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Highly diastereo- and enantioselective direct aldol reactions promoted by water-compatible organocatalysts bearing a pyrrolidinyl-camphor structural scaffold

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ABSTRACT

Efficient synthetic routes have been developed for the synthesis of a series of pyrrolidinyl-camphor containing organocatalysts (**1**–**10**). Structural modifications were made by varying the stereo- and electronic properties of the camphor scaffold and the aromatic substituents. These readily tunable and amphiphilic organocatalysts were evaluated for the direct asymmetric aldol reaction of various aromatic aldehydes and cyclohexanone either in organic solvents or in the presence of water. The aldol reaction proceeded smoothly with excellent chemical yields (up to 99%), enantioselectivities (up to 99% ee), and *anti*-diastereoselectivities (up to 99:1) with a catalytical amount of the bifunctional organocatalysts (20 mol %) under optimal reaction conditions. Mechanistic transition models are proposed and the stereochemical bias of the asymmetric aldol reaction is presented.

1. Introduction

In recent years, the development of small, metal-free privileged organic molecules that catalyze enantioselective reactions has emerged as one of the viable strategies for the preparation of chiral building blocks.[1,2] The aldol reaction is one of the most useful methods for the formation of carbon–carbon bond in organic chemistry.[3,4] Direct asymmetric aldol reactions provide an atom-economical approach to form β-hydroxyl carbonyls whilst various organocatalysts have been developed to achieve high diastereo- and enantioselectivities.[5] The stereoselective transformation in water or aqueous media[6] is an important research subject because water is an environmentally friendly, safe medium, which avoids issues of pollution that are inherent with organic solvents. Water often inhibits the catalyst's activity or alters enantioselectivity by interfering with the formation of transition states. Although the addition of large amount of water generally resulted in low chemical yields and enantioselectivities of the aldol products,[7] excellent stereoselectivities were achieved when the reaction was carried out in the presence of small amount of water.[8] Therefore, utilizing pure water as a reaction medium for asymmetric aldol reactions is needed, especially for the discovery of new small privileged organic molecules as a catalyst. Recently, many research groups have demonstrated direct asymmetric aldol reactions catalyzed by a variety of organocatalysts with high diastereo- and enantioselectivities in water[9] or in the presence of water.[10] Thus, the design and synthesis of small organic molecules that catalyze enantioselective reactions in water or in the presence of water is currently a promising research topic in organic chemistry.

In a previous study, we have developed recently, pyrrolidinyl-camphor based organocatalysts for asymmetric organocatalysis.[11] These catalysts were found to be efficient for direct aldol reactions on water with high diastereo- and enantioselectivities (up to >99:1 dr and >99% ee). We envision that the assembly of a well-defined structural camphor scaffold[12] with a thiourea motif[13] and amine functionalities could constitute a new class of bifunctional organocatalysts.[14] It is postulated that they synergistically activate both the nucleophilic and electrophilic substrates via enamine formation and hydrogen bond activation. In addition, the neighboring rigid bicyclic camphor structural scaffold can serve as an efficient stereocontrolling element. We would like to describe here the design and synthesis of a series of camphor-based organocatalysts (**1**–**10**) for the asymmetric aldol reaction. High to excellent levels of chemical yields (up to 95%) and stereoselectivities (up to >99:1 dr and >99% ee) were obtained and the stereochemical pathway of the reactions is proposed.

2. Results and discussion

2.1. Design and preparation of organocatalysts 1–10

The synthesis of organocatalysts **1**–**4** began with (*S*)-*tert*-butyl 2-(2-aminophenylcarbamoyl)pyrrolidine-1-carboxylate (**A**), which

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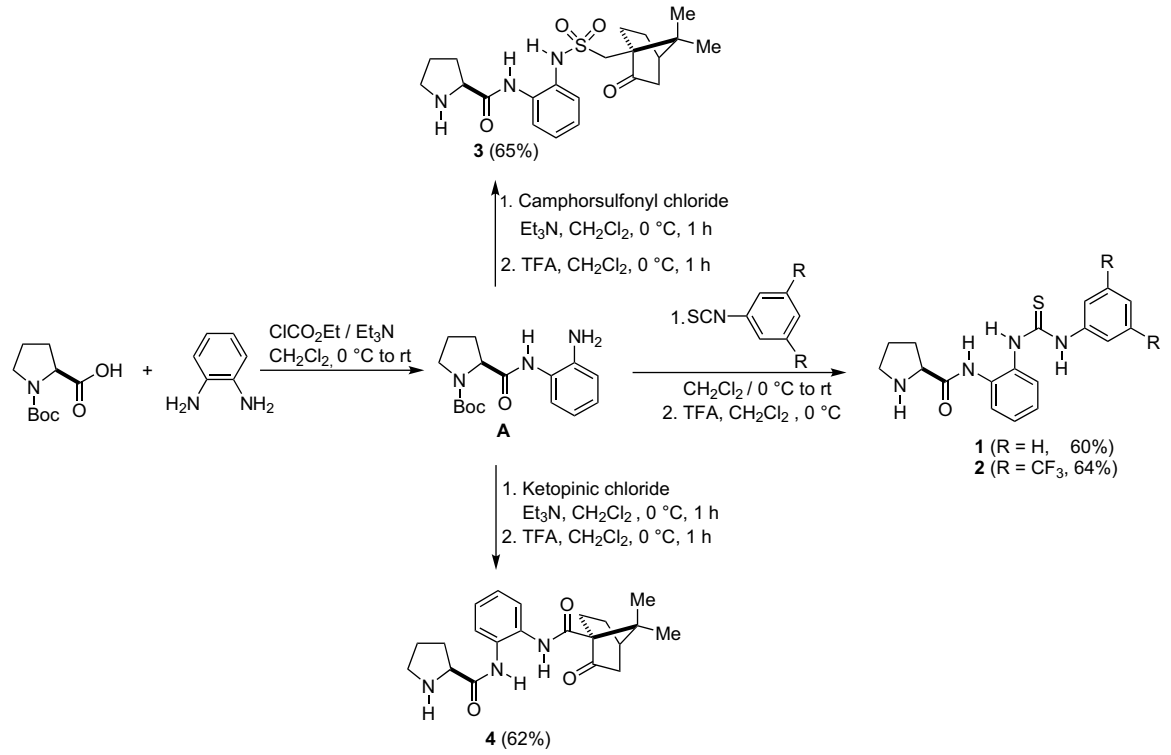
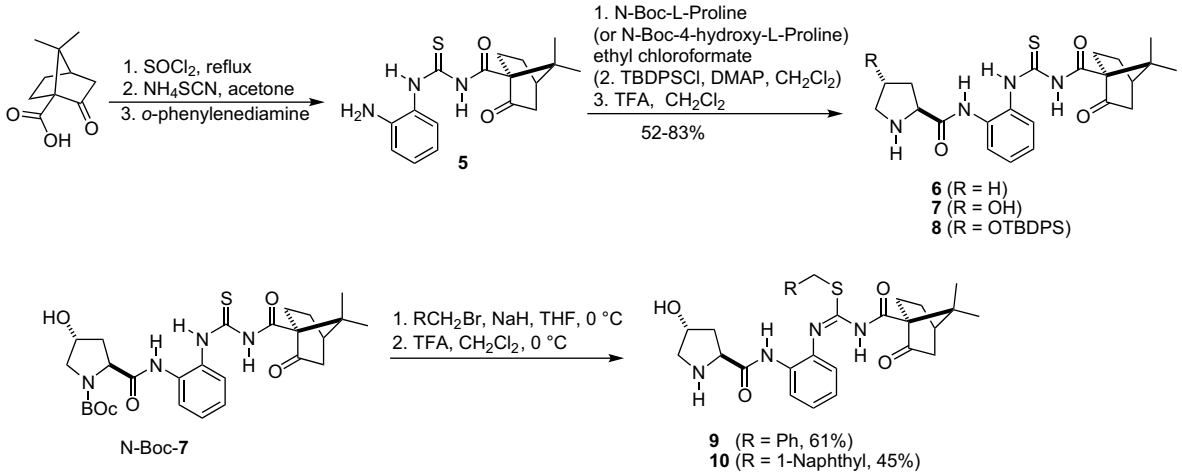
was readily prepared from the Boc-protected L-proline and *o*-phenylenediamine in CH_2Cl_2. Treatment of compound **A** with phenyl isothiocyanate and 3,5-bis(trifluoromethyl)phenyl isothiocyanate in CH_2Cl_2 to give Boc protected 1-(2-aminophenyl)-3-phenylthiourea and 1-[3,5-bis(trifluoromethyl)phenyl]-3-(2-aminophenyl)-thiourea derivatives, which was followed by the addition of TFA to give the desired organocatalysts **1** and **2** with overall yields of 60% and 64%, respectively (Scheme 1). The organocatalyst **3** can be prepared by conventional coupling between **A** and camphorsulfonyl chloride followed by TFA treatment to produce **3** with a 65% overall yield. A similar synthetic route was developed for the preparation of organocatalyst **4** in 62% overall yield by reacting ketopinic acid chloride with compound **A**.

On the other hand, the in situ prepared ketopinic acid derived isothiocyanate ($SOCl_2$ and NH_4SCN) was reacted with *o*-phenylenediamine to afford **5** (51% yield), which was then converted to a thiourea-amine catalyst **6** (R=H) with a relatively high yield (81%) (Scheme 2). A similar synthetic route was used to prepare the analogous 4-hydroxy L-proline organocatalyst **7**, which was subsequently protected as its *tert*-butyldiphenylsilyl ether **8**. Attempts to protect the 4-hydroxyl group of the pyrrolidine ring in *N*-Boc-**7** as its benzyl ether failed, which of worth noting, resulted in the formation of an unexpected benzylisothiourea **9** with a reasonable chemical yield (61% yield) after removal of the Boc group. A similar reaction affords (naphthalen-1-yl)methylisothiourea **10** by using 1-(bromomethyl)naphthalene under the same reaction conditions.



Scheme 1. Synthesis of prolinamide derivatives as an organocatalysts **1**–**4**.



Scheme 2. Synthesis of camphor containing thiourea-prolinamide catalysts **5**–**10**.

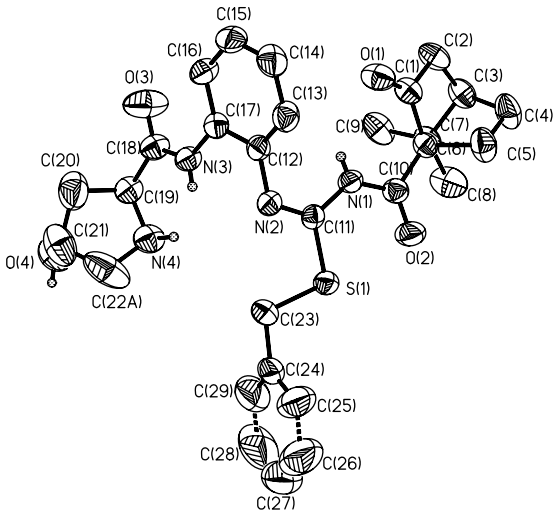


Figure 1. ORTEP diagram (50% probability level) of **9** (hydrogen atoms are omitted for clarity, expect at NH and OH).

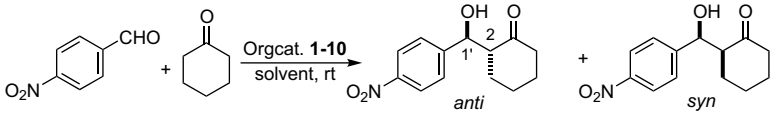
The structures of these organocatalysts were fully characterized by IR, ^{1}H, ^{13}C NMR, and HRMS analyses and compound **9** was further confirmed by single crystal X-ray data analysis (Fig. 1).[15]

2.2. Screening of organocatalysts and optimization of reaction conditions

As a model study, we explored the aldol reaction using cyclohexanone and 4-nitrobenzaldehyde in the presence of the organocatalysts **1**–**10** (Table 1). The probe substrate was treated with a catalytical amount of **1** (20 mol %) in toluene to give the desired product with 38% yield in 2 days. The *anti*-products were obtained with a reasonable diastereomeric ratio (*anti*/*syn*=73:27) and 51% enantiomeric excess (Table 1, entry 1). The powerful electron-withdrawing groups of CF_3 substituents in **2** augment the acidity of the N–H protons of thiourea, which resulted in an increase in chemical yield and enantioselectivity (Table 1, entry 2). An appreciable increase in reactivity was achieved when a camphorsulfonyl derived L-proline catalyst (**3**) was used (Table 1, entry 3). This may due to the enhanced N–H acidity by the sulfonyl group, which activates the electrophile. Low chemical yields and moderate selectivities were observed when organocatalyst **4** was used in toluene (Table 1, entry 4). No desired product was obtained when organocatalyst **5** was used. This demonstrated the vital role of the nucleophilic amine in the pyrrolidinyl moiety in the aldol reaction (Table 1, entry 5). The reaction proceeded smoothly to afford the *anti*-aldol product with a 78% yield and good stereoselectivities when a camphor moiety was incorporated into the thiourea-amine motif (Table 1, entry 6). Slight improvements in selectivity were observed when organocatalysts **7** and **8** were used in toluene (Table 1, entries 7 and 8). By screening all the organocatalysts using these conditions, it was observed that the *anti*-aldol products dominated with the newly generated absolute stereochemistry to be (2*R*,1′*S*). The assignment of the absolute configuration (2*R*,1′*S*) of *anti*-aldol product is determined on the bases of the literature reports.[5j,9a,16a]

By analyzing the preliminary data obtained, it is obvious that the presence of the bifunctional group is essential for the catalytical reaction. Attention was also paid to the solvent effect of organocatalysts **6**–**10** under similar reaction conditions. Reasonable to excellent yields and stereoselectivities were obtained under neat conditions (Table 1, entries 9–11). Reactivity was significantly improved with the organocatalysts (**6**–**10**) when hexanes were used as the solvent (Table 1, entries 12–16). Subsequently, the aldol reaction was carried out using organocatalysts **6**–**8** in CH_2Cl_2 to improve the reactivities and the stereoselectivities (Table 1, entries 17–19). Good diastereo- and enantioselectivities were obtained when catalyst **8** was used (Table 1, entry 18). The products were obtained with low reactivities and good stereoselectivities when catalyst **7** was used in THF (Table 1, entries 20–22). No significant improvements were observed when the reaction was carried out in CH_3CN and DMSO (Table 1, entries 23–25 and entries 26–28). Surprisingly, when using H_2O as the reaction medium, high chemical yields and selectivities were obtained for organocatalysts

Table 1
Diastereo- and enantioselective aldol reaction of cyclohexanone and 4-nitrobenzaldehyde catalyzed by organocatalysts **1**–**10** in various solvents (1 mL) at ambient temperature[a]



Entry	Cat.	Solvent	*t* (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)	Entry	Cat.	Solvent	*t* (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	**1**	Toluene	48	38	73:27	51	18	**7**	CH_2Cl_2	96	62	93:7	88
2	**2**	Toluene	48	48	63:37	66	19	**8**	CH_2Cl_2	96	97	86:14	80
3	**3**	Toluene	24	95	66:34	65	20	**6**	THF	96	26	90:10	86
4	**4**	Toluene	72	14	79:21	71	21	**7**	THF	48	91	94:6	89
5	**5**	Toluene	60	NR	—	—	22	**8**	THF	48	37	87:13	90
6	**6**	Toluene	72	78	76:24	74	23	**6**	CH_3CN	96	21	86:14	70
7	**7**	Toluene	48	87	95:05	84	24	**7**	CH_3CN	96	59	92:8	88
8	**8**	Toluene	48	52	88:12	84	25	**8**	CH_3CN	96	73	89:11	82
9	**6**	Neat	96	65	68:32	73	26	**6**	DMSO	96	31	81:19	77
10	**7**	Neat	96	90	90:10	90	27	**7**	DMSO	48	68	95:5	88
11	**8**	Neat	96	98	85:15	86	28	**8**	DMSO	48	43	82:18	76
12	**6**	Hexanes	72	98	76:24	57	29	**6**	H_2O	24	92	76:24	77
13	**7**	Hexanes	72	97	83:17	72	30	**6**	Brine	24	90	76:24	79
14	**8**	Hexanes	72	99	86:14	85	31	**7**	H_2O	48	89	88:12	81
15	**9**	Hexanes	72	99	91:9	86	32	**8**	H_2O	48	79	86:14	76
16	**10**	Hexanes	72	99	89:11	80	33	**9**	H_2O	72	99	91:9	85
17	**6**	CH_2Cl_2	96	29	84:16	68	34	**10**	H_2O	72	99	89:11	81

[a] All reactions were carried out using 4-nitrobenzaldehyde (75.5 mg, 0.5 mmol), cyclohexanone (0.1 mL, 1 mmol), and 20 mol % organocatalysts (**1**–**10**).
[b] Isolated yield.
[c] Determined by analysis of the crude products with chiral HPLC.
[d] *anti*-product % of ee was determined by Chiralpak AD-H.

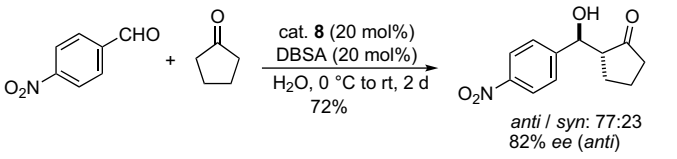
6–**10** (Table 1, entries 29 and 31–34). A comparable result was achieved when the aldol reaction was carried out in brine (Table 1, entry 30). The use of a co-solvent system (THF/H_2O) was also studied, but failed to improve the chemical outcomes (data not shown). Although excellent chemical yields can be obtained by carrying out the aldol reaction on H_2O, the stereochemical results need further improvement. Thus, we focus our subsequent investigations on the additive effect and using H_2O as the reaction medium.

As mentioned, our aim is to develop an environmentally benign synthetic method for asymmetric reactions. We envision that the presence of an additional proton source may help to build the framework of the hydrogen bonds between substrates and the catalyst. This may consequently enhance the outcomes of the stereoselectivities. Excellent chemical yields and good to high stereoselectivities were obtained when catalyzed by organocatalyst **6** with the addition of 20 mol % of HCl (0.033 M, 1.0 mL) and citric acid (0.033 M, 1.0 mL) (Table 2, entries 1 and 2). Comparable results were observed when acetic acid was added (Table 2, entry 3). The stereoselectivities were further improved when TFA was added as an additive (Table 2, entry 4). The reactivity decreased when 20 mol % of camphorsulfonic acid was added (Table 2, entry 5). Both the chemical yields and selectivities were improved by organocatalysts **6**–**8** in the presence of NH_4Cl (0.033 M, 1.0 mL) (Table 2, entries 6–10). Satisfactory results were achieved when dodecylbenzenesulfonic acid (DBSA) was added as it serves dual functions as both an acid promoter and a surfactant to improve the chemical outcomes. To this end, when organocatalyst **6** was employed in H_2O and DBSA (20 mol %), the *anti*-product was obtained with excellent chemical yield (97%) and high stereoselectivity (93:7 *anti*/*syn* ratio and 92% ee) (Table 2, entry 11). Slight improvements in stereoselectivities were observed when organocatalysts **7** and **8** were used (Table 2, entries 12–14). It is worth mentioning that only 2.0 equiv of the donor cyclohexanone to the acceptor aldehyde was used for the catalytical process using organocatalysts **6**–**8**, which represented a significant improvement over the conventional aldol condensation in organic solvents.

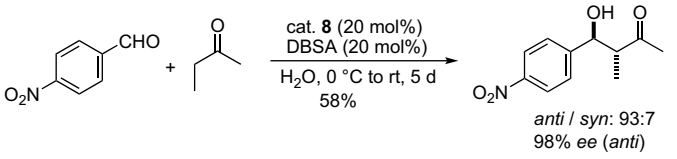
2.3. Substrate generality

The substrate generality of this aldol reaction using cyclohexanone and catalyzed by **8**–**10** with a series of aromatic aldehydes was then examined under optimum reaction conditions. In most cases, *anti*-aldol products with high to excellent diastereo- and enantioselectivities were obtained. The reaction rate depended upon the nature of the substituent on the aromatic group. Excellent selectivities were observed when 2-nitrobenzaldehyde was employed as the acceptor while the use of 3-nitrobenzaldehyde resulted in a decrease in both the reactivities and selectivities (Table 3, entries 1 and 2). Excellent enantioselectivity but diminished reactivity was observed when 4-cyanobenzaldehyde was used (Table 3, entry 3). The chemical yield was further decreased to 55% when benzaldehyde was used (Table 3, entry 4). High enantioselectivities of the *anti*-product were observed, for electron-donating substituent acceptor aldehydes the reactivity decreased dramatically as expected (Table 3, entries 5–7). High to excellent diastereo- and enantioselectivities were obtained when the reaction with 4-fluorobenzaldehyde was catalyzed by organocatalysts **8**–**10** in the presence of water with chemical yields of only 29–32% (Table 3, entries 8, 11, and 14). On the other hand, 4-chloro and 4-bromobenzaldehydes provide low reactivities and low to moderate selectivities when catalyzed by organocatalysts **8**–**10** (Table 3, entries 9, 10, 12, 13, 15, and 16). To improve reactivities and stereoselectivities of 4-halosubstituent acceptors, we have carried out reaction in hexanes catalyzed by organocatalysts **9** and **10**. 4-Fluorobenzaldehyde provides low chemical yields and excellent stereoselectivities (Table 3, entries 17 and 20), whereas, 4-chloro and 4-bromobenzaldehydes afford low reactivities and low to moderate selectivities in hexanes (Table 3, entries 18, 19, 21, and 22). The reactivity for aldehydes with electron-donating substituents and 4-halobenzaldehydes was dramatically decreased. This may be depending upon the nature of less reactivity of aldehyde acceptors having electron-donating and 4-halosubstituent group on the aromatic ring.

Cyclopentanone and butanone were also successfully explored as aldol donors. The reaction of cyclopentanone and butanone with 4-nitrobenzaldehyde proceeded smoothly in the presence of water when catalyzed by **8** to give the corresponding aldol products with isolated yields of 72% and 58%, respectively. The diastereomeric ratio of *anti*/*syn* was 77:23 and 93:7 with enantioselectivities of 82% and 98% observed for *anti*-isomer, respectively (Eqs. 1 and 2). Unfortunately, inferior results were observed, when we study for acetone (63% yield and 48% ee) and 2-hydroxyacetone (60% yield, *anti*/*syn* ratio 55:45 and 13% ee) donors with 4-nitrobenzaldehyde under the same reaction conditions.



(1)



(2)

Table 2
Optimization of enantioselective aldol reaction of cyclohexanone and 4-nitrobenzaldehyde catalyzed by **6**–**8** on water in the presence of various additives[a]

Entry	Cat.	Additive	*t* (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	**6**	HCl	40	91	86:14	90
2	**6**	Citric acid	24	96	80:20	80
3	**6**	CH_3CO_2H	24	91	84:16	80
4	**6**	TFA	24	93	93:7	93
5	**6**	(+)-CSA[e]	40	57	90:10	90
6	**6**	NH_4Cl	40	94	91:9	94
7	**7**	NH_4Cl	12	94	94:6	89
8	**8**	NH_4Cl (rt)	36	99	86:14	83
9	**8**	NH_4Cl (0 °C to rt)	36	92	91:9	85
10	**8**	NH_4Cl (rt, THF)	96	65	88:12	94
11	**6**	DBSA[f]	24	97	93:7	92
12	**7**	DBSA[f]	36	99	95:5	94
13	**8**	DBSA (rt)	36	89	96:4	98
14	**8**	**DBSA**[f]	**36**	**95**	**96:4**	**>99**

[a] Unless otherwise specified, all reactions were carried out using 4-nitrobenzaldehyde (0.5 mmol), cyclohexanone (1.0 mmol), additive (20 mol %), and catalyst (20 mol %) on water (1 mL) at ambient temperature.
[b] Total isolated yield.
[c] Determined by analysis of the crude products by chiral HPLC.
[d] Determined by chiral HPLC analysis (Chiralpak AD-H).
[e] D-(+)-10-Camphorsulfonic acid.
[f] The reaction was carried out at 0 °C with DBSA (dodecylbenzenesulfonic acid).

2.4. Transition state models for direct aldol reaction

The mechanistic understanding of the catalytical aldol reaction remains unclear and the transition state models were proposed to explain the asymmetric induction. The transition state

Table 3
Enantioselective aldol reaction of cyclohexanone and various aromatic aldehydes catalyzed by organocatalysts **8**–**10**[a]

Entry	R	Cat.	*t* (d)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	2-NO_2	**8**	2	87	99:1	98
2	3-NO_2	**8**	2	83	81:19	80
3	4-CN	**8**	2	75	88:12	94
4	H	**8**	7	55	97:3	94
5	4-Me	**8**	7	42	91:9	85
6	4-OMe	**8**	7	26	85:15	80
7	1-Naphthyl	**8**	7	35	90:10	89
8	4-F	**8**	7	32	89:11	73
9	4-Cl	**8**	7	25	42:58	29
10	4-Br	**8**	7	16	33:67	24
11	4-F	**9**	7	29	98:2	98
12	4-Cl	**9**	7	18	91:9	83
13	4-Br	**9**	7	30	86:14	23
14	4-F	**10**	7	29	93:7	>99
15	4-Cl	**10**	7	27	92:8	83
16	4-Br	**10**	7	34	40:60	41
17[e]	4-F	**9**	7	30	87:13	94
18[e]	4-Cl	**9**	7	24	95:5	83
19[e]	4-Br	**9**	7	35	39:61	33
20[e]	4-F	**10**	7	26	85:15	99
21[e]	4-Cl	**10**	7	44	33:67	61
22[e]	4-Br	**10**	7	40	31:69	22

[a] Unless otherwise specified, all reactions were carried out using aldehyde (0.5 mmol), cyclohexanone (1.0 mmol), additive (20 mol %), and catalyst (20 mol %) on water (1 mL for entries 1–16).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralpak AD-H).
[d] Determined by chiral HPLC analysis.
[e] Reactions were carried out in hexanes (1 mL for entries 17–22).

conformation was organized by the hydrogen bond formation involving the organocatalyst and the substrate. These together with the electrostatic as well as the steric interactions may account for the stereochemical bias of the reaction. The results are in agreement with earlier reports,[16] which suggested that the presence of additional hydrogen bond donors can have a beneficial effect on the prolinamide catalysts in aldol reactions. As proposed in Figure 2, the bifunctional organocatalyst (**6**) pyrrolidine moiety reacts with the cyclohexanone to form the nucleophilic enamine in the presence of an acidic additive. The aldehyde is activated by bifurcated H-bonding with NH of amide as well as NH of thiourea through hydrogen bond interactions.

We anticipated that in organic solvents, since there is a direct H-bonding between the aldehyde and the N–H groups of amide and thiourea, there may be an observed effect of stereochemistry (model I). On the other hand, when the reaction was carried out in an aqueous medium, the water molecules form H-bonding with the nitro and amide group in a favored transition state model II.[6a,9k,10g] In the case of organic solvent, the nucleophilic addition of the enamine to the *si*-face of the carbonyl group leading to the major (2*R*,1′*S*)-product. The aromatic substituent of the aldehyde is oriented to avoid the steric interactions with the camphor scaffold. However, the more fixed transition state model II is established in the presence of a nitro group. The approach of the enamine to the *si*-face of the carbonyl group yields the desired *anti*-product.

3. Conclusions

In conclusion, we have developed a practical alternative method for the organocatalytic direct aldol reaction using bifunctional

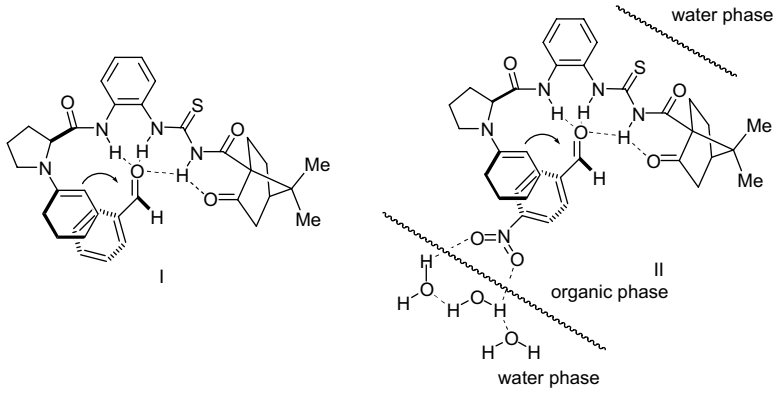


Figure 2. Proposed transition state models for the asymmetric aldol reaction was carried out in organic solvent (I) and in aqueous medium (II) using organocatalyst **6**.

thiourea-amine organocatalysts (**1**–**10**) bearing a hydrophobic camphor scaffold structural units. These catalysts are readily prepared from inexpensive starting materials with good overall chemical yields. The organocatalytic direct asymmetric aldol reaction was evaluated by employing these structurally tunable and amphiphilic structural organocatalysts either in organic solvents or in the presence of water. The *anti* aldol products were obtained with excellent chemical yields (up to 99%), and diastereo- and enantioselectivity (up to 99:1 dr and 99% ee) on water. A reasonable mechanistic explanation was proposed for the stereochemical bias of the asymmetric aldol reaction. Further study of these newly developed camphor containing bifunctional organocatalysts in asymmetric organocatalysis is under investigation.

4. Experimental section

4.1. General remarks

All reagents were used as purchased from commercial suppliers without additional purification. IR spectra were recorded on a Perkin–Elmer 500 spectrometer. NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Chemical shifts are reported in δ parts per million referenced to an internal TMS standard for ^{1}H NMR and chloroform-*d* (77.0 ppm) for ^{13}C NMR. Optical rotations were measured on a JASCO P-1010 polarimeter. HRMS were recorded on JEOL SX-102A. The X-ray diffraction measurements were carried out at 298 K on a KAPPA APEX II CCD area detector system equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube (λ=0.71073 Å). Routine monitoring of reactions was performed using silica gel, glass-backed TLC plates (Merck Kieselgel 60 F_{254}) and visualized by UV light (254 nm). Solutions were evaporated to dryness under reduced pressure on a rotary evaporator and the residues purified by flash column chromatography on silica gel (230–400 mesh) with the indicated eluents. Air and/or moisture sensitive reactions were performed under the inert atmospheric conditions.

4.2. Synthesis of organocatalysts 1–10

*4.2.1. Pyrrolidine-2-carboxylic acid-[2-(3-phenylthioureido)-phenyl]-amide (**1**)*

To a stirred solution of Boc-protected L-proline (1.61 g, 7.47 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C were added ethyl chloroformate (0.75 mL, 7.84 mmol) and Et_3N (1.09 mL, 7.84 mmol) dropwise. To this *o*-phenylenediamine (0.85 g, 7.84 mmol) was added and the resulting mixture was heated to the ambient temperature and then stirred for 30 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and H_2O was added (10 mL). The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo to give product **A** as a colorless liquid (1.94 g, 85%). To a solution of crude product **A** (1.94 g, 6.36 mmol) in dry CH_2Cl_2 (20 mL) were added phenyl isothiocyanate (0.91 mL, 7.63 mmol) and Et_3N (1.08 mL, 7.63 mmol) dropwise at 0 °C and stirred for 1 h. The mixture was extracted with CH_2Cl_2 (2×20 mL) and the combined organic layer was washed with brine (20 mL), dried over $MgSO_4$, and filtered. The solvent was removed under vacuo. The resulting crude product was dissolved in CH_2Cl_2 (10 mL) and was added TFA (2 mL) dropwise at 0 °C. After the consumption of the starting material as indicated by TLC analysis, the reaction mixture was diluted with H_2O (10 mL) and the resulting solution was adjusted to pH=~7 with aqueous $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (2×20 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel using MeOH/CH_2Cl_2 (1:20) as the eluent to furnish pure product **1** as a yellowish liquid (1.51 g, 70% for 2 steps; overall yield 60% for 3 steps). $[\alpha]_D^{27}$ −7.9 (*c* 2.9, $CHCl_3$); IR ($CHCl_3$): ν 3415, 2969, 2868, 1650, 1531, 1099 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (br s, 1H), 8.52 (br s, 1H), 7.72 (d, *J*=8.0 Hz, 1H), 7.44–7.32 (m, 5H), 7.30–7.25 (m, 1H), 7.24–7.21 (m, 1H), 7.17 (td, *J*=7.6 and 1.2 Hz, 1H), 3.76 (dd, *J*=8.8 and 4.8 Hz, 1H), 2.97 (td, *J*=6.8 and 2.0 Hz, 2H), 2.11–2.00 (m, 1H), 1.89–1.78 (m, 1H), 1.72–1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.61, 173.97, 137.46, 133.28, 129.44, 129.35, 128.75, 128.20, 126.68, 125.75, 124.92, 123.33, 60.80, 47.16, 30.93, 26.10; HRMS *m*/*z* 340.1367 (calcd for $C_{18}H_{20}N_4OS$: 340.1358).

*4.2.2. Pyrrolidine-2-carboxylic acid-{2-[3-(3,5-bistrifluoromethylphenyl)thioureido]phenyl}-amide (**2**)*

To a solution of the crude product **A** (1.00 g, 3.28 mmol) in dry CH_2Cl_2 (10 mL) were added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.63 mL, 3.44 mmol) and Et_3N (0.93 mL, 6.56 mmol) dropwise at 0 °C. After stirring for 1 h, the reaction mixture was extracted with CH_2Cl_2 (2×20 mL). The combined organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and the solvent was removed in vacuo to give the Boc-protected crude product **2**. The crude adduct was treated with TFA (1 mL) in CH_2Cl_2 (5 mL) at 0 °C for 1 h. The mixture was diluted with H_2O (10 mL) and the resulting solution pH was adjusted to ~7 with aqueous $NaHCO_3$. The mixture was then extracted with CH_2Cl_2 (2×10 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The product was purified by flash column chromatography on silica gel using MeOH/CH_2Cl_2 (1:20) as the eluent to yield **2** as a colorless liquid (1.17 g, 75% for 2 steps; overall yield 60% for 3 steps). $[\alpha]_D^{27}$ −25.4 (*c* 4.13, $CHCl_3$); IR ($CHCl_3$): ν 3417, 1633, 1519, 1471, 1380, 1278, 1177, 1131 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (br s, 1H), 8.04 (s, 2H), 7.63 (s, 1H), 7.53 (d, *J*=7.6 Hz, 1H), 7.36–7.29 (m, 1H), 7.23 (d, *J*=4.4 Hz, 2H), 3.85 (dd, 1H, *J*=9.2 and 5.2 Hz), 3.08–2.92 (m, 2H), 2.18–2.06 (m, 1H), 1.88–1.76 (m, 1H), 1.73–1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.66, 175.64, 140.17, 133.05, 131.80 (q, *J*=33 Hz), 130.53, 128.64, 128.39, 126.99, 125.22, 124.38, 123.61, 121.67, 118.54 (q, *J*=37 Hz), 60.69, 47.27, 30.81, 26.15; HRMS *m*/*z* 476.1115 (calcd for $C_{20}H_{18}F_6N_4OS$: 476.1106).

*4.2.3. Pyrrolidine-2-carboxylic acid-[2-(7,7-dimethyl-2-oxo-bicyclo-[2.2.1]hept-1-ylmethanesulfonylamino)phenyl]-amide (**3**)*

To a mixture of camphorsulfonic acid chloride [prepared from camphorsulfonic acid (1.00 g, 4.31 mmol) and $SOCl_2$ (20 mL)] in dry CH_2Cl_2 (10 mL) were added the common intermediate **A** (1.00 g, 3.28 mmol) and Et_3N (1.86 mL, 13.12 mmol) at 0 °C. After stirring for an additional 1 h, the mixture was extracted with CH_2Cl_2 (2×20 mL). The combined organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and the solvent was removed under vacuo to give the Boc-protected product **3**. This was dissolved in CH_2Cl_2 (5 mL) and TFA (1 mL) was added dropwise at 0 °C. After stirring for 1 h, the mixture was diluted with H_2O (10 mL) and the solution was adjusted to pH=~7 with aqueous $NaHCO_3$. The mixture was then extracted with CH_2Cl_2 (2×10 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel using MeOH/CH_2Cl_2 (1:20) as the eluent to afford the pure product **3** as a white solid (0.89 g, 65% for 3 steps); mp: 70–72 °C. $[\alpha]_D^{29}$ +60.7 (*c* 1.9, $CHCl_3$); IR ($CHCl_3$): ν 3576, 3244, 2962, 2884, 1743, 1668, 1595, 1521, 1455, 1336, 1150 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.38 (br s, 1H), 7.88 (dd, *J*=7.8 and 1.4 Hz, 1H), 7.34–7.24 (m, 3H), 7.14 (td, *J*=7.8 and 1.4 Hz, 1H), 3.92 (dd, *J*=9.2 and 5.2 Hz, 1H), 3.58 (d, *J*=15.2 Hz, 1H), 3.09 (t, *J*=6.8 Hz, 2H), 2.90 (d, *J*=15.2 Hz, 1H), 2.45 (dt, *J*=18.0 and 4.4 Hz, 1H), 2.32–2.12 (m, 3H), 2.10–1.94 (m, 5H), 1.88–1.70 (m, 2H), 1.52–1.42 (m, 1H), 1.04 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 217.01, 174.64, 134.27, 128.19, 127.86, 126.44, 125.22, 123.28, 61.07, 59.56, 49.57, 48.70, 47.31, 42.93, 42.88, 30.92, 27.01, 26.89, 26.19, 19.91, 19.63; HRMS *m*/*z* (MH^+) 420.1949 (calcd for $C_{21}H_{30}N_3O_4S$: 420.1952).

4.2.4. Pyrrolidine-2-carboxylic acid-{2-[(7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptane-1-carbonyl)amino]phenyl}-amide (**4**)

The same procedure as described in Section 4.2.3 was followed with ketopinic acid chloride [prepared from ketopinic acid (0.90 g, 4.94 mmol) and $SOCl_2$ (1.4 mL)] being used instead of camphorsulfonic acid chloride to afford organocatalyst **4** as a colorless liquid (0.75 g, 62% for 3 steps). $[\alpha]_D^{27}$ −6.32 (*c* 1.9, $CHCl_3$); IR ($CHCl_3$): ν 3427, 2969, 2873, 1726, 1651, 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 9.40 (s, 1H), 7.72–7.63 (m, 2H), 7.20–7.12 (m, 2H), 3.92 (dd, *J*=9.2 and 5.6 Hz, 1H), 3.08–2.94 (m, 2H), 2.63–2.53 (m, 2H), 2.27–2.04 (m, 5H), 2.00 (d, *J*=13.2 Hz, 1H), 1.88–1.68 (m, 3H), 1.48 (td, *J*=9.2 and 4.0 Hz, 1H), 1.31 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.49, 174.41, 168.06, 130.08, 129.80, 125.87, 125.52, 124.84, 124.12, 65.51, 61.12, 50.27, 47.32, 43.77, 43.44, 30.72, 28.88, 27.73, 26.29, 20.83, 20.57; HRMS *m*/*z* 369.2068 (calcd for $C_{21}H_{27}N_3O_3$: 369.2052).

4.2.5. 1-(2-Aminophenyl)-3-(7,7-dimethyl-2-oxo-bicyclo-[2.2.1]heptane-1-carbonyl)thiourea (**5**)

To a mixture of ketopinic acid (10.0 g, 54.9 mmol) and $SOCl_2$ (13.4 mL, 164.7 mmol) was stirred at reflux temperature (60 °C) for 2 h. The mixture was cooled to ambient temperature and the excess of $SOCl_2$ was removed in vacuo. The crude product was dissolved in acetone (200 mL) and NH_4SCN (8.4 g, 109.8 mmol) was added at 0 °C. The mixture was then stirred for 30 min. To this *o*-phenyldiamine (11.9 g, 109.8 mmol) was added at the same temperature and stirred for an additional 30 min. The mixture was concentrated, water (50 mL) was added, and extracted with EtOAc (2×50 mL). The combined organic layer was washed with brine (20 mL), dried over $MgSO_4$, and filtered, after which the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel using CH_2Cl_2/hexanes (1:1) as the eluent to yield **5** as a white solid (12.0 g, 66% for 3 steps); mp 180–181 °C. $[\alpha]_D^{22}$ +16.9 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): ν 3421, 2969, 1730, 1633, 1531, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.84 (s, 1H), 10.82 (s, 1H), 7.27 (d, *J*=8.0 Hz, 1H), 7.18–7.10 (m, 1H), 6.87–5.98 (m, 2H), 3.95 (s, 2H), 2.62 (dt, *J*=14.9, 4.0 Hz, 1H), 2.51 (td, *J*=14.9, 3.5 Hz, 1H), 2.29–2.13 (m, 2H), 2.08 (d, *J*=18.9 Hz, 1H), 1.87–1.76 (m, 1H), 1.58–1.47 (m, 1H), 1.30 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.61, 179.17, 170.65, 141.88, 128.75, 126.99, 124.08, 119.04, 117.42, 64.54, 51.07, 43.45, 43.37, 29.39, 27.79, 20.80, 20.45; HRMS *m*/*z* 331.1344 (calcd for $C_{17}H_{21}N_3O_2S$: 331.1354).

4.2.6. Pyrrolidine-2-carboxylic acid-{2-[3-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptane-1-carbonyl)thioureido]phenyl}-amide (**6**)

To a solution of Boc-protected L-proline (16.1 g, 74.7 mmol) in dry CH_2Cl_2 (200 mL) were added ethyl chloroformate (7.5 mL, 78.4 mmol) and Et_3N (10.9 mL, 78.4 mmol) dropwise at 0 °C. After 15 min stirring, a solution of compound **5** (22.3 g, 67.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 °C. The resulting mixture was allowed to warm up to ambient temperature and stirred for 6 h. To the reaction mixture were added H_2O (100 mL) and CH_2Cl_2 (200 mL) and the layers were separated. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product obtained was dissolved in CH_2Cl_2 (200 mL) and was treated with TFA (55.2 mL, 747.0 mmol) in a dropwise fashion at 0 °C for 4 h. The mixture was diluted with H_2O (50 mL) and the solution was adjusted to pH=∼7 with aqueous $NaHCO_3$. This was extracted with CH_2Cl_2 (2×200 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel containing 1% Et_3N of EtOAc/hexanes (1:4) as the eluent to furnish organocatalyst **6** as a white solid (24.0 g, 83% for 2 steps); mp 108–110 °C. $[\alpha]_D^{22}$ −3.5 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): ν 3215, 2968, 1731, 1516, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.83 (s, 1H), 10.81 (s, 1H), 9.98 (s, 1H), 8.06 (d, *J*=8.0 Hz, 1H), 7.50 (d, *J*=7.8 Hz, 1H), 7.38–7.32 (m, 1H), 7.20–7.14 (m, 1H), 3.87 (dd, *J*=9.2 and 4.9 Hz, 1H), 3.05–2.92 (m, 2H), 2.63 (dt, *J*=18.9 and 3.6 Hz, 1H), 2.52 (td, *J*=11.8 and 3.6 Hz, 1H), 2.29–2.00 (m, 6H), 1.87–1.65 (m, 3H), 1.59–1.50 (m, 1H), 1.31 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.31, 179.55, 173.40, 170.01, 133.56, 128.37, 127.78, 126.60, 124.04, 122.03, 64.11, 60.47, 50.43, 46.66, 42.87, 42.72, 30.19, 28.76, 27.18, 25.64, 20.23, 19.81; HRMS *m*/*z* 428.1878 (calcd for $C_{22}H_{28}N_4O_3S$: 428.1882).

4.2.7. 4-Hydroxypyrrolidine-2-carboxylic acid-{2-[3-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptane-1-carbonyl)thioureido]-phenyl}-amide (**7**)

The same procedure as described in Section 4.2.6 was followed with 4-hydroxy-L-proline (10.0 g, 76.3 mmol) being used instead of L-proline to give organocatalyst **7** as a white solid (15.5 g, 79% for 2 steps); mp 97–98 °C. $[\alpha]_D^{22}$ −10.9 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): ν 3226, 2968, 2929, 1731, 1676, 1594, 1517, 1161, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.84 (s, 1H), 10.77 (s, 1H), 9.98 (s, 1H), 8.04 (d, *J*=8.1 Hz, 1H), 7.51 (d, *J*=7.8 Hz, 1H), 7.37–7.32 (m, 1H), 7.22–7.16 (m, 1H), 4.44 (s, 1H), 4.13 (t, *J*=8.3 Hz, 1H), 3.01 (d, *J*=12.3 Hz, 1H), 2.92 (dd, *J*=12.3 and 2.9 Hz, 1H), 2.68–2.44 (m, 3H), 2.38–2.00 (m, 6H), 1.87–1.78 (m, 1H), 1.58–1.48 (m, 1H), 1.32 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.57, 180.16, 173.34, 170.56, 132.83, 128.84, 128.56, 127.07, 124.89, 122.82, 73.26, 64.73, 60.28, 55.18, 51.01, 43.47, 43.36, 39.81, 29.28, 27.76, 20.80, 20.44; HRMS *m*/*z* 444.1830 (calcd for $C_{22}H_{28}N_4O_4S$: 444.1831).

4.2.8. 4-(tert-Butyldiphenylsilanyloxy)pyrrolidine-2-carboxylic acid-2-[3-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptane-1-carbonyl)thioureido]phenyl}-amide (**8**)

To a stirred solution of *N*-Boc-protected adduct **7** (5.0 g, 9.2 mmol) in CH_2Cl_2 (50 mL) were added Et_3N (1.5 mL, 11.0 mmol), TBDPSCl (2.6 mL, 10.1 mmol), and DMAP (0.2 g, 1.8 mmol) at the ambient temperature. The reaction mixture was allowed to stir for 2 d and was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (2×50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The residue obtained was dissolved in CH_2Cl_2 (50 mL), and TFA (7.0 mL, 92.0 mmol) was added dropwise at 0 °C and stirred for 4 h. The mixture was diluted with H_2O (20 mL) and the solution was adjusted to pH=∼7 with aqueous $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (2×50 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:2) as the eluent to yield catalyst **8** as a white solid (3.3 g, 52% for 3 steps); mp 102–103 °C. $[\alpha]_D^{22}$ +0.5 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): ν 3225, 2959, 2931, 1732, 1682, 1593, 1533, 1516, 1111, 750, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.80 (s, 1H), 10.75 (s, 1H), 9.94 (s, 1H), 8.02 (d, *J*=8.0 Hz, 1H), 7.66–7.59 (m, 4H), 7.52 (d, *J*=7.7 Hz, 1H), 7.47–7.29 (m, 7H), 7.20–7.14 (m, 1H), 4.41 (s, 1H), 4.18 (t, *J*=8.5 Hz, 1H), 2.91 (d, *J*=12.0 Hz, 1H), 2.68 (dd, *J*=12.0 and 2.6 Hz, 1H), 2.59 (dt, *J*=19.0 and 3.4 Hz, 1H), 2.46 (td, *J*=14.9 and 3.4 Hz, 1H), 2.36 (dd, *J*=13.5 and 8.6 Hz, 1H), 2.25–2.13 (m, 2H), 2.08 (d, *J*=19.0 Hz, 1H), 1.88–1.71 (m, 2H), 1.58–1.48 (m, 1H), 1.23 (s, 3H), 1.06 (s, 9H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.39, 180.05, 173.40, 170.44, 135.59, 135.54, 133.94, 133.60, 132.83, 129.79, 129.71, 128.87, 128.47, 127.73, 127.69, 126.95, 124.76, 122.88, 75.10, 64.56, 60.58, 55.65, 50.95, 43.43, 43.31, 39.88, 29.25, 27.78, 26.89, 20.76, 20.32, 19.07; HRMS *m*/*z* 682.3004 (calcd for $C_{38}H_{46}N_4O_4SSi$: 682.3009).

*4.2.9. 4-Hydroxypyrrolidine-2-carboxylic acid-{2-[2-benzyl-3-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptane-1-carbonyl)-isothioureido]phenyl}-amide (**9**)*

To a solution of *N*-Boc-protected adduct **7** (5.0 g, 9.2 mmol), NaH (60% in mineral oil, 0.7 g, 18.4 mmol) in THF (50 mL) benzyl bromide (1.3 mL, 11.0 mmol) was added in a dropwise fashion at 0 °C and was stirred for 3 h. The mixture was diluted with H_2O (20 mL) and the solution was acidified to a pH=6–7 using a saturated aqueous NH_4Cl solution. The reaction mixture was extracted with EtOAc (2×100 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The resulting crude adduct was dissolved in CH_2Cl_2 (50 mL) and TFA (7.0 mL, 92.0 mmol) was added dropwise at 0 °C for 4 h. The mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (2×50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under vacuo. The crude product was purified by flash column chromatography on silica gel using EtOAc/hexanes (4:1) as the eluent to give **9** as a white solid (3.0 g, 61% for 3 steps); mp 192–193 °C. $[\alpha]_D^{22}$ +73.9 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): ν 3427, 2969, 2929, 1731, 1644, 1591, 1514, 1197 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.22 (s, 1H), 10.16 (s, 1H), 8.45 (d, *J*=7.7 Hz, 1H), 7.40 (d, *J*=7.2 Hz, 2H), 7.34–7.27 (m, 2H), 7.25–7.10 (m, 3H), 6.90 (d, *J*=7.2 Hz, 1H), 4.48–4.33 (m, 3H), 4.09 (t, *J*=7.6 Hz, 1H), 3.02 (d, *J*=12.3 Hz, 1H), 2.84 (dd, *J*=12.3 and 2.6 Hz, 1H), 2.48–2.23 (m, 5H), 2.15–1.94 (m, 3H), 1.89 (d, *J*=19.0 Hz, 1H), 1.62–1.51 (m, 1H), 1.43–1.32 (m, 1H), 1.21 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.70, 172.86, 168.03, 152.45, 136.21, 136.14, 130.36, 129.56, 128.51, 127.30, 125.09, 124.08, 120.03, 73.26, 64.96, 60.59, 55.33, 50.60, 43.32, 43.20, 39.87, 36.14, 29.64, 29.20, 27.67, 20.67, 20.20; HRMS *m*/*z* (MH^+) 535.2370 (calcd for $C_{29}H_{35}N_4O_4S$: 535.2374). Crystal data for **9** at 296 K: $C_{29}H_{34}N_4O_4S$, *M* 534.66, orthorhombic, P_{212121}, *a*=12.1093(9) Å, *b*=12.4874(9) Å, *c*=18.4317(13) Å, *V*=2787.1(3) $Å^3$, *Z*=4, λ=0.71073 Å, D_c=1.274 Mg/m^3, μ=0.157 mm^{-1}, 19,795 reflections, 339 parameters, *R*=0.1037, R_w=0.1282 for all data.

*4.2.10. 4-Hydroxypyrrolidine-2-carboxylic acid-{2-[3-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptane-1-carbonyl)-2-naphthalen-1-ylmethylisothioureido]phenyl}-amide (**10**)*

The same procedure as described in Section 4.2.9 was followed with 1-(bromomethyl)naphthalene (2.4 g, 11.0 mmol) being used instead of benzyl bromide to furnish organocatalyst **10** as a white solid (1.3 g, 45% for 3 steps); mp 104–106 °C. $[\alpha]_D^{22}$ +53.2 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): ν 3360, 3252, 2967, 2933, 1731, 1695, 1666, 1605, 1590, 1513, 1448, 1212, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.24 (s, 1H), 10.19 (s, 1H), 8.46 (d, *J*=7.8 Hz, 1H), 7.85 (s, 1H), 7.80–7.71 (m, 3H), 7.50 (d, *J*=8.2 Hz, 1H), 7.45–7.37 (m, 2H), 7.22–7.10 (m, 2H), 6.91 (d, *J*=7.4 Hz, 1H), 4.55 (q, *J*=12.8 Hz, 2H), 4.30 (s, 1H), 4.00 (t, *J*=8.2 Hz, 1H), 2.95 (d, *J*=12.1 Hz, 1H), 2.75 (d, *J*=10.2 Hz, 2H), 2.43–2.23 (m, 3H), 2.10–1.95 (m, 2H), 1.94–1.79 (m, 2H), 1.58–1.47 (m, 1H), 1.37–1.21 (m, 1H), 1.17 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.78, 173.26, 168.14, 152.44, 136.36, 133.79, 133.39, 132.64, 130.43, 128.36, 128.29, 127.68, 126.29, 125.99, 125.19, 124.26, 120.17, 73.12, 65.05, 60.66, 55.36, 50.66, 43.37, 43.24, 39.86, 36.39, 29.71, 29.23, 27.71, 20.73, 20.27; HRMS *m*/*z* (MH^+) 585.2529 (calcd for $C_{33}H_{37}N_4O_4S$: 585.2536).

4.3. General procedure for the direct aldol reaction

To a solution of dodecylbenzenesulfonic acid (DBSA, 0.1 mmol) and H_2O (1 mL) were added aldehyde (0.5 mmol) and organocatalyst (0.1 mmol) at 0 °C. Cyclohexanone (1.0 mmol) was added and the mixture was allowed to warm up to the ambient temperature for 1–7 days. The mixture was diluted with brine (5 mL) and then was extracted with EtOAc (2×15 mL). The combined organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:5) as the eluent to afford the pure aldol adducts.

4.3.1. (2R,1′S)-2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone

anti-Diastereomer:[5i,9a] ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J*=8.5 Hz, 2H), 7.51 (d, *J*=8.5 Hz, 2H), 4.90 (dd, *J*=8.2 and 2.6 Hz, 1H), 4.10 (d, *J*=2.6 Hz, 1H), 2.65–2.55 (m, 1H), 2.53–2.44 (m, 1H), 2.37 (td, *J*=13.0, 5.9 Hz, 1H), 2.16–2.06 (m, 1H), 1.88–1.78 (m, 1H), 1.75–1.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.59, 148.38, 147.48, 127.81, 123.46, 73.88, 57.10, 42.58, 30.67, 27.56, 24.60; HPLC analysis Chiralcel AD-H (*i*-PrOH/hexanes=5:95, 1.0 mL/min, 254 nm) t_R 43.7 min and t_R 58.8 min. *syn*-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J*=8.6 Hz, 2H), 7.49 (d, *J*=8.6 Hz, 2H), 5.49 (s, 1H), 3.20 (d, *J*=3.2 Hz, 1H), 2.68–2.60 (m, 1H), 2.53–2.45 (m, 1H), 2.40 (td, *J*=13.2 and 6.0 Hz, 1H), 2.17–2.06 (m, 1H), 1.90–1.82 (m, 1H), 1.80–1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.98, 149.17, 147.07, 126.63, 123.44, 70.13, 56.80, 42.60, 27.83, 25.92, 24.78; HPLC analysis Chiralcel AD-H (*i*-PrOH/hexanes=5:95, 1.0 mL/min, 254 nm) t_R 29.9 min and t_R 40.0 min.

4.3.2. (2R,1′S)-2-[Hydroxy(2-nitrophenyl)methyl]cyclohexanone

anti-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J*=8.2 Hz, 1H), 7.76 (d, *J*=7.9 Hz, 1H), 7.63 (t, *J*=7.4 Hz, 1H), 7.43 (t, *J*=7.4 Hz, 1H), 5.44 (d, *J*=7.1 Hz, 1H), 4.09 (br s, 1H), 2.81–2.71 (m, 1H), 2.50–2.40 (m, 1H), 2.35 (td, *J*=13.0 and 5.9 Hz, 1H), 2.14–2.03 (m, 1H), 1.89–1.52 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.77, 148.70, 136.52, 132.97, 128.96, 128.33, 123.97, 69.64, 57.24, 42.73, 31.01, 27.68, 24.89; HPLC analysis Chiralcel OD-H (*i*-PrOH/hexanes=5:95, 1.0 mL/min, 254 nm) t_R 16.5 min and t_R 19.6 min. *syn*-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J*=8.2 Hz, 1H), 7.84 (d, *J*=7.8 Hz, 1H), 7.65 (t, *J*=7.2 Hz, 1H), 7.43 (t, *J*=8.2 Hz, 1H), 5.96 (d, *J*=1.8 Hz, 1H), 3.22 (br s, 1H), 2.92–2.82 (m, 1H), 2.51–2.36 (m, 2H), 2.16–2.04 (m, 1H), 1.92–1.76 (m, 2H), 1.74–1.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.82, 147.07, 137.02, 133.05, 129.54, 127.85, 124.56, 66.54, 54.79, 42.46, 27.87, 26.40, 24.77; HPLC analysis Chiralcel OD-H (*i*-PrOH/hexanes=5:95, 1.0 mL/min, 254 nm) t_R 12.0 min and t_R 12.5 min.

4.3.3. (2R,1′S)-2-[Hydroxy(3-nitrophenyl)methyl]cyclohexanone

anti-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 8.15 (d, *J*=8.1 Hz, 1H), 7.67 (d, *J*=7.6 Hz, 1H), 7.53 (t, *J*=8.1 Hz, 1H), 4.90 (dd, *J*=8.4 and 2.7 Hz, 1H), 4.14 (d, *J*=2.7 Hz, 1H), 2.69–2.58 (m, 1H), 2.55–2.44 (m, 1H), 2.38 (td, *J*=13.0 and 6.1 Hz, 1H), 2.18–2.05 (m, 1H), 1.88–1.78 (m, 1H), 1.77–1.51 (m, 3H), 1.47–1.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.75, 148.24, 143.27, 133.15, 129.23, 122.78, 121.95, 73.94, 57.07, 42.59, 30.68, 27.57, 24.59; HPLC analysis Chiralcel AD-H (*i*-PrOH/hexanes=5:95, 1.0 mL/min, 254 nm) t_R 32.6 min and t_R 41.5 min. *syn*-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 8.11 (d, *J*=8.1 Hz, 1H), 7.67 (d, *J*=7.7 Hz, 1H), 7.52 (t, *J*=8.1 Hz, 1H), 5.48 (s, 1H), 3.28 (d, *J*=3.2 Hz, 1H), 2.67 (ddd, *J*=12.6, 5.6, and 1.9 Hz, 1H), 2.53–2.34 (m, 2H), 2.18–2.06 (m, 1H), 1.92–1.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.06, 148.33, 143.94, 132.00, 129.15, 122.07, 120.90, 69.91, 56.77, 42.59, 27.85, 25.92, 24.75; HPLC analysis Chiralcel AD-H (*i*-PrOH/hexanes=5:95, 1.0 mL/min, 254 nm) t_R 25.6 min and t_R 29.2 min.

4.3.4. (2R,1′S)-2-[Hydroxy(4-cyanophenyl)methyl]cyclohexanone

anti-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J*=8.2 Hz, 2H), 7.44 (d, *J*=8.2 Hz, 2H), 4.83 (dd, *J*=8.4 and 3.0 Hz, 1H), 4.05 (d, *J*=3.0 Hz, 1H), 2.62–2.43 (m, 2H), 2.36 (td, *J*=13.0 and 5.7 Hz, 1H), 2.16–2.04 (m, 1H), 1.88–1.76 (m, 1H), 1.74–1.48 (m, 3H), 1.43–1.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.71, 146.36, 132.13, 127.73, 118.66, 111.66, 74.16, 57.09, 42.61, 30.68, 27.59, 24.64; HPLC analysis Chiralcel AD-H (*i*-PrOH/hexanes=10:90, 0.5 mL/min, 254 nm) t_R 47.8 min and t_R 60.8 min. *syn*-Diastereomer: ^1H NMR

(400 MHz, $CDCl_3$): δ 7.62 (d, J=8.2 Hz, 2H), 7.43 (d, J=8.2 Hz, 2H), 5.43 (s, 1H), 3.27 (s, 1H), 2.64–2.56 (m, 1H), 2.51–2.32 (m, 2H), 2.14–2.04 (m, 1H), 1.92–1.82 (m, 1H), 1.80–1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.84, 147.14, 131.89, 126.47, 118.76, 110.66, 70.01, 56.65, 42.45, 27.67, 25.77, 24.63; HPLC analysis Chiralcel AD-H (*i*-PrOH/hexanes=10:90, 0.5 mL/min, 254 nm) t_R 35.4 min and t_R 41.4 min.

4.3.5. (2R,1′S)-2-(Hydroxyphenylmethyl)cyclohexanone

anti-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.25 (m, 5H), 4.77 (dd, J=8.8 and 2.6 Hz, 1H), 3.99 (d, J=2.6 Hz, 1H), 2.66–2.55 (m, 1H), 2.50–2.42 (m, 1H), 2.34 (td, J=12.9 and 6.0 Hz, 1H), 2.10–2.01 (m, 1H), 1.80–1.44 (m, 4H), 1.34–1.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.26, 140.90, 128.20, 127.70, 126.88, 74.52, 57.28, 42.47, 30.67, 27.65, 24.52; HPLC analysis Chiralcel OD-H (*i*-PrOH/hexanes=10:90, 1 mL/min, 254 nm) t_R 7.2 min and t_R 11.8 min. *syn*-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.21 (m, 5H), 5.38 (s, 1H), 3.12 (d, J=2.7 Hz, 1H), 2.58 (td, J=10.2 and 1.6 Hz, 1H), 2.47–2.40 (m, 1H), 2.35 (td, J=13.2 and 5.8 Hz, 1H), 2.10–2.00 (m, 1H), 1.87–1.58 (m, 4H), 1.56–1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.53, 141.51, 128.02, 126.83, 125.67, 70.47, 57.09, 42.52, 27.78, 25.89, 24.73; HPLC analysis Chiralcel OD-H (*i*-PrOH/hexanes=10:90,1 mL/min, 254 nm) t_R 5.6 min and t_R 6.3 min.

4.3.6. (2R,1′S)-2-[Hydroxy(4-methylphenyl)methyl]cyclohexanone

anti-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, J=8.0 Hz, 2H), 7.14 (d, J=8.0 Hz, 2H), 4.74 (dd, J=8.7 and 2.5 Hz, 1H), 3.90 (d, J=2.5 Hz, 1H), 2.65–2.55 (m, 1H), 2.51–2.42 (m, 1H), 2.40–2.29 (m, 4H), 2.12–2.02 (m, 1H), 1.82–1.73 (m, 1H), 1.72–1.46 (m, 3H), 1.34–1.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.52, 137.98, 137.48, 129.00, 126.88, 74.48, 57.41, 42.62, 30.83, 27.78, 24.68, 21.10; HPLC analysis Chiralcel OD-H (*i*-PrOH/hexanes=3:97, 1 mL/min, 254 nm) t_R 14.3 min and t_R 20.7 min. *syn*-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J=8.1 Hz, 2H), 7.13 (d, J=8.1 Hz, 2H), 5.34 (s, 1H), 2.99 (d, J=3.2 Hz, 1H), 2.61–2.53 (m, 1H), 2.49–2.28 (m, 5H), 2.11–2.02 (m, 1H), 1.88–1.59 (m, 4H), 1.57–1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.72, 138.51, 136.48, 128.79, 125.66, 70.51, 57.21, 42.63, 27.90, 26.06, 24.84, 21.03; HPLC analysis Chiralcel OD-H (*i*-PrOH/hexanes=3:97, 1 mL/min, 254 nm) t_R 10.4 min and t_R 11.1 min.

4.3.7. (2R,1′S)-2-[Hydroxy(4-methoxyphenyl)methyl]-cyclohexanone

anti-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, J=8.6 Hz, 2H), 6.79 (d, J=8.6 Hz, 2H), 4.66 (d, J=8.8 Hz, 1H), 3.86 (d, J=2.2 Hz, 1H), 3.72 (s, 3H), 2.57–2.47 (m, 1H), 2.43–2.34 (m, 1H), 2.28 (td, J=12.8 and 5.9 Hz, 1H), 2.04–1.93 (m, 1H), 1.79–1.39 (m, 4H), 1.24–1.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.59, 159.28, 133.25, 128.17, 113.78, 74.24, 57.54, 55.27, 42.64, 30.84, 27.82, 24.71; HPLC analysis Chiralcel AD-H (*i*-PrOH/hexanes=5:95, 1 mL/min, 254 nm) t_R 35.3 min and t_R 36.4 min. *syn*-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, J=8.6 Hz, 2H), 6.79 (d, J=8.6 Hz, 2H), 5.23 (s, 1H), 3.71 (s, 3H), 2.97 (d, J=2.9 Hz, 1H), 2.52–2.43 (m, 1H), 2.39–2.21 (m, 2H), 2.04–1.93 (m, 1H), 1.81–1.51 (m, 4H), 1.50–1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.78, 158.62, 133.74, 126.95, 113.58, 70.39, 57.30, 55.26, 42.67, 27.96, 26.22, 24.88; HPLC analysis Chiralcel AD-H (*i*-PrOH/hexanes=5:95, 1 mL/min, 254 nm) t_R 19.0 min and t_R 22.3 min.

4.3.8. (2R,1′S)-2-(Hydroxy-1-naphthylmethyl)cyclohexanone

anti-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J=9.0 Hz, 1H), 7.89–7.77 (m, 2H), 7.55 (d, J=6.8 Hz, 1H), 7.53–7.43 (m, 3H), 5.82 (dd, J=8.7 and 3.1 Hz, 1H), 4.13 (d, J=3.1 Hz, 1H), 3.03–2.93 (m, 1H), 2.54–2.47 (m, 1H), 2.38 (td, J=13.1 and 6.1 Hz, 1H), 2.12–2.02 (m, 1H), 1.74–1.58 (m, 1H), 1.55–1.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.71, 136.83, 133.95, 131.39, 128.92, 128.45, 125.97, 125.52, 125.36, 125.26, 123.96, 72.11, 57.45, 42.83, 31.39, 27.94, 24.90; HPLC analysis Chiralcel OJ-H (*i*-PrOH/hexanes=10:90, 0.5 mL/min, 254 nm) t_R 23.3 min and t_R 28.1 min. *syn*-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.90–7.84 (m, 1H), 7.82–7.73 (m, 2H), 7.70 (d, J=7.2 Hz, 1H), 7.52–7.44 (m, 3H), 6.24 (s, 1H), 3.14 (s, 1H), 2.77 (dd, J=12.8 and 5.6 Hz, 1H), 2.54–2.48 (m, 1H), 2.38 (td, J=13.6 and 6.1 Hz, 1H), 2.10–2.00 (m, 1H), 1.90–1.52 (m, 4H), 1.45–1.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.61, 136.56, 133.63, 129.49, 129.10, 127.46, 125.99, 125.32, 125.29, 124.06, 122.34, 66.89, 55.35, 42.61, 27.73, 26.02, 24.73; HPLC analysis Chiralcel OJ-H (*i*-PrOH/hexanes=10:90, 0.5 mL/min, 254 nm) t_R 20.7 min and t_R 28.9 min.

4.3.9. (2R,1′S)-2-[Hydroxy(4-fluorophenyl)methyl]cyclohexanone

anti-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.25 (m, 2H), 7.02 (t, J=8.7 Hz, 2H), 4.77 (d, J=8.7 Hz, 1H), 4.03 (d, J=1.7 Hz, 1H), 2.62–2.52 (m, 1H), 2.51–2.42 (m, 1H), 2.35 (td, J=12.9, 6.0 Hz, 1H), 2.13–2.02 (m, 1H), 1.88–1.45 (m, 4H), 1.34–1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.32, 163.59 (d, J=244.4 Hz), 136.90 (d, J=3.1 Hz), 128.69 (d, J=7.9 Hz), 115.31 (d, J=21.1 Hz), 74.06, 57.47, 42.63, 30.75, 27.73, 24.68; HPLC analysis Chiralcel OD-H (*i*-PrOH/hexanes=5:95, 1 mL/min, 254 nm) t_R 12.9 min and t_R 25.9 min. *syn*-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.23 (m, 2H), 7.01 (t, J=8.7 Hz, 2H), 5.35 (s, 1H), 3.17 (s, 1H), 2.62–2.51 (m, 1H), 2.50–2.30 (m, 2H), 2.13–2.02 (m, 1H), 1.92–1.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.48, 162.96 (d, J=243.2 Hz), 137.23 (d, J=3.0 Hz), 127.32 (d, J=7.8 Hz), 114.96 (d, J=21.1 Hz), 70.04, 57.05, 42.53, 27.64, 25.93, 24.73; HPLC analysis Chiralcel OD-H (*i*-PrOH/hexanes=5:95, 1 mL/min, 254 nm) t_R 9.6 min and t_R 9.8 min.

4.3.10. (2R,1′S)-2-[Hydroxy(4-chlorophenyl)methyl]cyclohexanone

anti-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J=8.4 Hz, 2H), 7.25 (d, J=8.4 Hz, 2H), 4.76 (d, J=8.7 Hz, 1H), 4.00 (s, 1H), 2.60–2.43 (m, 2H), 2.35 (td, J=12.9 and 6.0 Hz, 1H), 2.13–2.03 (m, 1H), 1.83–1.75 (m, 1H), 1.71–1.47 (m, 3H), 1.35–1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.20, 139.59, 133.57, 128.54, 128.41, 74.11, 57.38, 42.66, 30.76, 27.73, 24.71; HPLC analysis Chiralcel OD-H (*i*-PrOH/hexanes=5:95, 1 mL/min, 254 nm) t_R 13.7 min and t_R 21.9 min. *syn*-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J=8.4 Hz, 2H), 7.23 (d, J=8.4 Hz, 2H), 5.35 (s, 1H), 3.10 (d, J=3.2 Hz, 1H), 2.56 (td, J=9.8 and 1.5 Hz, 1H), 2.50–2.30 (m, 2H), 2.14–2.04 (m, 1H), 1.89–1.80 (m, 1H), 1.74–1.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.45, 140.01, 132.62, 128.26, 127.14, 70.07, 56.99, 42.59, 27.85, 25.93, 24.80; HPLC analysis Chiralcel OD-H (*i*-PrOH/hexanes=5:95, 1 mL/min, 254 nm) t_R 10.2 min and t_R 10.6 min.

4.3.11. (2R,1′S)-2-[Hydroxy(4-bromophenyl)methyl]cyclohexanone

anti-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J=8.4 Hz, 2H), 7.20 (d, J=8.4 Hz, 2H), 4.75 (dd, J=8.6 and 2.8 Hz, 1H), 3.98 (d, J=2.8 Hz, 1H), 2.60–2.43 (m, 2H), 2.35 (td, J=13.0 and 6.1 Hz, 1H), 2.13–2.04 (m, 1H), 1.84–1.47 (m, 4H), 1.36–1.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.21, 140.08, 131.50, 128.76, 121.72, 74.19, 57.35, 42.67, 30.77, 27.73, 24.73; HPLC analysis Chiralcel OD-H (*i*-PrOH/hexanes=5:95, 1 mL/min, 254 nm) t_R 14.7 min and t_R 21.0 min. *syn*-Diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J=8.4 Hz, 2H), 7.18 (d, J=8.4 Hz, 2H), 5.33 (s, 1H), 3.10 (d, J=3.2 Hz, 1H), 2.55 (td, J=9.7 and 1.2 Hz, 1H), 2.49–2.41 (m, 1H), 2.36 (td, J=13.2 and 5.8 Hz, 1H), 2.14–2.04 (m, 1H), 1.88–1.80 (m, 1H), 1.74–1.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.49, 140.61, 131.27, 127.58, 120.78, 70.16, 57.01, 42.65, 27.92, 25.98, 24.86; HPLC analysis Chiralcel OD-H (*i*-PrOH/hexanes=5:95, 1 mL/min, 254 nm) t_R 10.9 min and t_R 11.3 min.

4.3.12. (2R,1′S)-2-(Hydroxy(4-nitrophenyl)methyl)cyclopentanone

anti-Diastereomer:[5i] ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J=8.6 Hz, 2H), 7.54 (d, J=8.6 Hz, 2H), 4.85 (d, J=9.2 Hz, 1H), 4.76 (s,

1H), 2.53–2.34 (m, 2H), 2.33–1.90 (m, 3H), 1.85–1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.33, 150.05, 148.62, 126.36, 123.64, 70.53, 56.04, 38.88, 22.44, 20.30; HPLC analysis Chiralcel AS-H (*i*-PrOH/hexanes=15:85, 0.6 mL/min, 254 nm) t_R 35.6 min and t_R 47.4 min.

4.3.13. (2R,1′S)-4-Hydroxy-3-methyl-4-(4-nitrophenyl)-butan-2-one

anti-Diastereomer:[5j] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J=8.7 Hz, 2H), 7.52 (d, J=8.7 Hz, 2H), 4.86 (d, J=8.0 Hz, 1H), 3.21 (br s, 1H), 2.96–2.87 (m, 1H), 2.22 (s, 3H), 1.00 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.78, 149.32, 147.45, 127.44, 123.57, 75.32, 53.22, 30.00, 13.95; HPLC analysis Chiralcel AS-H (*i*-PrOH/hexanes=15:85, 0.6 mL/min, 254 nm) t_R 32.5 min and t_R 41.9 min.

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