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PAPER

Highly diastereo- and enantioselective direct Barbas–List aldol reactions promoted by novel benzamidoethyl and benzamidopropyl prolinamides in water

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Four novel benzamido-functionalized prolinamides have been prepared and tested as organocatalysts for enantioselective aldol reaction of aldehydes and cyclic ketones in water. In particular, prolinamide derived from achiral ethylene diamine was the best catalyst leading to *anti* aldols in excellent diastereomeric (up to 98/2) and enantiomeric (up to 99/1) ratios, thereby showing that lateral amide functionalities might be a key issue for facilitating "in water" chemistry. These catalysts are cheaper and easier to prepare than those previously described.

Introduction

The aldol reaction is a fundamental organic reaction used by nature to build carbon-based skeletons having a 3-hydroxycarbonyl arrangement and, where appropriate, two contiguous stereocenters. The control of diastereo- and enantioselectivity of the reaction is a major objective for organic chemists,[1] and recently the design of catalysts for the stereoselective Barbas–List aldol reactions has attracted a lot of interest. Although the reaction is normally carried out in organic solvents, it has been demonstrated that the addition of some water has a positive effect on the process[2] but the use of an excess, decreases the reactivity and stereocontrol of the reaction.[3] The search for small chiral molecules capable of promoting enantioselective aldol reactions in water has seen a burst of activity.[4]

To this end, a variety of catalysts, such as chiral bifunctional diamines[5] and proline derivatives, have been employed. Proline itself catalyzes the Barbas–List aldol reaction in water though it leads to racemic aldols,[6] but 4-hydroxyproline derivatives,[7] including polymer supported[8] or ionic liquid modified prolines,[9] have been shown to be excellent catalysts for the reaction. In addition, amino acids,[10] amino amides,[11] modified amino acids,[12] small peptides,[13] or prolinothioamides[14] also give good results. Arguably prolinamide and its derivatives appear to be the most efficient organocatalysts for Barbas–List aldol reactions.[15] In this way, prolinamides derived from amino alcohols or amino phenols,[16] amines, diamines,[17] and prolyl sulfonamides[18] have been explored as bifunctional catalysts to promote stereoselective aldol reactions in water. These catalysts differ from each other in the appendage attached to the carboxylic group, searching to tune the pK_a of the catalyst, to improve its solubility "in water" and to get better diastereo- and enantioselectivity.

All these catalysts have two relevant modules: a chiral polar core where the ketone will be temporarily attached in a covalent manner and a hydrophobic moiety that assures the stereochemically controlled confinement of the aldehyde unit. Recent observations have shown that the stereochemistry of the final aldol is dictated by the configuration of the proline component, whilst the structure of the amine appendage has only a minor influence on the diastereo- and enantioselectivity of the reaction.[19] Accordingly, we decided to explore benzamidoethyl- and benzamidopropyl-derived prolinamides on the expectation that hydrophobicity will perhaps induce a favorable conformational pocket for the aldehyde component and lead to highly stereoselective Barbas–List aldol reactions.

To test this hypothesis we have prepared[20] prolinamide **I** and its enantiomer *ent*-**I** from *p*-toluoyl ethylenediamine and L- or D-proline respectively, as well as its homologous **II** from L-proline and the corresponding 1,3-propanediamine derivative. Prolinamide **III**, which has an additional stereocenter at the amine component, was also synthesized for the purpose of examining the effect of the additional stereocenter on the stereocontrol of the Barbas–List aldol reaction (Fig. 1).

Results and discussion

Compounds **I–III** were evaluated as organocatalysts for the direct aldol reaction of *p*-nitrobenzaldehyde and cyclohexanone in water. Initially, a comparative study was made to test the ability to promote the reaction in good yield and stereoselectivity (diastereo- and enantioselectivity). For this purpose, the reactions were carried out with a catalyst load of 20 mol% (relative to aldehydes), 40 mol% of acetic acid as co-catalyst and 5 equivalents of cyclohexanone at 1 °C (Scheme 1 and Table 1). As illustrated

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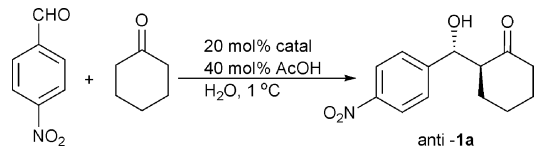
† Dedicated to Professor Carmen Nájera on occasion of her 60th birthday.

‡ Electronic supplementary information (ESI) available: Preparation and characterization data of the catalysts, ^{1}H NMR, ^{13}C NMR spectra for all compounds, HRMS for all new compounds, and HPLC chromatograms for the mixtures. See DOI: 10.1039/c0ob00688b

Table 1 Screening of organocatalysts **I–III** for direct Barbas-List aldol reaction in water[a]

Entry	Catalyst	*t*/h	Yield[b] (%)	*anti*/*syn*[c]	E.r.[d] (*anti*)	Major
1	**I**	48	90	98/2	97 : 3	(2*S*,1′*R*)
2	*ent*-**I**	48	94	98/2	3 : 97	(2*R*,1′*S*)
3	**II**	46	98	97/3	95 : 5	(2*S*,1′*R*)
4	**III**	22	95	96/4	95 : 5	(2*S*,1′*R*)

[a] *Reaction conditions*: 1 mL of water, 2.5 mmol cyclohexanone, 0.5 mmol aldehyde, 20 mol% catalyst, 40 mol% HOAc, 1 °C. [b] Yields determined after chromatographic purifications. [c] Diastereomeric excess determined by ^{1}H NMR of crude reaction mixture. [d] Enantiomeric ratio determined by chiral HPLC analysis for *anti*-diastereomer.



Scheme 1 Reaction of 4-nitrobenzaldehyde with cyclohexanone catalyzed by **I–III**.

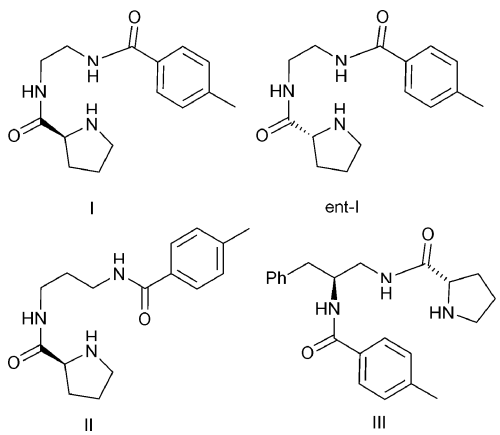


Fig. 1 Catalysts used in this work.

in Table 1, the best diastereo- and enantiocontrol was reached with benzamidoethyl-derived prolinamide catalyst **I**, and *ent*-**I**. Benzamidopropyl-derived prolinamide **II**, was even better in terms of rate and chemical yield though unfortunately diastereo- and enantioselectivities were worse. Catalyst **III**, with an additional stereocenter at the amine component and presumably more hydrophobic than **I** or **II**, did in fact accelerate the reaction (entry 4, Table 1), though both chemical yield and stereoselection were poorer.

Having found **I** to be our best catalyst for aldol reactions in water we optimized the reaction conditions, and the results are summarized in Table 2. It is worth noting that in the absence of catalyst the reaction did not take place even after stirring a mixture of 4-nitrobenzaldehyde and cyclohexanone in water and 40 mol% of acetic acid at rt for one month (entry 1). In contrast, an 85% mixture of *anti* and *syn* aldols (83/17) was obtained after 48 h. when working in the presence of 20 mol% of **I**, without co-catalyst (entry 2).

The presence of acetic acid as co-catalyst not only accelerated the reaction but also improved the stereoselectivity as illustrated in entry 3 (20 mol% of both catalyst and acetic acid) and entry

Table 2 Optimization of enantioselective direct Barbas–List aldol reaction of cyclohexanone and 4-nitrobenzaldehyde catalyzed by **I** in water

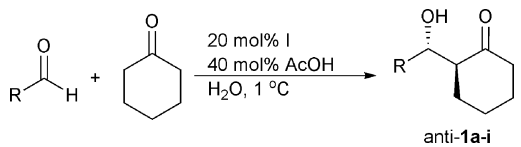
	mol%						
Entry	Cat.	AcOH	*t*/h	*T*/°C	Yield[a] (%)	*anti*/*syn*[b]	E.r.[c]
1	—	40	720	20	—	—	—
2	20	—	48	20	85	83/17	87/13
3	20	20	20	20	65	90/10	91/9
4	20	40	21	20	94	90/10	92/8
5	20	40 (TFA)	72	20	28	74/26	80/20
6	5	10	22	20	92	93/7	91/9
7	20	40	48	1	90	98/2	97/3
8[d]	20	40	22	1	85	96/4	97/3
9[e]	20	40	22	1	92	88/12	89/11
10	10	20	76	1	77	96/4	95/5
11	5	10	168	1	63	97/3	94/6
12[f]	20	40	72	1	90	98/2	94/6

[a] Yields determined after chromatographic purifications. [b] Diastereomeric excess determined by ^{1}H NMR of crude reaction mixture. [c] Enantiomeric excesses determined by chiral HPLC analysis for *anti*-diastereomer. [d] Reaction performed in brine. [e] Reaction performed "neat" without solvent. [f] Reaction was performed using 5 mmol of *p*-nitrobenzaldehyde.

4 (20 mol% of **I** and 40 mol% of acetic acid), as it is generally accepted that an acid co-catalyst promotes the formation of the intermediate enamine species.[21] Using the stronger trifluoroacetic acid led to a decrease of reactivity as well as both the diastereo- and enantioselectivities (entry 5).[22] Excellent yield and diastereomeric and enantiomeric ratios were obtained with only *5 mol%* of catalyst (entry 6), at room temperature.

The best results were obtained when the reaction was carried out at 1 °C, although reaction time needed to be increased to 48 h (entry 7). Under these conditions catalyst loading can be diminished to 10 mol% or even 5 mol%, without loss of stereocontrol, but unfortunately with a significant drop in chemical yield (entries 10 and 11). Contrary to previously described results,[4] lower yield and stereoselection were observed when brine was used as reaction medium (entry 8). Under solvent-free conditions, the reaction works well at 1 °C giving the aldol in high yield, although in moderate diastereo- and enantioselectivity (entry 9). The reaction can be scaled-up without loss of stereoselectivity. In this way, a mixture of 4-nitrobenzaldehyde (0.805 g, 5 mmol), cyclohexanone (2.45 g, 25 mmol), catalyst **I** (275 mg, 1 mmol, 20 mol%) and AcOH (0.116 mL, 40 mol%) in 10 mL of water was stirred for 72 h. at 1 °C. After work-up, the aldol was obtained in excellent yield and diastereo- and enantioselectivity (entry 12).

A variety of aromatic aldehydes were then tested to study the electronic effects of substituents upon the aldol reaction with cyclohexanone using prolinamide **I** as catalyst. The results collected in Scheme 2 and Table 3 show that in fact chemical yields are dramatically dependant upon aldehyde substitution. Thus benzaldehyde itself (entry 7) as well as 2-naphthaldehyde and 4-methylbenzaldehyde furnished the corresponding aldols in



Scheme 2 Aldol reaction of cyclohexanone and different aldehydes catalyzed by **I**.

Table 3 Direct aldol reaction of different aldehydes and cyclohexanone by using catalyst **I**.[a]

Entry	R	*t*/h	Yield[b] (%)	Product	*anti*/*syn*[c,d]	E.e.[e,f]
1	4-CNC_6H_4	16	82	**1b**	95/5 (91/9)	94 (91)
2	4-$CF_3C_6H_4$	48	96	**1c**	97/3	94
3	4-$NO_2C_6H_4$	48	90	**1a**	98/2 (95/5)	94 (93)
4	2-$NO_2C_6H_4$	168	75	**1d**	97/3 (99/1)	94 (96)
5	3-$NO_2C_6H_4$	144	96	**1e**	97/3 (96/4)	98 (96)
6	4-ClC_6H_4	144	84	**1f**	98/2 (95/5)	94 (92)
7	Ph	168	40	**1g**	99/1 (85/15)	94 (83)
8	4-MeC_6H_4	192	10	**1h**	94/6	92
9[g]	4-MeC_6H_4	216	38	**1h**	88/12	84
10	2-Naphthyl	168	16	**1i**	99/1	92
11[g]	2-Naphthyl	240	44	**1i**	92/8	86

[a] Unless otherwise mentioned, the reaction was performed with aldehyde (0.5 mmol), cyclohexanone (0.26 mL, 2.5 mmol), catalyst (28 mg, 0.1 mmol), HOAc (11.6 mL, 0.2 mmol) and H_2O (1 mL) at 1 °C. [b] Yields determined after chromatographic purifications. [c] Diastereomeric excess determined by ^1H NMR of crude reaction mixture. [d] Numbers in parenthesis refer to the best d.r. previously described by using a diamide in water.[17b] [e] Enantiomeric excess by chiral HPLC analysis for *anti*-diastereomer. [f] Numbers in parenthesis refer to the best e.e. described by using a diamide in water.[19b] [g] Reaction performed at room temperature.

Table 4 Direct aldol reaction of 4-nitrobenzaldehyde with different ketones using catalyst **I**[a]

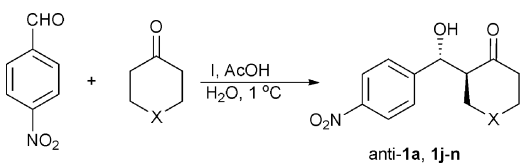
Entry	X/(Eq.)	*t*/h	Yield[b] (%)	Product	*anti*/*syn*[c]	E.r.[d]
1	—/(5)	18	85	**1j**	34/66	93/7 (61/39)[e]
2	CH_2/(5)	48	75	**1a**	98/2	97/3
3	CHMe/(5)	22	88	**1k**	98/2	96/4
4	O/(2)	142	61	**1l**	80/20	90/10
5	S/(2)	192	21	**1m**	96/4	93/7
6[f]	S/(2)	72	64	**1m**	98/2	97 : 3
7[g]	S/(2)	120	72	**1m**	97/3	96/4
8	NBoc/(2)	192	—	**1n**	—	—
9[f]	NBoc/(2)	118	66	**1n**	97/3[h]	94/6[h]

[a] Unless otherwise illustrated, the reaction was performed with aldehyde (0.5 mmol), ketone (1 or 2.5 mmol), catalyst (28 mg, 0.1 mmol), HOAc (11.6 mL, 0.2 mmol) and H_2O (1 mL) at 1 °C. [b] Yields determined after chromatographic purifications. [c] Diastereomeric excess determined by ^1H NMR of crude reaction mixture. [d] Enantiomeric excess determined by chiral HPLC analysis for *anti*-diastereomer. [e] E.r. for the *syn* isomer in parenthesis. [f] Solvent: H_2O–EtOH (1 : 1). [g] Solvent: H_2O–THF (1 : 1). [h] Measured on the reaction mixture.

medium or low yields (entries 8 and 10), respectively. Excellent diastereo- and enantioselectivities were obtained in all cases, though reactions carried out at rt (entries 9 and 11) showed a decline in stereoselection. These results clearly indicate the importance of electronic effects on the reaction rate: rapid for 4-substituted benzaldehydes with electro-withdrawing groups (entries 1–3), but much slower for unsubstituted aldehydes or for those substituted with electron-donating groups.

For comparative purposes, entries 1–7 in Table 3 (numbers in parenthesis) summarize the best stereochemical results previously obtained for the same reactions by using a catalyst derived from (1*R*,2*R*)-1,2-cyclohexane diamine.[17b] It can be observed that both the diastereomeric ratio and the enantiomeric excesses are better for the reactions promoted by **I** than those previously described in the same reaction conditions. The only exception refers to the aldol reaction between cyclohexanone and 2-nitrobenzaldehyde (entry 4).

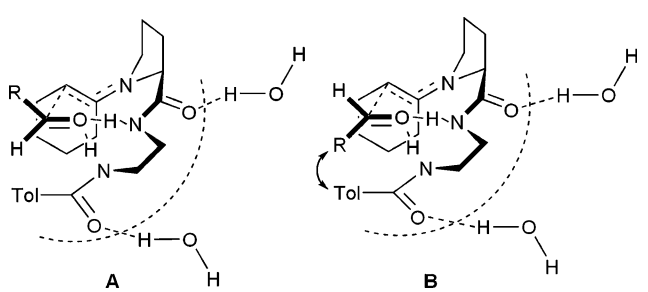
In order to increase the scope of catalyst **I**, the above reaction conditions were applied to several cyclic or heterocyclic ketones (Scheme 3 and Table 4). All six-membered ring ketones yielded the *anti* aldol as the major diastereoisomer whereas cyclopentanone yielded the *syn* aldol as the major product in low d.r. and e.r., although the minor *anti* stereoisomer was obtained with good e.r. (entry 1 in Table 4). In particular, good diastereo- and enantioselectivity were obtained with cyclohexanone and 4-methylcyclohexanone (entries 2 and 3), whereas tetrahydropyranone yielded the *anti* aldol **1l** with good enantioselectivity but only moderate diastereoselection (entry 4). On the other hand, tetrahydrothiopyranone reacted very slowly yielding the aldol **1m** with high diastereo- and enantioselection but in low yield (entry 5), and the piperidone derivative was not transformed after 192 h of reaction time (entry 8). Both of them led to the aldols **1m** and **1n** in good yields when the reactions were carried out in a mixture of water–ethanol (1 : 1, v/v) or water–THF (1 : 1, v/v) (entries 6, 7 and 9), thereby showing that solubility problems retard the reaction.



Scheme 3 Reaction of 4-nitrobenzaldehyde with different ketones.

The excellent levels of diastereo- and enantiocontrol can be attributed to the formation of hydrogen bonds between the water molecules surrounding the complex and the oxygen of the amide groups.[16e] These hydrogen bonds also increase the acidity of the NH groups making a more compact transition state and increasing the rate of the reactions.[11a,26]

The stereochemical outcome of the reaction can be explained in agreement with a simplified transition state as depicted in Scheme 4. That model indicates that the stereochemistry of the major isomer is determined by the stereocenter of the proline component of the catalyst. The presence of additional stereocenters at the amine counterpart of the prolinamides has little or no influence in the stereo-discrimination. Our results can be explained by accepting that transition state **A** is more favorable than **B** probably because of non-bonding repulsions between the R group of the aldehyde and the *p*-tolyl substituent of the amide. In this way, the major enantiomers are formed by reaction of the *re* face of the activated aldehyde with the *re* face of the enamine.



Scheme 4 Proposed TS for diastereo- and enantioselective aldol reaction.

Summary

Benzamidoethyl prolinamide **I** is an excellent catalyst for the diastereo- and enantioselective direct Barbas–List aldol reaction of six-membered ring ketones with aryl aldehydes in water as solvent. **I** and its enantiomer (*ent*-**I**) can be prepared in high yields from easily accessible L- or D-proline, respectively, and ethylenediamine. The homologous benzamidopropyl prolinamide (**II**), available from L-proline and 1,3-propane diamine, is also an excellent catalyst for asymmetric aldol reaction in water. It has been demonstrated that these prolinamides behave in the same way as more complex and expensive prolinamides derived from chiral diamines such as **III**, which was also prepared and tested in this work. The summarized results have also shown that it is not necessary to introduce additional stereocenters in the amine component of the prolinamide to get excellent diastereo- and enantiocontrol in the aldol reaction.

Experimental section

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ as solvent. Chemical shifts for protons are reported in ppm from TMS with the residual $CHCl_3$ resonance as internal reference. Chemical shifts for carbons are reported in ppm from TMS and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet m = multiplet, br = broad), coupling constants in Hertz, and integration. Specific rotations were measured using a 5-mL cell with a 1-dm path length, and a sodium lamp, and concentration is given in g per 100 mL. Infrared spectra are reported in wavenumbers. Melting points were obtained with open capillary tubes and are uncorrected. Flash chromatography was carried out using silica gel (230–240 mesh). Chemical yields refer to pure isolated substances. TLC analysis was performed on glass-backed plates coated with silica gel 60 and an F_{254} indicator, and visualized by either UV irradiation or by staining with phosphomolybdic acid solution. Chiral HPLC analysis was performed on a Hewlett–Packard 1090 Series II instrument equipped with a quaternary pump, using a Daicel Chiralcel OD Column (250 × 4.6 mm) or Chiralpak AS-H, AD-H Column (250 × 4.6 mm). UV detection was monitored at 220 or at 254 nm. Racemic samples were prepared by using racemic proline as the catalyst in DMF[23] or DMSO.[24]

Organic compounds were purchased from Aldrich and used as received. Solvents were dried and stored over microwave–activated 4 Å molecular sieves.

Typical procedure for enantioselective aldol reaction

To a mixture of catalyst (0.1 mmol), ketone (2.5 mmol) and water (1 mL), acetic acid (0.12 mL, 0.2 mmol) was added at 0 °C. The reaction mixture was stirred for 15 min in a closed vial, and then aldehyde (0.5 mmol) was added. The reaction mixture was stirred until the reaction was finished, then the reaction was quenched by addition of saturated ammonium chloride solution (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give pure aldol adduct after flash column chromatography on silica gel. Diastereoselectivity was determined by ^{1}H NMR analysis of the crude aldol product after short column chromatography purification to remove the cyclohexanone and the catalyst. The enantiomeric excess was determined by chiral-phase HPLC analysis using mixtures of hexane–isopropanol as eluting solvents. Absolute stereochemistry was determined by comparison with the literature data.

2-[Hydroxy(4-nitrophenyl)methyl]cyclohexan-1-one (1a)[25,26]. Yield: 90%; *anti*/*syn*: 98/2; *anti*-diastereomer (2*S*,1′*R*), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22–1.84 (m, 6H); 2.30–2.41 (m, 1H); 2.46–2.63 (m, 2H); 4.11 (d, J = 3.0 Hz, 1H); 4.89 (dd, J = 8.3 Hz, J = 2.9 Hz, 1H); 7.50 (d, J = 8.6 Hz, 2H); 8.19 (d, J = 8.6 Hz, 2H); HPLC analysis: Chiracel OD (hexanes/i-PrOH = 95/5, 1.5 mL min^{-1}, 220 nm, 20 °C): t_R = 18.8 min (major) and t_R = 25.8 min (minor); e.r.: 97 : 3, $[\alpha]_D^{23}$ = +10.9 (*c* 0.5, $CHCl_3$); *syn*-diastereomer, ^{1}H NMR ($CDCl_3$): δ 1.52–2.12 (m, 6H); 2.33–2.50 (m, 2H); 2.57–2.61 (m, 1H); 3.20 (br s, 1H); 5.43 (s, 1H); 7.43 (d, J = 8.0 Hz, 2H); 7.63 (d, J = 8.3 Hz, 2H).

2-[Hydroxy(4-cyanophenyl)methyl]cyclohexan-1-one (1b)[26,27]. Yield: 82%; *anti*/*syn*: 95/5; *anti*-diastereomer (2*S*,1′*R*), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35–2.14 (m, 6H); 2.30–2.50 (m, 2H); 2.53–2.61 (m, 1H); 4.07 (br s, 1H); 4.83 (d, J = 8.8 Hz, 1H); 7.45 (d, J = 8.3 Hz, 2H); 7.65 (d, J = 8.3 Hz, 2H); HPLC analysis: Chiracel OD (hexanes/i-PrOH = 95/5, 1.0 mL min^{-1}, 220 nm, 20 °C): t_R = 30.2 min (major) and t_R = 44.8 min (minor); er: 97 : 3, $[\alpha]_D^{23}$ = +21.4 (*c* 0.6, $CHCl_3$); *syn*-diastereomer, ^{1}H NMR ($CDCl_3$): δ 1.52–2.12 (m, 6H); 2.33–2.50 (m, 2H); 2.57–2.61 (m, 1H); 3.20 (br s, 1H); 5.43 (s, 1H); 7.43 (d, J = 8.0 Hz, 2H); 7.63 (d, J = 8.3 Hz, 2H).

2-[Hydroxy(4-trifluoromethylphenyl)methyl]cyclohexan-1-one (1c)[28]. Yield: 96%; *anti*/*syn*: 97/3; *anti*-diastereomer (2*S*,1′*R*), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26–1.36 (m. 1H); 1.54–1.80 (m, 4H); 2.05–2.10 (m, 1H); 2.35–2.60 (m, 3H); 4.07 (br s, 1H); 4.85 (d, J = 8.3 Hz, 1H); 7.45 (d, J = 7.9 Hz, 2H); 7.61 (d, J = 7.9 Hz, 2H); HPLC analysis: Chiralpak AD-H (hexanes/i-PrOH = 90/10, 0.5 mL min^{-1}, 254 nm, 20 °C): t_R = 21.0 min (minor) and t_R = 25.8 min (major); e.r.: 97 : 3, $[\alpha]_D$ = +20.0 (*c* = 1.0, $CHCl_3$).

2-[Hydroxy(2-nitrophenyl)methyl]cyclohexan-1-one (1d)[25,27]. Yield: 75%; *anti*/*syn*: 97/3; *anti*-diastereomer (2*S*,1′*R*), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57–1.88 (m, 6H); 2.07–2.13 (m, 1H); 2.33–2.49 (m, 2H); 2.74–2.78 (m, 1H); 5.45 (d, J = 7.0 Hz, 1H); 7.44 (t, J = 7.5 Hz, 1H); 7.76 (t, J = 7.5 Hz, 1H); 7.77 (d, J = 8.1 Hz, 1H); 7.85 (d, J = 8.1 Hz, 1H); HPLC analysis: Chiracel OD (hexanes/i-PrOH = 95/5, 1.0 mL min^{-1}, 220 nm, 20 °C) t_R = 18.0 min (major) and t_R = 21.5 min (minor); e.r.: 97 : 3, $[\alpha]_D^{23}$ = +21.9 (*c* 0.3, $CHCl_3$); *syn*-diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50–1.89 (m, 6H); 2.08–2.14 (m, 1H); 2.41–2.47 (m, 2H); 2.85–2.92 (m, 1H); 5.96 (d, J = 2.2 Hz, 1H); 7.43 (t, J = 7.5 Hz, 1H); 7.65 (t, J = 7.5 Hz, 1H); 7.84 (d, J = 7.9 Hz, 1H); 8.01 (d, J = 7.9 Hz, 1H).

2-[Hydroxy(3-nitrophenyl)methyl]cyclohexan-1-one (1e)[25,27]. Yield: 96%; *anti*/*syn*: 97/3; *anti*-diastereomer (2*S*,1′*R*), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30–1.85 (m, 6H); 2.32–2.43 (m, 1H); 2.48–2.53 (m, 1H); 2.58–2.67 (m, 1H); 4.13 (br s, 1 H); 4.90 (d, J = 9.0 Hz, 1H); 7.53 (t, J = 7.9 Hz, 1H); 7.67 (d, J = 7.5 Hz, 1H); 8.16 (d, J = 7.9 Hz, 1H); 8.21 (d, J = 1.7 Hz, 1H); HPLC analysis: Chiracel OD (hexanes/i-PrOH = 95/5, 1.5 mL min^{-1}, 220 nm,

20 °C): t_R = 15.2 min (major) and t_R = 20.9 min (minor); e.r.: 99 : 1, $[\alpha]_D^{23}$ = +31.5 (*c* 0.5, $CHCl_3$); *syn*-diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50–1.90 (m, 6H); 2.39–2.52 (m, 2H); 2.62–2.69 (m, 1H); 3.23 (br s, 1H); 5.48 (s, 1H); 7.52 (t, *J* = 7.9 Hz, 1H); 7.67 (t, *J* = 7.5 Hz, 1H); 8.12 (d, *J* = 8.3 Hz, 1H); 8.19 (s, 1H).

2-[Hydroxy(4-chlorophenyl)methyl]cyclohexan-1-one (1f)[16f,26]. Yield: 84%; *anti*/*syn*: 98/2; *anti*-diastereomer (2*S*,1′*R*), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26–2.11 (m, 6H); 2.31–2.49 (m, 2H); 2.52–2.59 (m, 1H); 3.61 (s, 1H); 4.76 (d, *J* = 8.4, 1H); 7.25 (d, *J* = 8.4 Hz, 2H); 7.31 (d, *J* = 8.8 Hz, 2H); HPLC analysis: Chiracel OD (hexanes/i-PrOH = 95/5, 1.0 mL min^{-1}, 220 nm, 20 °C): t_R = 13.4 min (major) and t_R = 19.4 min (minor); e.r.: 97 : 3; $[\alpha]_D^{23}$ = +22.5 (*c* 0.7, $CHCl_3$); *syn*-diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49–2.09 (m, 6H); 2.32–2.46 (m, 2H); 2.53–2.57 (m, 1H); 2.92 (br s, 1H); 5.34 (d, *J* = 2.0 Hz, 1H); 7.23 (d, *J* = 8.4 Hz, 2H); 7.30 (d, *J* = 8.4 Hz, 2H).

2-[Hydroxy(phenyl)methyl]cyclohexan-1-one (1g)[25,26]. Yield: 40%; *anti*/*syn*: 99/1; *anti*-diastereomer (2*S*,1′*R*), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27–2.13 (m, 6H); 2.31–2.52 (m, 2H); 2.55–2.67 (m, 1H); 3.99 (br s, 1H); 4.79 (d, *J* = 8.8 Hz, 1H); 7.29–7.40 (m, 5H); HPLC analysis: Chiracel OD (hexanes/i-PrOH = 90/10, 1.0 mL min^{-1}, 220 nm, 20 °C): t_R = 9.6 min (major) and t_R = 13.3 min (minor); e.r.: 97 : 3, $[\alpha]_D^{23}$ = +28.5 (*c* 0.4, $CHCl_3$); *syn*-diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48–2.12 (m, 6H); 2.33–2.48 (m, 2H); 2.50–2.64 (m, 1H); 3.05 (br s, 1H); 5.41 (s, 1H); 7.25–7.41 (m, 5H).

2-[Hydroxy(4-methylphenyl)methyl]cyclohexanone (1h)[16f,27]. Yield: 38%; *anti*/*syn*: 88 : 12; *anti*-diastereomer (2*S*,1′*R*), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51–1.80 (m, 5H); 2.05–2.11 (m, 1H); 2.34 (s, 3H); 2.41–2.50 (m, 2H); 2.57–2.64 (m, 1H); 3.94 (br s, 1H); 4.76 (d, *J* = 8.8 Hz, 1H); 7.16 (d, *J* = 8.3 Hz, 2H); 7.21 (d, *J* = 8.3 Hz, 2H); HPLC analysis: Chiracel OD (hexanes/i-PrOH = 95/5, 1.0 mL min^{-1}, 220 nm, 20 °C): t_R = 11.7 min (major) and t_R = 15.6 min (minor), e.r.: 92 : 8, $[\alpha]_D^{23}$ = +17.4 (*c* 0.7, $CHCl_3$); *syn*-diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48–1.88 (m, 5H); 2.05–2.12 (m, 1H); 2.35 (s, 3H); 2.38–2.48 (m, 2H); 2.55–2.62 (m, 1H); 2.99 (br s, 1H); 5.36 (s, 1H); 7.15 (d, *J* = 8.3 Hz, 2H); 7.20 (d, *J* = 8.3 Hz, 2H).

2-[Hydroxy(naphthalene-2-yl)methyl]cyclohexan-1-one (1i)[26,27]. Yield: 44%; *anti*/*syn*: 92/8; *anti*-diastereomer (2*S*,1′*R*), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27–1.41 (m, 1H); 1.50–1.78 (m, 4H); 2.07–1.12 (m, 1H); 2.33–2.44 (m, 1H); 2.49–2.54 (m, 1H); 2.68–2.77 (m, 1H); 4.10 (br s, 1H); 4.98 (d, *J* = 8.8 Hz, 1H); 7.48–7.51 (m, 3H); 7.77 (s, 1H); 7.83–7.87 (m, 4H); HPLC analysis: Chiralpak AS-H (hexanes/i-PrOH = 98/2, 1.0 mL min^{-1}, 220 nm, 20 °C): t_R = 40.3 min (major) and t_R = 45.3 min (minor), e.r.: 93 : 7, $[\alpha]_D^{23}$ = +17.2 (*c* = 0.6, $CHCl_3$); *syn*-diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46–1.56 (m, 1H); 1.63–1.85 (m, 4H); 2.08–2.12 (m, 1H); 2.35–2.52 (m, 2H); 2.69–2.75 (m, 1H); 3.19 (br s, 1H); 5.58 (s, 1H); 7.37 (d, *J* = 9.2 Hz, 1H); 7.46–7.50 (m, 2H); 7.81–7.84 (m, 4H).

2-[Hydroxy(4-nitrophenyl)methyl]cyclopentan-1-one (1j)[29]. Yield: 85%; *anti*/*syn*: 34/66; *anti*-diastereomer (2*S*,1′*R*), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51–1.80 (m, 3H); 1.98–2.07 (m, 1H); 2.21–2.52 (m, 3H); 4.78 (s, 1H); 4.85 (d, *J* = 9.2 Hz, 1H); 7.54 (d, *J* = 8.8 Hz, 2H); 8.22 (d, *J* = 8.8 Hz, 2H); HPLC analysis: Chiralpak AD-H (hexanes/i-PrOH = 90/10, 0.5 mL min^{-1}, 254 nm, 20 °C): t_R = 46.9 min (minor) and t_R = 48.7 min (major); e.r.: 93 : 7, $[\alpha]_D^{23}$ = −88.5 (*c* 0.95, $CHCl_3$); *syn*-diastereomer, ^{1}H NMR ($CDCl_3$): δ 1.65–1.76 (m, 2H); 1.96–2.22 (m, 3H); 2.36–2.52 (m, 2H); 2.69 (br s, 1H); 5.43 (d, *J* = 2.2 Hz, 1H); 7.53 (d, *J* = 8.8 Hz, 2H); 8.22 (d, *J* = 8.8 Hz, 2H). HPLC analysis: Chiralpak AD-H (hexanes/i-PrOH = 90/10, 0.5 mL min^{-1}, 254 nm, 20 °C): t_R = 28.5 min (major) and t_R = 36.6 min (minor); e.r.: 61 : 39, $[\alpha]_D^{23}$ = +49.0 (*c* 0.6, $CHCl_3$).

2-[Hydroxy(4-nitrophenyl)methyl]-4methylcyclohexan-1-one (1k)[5b,29]. Yield: 88%; *anti*/*syn*: 98/2; *anti*-diastereomer (2*S*,1′*R*), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, *J* = 7.0 Hz, 3H); 1.30–2.12 (m, 5H); 2.36–2.79 (m, 3H); 3.94 (br s, 1H); 4.93 (d, *J* = 8.8 Hz, 1H); 7.51 (d, *J* = 8.8 Hz, 2H); 8.22 (d, *J* = 8.8 Hz, 2H); HPLC analysis: Chiralpak AD-H (hexanes/i-PrOH = 90/10, 1.0 mL min^{-1}, 254 nm, 20 °C): t_R = 32.5 min (major) and t_R = 35.9 min (minor), e.r.: 96 : 4, $[\alpha]_D^{23}$ = −42.0 (*c* 0.7, EtOAc); *syn*-diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (d, *J* = 7.0 Hz, 3H); 1.78–2.12 (m, 5H); 2.30–2.85 (m, 3H); 3.15 (br s, 1H); 5.49 (d, *J* = 2.2 Hz); 7.49 (d, *J* = 8.8 Hz, 2H); 8.21 (d, *J* = 8.8 Hz, 2H).

(3*S*,1′*R*)-3-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]tetrahydropyran-4-one (1l)[30]. Yield: 61%; mixture of *anti*/*syn*: 80/20, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50–2.57 (m, 1H); 2.64–2.74 (m, 1H); 2.85–2.93 (m, 1H); 3.42–3.49 (m, 1H); 3.70–3.79 (m, 3H); 4.18–4.24 (m, 1H); 4.99 (d, *J* = 7.9 Hz, 0.8H, *anti*); 5.54 (d, *J* = 2.6 Hz, 0.2H, *syn*); 7.52 (d, *J* = 8.8 Hz, 2H); 8.23 (d, *J* = 8.8 Hz, 2H); analysis Chiralpak AD-H (hexanes/i-PrOH = 80/20, 1.0 mL min^{-1}, 254 nm, 20 °C): t_R = 20.3 min (minor) and t_R = 23.8 min (major), e.r.: 90 : 10, $[\alpha]_D^{23}$ = + 6.8 (*c* 0.9, $CHCl_3$).

(3*S*,1′*R*)-3-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]tetrahydrothiopyran-4-one (1m)[31]. Yield: 64%; *anti*/*syn*: 98/2; *anti*-diastereomer (3*S*,1′*R*), ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49–2.54 (m, 1H); 2.65–2.73 (m, 1H); 2.78–2.85 (m, 2H); 2.98–2.06 (m, 3H); 3.64 (br s, 1H); 5.06 (d, *J* = 7.9 H, 1H); 7.55 (d, *J* = 8.8 Hz, 2H); 8.25 (d, *J* = 8.8 Hz, 2H); HPLC analysis: Chiralpak AD-H (hexanes/i-PrOH = 90/10, 1.0 mL min^{-1}, 254 nm, 20 °C): t_R = 45.5 min (minor) and t_R = 80.5 min (major), e.r.: 97 : 3, $[\alpha]_D^{23}$ = +15.0 (*c* = 0.6, $CHCl_3$); *syn*-diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50–2.55 (m, 1H); 2.81–2.84 (m, 2H); 2.96–3.06 (m, 6H); 3.12 (br s, 1H); 5.53 (s, 1H); 7.53 (d, *J* = 8.8 Hz, 2H); 8.24 (d, *J* = 8.8 Hz, 2H).

(3*S*,1′*R*)-3-[1′-Hydroxy-1′-(4-nitrophenyl)methyl]-4-oxopiperidine-1-carboxylic acid *tert*-butyl ester (1n)[32]. Yield: 66%; mixture of *anti*/*syn*: 96/4, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (br s, 9H); 2.49–2.56 (m, 2H); 2.77 (br s, 1H); 2.93 (t, *J* = 11.0 Hz, 1H); 3.27 (br s, 1H); 3.70–3.83 (m, 1H); 3.87 (d, *J* = 3.6 Hz, 1H); 4.19 (m, 1H); 4.97 (dd, *J* = 7.9 Hz, *J* = 3.1 Hz, 0.96H, *anti*); 5.48 (br s, 0.04H, *syn*); 7.56 (d, *J* = 8.4 Hz, 2H); 8.24 (d, *J* = 8.8 Hz, 2H); HPLC analysis: Chiralpak AD-H (hexanes/i-PrOH = 97 : 3, 1.0 mL min^{-1}, 220 nm, 20 °C): t_R = 75.0 min (major) and t_R = 85.0 min (minor), e.r.: 94 : 6, $[\alpha]_D^{23}$ = +17.2 (*c* 1.1, $CHCl_3$).

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