hz, 1H, –C*H*OH), 3.58 (s, 1H, –O*H*), 3.05–2.90 (m, 1H, –CH_2CO), 2.73–2.53 (m, 1H, –CH_2CO), 2.22 (s, 3H, –COCH_3); Mass (EI): m/z 198 (M^+), 43; IR (neat): 3410, 2930, 1712, 1440, 840 cm^{-1}; $[\alpha]_D^{25}$ +97.0 (c 1,

$CHCl_3$) for 85% ee [lit. value]. Enantiomeric excess: 60% by procedure A and procedure B, which was determined by optical rotation (compared with the literature value).

4.3.8. (4*R*)-Hydroxy-5-methyl-hexan-2-one (8b).[21] Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.85–3.75 (m, 1H, –C*H*OH); 2.90 (br s, 1H, –O*H*), 2.58–2.50 (m, 2H, –CH_2CO), 2.20 (s, 3H, –CO CH_3), 1.76–1.58 (m, 1H, $(CH_3)_2$C*H*), 1.00–0.85 (m, 6H, –CH(CH_3)$_2$); IR (neat): 3410, 2929, 1710, 1350, 702 cm^{-1}; $[\alpha]_D^{25}+75.5$ (*c* 1.2, $CHCl_3$) for 99% ee [lit. value]. Enantiomeric excess: 84% by procedure A and 84% by procedure B, which was determined by optical rotation (compared with the literature value).

4.3.9. (4*R*)-4-(Cyclohexyl)-4-hydroxy-2-butanone (9b).[21] Colourless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83–3.76 (m, 1H, –C*H*OH), 2.60–2.50 (m, 2H, –CH_2CO), 2.40–2.25 (m, 1H, –O*H*), 2.18 (s, 3H, –COCH_3), 1.77–1.62 (m, 5H, –$CH_2CH_2CHCH_2CH_2$), 1.25–0.97 (m, 6H, –(CH_2)$_3$); Mass (EI): *m*/*z* 169 (M^+-1), 87, 43; IR (neat): 3419, 2930, 1715, 1450, 1364, 1165 cm^{-1}; $[\alpha]_D^{25}+45.9$ (*c* 1.2, $CHCl_3$) for 97% ee [lit. value]. Enantiomeric excess: 71% by procedure A and 86% by procedure B, which was determined by optical rotation (compared with the literature value).

4.3.10. (4*R*)-Hydroxy-4-(4′-methoxyphenyl)-butan-2-one (10b).[35] Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, $J=8.8$ Hz, 2H, Ar-*H*), 6.88 (d, $J=8.8$ Hz, 2H, Ar-*H*), 5.10 (dd, $J=9.0$, 3.3 Hz, 1H, –C*H*OH), 3.80 (s, 3H, –OCH_3), 3.22 (br s, 1H, –O*H*), 2.86–2.78 (m, 2H, –CH_2CO), 2.19 (s, 3H, –COCH_3); Mass (EI): *m*/*z* 194 (M^+), 43; IR (neat): 3424, 2917, 1730, 1450, 1100, 1070 cm^{-1}; $[\alpha]_D^{25}+38.5$ (*c* 0.7, $CHCl_3$) for 48% ee. Enantiomeric excess: 48% by procedure B, which was determined by HPLC analysis using chiralcel OB-H column (isopropyl alcohol/hexane 15:85).

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