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Proline–calixarene thiourea host–guest complex catalyzed enantioselective aldol reactions: from nonpolar solvents to the presence of water

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ABSTRACT

A proline–calix[4]arene thiourea host–guest complex catalyzed intermolecular aldol reaction of aromatic aldehydes with cyclohexanone has been developed. The *anti*-configured products were obtained in good yields and with high enantioselectivities. The reaction is proposed to work via a modified Houk–List model, where the carboxylate part of the proline constitutes as a supramolecular system with the thiourea. The outcome of the study indicates the influence of the calix[4]arene thiourea on both the reactivity and selectivity in a non-polar reaction medium, even in the presence of water at moderate temperatures.

1. Introduction

The aldol reaction is one of the most commonly applied methods inspired by Nature, for C—C bond construction in synthetic organic chemistry.[1] The catalytic potential of enamine catalysis with L-proline, 'the simplest enzyme',[2] for intermolecular enantioselective direct aldol reactions between unmodified ketones and aldehydes was first introduced by List et al.[3] L-proline is environmentally friendly, easily available, inexpensive, and easy to handle; as a result, it is a first-choice catalyst for diastereo- and enantioselective aldol reactions. Despite the fact that L-proline is still an attractive organocatalyst, it has some potential issues such as (i) limited reactivity and solubility in nonpolar organic solvents; (ii) potential parasitic side reactions; and (iii) low selectivities with aromatic aldehydes in direct aldol reactions.[4] Although there have been extensive efforts to develop new and efficient strategies including new types of organocatalysts for improving the enantioselectivities of the aldol reaction products, it is still a thriving area in research.

After considerable efforts devoted to the development of proline derivatives in order to improve their reactivity and selectivity, it was found that the addition of catalytic or substoichiometric additives as a cocatalyst allowed the introduction of new, effective, and highly enantioselective organocatalytic systems. For instance, Shan et al. reported that using chiral diols as additives can improve the enantioselectivity of proline catalyzed aldol reactions, possibly through their involvement in the transition state, via the formation of a hydrogen-bonding network.[5] In 2007, Clarke et al. established an enhancement in the reactivity and selectivity of a proline-derived amide with a hydrogen bond acceptor site, which could then self-assemble with hydrogen bond donor additives, thereby turning a poor catalyst into a very good one via a Michael-type addition of ketones to nitro olefins.[6] Taking inspiration from the use of supramolecular self-assembly units used by Clarke to make a good asymmetric catalyst perfect, we have previously reported the proof-of-principle results of proline-catalyzed direct aldol reactions between cyclic ketones and aldehydes using Schreiner's thiourea as the additive.[7] We proposed that the reaction may proceed according to a modified Houk–List model,[8] in which the carboxylate moiety of the proline forms an assembly with the thiourea, in turn enhancing the reactivity and selectivity of the catalyst. Furthermore, the thiourea is treated as a non-polar counterpart to proline, increasing its solubility limits in non-polar solvents, such as hexane or toluene. Since then, great efforts have been made to show the role of suitable additives in enhancing the reactivity and stereoselectivity of the catalytic systems.[9] These approaches are clearly useful in avoiding tedious chemical syntheses and could eventually allow the construction of libraries of structurally diverse catalyst systems. Due to these features, there is still a considerable demand for investigations into novel self-assembled organocatalysts.

Due to the advantages of water as compared to commonly used organic solvents, reactions in aqueous media have recently

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attracted a great deal of attention from a synthetic point of view in recent years.[10] In Nature, the hydrophobic active part of an enzyme is responsible for the occurrence of the reactions in Class *I* Aldolase type reactions.[11] The hydrophobic 'reaction flask' of natural enzymes at their active site has inspired organic chemists to develop entirely new hydrophobic proline derivatives as organocatalysts for asymmetric aldol reactions 'in the presence of water'.[12] Under such reaction conditions, the catalysts were used to promote the reaction in a hydrophobic cavity, away from water molecules, therefore giving better results than L-proline.

Based on our previous research,[7,13] we decided herein to investigate direct asymmetric aldol reaction catalyzed by an L-proline–calixarene-derived achiral thiourea host guest complex. On this basis, it was thought that the hydrophobic cavity of calix[4]arene could be used for the reaction to proceed and increase the solubility of proline with the help of thioureas attached to the calix[4] arene molecule, which could also stabilize the transition state due to hydrogen bonding interactions, which can be seen in Figure 1.

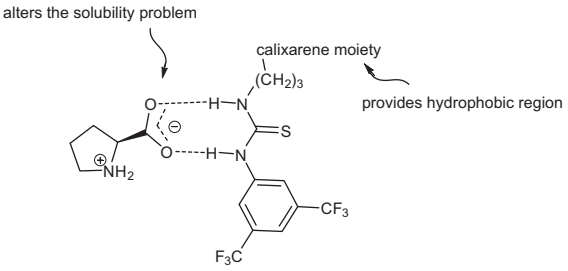


Figure 1. Self-assembled organocatalyst.

The hydrophobic cavities of calix[4]arenes make them good candidates in host–guest chemistry due to possible noncovalent interactions and the possibility of holding smaller molecules. Therefore, the effect of calix[4]arene with a hydrophobic cavity on the selectivity of the reaction in the presence of water was also investigated.

2. Results and discussion

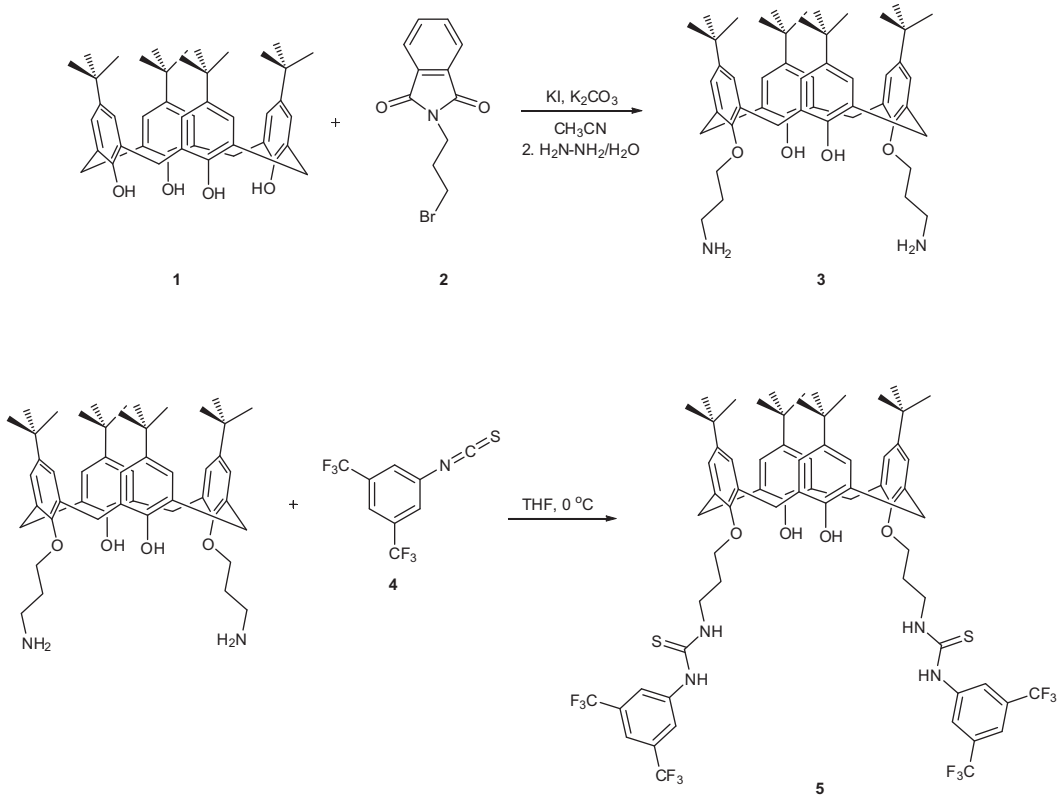
2.1. Synthesis of calix[4]arene derived achiral thiourea

The (thio)urea functionalized calix[4]arene **5** was synthesized from calixarene diamine **3** according to a procedure similar to that reported for the synthesis of calix[4]arene derived thioureas.[13] As shown in Scheme 1, the synthesis commenced with the preparation of the bis(3-phthalimidopropoxy)calix[4]arene, which then was transformed into the corresponding bis(3-aminopropoxy)calix[4]arene **3**. Compound **3** was then reacted with 3,5-bis(trifluoromethyl)phenyl isothiocyanate to give (thio)urea functionalized calix[4]arene **5**.

2.2. Direct asymmetric aldol reaction in nonpolar solvents

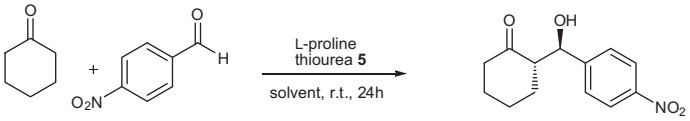
Herein, we first report the ability of the proline–thiourea **5** host–guest catalyst in promoting enantioselective direct asymmetric aldol reactions in nonpolar solvents, taking the reaction of cyclohexanone and *p*-nitrobenzaldehyde as a model. To this end, a mixture of cyclohexanone (1 mmol), *p*-nitro-benzaldehyde (0.5 mmol), and proline–thiourea **5** host–guest catalyst was stirred in the corresponding solvent at ambient temperature for 24 h; the results are shown in Table 1.

The reaction in DMSO, which is a classic polar solvent for this type of reaction, furnished the same level of selectivity and product



Scheme 1. Synthetic pathway for the preparation of compound **5**.

Table 1
Optimization of the reaction conditions for the direct enantioselective aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde catalyzed by proline/thiourea **5**



Entry	Solvent	Catalyst[a] (%)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
1	MeCN	10:5	32	68:32	90
2	$CHCl_3$	10:5	90	80:20	92
3	CH_2Cl_2	10:5	87	77:23	89
4	Toluene	10:5	95	87:13	90
5	Cyclohexane	10:5	95	88:12	92
6	Hexane	20:20	97	90:10	91
7	Hexane	20:10	97	86:14	96
8	Hexane	10:10	97	88:12	96
9	Hexane	10:5	99	95:5	99
10	Hexane	5:5	45	90:10	98
11[e]	Hexane	10:5	82	88:12	89
12[f]	Hexane	10:5	36	77:23	84

[a] L-Proline:thiourea **5** (mol %).
[b] Isolated yield after flash column chromatography on silica gel.
[c] Determined by ^{1}H NMR of the crude mixture.
[d] The ee value of the *anti*-isomer was determined by chiral HPLC analysis in comparison with an authentic racemic material.
[e] (*S*)-*tert*-Leucine was used as the catalyst.
[f] (*S*)-Tryptophan was used as the catalyst.

purity with or without the urea additive. When MeCN was used, the reaction was slow and the selectivity was low (Table 1, entry 1). This was, of course, not unexpected when considering the possibility of hydrogen bonding in polar solvents.

When we moved to non-polar solvents, both the efficiency and selectivity were enhanced remarkably. The results show that the optimum conditions, in terms of stereoselection and chemical yield, were obtained with hexane. Thiourea functionalized calix[4]arene **5** loading was also found to be critical for high enantioselectivity. With greater than 20 mol % loading, poorer enantioselectivities of the products were obtained. For example, with a 20 mol % loading, an enantiomeric excess of 91% was obtained for the *para*-NO_2 derivative (Table 1, entry 7); a similar reaction with 5 mol % loading produced a product with 99% ee (Table 1, entry 6). The optimum amount of catalyst (proline:thiourea **5**) was determined as 10:5 (%) relative to the aldehyde, and afforded the product with high yield and stereoselectivity (Table 1, entry 9).

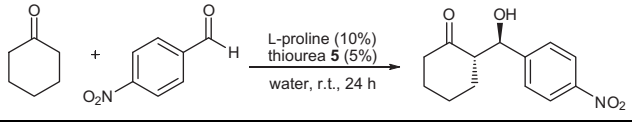
We also found that primary amino acids such as (*S*)-tryptophan and (*S*)-*tert*-leucine were very good catalysts for this transformation (Table 1, entries 7 and 8), although proline was superior. These results evidently show the great effect of the thiourea moiety on the reactivity and selectivity, even in an unconventional nonpolar reaction medium, without the need to use low temperatures. It is also noteworthy that the sense of stereoselection is the same as that with proline as the sole catalyst.

2.3. Direct asymmetric aldol reaction in the presence of water

Using water as the reaction medium, we decided to investigate the effect of the hydrophobic part of the calix[4]arene moiety of the thiourea guest molecule. For this purpose, the reaction of cyclohexanone and 4-nitrobenzaldehyde was tested in the presence of water under various conditions (Table 2).

As summarized in Table 2, when 18 equiv of water and 8 equiv of donor were employed, the reaction proceeded efficiently to give the aldol product in 51% yield, with a dr of 52:48 in favor of the *anti* stereochemistry and 80% ee (Table 2, entry 1). From a practical point of view, the direct asymmetric aldol reaction usually requires a large (16-fold) excess of the donor. However, herein only 3 equiv.

Table 2
L-Proline/thiourea **5** host guest complex catalyzed direct aldol reactions in the presence of water



Entry	Water (equiv)	Cyclohexanone (equiv)	Yield[a] (%)	*anti*:*syn*[b]	ee[c] (%)
1	18	8	51	52:48	80
2	18	3	60	65:35	92
3	9	3	54	54:46	88
4	36	3	35	52:48	82
5	108	3	Trace	n.d	n.d
6[d]	18	3	Trace	n.d	n.d

[a] Isolated yield after flash column chromatography on silica gel.
[b] Determined by ^{1}H NMR of the crude mixture.
[c] The ee value of the *anti*-isomer was determined by chiral HPLC analysis in comparison with an authentic racemic material.
[d] Schreiner's thiourea was used.

of the donor were used, and good results were obtained with 60% yield and 92% ee, although the dr value was moderate (65:35) (Table 2, entry 2). The reaction yield decreased sharply when a large excess of water was used (Table 2, entries 4 and 5). Tolerable results were also obtained when 9 equiv of water were used (Table 2, entry 3). It was also shown that the reaction did not take place when 1,3-bis(3,5-bis(trifluoromethyl)phenyl) thiourea (Schreiner's thiourea) was used, which clearly demonstrated the importance of the hydrophobic part of the calix[4]arene skeletons in compound **5**, for the reaction to proceed in the presence of water.

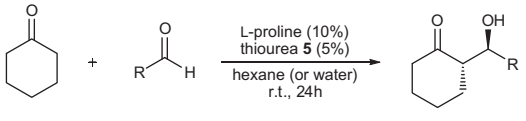
With these optimized conditions in hand, the scope and limitations of the direct asymmetric aldol reactions between a series of aromatic aldehydes and cyclohexanone were examined (Table 2). We chose nitro, cyano, trifluoromethyl, and halogen substituents as demonstrative electron-withdrawing groups and a methoxy substituent as an electron-donating group on the phenyl ring.

As can be seen in Table 3, using hexane as the solvent, the reactions between aromatic aldehydes with electron-withdrawing and donating substituents on the phenyl ring and cyclohexanone resulted in the corresponding *anti*-aldol products with good to excellent diastereoselection and with 80–99% ee (Table 2, Method A). With the exception of the cyano substituent, electron-withdrawing groups generally gave excellent enantioselectivity. An electron-donating methoxy group at the *para*-position on the phenyl ring decreased the reaction rate and both the diastereoselectivty and enantioselectivty (entry 9).

Moreover, we also studied the reactions between aldehydes and cyclohexanone in the presence of water (Table 2, Method B). The reaction of aromatic aldehydes with electron withdrawing groups proceeded smoothly and were completed in 24 h with isolated yields ranging from 48% to 62% and with up to 92% ee.

All of the aforementioned results led us to propose a mechanism based on general enamine catalysis. The transition state can be explained according to a modified Houk–List model,[8a,b] because thiourea generates a supramolecular unit due to hydrogen bonding with the carboxylic acid moiety of the proline, which participates in improving the catalytic properties of proline (Fig. 2, Model A). Furthermore, the hydrogen on the amine moiety of the proline becomes much more acidic, which also assists in stabilizing the transition state. Furthermore, the chair conformation in the transition state explains the stability and stereoselectivity seen in the reaction. Lastly, a nonpolar thiourea moiety helps to increase the solubility properties of proline in non-polar solvents such as hexane or toluene.

Table 3
Aldol reaction of different aldehydes with cyclic ketones catalyzed by L-proline/thiourea **5**



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Entry[a]	Aldehyde (R)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
1	4-NO_2Ph (A)	95	97:3	99
	(B)	60	65:35	92
2	4-BrPh (A)	80	94:6	99
	(B)	55	62:38	81
3	4-CNPh (A)	78	80:20	87
	(B)	53	59:41	81
4	4-CF_3Ph (A)	78	94:6	95
	(B)	58	60:40	80
5	3-CF_3Ph (A)	90	94:6	99
	(B)	60	58:42	86
6	3-NO_2Ph (A)	90	96:4	99
	(B)	62	60:40	87
7	2-BrPh (A)	83	96:4	99
	(B)	54	62:38	77
8	2-FPh (A)	84	90:10	94
	(B)	50	61:39	82
9	4-MeOPh (A)	70	81:19	80
	(B)	30	53:47	35

[a] (A): Method A (in hexane), (B): Method B (in the presence of water).
[b] Isolated yield after flash column chromatography on silica gel.
[c] Determined by ^{1}H NMR of the crude mixture.
[d] The ee value of the *anti*-isomer was determined by chiral HPLC analysis in comparison with an authentic racemic material.

When the reaction was performed in the presence of water, we again assumed that the asymmetric aldol reaction occurred via an enamine mechanism (Fig. 2, Model B). As depicted in Figure 2, Model B, a hydrophobic region and a hydrophilic region can be created by the formation of hydrogen bonds between free OH groups of interfacial water molecules and OH groups of the calixarene moiety, which enhances the activity of organic catalysis on water.

3. Conclusion

In conclusion, we have shown that the host–guest proline–thiourea functionalized calix[4]arene **5** complex can directly catalyze enantioselective aldol reactions in nonpolar solvents. Under the optimal conditions, high yields (up to 95%), enantioselectivities (up to >99% ee), and diastereoselectivities (up to 97:3) were obtained. The reaction is proposed to proceed via a modified Houk–List model, where the carboxylate part of the proline constitutes a supramolecular system with the thiourea. We have also found that these self-assembled organocatalysts can catalyze direct aldol reactions in the presence of water with moderate diastereoselectivities (up to 65:35) and with high enantioselectivities (up to 92% ee). Considering the catalytic inefficiency of proline for the aldol reaction in water, these results clearly demonstrate the effect of the hydrophobic part of calix[4]arene thiourea **5** on both reactivity and selectivity, in the presence of water, without the need to use low temperatures.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker DPX 400. ^{1}H NMR spectra are reported in ppm using solvent as an internal standard ($CHCl_3$ at 7.26 ppm). Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a 100 MHz spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Column chromatography was conducted on silica gel 60 (mesh size 40–63 μm). TLC was carried out on aluminum sheets precoated with silica gel 60F254 (Merck). Visualization was accomplished with UV light and anisaldehyde followed by heating. HRMS were recorded on Agilent 6224 TOF LC/MS. The enantiomeric excess (ee) of the products was determined by chiral-phase HPLC analysis. Optical rotations were measured with a Krüss P3002RS automatic polarimeter at 589 nm.

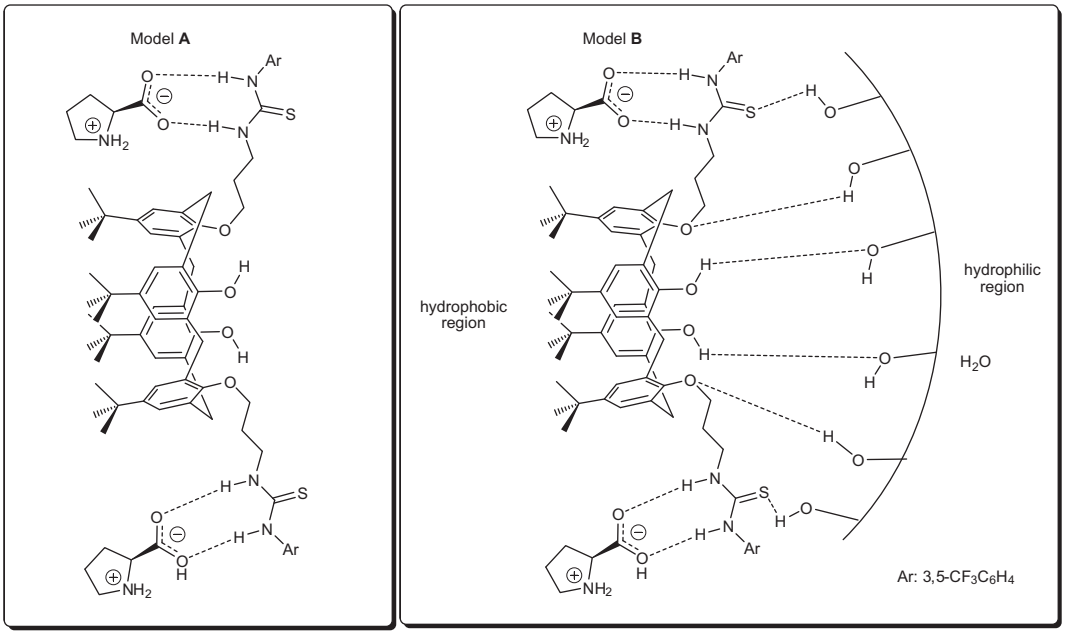

Figure 2. The proposed interaction of the thiourea moiety with proline (a) in nonpolar solvents and (b) in the presence of water.

4.2. Synthesis of *p-tert*-butyl calix[4]arene thiourea 3

p-t-Butylcalix[4]arene diamine (1.0 mmol, 0.762 mg) was dissolved in 30 ml of dried THF. Then, 3,5-bis(trifluoromethyl)phenyl isothiocyanate (2.2 mmol, 400 μL) was added via syringe in an ice bath and the mixture was stirred at room temperature until the completion of the reaction (monitored by TLC). After completion of the reaction, the volatile material was removed and the remaining solid was dissolved in a minimum amount of EtOAc. By using column chromatography, the desired product was taken in a 4:1 (Hexane/EtOAc) solvent system. Finally, *n*-hexane was added for precipitation. The solid product was filtered and washed with hexane several times. The crystallization procedure was then applied to the filtered product. ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 9.17–9.07 (m, 2H), 7.87–7.85 (m, 4H), 7.81–7.74 (m, 2H), 7.61–7.57 (m, 2H), 7.57–7.53 (m, 2H), 7.18–7.16 (m, 4H), 6.86–6.81 (m, 4H), 4.10–3.97 (m, 12H), 3.51–3.39 (m, 4H), 2.24–2.03 (m, 4H), 1.35–1.27 (m, 18H), 0.99–0.93 (m, 18H) ^{13}C NMR (101 MHz, $CDCl_3$ δ ppm): 181.6, 148.6, 148.5, 148.0, 144.7, 140.4, 132.0, 131.7, 126.18 126.2, 124.4, 122.7, 117.9, 44.7, 34.1, 31.9, 30.9, 28.3. HRMS: Calculated mass: 1304.2003 g/mole Measured $[M-H]^+$: 1305.5212 g/mole.

4.3. General procedure for the enantioselective direct aldol Reaction

Method A: L-Proline (0.025 mmol, 2.8 mg), calix[4]arene thiourea (0.0125 mmol, 16.25 mg), and 45 μL of hexane were placed in a screw capped vial, then cyclohexanone (2 mmol, 0.2 mL) was added, in which the resulting mixture was stirred for 15 min. at ambient temperature followed by the addition of aldehyde (0.25 mmol) after which stirring was continued until no further conversion was observed by TLC. After completion of the reaction, the reaction mixture was treated with saturated aqueous ammonium chloride solution and the whole mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated to give a crude residue, which was purified by column chromatography over silica gel using hexane–ethyl acetate as an eluent to afford a pure product.

Method B: At first, L-proline (0.025 mmol, 2.8 mg), calix[4]arene thiourea (0.0125 mmol, 16.25 mg) and 45 mL of hexane were placed in a screw capped vial, then cyclohexanone (0.75 mmol, 75 μL) was added, in which the resulting mixture was stirred for 15 min at ambient temperature followed by the addition of aldehyde (0.25 mmol) after which stirring was continued until no further conversion was observed by TLC. After completion of the reaction, work-up was carried out in the usual manner as described above.

4.3.1. (*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one 8a[14a,b]

This compound was obtained in a maximum of 95% yield and 99% ee; $[\alpha]_D^{rt} = +11.5$ (*c* 1.0 $CHCl_3$) {lit. $[\alpha]_D^{rt} = +11.8$ (*c* 1.0, $CHCl_3$) 95% ee};[15a] *anti*/*syn*: 97/3, *anti*-diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.46–1.31 (m, 1H), 1.71–1.52 (m, 3H), 1.93–1.77 (m, 1H), 2.16–2.07 (m, 1H), 2.42–2.31 (m, 1H), 2.54–2.45 (m, 1H), 2.66–2.55 (m, 1H), 4.09 (s, 1H), 4.90 (d, *J* = 8.3 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 2H). The enantiomeric purity was determined by HPLC on a chiralpak AD-H column [hexane/2-propanol 90:10]; flow rate 1.0 mL/min, *anti*: t_{minor} = 24.6 min and t_{major} = 32.3 min

4.3.2. (*S*)-2-((*R*)-Hydroxy(4-bromophenyl)methyl)cyclohexan-1-one 8b[14a,b]

This compound was obtained in a maximum of 80% yield and 99% ee; $[\alpha]_D^{rt} = +11.5$ (*c* 0.8 $CHCl_3$) {lit. $[\alpha]_D^{rt} = +11.3$ (*c* 1.0, $CHCl_3$) 98% ee};[15b] *anti*/*syn*: 94/6, *anti*-diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.37–1.21 (m, 1H), 1.62–1.54 (m, 3H), 1.86–1.75 (m, 1H), 2.15–2.04 (m, 1H), 2.34 (d, *J* = 7.2 Hz, 1H), 2.64–2.43 (m, 2H), 3.98 (d, *J* = 2.72 Hz, 1H), 4.75 (d, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H) 99% ee was obtained. The enantiomeric purity was determined by HPLC on a chiralpak AD-H column [hexane/2-propanol 90:10]; flow rate 1.0 mL/min, *anti*: t_{major} = 14.4 min and t_{minor} = 16.7 min.

4.3.3. 4-[Hydroxy(2-oxocyclohexyl)methyl]benzonitrile 8c[14a]

This compound was obtained in a maximum of 78% yield and 87% ee; $[\alpha]_D^{rt} = +19.2$ (*c* 1.0 $CHCl_3$) {lit. $[\alpha]_D^{25} = +20.1$ (*c* 1.4, $CHCl_3$) 85% ee};[15c] *anti*/*syn*: 80/20, *anti*-diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.43–1.30 (m, 1H), 1.64–1.51 (m, 1H), 1.90–1.77 (m, 1H), 2.16–2.07 (m, 1H), 2.42–2.30 (m, 1H), 2.62–2.45 (m, 1H), 4.07 (d, 1H), 4.84 (d, *J* = 8.5 Hz, 1H), 7.46–7.43 (m, 2H), 7.68–7.63 (m, 1H). The enantiomeric purity was determined by HPLC on a chiralpak AD-H column [hexane/2-propanol 90:10]; flow rate 1.0 mL/min, *anti*: t_{major} = 24.5 min and t_{minor} = 31.1 min.

4.3.4. (*S*)-2-((*R*)-Hydroxy(4-trifluoromethylphenyl)methyl)cyclohexan-1-one 8d[14b]

This compound was obtained in a maximum of 78% yield and 95% ee; $[\alpha]_D^{rt} = +2.3$ (*c* 1.0 $CHCl_3$) {lit. $[\alpha]_D^{25} = +2.8$ (*c* 1.3, $CHCl_3$ 99% ee)};[15c] *anti*/*syn*: 94/6, *anti*-diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.66–1.51 (m, 4H), 1.86–1.76 (m, 1H), 2.16–2.05 (m, 1H), 2.43–2.31 (m, 1H), 2.54–2.44 (m, 1H), 2.66–2.55 (m, 1H), 4.04 (d, *J* = 2.8 Hz, 1H), 4.85 (d, *J* = 8.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H). The enantiomeric purity was determined by HPLC on a chiralpak OD-H column [hexane/2-propanol 95:5]; flow rate 0.5 mL/min, *anti*: t_{major} = 11.5 min and t_{minor} = 14.9 min.

4.3.5. (*S*)-2-((*R*)-Hydroxy(3-trifluoromethylphenyl)methyl)cyclohexan-1-one 8e[14c,d]

This compound was obtained in a maximum of 90% yield and 99% ee; $[\alpha]_D^{rt} = +10.2$ (*c* 1.0 $CHCl_3$); *anti*/*syn*: 94/6, *anti*-diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.33–1.14 (m, 2H), 1.68–1.55 (m, 2H), 1.80–1.69 (m, 1H), 2.10–1.99 (m, 1H), 2.37–2.24 (m, 1H), 2.47–2.37 (m, 1H), 2.59–2.5 (m, 1H), 4.01 (d, 1H(*syn*)), 4.77 (d, *J* = 8.7 Hz, 2H), 7.46–7.37 (m, 1H), 7.55–7.47 (m, 2H) The enantiomeric purity was determined by HPLC on a chiralpak AS-H column [hexane/2-propanol 95:5]; flow rate 0.5 mL/min, *anti*: t_{major} = 19.6 min, t_{minor} = 23.8 min.

4.3.6. (*S*)-2-((*R*)-Hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one 8f[14a]

This compound was obtained in a maximum of 90% yield and 99% ee; $[\alpha]_D^{rt} = +38.4$ (*c* 1.0 $CHCl_3$) {lit. $[\alpha]_D^{rt} = +37.6$ (*c* 1.0, $CHCl_3$) 96% ee};[15b] *anti*/*syn*: 96/4, *anti*-diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.47–1.32 (m, 1H) 1.76–1.51 (m, 4H), 1.91–1.78 (m, 1H), 2.17–2.07 (m, 1H), 2.44–2.31 (m, 1H), 2.56–2.46 (m, 1H), 2.72–2.58 (m, 1H), 4.13 (d, *J* = 3.0 Hz, 1H), 4.91 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 8.22 (s, 1H). The enantiomeric purity was determined by HPLC on a chiralpak AD-H column [hexane/2-propanol 90:10]; flow rate 1.0 mL/min, *anti*: t_{major} = 19.9 min. and t_{minor} = 25.2 min.

4.3.7. (*S*)-2-((*R*)-Hydroxy(2-bromophenyl)methyl)cyclohexan-1-one 8g[14e]

This compound was obtained in a maximum of 83% yield and 99% ee; $[\alpha]_D^{rt} = +20.2$ (*c* 1.0 $CHCl_3$) {lit. $[\alpha]_D^{25} = +20.1$ (*c* 0.5, $CHCl_3$) 97% ee)};[15b] *anti*/*syn*: 96/4, *anti*-diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 2.14–2.05 (m, 1H), 2.41–2.28 (m, 1H), 2.52–2.41 (m, 1H), 2.76–2.62 (m, 1H), 4.04 (d, *J* = 4.09 Hz, 1H), 5.30 (dd, *J* = 7.96 Hz, 1H), 7.13 (t, *J* = 7.44 Hz, 1H), 7.34 (t, *J* = 7.70 Hz, 1H),

7.52 (d, J = 7.97 Hz, 1H). The enantiomeric purity was determined by HPLC on a chiralpak AD-H column [hexane/2-propanol 90:10]; flow rate 0.3 mL/min, *anti*: t_{major} = 37.2 min. and t_{minor} = 43.5 min.

4.3.8. (*S*)-2-((*R*)-Hydroxy(2-fluorophenyl)methyl)cyclohexan-1-one 8h[14f]

This compound was obtained in a maximum of 84% yield and 94% ee; $[\alpha]_D^{rt} = +20.8$ (c 1.0 $CHCl_3$) {lit. $[\alpha]_D^{25} = +22.6$ (c 0.6, $CHCl_3$) 99% ee};[15d] *anti*/*syn*: 90/10, *anti*-diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 2.42–2.30 (m, 1H), 2.53–2.44 (m, 1H), 2.75–2.60 (m, 1H), 3.99 (d, J = 3.4 Hz, 1H), 5.18 (d, J = 8.7 Hz, 1H), 7.06–6.97 (m, 1H), 7.21–7.13 (m, 1H), 7.30–7.23 (m, 1H), 7.53–7.43 (m, 1H). The enantiomeric purity was determined by HPLC on a chiralpak AD-H column [hexane/2-propanol 95:5]; flow rate 1.0 mL/min, *anti*: t_{major} = 8.9 min and t_{minor} = 12.0 min.

4.3.9. (*S*)-2-((*R*)-Hydroxy(4-methoxyphenyl)methyl)cyclohexan-1-one 8i[14a,b]

This compound was obtained in a maximum of 70% yield and 80% ee; $[\alpha]_D^{rt} = +26.3$ (c 1.0 $CHCl_3$) {lit. $[\alpha]_D^{25} = +30.5$ (c 1.7, $CHCl_3$) 91% ee};[15c] *anti*/*syn*: 81/19, *anti*-diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.43–1.51 (m, 1H), 1.63–1.82 (m, 3H), 2.07–2.11 (m, 1H), 2.30–2.61 (m, 4H), 3.81 (s, 3H), 3.92–3.94 (d, 1H, J = 2.4 Hz), 4.73–4.76 (dd, 1H, J = 1.6, 8.9 Hz), 6.87–6.89 (dd, 2H, J = 1.9, 6.7 Hz), 7.25 (d, 2H, J = 2.0 Hz). The enantiomeric purity was determined by HPLC on a chiralpak AD-H column [hexane/2-propanol 95:5]; flow rate 0.8 mL/min, *anti*: t_{major} = 30.1 min and t_{minor} = 31.7 min.

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