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A highly enantio- and diastereoselective direct aldol reaction in aqueous medium catalyzed by thiazolidine-based compounds

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ABSTRACT

Taking L-aminoacids as starting materials, a new set of enantiopure thiazolidine-based organocatalysts were prepared using a simple synthetic approach and successfully applied in the asymmetric direct aldol reaction between various cyclic ketones and aldehydes in a saturated aqueous medium. The aldol adducts were obtained with excellent enantioselectivity (up to >99% ee) and diastereoselectivity (dr >20:1).

1. Introduction

Asymmetric organocatalysis, which is based on use of small organic molecules in the absence of transition metals, is now a well-established research area and recognized as the third column of organic synthesis due to its versatility and efficiency. To date, more than 300 reactions and methodologies have been developed using organocatalyzed processes.[1] Since the seminal article published by List, Barbas et al.,[2] which reported the use of L-proline to catalyze the direct intermolecular asymmetric aldol reaction, this research area has experienced an exponential growth. Great effort has been devoted to the development of new organocatalysts and organocatalytic processes that can be used toward the synthesis of lead products in high yield and stereoselectivity including the synthesis of natural products and compounds with interesting biological properties.[1a–g]

The amino acid L-proline has been intensively studied and used to catalyze more than ten different reactions and has therefore achieved a 'privileged catalyst' status.[3] Consequently, over the past few years, a great deal of attention has been devoted to the use of naturally occurring amino acids in organocatalysis due to their low cost and availability in an enantiopure form.[4]

Further studies reported by Barbas et al.[2a] have shown that (*R*)-thiazolidine-4-carboxylic acids can also promote the aldol reaction with high enantioselectivity. However, the use of this type of heterocycle as a chiral modifier in organocatalysis has been rarely reported.[2,5] Despite the lack of literature precedent, during the course of our work in the field of asymmetric catalysis we have reported the successful use of thiazolidines as chiral ligands in several organometallic reactions.[6–8]

Recently, our group has developed a new class of thiazolidine-based organocatalysts, which are readily obtained from L-cysteine and successfully applied them in the direct asymmetric aldol reaction between propanone and a variety of aldehydes **3d–g** (Fig. 1).[9] In this context and in connection with our continuing interest in the development and application of new organocatalysts, we now report the synthesis of three new thiazolidine-based compounds **3a–c** (Fig. 1) in an attempt to improve the activity and selectivity of thiazolidine-based organocatalysts. We have also expanded the application of these compounds by evaluating their catalytic activity in the direct asymmetric aldol reaction between various cyclic ketones and aldehydes in an aqueous medium.

2. Results and discussion

The organocatalysts **3a–f** were synthesized via a short and high yielding sequence using L-amino acids as the starting materials. Most importantly, this synthetic strategy can readily generate a high degree of structural diversity, which is important for the systematic optimization of the catalysts structure.

L-Cysteine was initially reacted with formaldehyde and subsequently protected with Boc_2O to give the unsubstituted thiazolidine carboxylic acid **1a** (Scheme 1). In order to study the influence of substituents on the heterocyclic moiety, compound **1b** was also synthesized by refluxing L-cysteine in propanone followed by protection with Boc_2O.

A double Grignard addition or reduction of an aminoester afforded the desired range of aminoalcohols, which were reacted with the thiazolidine carboxylic acids **1a** and **1b** in the presence of stoichiometric amounts of $ClCO_2Et$ and NMM to give the corresponding amides **2a–c** (Scheme 2). In order to understand the role of the different substituents (R, R′, and R″), different amino acids were used including L-methionine and L-cysteine for compounds

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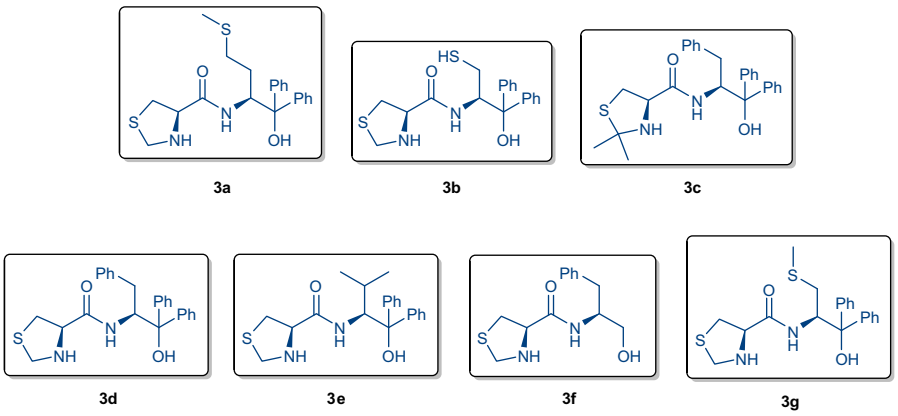
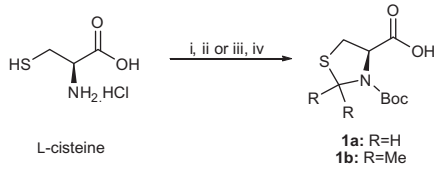


Figure 1. Thiazolidine-based organocatalysts **3a–g**.



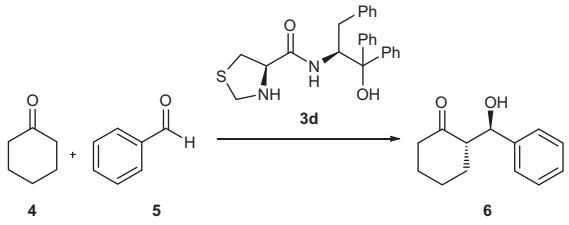
Scheme 1. Synthesis of the thiazolidine carboxylic acids **1a–b**. Reagents and conditions: (i) 37% HCHO, 1 M NaOH; (ii) Boc_2O, 1 M NaOH, 1,4-dioxane/H_2O (95%); (iii) Me_2CO, reflux; (iv) Boc_2O, DIPEA, MeCN (40%).

3a and **3b**, respectively, and L-phenylalanine for compound **3c**. Removal of the Boc group delivered the desired organocatalysts **3a–c** in good overall yield. Compounds **3d** and **3g** (Fig. 1) were synthesized using the same synthetic strategy. All spectroscopic data are in accordance with those reported in the literature.[9]

With the target compounds **3a–c** in hand, together with the known organocatalysts **3d–f**, we focused our attention toward the optimization of the aldol reaction with an aim of controlling the stereochemistry of the two stereocenters formed during the reaction. As a model reaction, we elected to investigate the aldol reaction between cyclohexanone and benzaldehyde catalyzed by compound **3d**. Organocatalyst **3d** had furnished the best results in a previously reported study[9] and the results depicted in Table 1.

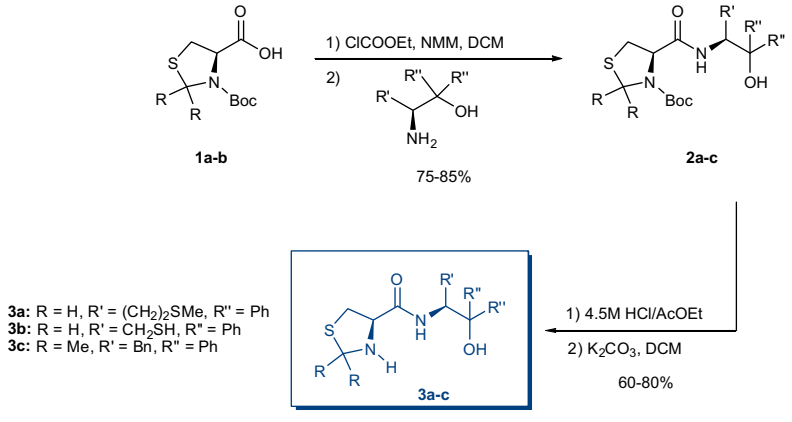
Initially, we investigated the effect of catalyst loading, reaction time, and temperature on the yield, diastereomeric ratio (dr) and enantiomeric excess (ee). As expected, lower yields were obtained with shorter reaction times (Table 1, entries 1–5). By either increasing or decreasing the catalyst loading from 10 mol %, inferior results were achieved. In the case of 5 mol % of catalyst **3d**, a dramatic decrease in the yield and ee was observed (Table 1, entries 6 and 7). Using 15 mol % of catalyst, no significant

Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst (mol %)	Time (h)	Temp (°C)	Yield[b] (%)	ee[c] (%)	dr[d] (*anti*/*syn*)
1	10	24	rt	16	99	10:1
2	10	48	rt	23	99	10:1
3	10	72	rt	25	99	10:1
4	10	96	rt	58	99	10:1
5	10	120	rt	66	99	10:1
6	5	120	rt	24	92	>20:1
7	15	120	rt	55	80	>20:1
8	10	120	40	54	94	8:1

[a] Reaction performed with 1.0 mL of cyclohexanone, 1.0 mmol (0.101 mL) of benzaldehyde and 5–15 mol % of organocatalyst **3d**.
[b] Isolated yield.
[c] Determined by HPLC using chiral stationary phase.
[d] Determined by ^1H NMR spectroscopy of the crude reaction mixture.



Scheme 2. Synthesis of organocatalysts **3a–c**.

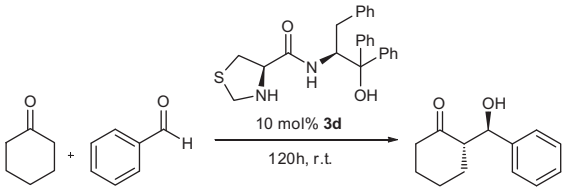
increase in product yield was observed, however a great reduction in ee was observed. No changes in product yield were observed when the reaction was performed at 40 °C, but in terms of the stereoselectivity of the reaction, the results were poor (Table 1, entry 8).

After screening the experimental parameters, we performed the reaction with the optimized conditions using organocatalyst **3d** in different polar and non-polar solvents as well as in aqueous systems (Table 2). Performing the reaction in CH_2Cl_2 or toluene leads to a dramatic reduction in the product yield and stereoselectivity (Table 2, entries 2 and 3). Surprisingly, the use of DMSO, a broadly used solvent in organocatalytic systems,[4] did not promote the reaction and trace amounts of product were obtained (Table 2, entries 4 and 7). When considering the literature precedent, we discovered that the use of this type of organocatalyst in the direct aldol reaction has been shown to be influenced, in terms of the stereoselectivity of the reaction, by the use of a reaction system with equal amounts of water or brine and ketone.[5,11] Subsequently, we performed the reaction using water itself or aqueous solvent systems and good results were achieved (Table 2, entries 5 and 6 compared with entries 8 and 9). Indeed when brine was used as the solvent, an excellent ee (99%) and excellent dr (>20:1 (*anti*/*syn*)) were obtained (Table 2, entry 9).

Once we established the optimized catalyst loading and the reaction conditions, we evaluated the different characteristics of compounds **3a–f** in regard to their polarity, solubility, and hydrophobicity or hydrophilicity, in order to identify an organocatalyst with superior performance. For this purpose we used the two best reaction conditions: (1) using the ketone as solvent (Table 2, entries 1 and 2) using a brine/ketone mixture as the solvent (Table 2, entry 9). The results are summarized in Table 3 (please note the results in the parenthesis refer to reactions performed using a brine/ketone solvent system).

We observed that the catalysts possessing polar hydrophilic groups on the aminoalcohol moiety furnished the desired product in moderate yields and with high ee and dr (Table 3, entries 1 and 2). The presence of a *gem*-dimethyl group on the heterocycle in catalyst **3c** caused a dramatic reduction in the reaction yield, which was attributed to difficult enamine formation

Table 2
Solvent screen[a]

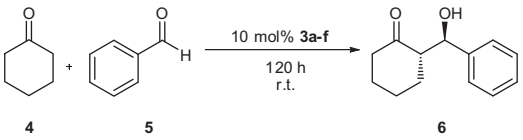


4 5 6

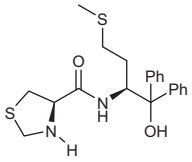
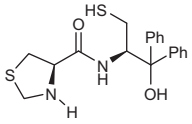
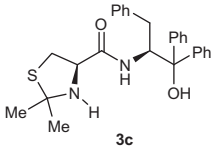
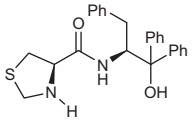
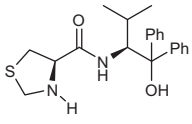
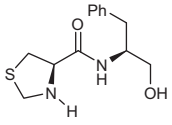
Entry	Solvent	Yield[b] (%)	ee[c] (%)	dr[d] (*anti*/*syn*)
1	**4**	66	99	10:1
2	CH_2Cl_2	15	71	6:1
3	PhMe	20	60	8:1
4	DMSO	Traces	—	—
5	H_2O	59	94	14:1
6	Brine	62	99	14:1
7	DMSO–**4** (1:1)	Traces	—	—
8	H_2O–**4** (1:1)	60	97	10:1
9	Brine–**4** (1:1)	64	99	>20:1

[a] Reaction performed with 1.0 mL of solvent or solvent combination, 1.0 mmol of benzaldehyde (0.101 mL) and 10 mol % (0.1 mmol, 0.042 g) of organocatalyst **3d**.
[b] Isolated yield.
[c] Determined by HPLC using chiral stationary phase.
[d] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Table 3
Direct asymmetric aldol reaction between cyclohexanone and benzaldehyde catalyzed by organocatalysts **3a–f**[a]



4 5 6

Entry	Catalyst	Yield[b] (%)	% ee[c]	dr[d] (*anti*/*syn*)
1	 **3a**	35 (69)	90 (99)	19:1 (19:1)
2	 **3b**	46 (35)	94 (99)	>20:1 (>20:1)
3	 **3c**	42 (20)	36 (96)	4:1 (19:1)
4	 **3d**	66 (64)	99 (99)	10:1 (>20:1)
5	 **3e**	75 (40)	92 (99)	10:1 (>20:1)
6	 **3f**	25 (33)	64 (92)	>20:1 (>20:1)

[a] Reaction performed with 1.0 mL of cyclohexanone, 1.0 mmol of benzaldehyde, and 0.1 mmol of organocatalyst.
[b] Isolated yield.
[c] Determined by HPLC using chiral stationary phase.
[d] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The results in the parenthesis refer to reactions performed using a brine/ketone solvent system.

(Table 1, entries 3 and 4). A similar result was found with the organocatalyst with no *gem*-diphenyl group on the amino alcohol moiety (Table 1, entry 6). According to previous reports, the *gem*-diaryl group plays a crucial role in the catalytic system.[10] These substituents act by facilitating the formation of cyclic intermediates through the Thorpe–Ingold effect. In addition, for the case of alcohols, this group contributes to an increase in the acidity of the hydroxyl group, which was required in the formation of hydrogen bonds. The best results were obtained with organocatalysts **3d** and **3e**, which contain hydrophobic groups (benzyl and isopropyl groups, respectively). Although catalyst **3e** furnished the aldol adduct in the highest yield, the stereoselectivity of the reaction was better using catalyst **3d** (entries 4 and 5).

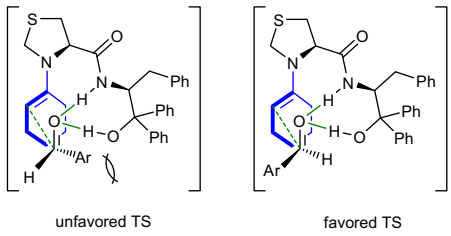


Figure 2. Proposed transition states.

As expected, performing the reaction in a ketone–brine solvent system gave improved results in terms of the reaction yield and stereoselectivity for the majority of the catalysts studied. Notably, an increase in ee was observed for all the catalysts, up to 99% ee in most cases and no less than 92% ee (catalyst **3f**). Also the dr values showed a remarkable improvement for catalysts **3c–e**, up to >20:1 and no less than 19:1. The reaction yield remained in the same range for the majority of the catalysts with the exception of catalyst **3a** where a considerable increase in yield from 35% to 69% was observed while when catalyst **3e** was used a decrease in yield from 75% to 40%, which was attributed to its low solubility in an aqueous medium was obtained.

Based on these experimental results and literature precedent, we propose that the stereoselectivity observed during the direct aldol reaction catalyzed by **3a–f** can be described by the transition state model depicted in Figure 2.[10,12] After enamine formation by the catalyst and ketone, the position of the aldehyde can be oriented via hydrogen bonding interactions. In this way, the C–C bond formation takes place from the *re* face of the aldehyde. The presence of the *gem*-diphenyl group on the amino alcohol moiety restricts the conformation of the transition state and makes the hydroxyl group a better hydrogen bond donor (Table 3, entries 4 and 6). Furthermore, the beneficial effect of water in the asymmetric aldol reaction was attributed to improved catalyst turnover due to faster hydrolysis of the intermediates in the enamine catalytic cycle and the suppression of catalyst inhibition.

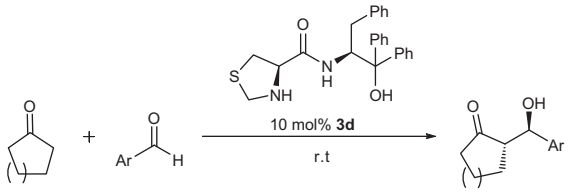
Having established the optimal reaction conditions, the scope and limitations of the direct aldol reaction catalyzed by **3d** were also examined (Table 4). The optimal reaction conditions were applied in the organocatalytic reaction and a wide range of aromatic aldehydes were found to react smoothly with cyclic ketones to give their corresponding aldol adducts with good to excellent results. The results listed in Table 4 confirm that ligand **3d** was a suitable catalyst for this asymmetric reaction.

Aldehydes with strong electron-donating groups in the *para* position, such as methyl and methoxyl groups (Table 4, entries 2 and 3, respectively), lead to a low yield of the desired product even when prolonged reaction times were used. However, excellent enantioselectivity (up to 99% ee for *p*-tolualdehyde) and good to excellent diastereoselectivity were observed. In the case of *para*-halogenated aldehydes, the aldol addition product was obtained in moderate to good yield after 120 h with excellent ee and dr (Table 4, entries 4 and 5).

The use of aromatic aldehydes with strong electron-withdrawing groups such as nitro or cyano groups (Table 4, entries 6–9), lead to a dramatic decrease in the reaction time and the products were obtained in an almost quantitative yield after 24 h. Regardless of the position and chemical nature of the substituent, the stereoselectivity obtained was excellent, with enantioselectivities >98% ee and diastereoselectivities between 10:1 and >20:1.

Using a smaller cyclic ketone, cyclopentanone (Table 4, entry 10), the organocatalyst was also effective giving the aldol product in excellent yield (90%) after 24 h and good enantioselectivity (90% ee) although the diastereoselectivity was lower (dr = 2:1). When the reaction was performed with a larger cyclic ketone, cycloheptanone (Table 4, entry 11), no product was isolated. This was attributed to the formation of an enamine that provided greater steric repulsion to the aldehyde (see the transition state shown in Fig. 2).

Table 4
Reaction scope: aldehydes and cyclic ketones[a]



Entry	Ketone (*n*)	Aldehyde (Ar)	Time (h)	Yield[b] (%)	% ee[c]	dr[d] (*anti*/*syn*)
1	**4a** (2)	Ph	120	**6a**: 66	99	>20:1
2	**4a** (2)	*p*-Me-Ph	120	**6b**: 25	>99	>20:1
3	**4a** (2)	*p*-MeO-Ph	120	**6c**: 15	98	>20:1
4	**4a** (2)	*p*-Cl-Ph	120	**6d**: 84	99	>20:1
5	**4a** (2)	*p*-Br-Ph	120	**6e**: 60	99	8:1
6	**4a** (2)	*p*-CN-Ph	24	**6f**: 96	98	>20:1
7	**4a** (2)	*o*-NO_2-Ph	24	**6g**: 97	>99	>20:1
8	**4a** (2)	*m*-NO_2-Ph	24	**6h**: 95	98	10:1
9	**4a** (2)	*p*-NO_2-Ph	24	**6i**: 90	98	10:1
10	**4b** (1)	*p*-NO_2-Ph	24	**6j**: 97	90	2:1
11	**4c** (3)	*p*-NO_2-Ph	120	**6k**: trace	—	—

[a] Reaction performed with 0.5 mL of cyclic ketone, 0.5 mL of brine, 1.0 mmol of aldehyde and 10 mol % (0.1 mmol, 0.042 g) of organocatalyst **3d**.
[b] Isolated yield.
[c] Determined by HPLC using chiral stationary phase.
[d] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

3. Conclusion

To summarize, three new thiazolidine amides derived from different L-amino alcohols were synthesized using a simple synthetic approach. A wide variety of substituents can be incorporated into the compounds and allowed us to explore the influence of their stereoelectronic effects in order to discover an efficient catalytic system. All the organocatalysts were evaluated for their ability to catalyze the direct aldol reaction between a variety of aromatic aldehydes and cyclic ketones. The results demonstrated that the organocatalyst **3d** was very efficient and furnished the desired aldol adducts with excellent enantioselectivity (up to 99% ee) and diastereoselectivity [dr = 99:1 (*anti*/*syn*)]. Expanding the scope of this organocatalyst in other asymmetric transformations is currently underway in our laboratory.

4. Experimental

4.1. General methods

The ^{1}H NMR, ^{13}C NMR, 2D-COSY NMR, and 2D-HMQC NMR spectra were recorded on 300 MHz spectrometers Varian Inova 300 and Varian VNMRS 300. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard in spectra made in $CDCl_3$. Coupling constants are reported in Hz. All enantiomeric excesses were obtained from HPLC using chiral stationary phase (Chiralcel OD-H or OJ-H columns and Chiralpak AD-H or AS-H columns) in a Shimadzu LC-20AT chromatograph. Optical rotations were obtained in a Perkin Elmer Polarimeter 341. Infrared spectra were obtained in a Varian 640-IR spectrometer. All the column

chromatography separations were done by using silica gel Fluka, 100–200 Mesh. Solvents were purified by usual methods.[13] Other reagents were obtained from commercial source and used without further purification. The organic extracts were dried over anhydrous sodium sulfate. Evaporation of solvent was performed under reduced pressure. Brine refers to saturated solution of NaCl in water at 25 °C.

4.2. General procedure for the synthesis of catalysts 3a-c

In 150 mL two necked round-bottomed flask, the *N*-protected thiazolidine **1a** or **1b** (15 mmol), anhydrous dichloromethane (30 mL) and *N*-methylmorpholine (1.62 mL, 15 mmol) were added under argon atmosphere at 0 °C. The solution was stirred for 30 min. then ethyl chloroformate (1.43 mL, 15 mmol) was added. After 30 min. the aminoalcohol (15 mmol) was added and the mixture was stirred for 24 h at rt. Then, the mixture was diluted in dichloromethane (20 mL) and washed with 1 M NaOH and aqueous solution of NaCl. The organic layer was dried over Na_2SO_4 and evaporated. The residue was dissolved in ethyl acetate (60 mL) and a solution of 4.5 M HCl in ethyl acetate (54 mL) was added dropwise at 0 °C. The suspension was stirred for 15 min. and then the solvent was evaporated. The residue was dissolved in dichloromethane and evaporated again. This procedure was repeated three times. The residue was then dissolved in a solution of CH_2Cl_2 1:1 H_2O, cold to 0 °C and neutralized with K_2CO_3. The organic layer was separated and the aqueous layer washed with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated. The residue was purified with column chromatography or recrystallization to furnish the product.

4.2.1. (*R*)-*N*-((*S*)-1-Hydroxy-4-(methylthio)-1,1-diphenylbutan-2-yl)thiazolidine-4-carboxamide 3a

This was prepared as per our general procedure to afford product **3a**. Recrystallization from CH_2Cl_2 furnished a white solid. Yield: 80%. Mp 152–154 °C. $[\alpha]_D^{20} = -57$ (*c* 1, CH_2Cl_2). IR (FT-IR/ATR, cm^{-1}): 1515, 1651, 3324. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.55 (m, 4H), 7.44 (d, 1H, *J* = 9.2 Hz), 7.23 (m, 6H), 4.98 (m, 1H), 4.73 (br s, 1H), 3.98 (d, 1H, *J* = 10 Hz), 3.78 (dd, 1H, *J* = 4.8 Hz, *J* = 7.3 Hz), 3.51 (d, 1H, *J* = 10 Hz), 2.97 (dd, 1H, *J* = 4.9 Hz, *J* = 10.9 Hz), 2.81 (dd, 1H, *J* = 7.3 Hz, *J* = 10.8 Hz), 2.58 (m, 2H), 2.33 (br s, 1H), 1.95 (s, 3H), 1.84 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 172.1, 146.2, 144.1, 128.8, 128.1, 127.7, 127.3, 124.9, 81.2, 65.9, 56.1, 53.6, 35.1, 31.1, 28.2, 15.3. HRMS calculated for $[C_{21}H_{26}N_2O_2S_2+Na]+$: 425.5626, obtained: 425.5620.

4.2.2. (*R*)-*N*-((*R*)-1-Hydroxy-3-mercapto-1,1-diphenylpropan-2-yl)thiazolidine-4-carboxamide 3b

This was prepared as per our general procedure to afford product **3b**. Recrystallization from EtOH furnished a white solid. Yield: 65%. Mp 128–131 °C. $[\alpha]_D^{20} = -151$ (*c* 1, CH_2Cl_2). IR (FT-IR/ATR, cm^{-1}): 1522, 1655, 2554, 3334. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.71 (m, 5H), 7.25 (m, 6H), 5.29 (br s, 2H), 4.01 (m, 1H), 3.76 (s, 2H), 3.08 (br s, 1H), 2.80 (m, 3H), 2.39 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 172.1, 145.2, 144.1, 129.1, 128.9, 127.9, 125.5, 81.1, 66.1, 57.5, 53.4, 38.2, 35.1. HRMS calculated for $[C_{19}H_{22}N_2O_2S_2+Na]+$: 397.5094, obtained: 397.5090.

4.2.3. (*R*)-*N*-((*S*)-1-Hydroxy-1,1,3-triphenylpropan-2-yl)-2,2-dimethylthiazolidine-4-carboxamide 3c

This was prepared as per our general procedure to afford product **3c**. The residue was concentrated in vacuum and purified by column chromatography with silica gel 230–400 Mesh with a mixture of hexanes/ethyl acetate (1:1) as eluent to furnish the product as a white solid. Yield: 50%. Mp 193–196 °C. $[\alpha]_D^{20} = -98$ (*c* 1, CH_2Cl_2). IR (FT-IR/ATR, cm^{-1}): 1517, 1656, 2960, 2980, 3320. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.71 (m, 2H), 7.58 (m, 2H), 7.39 (m, 2H), 7.24 (m, 7H), 7.17 (m, 3H), 5.40 (br s, 1H), 4.84 (m, 1H), 3.81 (m, 1H), 3.17 (m, 2H), 2.91 (dd, 2H, *J* = 3.4 Hz, *J* = 13.6 Hz), 2.79 (dd, 2H, *J* = 8.5 Hz, *J* = 11.9 Hz), 2.09 (br s, 1H), 1.63 (br s, 1H), 1.43 (s, 3H), 0.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 172.1, 145.7, 144.9, 139.1, 129.1, 128.8, 128.3, 127.4, 126.6, 126.2, 125.8, 125.4, 80.9, 80.2, 67.6, 60.8, 59.4, 36.1, 30.3, 28.3. HRMS calculated for $[C_{27}H_{30}N_2O_2S+Na]+$: 469.5935, obtained: 469.5940.

4.3. General procedure for organocatalytic asymmetric direct aldol addition

A solution of a catalyst **3** in dry cyclic ketone (0.5 mL) was stirred at the temperature indicated in the tables, for around 2 h. Aldehyde (1 mmol) was then slowly added and after addition of brine (0.5 mL) the resulting mixture was stirred for the indicated time. After that, the reaction mixture was treated with saturated aqueous ammonium chloride solution (10 mL) and the whole mixture was extracted with dichloromethane (3 × 20 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed under vacuum. The crude mixture was purified by column chromatography on silica gel with hexanes/ethyl acetate (80:20) being the eluant. The enantiomeric excess (ee) was determined by HPLC analysis using Chiracel OD-H or OJ-H and Chiralpak AD-H or AS-H columns and the diastereomeric ratio was determined by ^1H NMR analysis.

4.3.1. (*S*)-2-((*R*)-Hydroxy(phenyl)methyl)cyclohexanone 6a

This compound was obtained in a maximum yield of 66% with ee = 99% and dr = >20:1. The enantiomeric excess was determined by HPLC on Chiralcel OD-H (hexanes/2-propanol 90:10); 221 nm; flow rate 0.5 mL/min; $t_{R(major)}$ = 9.38 min (*S*, *R*), $t_{R(minor)}$ = 12.48 min (*R*, *S*). $[\alpha]_D^{20}$ = +18 (*c* 1, $CHCl_3$) {lit.[5] $[\alpha]_D^{25}$ = +19 (*c* 1, $CHCl_3$)}. ^1H NMR (300 MHz, $CDCl_3$, δ) 7.30 (5H, m), 4.79 (1H, d, *J* = 8.8 Hz), 4.05 (1H, s), 2.63 (1H, m), 2.49 (1H, m), 2.34 (1H, m), 2.06 (1H, m), 1.62 (4H, m), 1.28 (1H, m).

4.3.2. (*S*)-2-((*R*)-Hydroxy(*p*-tolyl)methyl)cyclohexanone 6b

This compound was obtained in a maximum yield of 25% with ee >99% and dr = 98:2. The enantiomeric excess was determined by HPLC with chiral stationary phase: $t_{R(major)}$ = 25.27 min (*S*, *R*), $t_{R(minor)}$ = 23.45 min (*R*, *S*). $[\alpha]_D^{25}$ = +17 (*c* 0.2, $CHCl_3$) {lit.[14] $[\alpha]_D^{24}$ = +12.9 (*c* 0.17, $CHCl_3$)}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–7.02 (4H, m), 4.67 (1H, d, *J* = 8.8 Hz), 2.58–2.46 (1H, m), 2.45–2.34 (1H, m), 2.34–2.17 (4H, m), 2.07–1.93 (1H, m), 1.77–1.63 (1H, m), 1.63–1.35 (3H, m), 1.30–1.12 (1H, m).

4.3.3. (*S*)-2-((*R*)-Hydroxy(4-methoxyphenyl)methyl)cyclohexanone 6c

This compound was obtained in a maximum yield of 15% with ee = 98% and dr = 89:11. The enantiomeric excess was determined by HPLC with chiral stationary phase: $t_{R(major)}$ = 33.85 min (*S*, *R*), $t_{R(minor)}$ = 30.60 min (*R*, *S*). $[\alpha]_D^{25}$ = +25 (*c* 1, $CHCl_3$) {lit.[5] $[\alpha]_D^{25}$ = +30.5 (*c* 1.7, $CHCl_3$)}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (2H, d, *J* = 8.7 Hz), 6.81 (2H, d, *J* = 8.5 Hz), 4.67 (1H, d, *J* = 9.0 Hz), 3.87 (1H, br s), 3.73 (3H, s), 2.60–2.21 (3H, m), 2.09–1.92 (1H, m), 1.83–1.38 (4H, m), 1.30–1.09 (1H, m).

4.3.4. (*S*)-2-((*R*)-(4-Chlorophenyl)(hydroxy)methyl)cyclohexanone 6d

This compound was obtained in a maximum yield of 84% with ee = 99% and dr = 96:4. The enantiomeric excess was determined by HPLC with chiral stationary phase: $t_{R(major)}$ = 32.63 min (*S*, *R*),

$t_{R(minor)}$ = 27.29 min (*R*, *S*). $[\alpha]_D^{25}$ = +20 (*c* 1, $CHCl_3$) {lit.[5] $[\alpha]_D^{25}$ = +23.4 (*c* 1.3, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.07 (4H, m), 4.66 (1H, d, *J* = 8.5 Hz), 4.04 (1H, br s), 2.58–2.17 (3H, m), 2.02–1.86 (1H, m), 1.73–1.33 (4H, m), 1.26–1.05 (1H, m).

4.3.5. (*S*)-2-((*R*)-(4-Bromophenyl)(hydroxy)methyl)cyclohexanone 6e

This compound was obtained in a maximum yield of 60% with ee = 99% and dr = 98:2. The enantiomeric excess was determined by HPLC with chiral stationary phase: $t_{R(major)}$ = 18.57 min (*S*, *R*), $t_{R(minor)}$ = 15.76 min (*R*, *S*). $[\alpha]_D^{25}$ = +24 (*c* 1, $CHCl_3$) {lit.[14] $[\alpha]_D^{24}$ = +22.6 (*c* 0.7, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 8.4 Hz), 7.11 (2H, d, *J* = 8.5 Hz), 4.66 (1H, d, *J* = 8.6 Hz), 3.98 (1H, br s), 2.58–2.19 (3H, m), 2.05–1.88 (1H, m), 1.75–1.26 (4H, m), 1.26–1.07 (1H, m).

4.3.6. 4-((*R*)-Hydroxy((*S*)-2-oxocyclohexyl)methyl)benzonitrile 6f

This compound was obtained in a maximum yield of 96% with ee = 98% and dr = 96:4. The enantiomeric excess was determined by HPLC with chiral stationary phase: $t_{R(major)}$ = 34.97 min (*S*, *R*), $t_{R(minor)}$ = 27.37 min (*R*, *S*). $[\alpha]_D^{25}$ = +19 (*c* 1, $CHCl_3$) {lit.[5,14] $[\alpha]_D^{25}$ = +20.1 (*c* 1.4, $CHCl_3$)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 8.3 Hz), 7.45 (2H, d, *J* = 8.0 Hz), 4.85 (1H, d, *J* = 8.3 Hz), 4.12 (1H, br s), 2.64–2.31 (3H, m), 2.14–2.06 (1H, m), 1.84–1.79 (1H, m), 1.70–1.50 (3H, m), 1.42–1.32 (1H, m).

4.3.7. (*S*)-2-((*R*)-Hydroxy(2-nitrophenyl)methyl)cyclohexanone 6g

This compound was obtained in a maximum yield of 97% with ee >99% and dr = 98:2. The enantiomeric excess was determined by HPLC with chiral stationary phase: $t_{R(major)}$ = 17.29 min (*S*, *R*), $t_{R(minor)}$ = 18.94 min (*R*, *S*). $[\alpha]_D^{25}$ = +15 (*c* 1, $CHCl_3$) {lit.[14] $[\alpha]_D^{24}$ = +19.8 (*c* 1.6, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 8.0 Hz), 7.77 (1H, d, *J* = 7.0 Hz), 7.64 (1H, t, *J* = 7.3 Hz), 7.43 (1H, t, *J* = 7.1 Hz), 5.43 (m, 1H), 4.20 (1H, d, *J* = 4.4 Hz), 2.83–2.68 (1H, m), 2.50–2.27 (2H, m), 2.16–2.02 (1H, m), 1.91–1.51 (5H, m).

4.3.8. (*S*)-2-((*R*)-Hydroxy(3-nitrophenyl)methyl)cyclohexanone 6h

This compound was obtained in a maximum yield of 95% with ee = 98% and dr = 91:9. The enantiomeric excess was determined by HPLC with chiral stationary phase: $t_{R(major)}$ = 41.25 min (*S*, *R*), $t_{R(minor)}$ = 53.82 min (*R*, *S*). $[\alpha]_D^{25}$ = +26 (*c* 1, $CHCl_3$) {lit.[14] $[\alpha]_D^{25}$ = +32.5 (*c* 1.35, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (1H, s), 8.14 (1H, d, *J* = 8.2 Hz), 7.68 (1H, d, *J* = 7.6 Hz), 7.42 (1H, t, *J* = 7.8 Hz), 4.92 (1H, d, *J* = 8.5 Hz), 4.20 (1H, br s), 2.72–2.58 (1H, m), 2.57–2.28 (1H, m), 2.20–2.00 (1H, m), 1.91–1.75 (1H, m), 1.75–1.47 (3H, m), 1.46–1.28 (1H, m).

4.3.9. (*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclohexanone 6i

This compound was obtained in a maximum yield of 90% with ee = 98% and dr = 91:9. The enantiomeric excess was determined by HPLC with chiral stationary phase: $t_{R(major)}$ = 31.55 min (*S*, *R*), $t_{R(minor)}$ = 23.24 min (*R*, *S*). $[\alpha]_D^{20}$ = +10 (*c* 1, $CHCl_3$) {lit.[14] $[\alpha]_D^{25}$ = +12.8 (*c* 1.85, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (2H, d, *J* = 8.4 Hz), 7.43 (2H, d, *J* = 8.8 Hz), 4.83 (1H, d, *J* = 8.2 Hz), 4.11 (1H, br s), 2.61–2.49 (1H, m), 2.40–2.24 (2H, m), 2.11–1.96 (1H, m), 1.83–1.64 (1H, m), 1.64–1.41 (3H, m), 1.38–1.23 (1H, m).

4.3.10. (*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclopentanone 6j

This compound was obtained in a maximum yield of 97% with ee = 90% and dr = 68:32. The enantiomeric excess was determined by HPLC with chiral stationary phase: $t_{R(major)}$ = 37.53 min (*S*, *R*), $t_{R(minor)}$ = 36.09 min (*R*, *S*). $[\alpha]_D^{25}$ = −25 (*c* 0.5, $CHCl_3$) {lit.[14] $[\alpha]_D^{25}$ = −30.6 (*c* 0.56, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$) (Mixture of *anti*/*syn*: 68:32) δ 8.28–8.13 (2H, m), 7.61–7.45 (2H, m), 5.41 (0.32H, s, CH of *syn* diastereomer), 4.86 (0.68H, d, *J* = 8.9 Hz, CH of *anti* diastereomer), 3.27 (1H, br s), 2.60–2.30 (2H, m), 2.19–1.89 (3H, m), 1.88–1.64 (2H, m).

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