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A new organocatalyst derived from abietic acid and 4-hydroxy-L-proline for direct asymmetric aldol reactions in aqueous media

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ABSTRACT

Enantioselective direct aldol reactions were carried out in aqueous media with a new organocatalyst that was derived from 4-hydroxy-L-proline and abietic acid via a simple and convenient synthetic protocol with a high overall yield (75%). The new organocatalyst was used for aldol reactions between substituted aromatic aldehydes and various ketones in the presence of several acid additives in aqueous media. The corresponding aldol products were obtained in high isolated yields (up to 99%) and with high *anti*-diastereoselectivities (up to 94%) and enantioselectivities (>99.9%). The catalyst loading can be efficiently reduced to only 1 mol %. The aldol reactions were found to be extremely fast which is very unusual in organocatalyzed reactions in water.

1. Introduction

Asymmetric organocatalysis is a metal free and environmentally benign catalysis, which is currently a high profile field of research in organic synthesis.[1] It is evident that the magnitude of research on asymmetric organocatalyzed aldol reaction is enormous compared to the other types of carbon—carbon bond forming reactions.[1] Initial studies on the development of asymmetric organocatalyzed aldol reactions were carried out by Hajos and Parrish in 1970s, followed by Barbas, List, and Lerner in 2000.[2] It was established that L-proline efficiently catalyzed intermolecular asymmetric aldol reactions in organic solvents,[2] but performed extremely poorly in water.[3] This changed entirely after the derivatization of L-proline and 4-hydroxy-L-proline structures.[4–9] Suitably modified derivatives of L-proline and 4-hydroxy-L-proline have been successfully employed as catalysts for asymmetric aldol reactions in water.[7–9] One modification was performed at the carboxylic acid functionality of either L-proline or 4-hydroxy-L-proline;[7] another modification was aimed at the hydroxyl group of 4-hydroxy-L-proline[8] while the third modification was carried out simultaneously on both the hydroxyl and carboxylic groups of 4-hydroxy-L-proline.[9] However, multistep and low yielding catalyst synthesis, slow catalysis in water, and the need for high catalyst loading remained as some of the fundamental limitations of the aforementioned derivatized organocatalysts.[7–9] It is believed that the creation of a hydrophobic environment by the introduction of a suitable moiety into the catalyst structure is a key factor for achieving excellent stereoselectivity.[8d] However, there is still a need to determine the ideal hydrophobic backbone for 4-hydroxy-L-proline. Some terpene structures have been found to be significant in this regard.[8g,10] The requirement of a carbonyl functionality in the terpene moiety for a better stereoselectivity was proposed by Tao et al.[8g] Herein we have found that an organocatalyst even without a carbonyl functionality in the terpene moiety is similarly effective. Organocatalyst **1** with an abietic acid attachment on the 4-hydroxy-L-proline was found to be successful with a lower catalyst loading in aqueous media. Moreover, organocatalyst **1** could solve most of the aforementioned disadvantages,[4–9] since the synthesis of organocatalyst **1** is simple, the catalyst loading is low, and the catalysis is extremely fast. Catalyst **1** was synthesized from two inexpensive naturally occurring components; 4-hydroxy-L-proline and abietic acid via a simple procedure with high overall yield and purity.

Herein we report that catalyst **1** with only 1 mol % loading provided aldol products with high isolated yields (up to 99%), high *anti* diastereoselectivities (up to 94%), and optimum enantioselectivities (>99.9%) within 2–6 h of reaction in water. The unusually fast rate of reaction in the presence of the new catalyst **1** with only 1 mol % loading is noteworthy in organocatalyzed asymmetric transformations since such a fast catalytic activity with an extremely low catalyst loading has been rarely observed in aqueous media.[7z]

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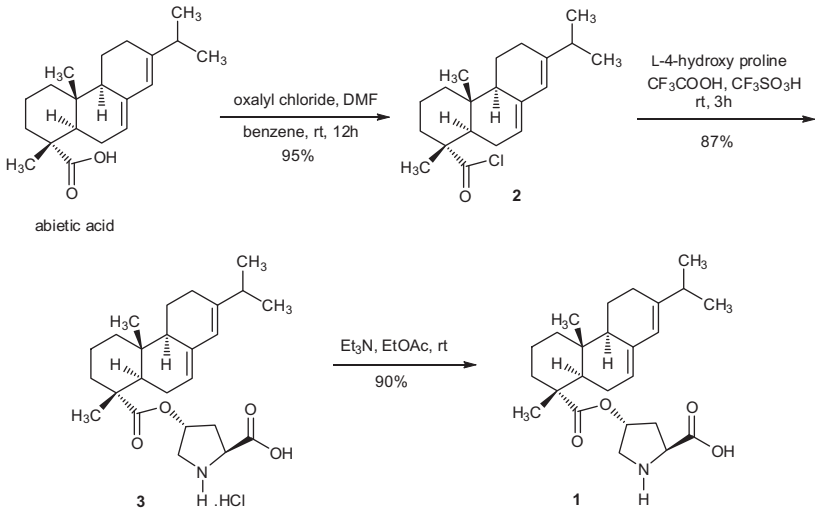


Scheme 1. Preparation of the catalyst **1**.

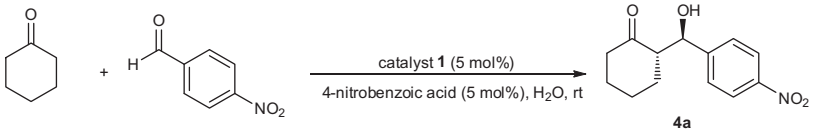
2. Results and discussion

Catalyst **1** was prepared in only three steps and under very mild and convenient reaction conditions. First abietic acid was converted into its acid chloride **2** with oxalyl chloride, then subsequent esterification between acid chloride **2** and 4-hydroxy-L-proline in the presence of trifluoroacetic acid and trifluoromethane sulfonic acid produced salt **3**, which after triethylamine treatment furnished the desired catalyst **1** in 75% overall yield (Scheme 1).

4-Hydroxy-L-proline derivative **1** was subsequently tested as an organocatalyst for direct aldol reactions between 4-nitrobenzaldehyde and cyclohexanone. During the optimization study of the aldol reaction between 4-nitrobenzaldehyde and cyclohexanone with a ratio of 1:3 or 1:10, 87% enantioselectivity was obtained under neat conditions (entries 2 and 7, Table 1). It should be noted that the addition of water (any volume) significantly enhanced the enantioselectivity under similar reaction conditions (Table 1).

When the aldol reactions were performed under same reaction conditions but without 4-nitrobenzoic acid as an additive, the enantioselectivity decreased from 92% to only 56% (entries 4 and 1, respectively, Table 1). This indicates that water and the acid additive play a crucial role for the enhancement of the enantioselectivity in the aldol products. In the presence of both 1:3 and 1:10 volume ratios of aldehyde and ketone, we observed that 0.5 ml was the optimum volume of water (entries 5 and 10, respectively, Table 1). When the amount of water was increased or decreased from 0.5 ml, the enantioselectivity as well as the diastereoselectivity decreased. The enantioselectivity was slightly better with a 1:10

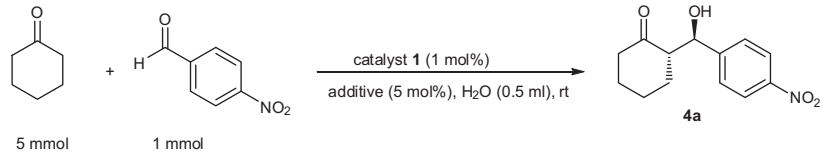
Table 1
Effect of water and the aldehyde–ketone ratio



Entry	Aldehyde/ketone (mmol)	Water (ml)	Time (h)	Yield[a] (%)	*anti*/*syn*[b]	ee[c] (%)
1[d]	1:3	0.1	2.5	95	70:30	56
2	1:3	—	2.5	93	93:7	87
3	1:3	0.01	2.5	94	91:9	90
4	1:3	0.1	3	99	92:8	92
5	1:3	0.5	4	92	95:5	97
6	1:3	1	4	96	93:7	96
7	1:10	—	9	92	89:11	87
8	1:10	0.01	7.5	94	93:7	93
9	1:10	0.1	5	96	92:8	99
10	1:10	0.5	6	96	93:7	99
11	1:10	1	5	98	94:6	98
12[e]	1:3	0.5	15	93	91:9	96
13[f]	1:3	0.5	14	86	93:7	97
14	1:5	0.5	6	95	95:5	97
15[e]	1:5	0.5	17	94	93:7	96
16[f]	1:5	0.5	16	98	96:4	98
17[g]	1:5	0.5	48	—	—	—

[a] Isolated yield after purification by column chromatography.
[b] Diastereomer ratios (*anti*/*syn*) were determined by ^{1}H NMR spectrum of the crude product mixture.
[c] Determined by chiral HPLC analysis.
[d] Reaction carried out in the absence of 4-nitrobenzoic acid.
[e] In the presence of 0.5 mol % of catalyst **1**.
[f] In the presence of 1 mol % of catalyst **1**.
[g] In the absence of catalyst **1**.

Table 2
Effect of various acid additives



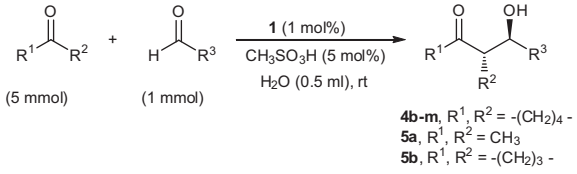
Entry	Additive (pK_a)	Time (h)	Yield[a] (%)	*anti*/*syn*[b]	ee[c] (%)
1	Benzoic acid (4.2)	16	94	92:8	93
2	Citric acid (3.14)	16	93	97:3	97
3	Tartaric acid (2.89)	16	96	91:9	97
4	Adipic acid (4.43)	14	92	96:4	94
5	Stearic acid (10.15)	15	96	92:8	94
6	2,4-Dinitrophenol (4.11)	15	95	92:8	93
7	Phthalic acid (2.98)	16	99	95:5	97
8	Picric acid (0.38)	16	93	93:7	80
9	Oleic acid (9.85)	18	87	96:4	95
10	TFA (0.23)	20	94	97:3	98
11	PTSA (−2.8)	6	99	95:5	97
12	Triflic (−12)	4	97	96:4	98
13	Methane sulfonic (−1.9)	4	89	97:3	99

[a] Isolated yield after column chromatography.
[b] Diastereomer ratios (*anti*/*syn*) were determined by ^{1}H NMR spectrum of the crude product mixture.
[c] Determined by chiral HPLC analysis of the *anti* isomer.

aldehyde–ketone ratio compared to 1:3 (entries 5 and 10, respectively, Table 1). Although the 1:10 aldehyde–ketone ratio was found to be better in affording the highest enantioselectivity (99%) in the aldol products, we adopted a 1:5 ratio of aldehyde–ketone for subsequent optimization studies to gain higher atom economy. It was also observed that this lower aldehyde and ketone ratio (1:5) not only kept the enantioselectivity (97%) almost unchanged, but also provided an enhanced *anti*/*syn* diastereoselectivity (entry 14, Table 1). During the catalyst loading optimization study, in the presence of 0.5 ml of water it was found that as low as 1 mol % of the catalyst was very effective and afforded as high as 98% enantioselectivity with 1:5 aldehyde–ketone ratio (entry 16, Table 1). This observation established the excellent catalytic activity of the newly developed organocatalyst **1**. An experiment without catalyst **1** was also performed, where even after a 48 h reaction time, no product formation was observed (entry 17, Table 1). Once the aldehyde–ketone ratio (1:5), volume of water (0.5 ml), and catalyst loading (1 mol %) were optimized, we next examined the effect of various acid additives in the same aldol reaction. A variety of acid additives with a wide range of pK_a, starting from aromatic to aliphatic acids such as benzoic acid, adipic acid, and so on afforded aldol adducts with enantioselectivities ranging from 80% to 99% (Table 2).

All acid additives, except for picric acid, afforded excellent enantioselectivities with a catalyst loading of only 1 mol %. The reactions were comparatively slower in the presence of fatty acids such as stearic and oleic acid, aromatic acids such as phthalic acid, benzoic acid and 2,4-dinitrophenol, and aliphatic acids such as tartaric acid, citric acid, and adipic acid, but excellent enantioselectiv-

Table 3
Direct aldol reaction between various aromatic aldehydes and cyclohexanone with organocatalyst **1**



Entry (aldol product)	R^3CHO	Time (h)	Yield[a] (%)	*anti*/*syn*[b]	ee[c] (%)
1 **4b**	*o*-Nitrobenzaldehyde	5	92	97:3	>99
2 **4c**	*m*-Nitrobenzaldehyde	6	89	92:8	96
3 **4d**	*o*-Chlorobenzaldehyde	4	87	97:3	>99
4 **4e**	*m*-Chlorobenzaldehyde	5	85	91:9	96
5 **4f**	*p*-Chlorobenzaldehyde	6	91	96:4	>99
6 **4g**	4-Methylbenzaldehyde	4	86	92:8	95
7 **4h**	*o*-Fluorobenzaldehyde	5	88	95:5	>99
8 **4i**	*m*-Fluorobenzaldehyde	4	85	97:3	98
9 **4j**	2-Naphthaldehyde	4	93	96:4	>99
10 **4k**	1-Naphthaldehyde	3	95	97:3	95
11 **4l**	*p*-(Trifluoro)methyl-benzaldehyde	2	97	92:8	>99
12 **4m**	*o*-Methoxy benzaldehyde	6	89	96:4	98
13 **5a**	*p*-Nitrobenzaldehyde	6	90	—	99
14 **5b**	*p*-Nitrobenzaldehyde	4	93	97:3	99.9

[a] Isolated yield after column chromatography.
[b] Diastereomer ratios (*anti*/*syn*) were determined by ^{1}H NMR spectrum of the crude product mixture.
[c] Determined by chiral HPLC analysis of the *anti* isomer.

ities were obtained (Table 2). Similar to other reports, sulfonic acid additives with a lower pK_a than carboxylic acid and phenol additives, furnished the aldol products with higher enantioselectivities.[7y,9g,11] With catalyst **1**, methanesulfonic acid afforded the highest enantioselectivity (99%) and the reaction was completed within 4 h (entry 13, Table 2). In these experiments, a non-linear relationship (specifically a non-monotonic relationship) was observed between the pK_a and obtained ees. The results of this comprehensive acid additive study clearly indicated the requirement of a strong sulfonic acid additive for achieving best results in terms of reactivity as well as selectivity with catalyst **1**. The requirement of a specific acid additive for a specific organocatalyst for optimum results is a well established fact in the literature.[7d,j–l,q–t,w,y,z,8a,9f,g,11,12] Nevertheless, we were unsure as to whether any unknown fundamental structural effect of the methane sulfonic acid was responsible for the fastest reactivity and highest selectivity in the present reaction, additional to known facts such as reactivity enhancement through hydrogen bonding and maintaining the pH of the reaction media.

Once all the parameters such as aldehyde–ketone ratio, water volume, catalyst loading, and acid additive were optimized, we next investigated the substituent effects of aromatic aldehydes in aldol reactions in order to identify the scope and limitations of catalyst **1**, as shown in Table 3.

As can be seen from the results shown in Table 3, almost all of the aromatic aldehyde substrates with either electron withdrawing or electron donating substitution furnished the corresponding aldol adducts with absolute enantiocontrol. It is also noteworthy that all of the substrates showed very fast chemical reactivity, which is very unusual in organocatalyzed aldol reactions in water.[4–9] We also checked the efficacy of catalyst **1** for aldol reactions between various aliphatic ketones and *p*-nitrobenzaldehyde under the same optimized reaction conditions. Two aliphatic ketones such as acetone and cyclopentanone provided the corresponding aldol adducts with excellent enantioselectivity and yields within 4–6 h only (entries 13 and 14, Table 3).

We assume that, under the reaction conditions employed, a hydrophobic region and a hydrophilic region formed in the presence of catalyst **1** (Fig. 1). A plausible transition state model is shown in Figure 1 to explain the stereochemical outcome in the present reaction. Theoretically it was established that free OH groups of interfacial water molecules are responsible for the catalysis through the activation of the aldehyde's carbonyl group via the formation of hydrogen bonds.[13] A hypothesis regarding the similar transition state has been discussed by Giacalone et al.[14]

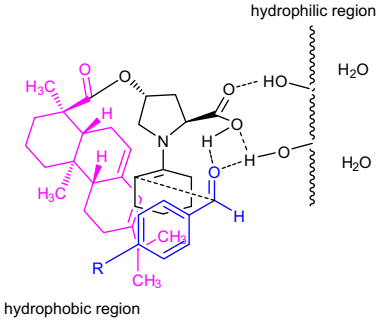


Figure 1. Possible transition state model for the formation of the major *anti* enantiomer.

This is the first time that such an unusually fast chemical reactivity with excellent stereoselectivity has been observed in the presence of only 1 mol % of organocatalyst in aqueous media.

3. Conclusion

In conclusion, we have reported a new catalyst derived from 4-hydroxy-L-proline that catalyzed a direct aldol reaction with excellent diastereo- and enantioselectivities. The simple, short, and inexpensive synthesis of organocatalyst **1** starting from readily available natural products, 4-hydroxy-L-proline and abietic acid, makes it a useful and practical catalyst for the synthesis of stereochemically pure aldol products. Unlike other organocatalysts reported so far, catalyst **1** can perform with great reactivity in water since most of the aldol reactions were completed in between 2 and 6 h at room temperature even with only 1 mol % of catalyst loading in the presence of sulfonic acid additives.[4–9] A single organocatalyst, similar to the present organocatalyst **1**, has not been found to solve simultaneously the major limitations such as multistep and low-yielding catalyst synthesis, slow catalysis in water, high catalyst loading, and poor to moderate selectivity in organocatalyzed asymmetric aldol reaction in water.[4–9] Herein we have used catalyst **1** with an abietic acid scaffold which has shown noteworthy results in asymmetric aldol reactions in water. Our results indicate that the attachment of abietic acid on 4-hydroxy-L-proline generates an ideal hydrophobic and as well as steric environment in the catalyst structure, which can interact with the substrate molecules resulting in excellent diastereo- and enantioselectivities.

4. Experimental

4.1. General

All reagents and starting materials were obtained from commercial sources and used as received.

All dry solvents were purified using a solvent purification system. Routine monitoring of the reaction was performed by TLC, using precoated silica gel TLC plates obtained by E-Merck. All column chromatographic separations were carried out by using silica gel (60–120 mesh). Petroleum ether used was of boiling range 60–80 °C. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a 400 MHz Bruker spectrometer. Chemical shifts are expressed in ppm downfield from TMS as internal standard. Infrared (IR) spectra were recorded on a FT-IR spectrometer (Shimadzu). Melting points were determined on a digital melting point apparatus. Analytical high performance liquid chromatography (HPLC) was carried out on (Shimadzu CLASS-VP V6.12 SP5) instrument using Chiralpak AD-H (4.6 mm × 250 mm), Chiralpak Kromasil 5-AmyCoat (4.6 mm × 250 mm), and Chiralcel OD-H (4.6 mm × 250 mm) columns. Optical rotations were measured on a Jasco Dip 360 digital polarimeter at λ = 589 nm.

4.2. Synthesis of abietic acid chloride 2

Oxalyl chloride (1.2 mmol, 0.1 ml) was added dropwise to a solution of abietic acid (1 mmol, 302 mg) in dimethyl formamide (0.004 mmol, 0.0003 ml) and dry benzene (0.72 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred for 12 h and then concentrated in vacuo to afford abietic acid chloride **2** (304 mg, 95% yield).

4.3. Synthesis of (2*S*,4*R*)-4-((1*R*,4a*R*,4b*R*,10a*R*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a decahydrophenanthrene-1-carbonyloxy)pyrrolidine-2-carboxylic acid 1

A 25 ml round bottomed flask was charged with CF_3CO_2H (0.259 mL, 0.02 mmol) and placed in an ice/water bath. Powdered *trans*-4-hydroxy-L-proline (70.7 mg, 0.54 mmol) was then added to it in small portions with vigorous stirring to give a viscous solution

(leaving some pieces of insoluble material). The reaction mixture was stirred for 5 min and then the ice/water bath was removed. To the resultant suspension, CF_3SO_3H (0.008 mL, 0.09 mmol) was added. After 5 min of stirring, abietic acid chloride **2** (346.7 mg, 1.08 mmol) was added in one portion. The reaction flask was fitted with a loose glass stopper, and the reaction mixture was stirred at room temperature for 3 h. The reaction flask was then cooled in an ice/water bath, and Et_2O (5 mL) was added under vigorous stirring over a period of 5 min. The resulting suspension was stirred at 0–5 °C for 10 min and then filtered to obtain a brown salt **3** as a solid product (211 mg, 87%). The crude brown salt **3** (211 mg, 0.47 mmol) was dissolved in the minimum volume of ethyl acetate, and an equivalent amount of Et_3N (0.06 ml, 0.47 mmol) was added. The resulting white suspension was allowed to return to room temperature after 5 min of stirring, and then filtered. The filtrate was evaporated to furnish **1** (179 mg, 90%) as a light yellow solid. Mp 68–69 °C; $[\alpha]_D^{20}$ = +10 (*c* 1.0, $CHCl_3$); IR (film, cm^{-1}): 3593, 2925, 2302, 1722, 1396, 1236, 1114, 883; ^1H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H) 5.32 (s, 1H), 4.67 (s, 1H), 3.82–3.9 (m, 1H), 2.9–2.96 (m, 2H) 2.24–2.37 (m, 7H) 1.84 (m, 3H) 1.68 (m, 2H) 1.25–1.30 (m, 12H) 0.84–1.03 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) 8.5, 16.2, 18.3, 19.7, 21.7, 23.9, 24.3, 25.0, 25.1, 30.0, 32.8, 33.3, 36.4, 36.8, 37.7, 44.7, 45.9, 47.3, 50.6, 124.0, 126.8, 134.4, 145.6, 177.8, 182.0; ESI-MS (*m*/*z*): calcd for $C_{25}H_{37}NO_4$ [M−H]: 414.2643; found: 414.2642.

4.4. General procedure for the enantioselective direct aldol reaction

To a mixture of catalyst **1** (0.01 mmol) and additive (0.05 mmol) in water (0.5 mL), ketone (5.0 mmol) followed by aromatic aldehydes (1.0 mmol) were added. The resulting mixture was stirred at room temperature to afford an emulsion. The asymmetric aldol reactions were found to occur in emulsions where the catalyst molecules were distributed in the water–oil interface. The reactions were monitored by TLC. After the disappearance of the starting aldehyde, the reaction mixture was quenched with 10 mL of saturated $NaHCO_3$ solution, extracted with EtOAc (3 × 10 mL), and the organic layer was treated with brine (15 mL), dried over Na_2SO_4, and concentrated under vacuum. Purification of the crude products by column chromatography afforded the corresponding pure aldol products. The ee of the products were determined by chiral HPLC analysis. The specific rotations were compared with the literature data.[7c,15]

4.4.1. (2*S*,1′*R*)-2-[Hydroxy(4-nitrophenyl)methyl]cyclohexan-1-one 4a

The spectroscopic NMR data were in agreement with the previously reported one.[15c] $[\alpha]_D^{25}$ = +6.5 (*c* 0.1, $CHCl_3$). The enantiomeric excess of this sample was determined to be >99% by chiral HPLC analysis Chiralpak Kromasil 5-CelluCoat, hexanes/*i*PrOH 95:5), Flow rate = 0.7 mL/min; λ = 254 nm; t_R (major) = 23.5 min, t_R (minor) = 33.1 min.

4.4.2. (2*S*,1′*R*)-2-[Hydroxy(2-nitrophenyl)methyl]cyclohexan-1-one 4b

The spectroscopic NMR data were in agreement with the previously reported one.[15c] $[\alpha]_D^{25}$ = +25.3 (*c* 0.1, $CHCl_3$). The enantiomeric excess of this sample was determined to be >99% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane (10:90), Flow rate = 0.7 mL/min; λ = 254 nm; t_R (major) = 15.9 min, t_R (minor) = 18.8 min.

4.4.3. (2*S*,1′*R*)-2-[Hydroxy(3-nitrophenyl)methyl]cyclohexan-1-one 4c

The spectroscopic NMR data were in agreement with the previously reported one.[16] $[\alpha]_D^{25}$ = +29.3 (*c* 0.1, $CHCl_3$). The enantiomeric excess of this sample was determined to be 96% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane (15:85), Flow rate = 0.7 mL/min; λ = 254 nm; t_R (major) = 14.3 min, t_R (minor) = 20 min.

4.4.4. (2*S*,1′*R*)-2-[Hydroxy(2-chlorophenyl)methyl]cyclohexan-1-one 4d

The spectroscopic NMR data were in agreement with the previously reported one.[15c] $[\alpha]_D^{25}$ = +21.5 (*c* 0.9, $CHCl_3$). The enantiomeric excess of this sample was determined to be >99% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane (05:95), Flow rate: 0.7 ml/min; λ = 254 nm; t_R (major) = 9.8 min, t_R (minor) = 12.5 min.

4.4.5. (2*S*,1′*R*)-2-[Hydroxy(3-chlorophenyl)methyl]cyclohexan-1-one 4e

The spectroscopic NMR data were in agreement with the previously reported one.[15c] $[\alpha]_D^{25}$ = +16.4 (*c* 1.1, $CHCl_3$). The enantiomeric excess of this sample was determined to be 96% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane (05:95), Flow rate: 0.7 ml/min; λ = 254 nm; t_R (major) = 33.4 min, t_R (minor) = 36.6 min.

4.4.6. (2*S*,1′*R*)-2-[Hydroxy(4-chlorophenyl)methyl]cyclohexan-1-one 4f

The spectroscopic NMR data were in agreement with the previously reported one.[15c] $[\alpha]_D^{25}$ = +25.2 (*c* 0.1, $CHCl_3$). The enantiomeric excess of this sample was determined to be >99% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane (15:85), Flow rate: 0.7 ml/min; λ = 254 nm; t_R (major) = 9.6 min, t_R (minor) = 12.9 min.

4.4.7. (2*S*,1′*R*)-2-[Hydroxy(4-mehylphenyl)methyl]cyclohexan-1-one 4g

The spectroscopic NMR data were in agreement with the previously reported one.[15c] $[\alpha]_D^{25}$ = +13.1 (*c* 0.2, $CHCl_3$). The enantiomeric excess of this sample was determined to be 95% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane (3:97), Flow rate: 1 ml/min; λ = 254 nm; t_R (major) = 12.6 min, t_R (minor) = 17.2 min.

4.4.8. (2*S*,1′*R*)-2-[Hydroxy(2-fluorophenyl)methyl]cyclohexan-1-one 4h

The spectroscopic NMR data were in agreement with the previously reported one.[14] $[\alpha]_D^{25}$ = +22 (*c* 1, $CHCl_3$). The enantiomeric excess of this sample was determined to be >99% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane (05:95), Flow rate: 0.7 ml/min; λ = 254 nm; t_R (major) = 12.2 min, t_R (minor) = 16.3 min.

4.4.9. (2*S*,1′*R*)-2-[Hydroxy(3-fluorophenyl)methyl]cyclohexan-1-one 4i

The spectroscopic NMR data were in agreement with the previously reported one.[7i] $[\alpha]_D^{25}$ = +16.4 (*c* 1, $CHCl_3$). The enantiomeric excess of this sample was determined to be 98% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane (05:95), Flow rate: 0.7 ml/min; λ = 254 nm; t_R (major) = 15.1 min, t_R (minor) = 20.9 min.

4.4.10. (2*S*,1′*R*)-2-[Hydroxy(naphthalen-2-yl)methyl]cyclohexan-1-one 4j

The spectroscopic NMR data were in agreement with the previously reported one.[16] $[\alpha]_D^{25}$ = +7.4 (*c* 0.1, $CHCl_3$). The enantiomeric excess of this sample was determined to be >99% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane

(10:90), Flow rate: 0.7 ml/min; λ = 254 nm; t_R (major) = 18.6 min, t_R (minor) = 23.8 min.

4.4.11. (2*S*,1′*R*)-2-[Hydroxy(naphthalen-1-yl)methyl]cyclohexan-1-one 4k

The spectroscopic NMR data were in agreement with the previously reported one.[16] $[\alpha]_D^{25}$ = +9.2 (*c* 1, $CHCl_3$). The enantiomeric excess of this sample was determined to be 95% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane (3:97), Flow rate: 1 ml/min; λ = 254 nm; t_R (major) = 34.2 min, t_R (minor) = 37.6 min.

4.4.12. (2*S*,1′*R*)-2-[Hydroxy(4-trifluoromethylphenyl)methyl] cyclohexan-1-one 4l

The spectroscopic NMR data were in agreement with the previously reported one.[16] $[\alpha]_D^{25}$ = +1.7 (*c* 0.1, $CHCl_3$). The enantiomeric excess of this sample was determined to be >99% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane (20:80), Flow rate: 0.5 ml/min; λ = 254 nm; t_R (major) = 12.1 min, t_R (minor) = 14.1 min.

4.4.13. (2*S*,1′*R*)-2-[Hydroxy(2-methoxyphenyl)methyl] cyclohexan-1-one 4m

The spectroscopic NMR data were in agreement with the previously reported one.[8g] $[\alpha]_D^{25}$ = −23.6 (*c* 1, EtOAc). The enantiomeric excess of this sample was determined to be 98% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane (05:95), Flow rate: 0.7 ml/min; λ = 254 nm; t_R (major) = 17.7 min, t_R (minor) = 24.1 min.

4.4.14. (4*R*)-4-Hydroxy-*p*-nitrophenylbutan-2-one 5a

The spectroscopic NMR data were in agreement with the previously reported one.[7w] $[\alpha]_D^{25}$ = +64.6 (*c* 0.5, $CHCl_3$). The enantiomeric excess of this sample was determined to be 99% by chiral HPLC analysis Chiralcel OD-H (250 × 4.6 mm), Mobile phase: IPA/*n*-Hexane (8.5:91.5), Flow rate: 0.7 ml/min; λ = 254 nm; t_R (major) = 38.7 min, t_R (minor) = 45.1 min.

4.4.15. (2*S*,1′*R*)-2-[Hydroxy(4-nitrophenyl)methyl]cyclopentan-1-one 5b

The spectroscopic NMR data were in agreement with the previously reported one.[7w] $[\alpha]_D^{25}$ = −30.8 (*c* 0.58, $CHCl_3$). The enantiomeric excess of this sample was determined to be >99.9% by chiral HPLC analysis Chiralpak Kromasil-5AmyCoat (254 × 4.6), Mobile phase: IPA/Pet Ether (10:90), Flow rate: 1 ml/min; λ = 265 nm; t_R (major) = 21.3 min.

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References

1. (a) GrÖger, H.; Wilken, J.; Berkessel, A. *Organic Synthesis Highlights V*; Wiley-VCH: Weinheim, 2003. pp 178–186; (b) Berkessel, A.; GrÖger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weiheim, 2005; (c) List, B. *Chem. Rev.* **2007**, *107*, 5413–5883; (d)*Modern Methods in Stereoselective Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2013.
2. (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621; (b) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; (c) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
3. Mase, N.; Barbas, C. F., III *Org. Biomol. Chem.* **2010**, *8*, 4043–4050.
4. For recent discussions on proline and proline-derived organocatalysts, see the reviews; (a) List, B.; Yamamoto, H. *Synlett* **2011**, 461–512; (b) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302–6337.
5. See the recent reviews (a) Bhowmick, S.; Bhowmick, K. C. *Tetrahedron: Asymmetry* **2011**, *22*, 1945–1979; (b) Hernández, J. G.; Juaristi, E. *Chem. Commun.* **2012**, 5396–5409; (c) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687–6703; (d) Heravi, M. M.; Asadi, S. *Tetrahedron: Asymmetry* **2012**, *23*, 1431–1465; (e) Mlynarski, J.; Bas, S. *Chem. Soc. Rev.* **2014**, *43*, 577–587; (f) Bisai, V.; Bisai, A.; Singh, V. K. *Tetrahedron* **2012**, *68*, 4541–4580.
6. See the very recent review on organocatalysis for C—C bond forming reactions: Scheffler, U.; Mahrwald, R. *Chem. Eur. J.* **2013**, *19*, 14346–14396.
7. (a) He, T.; Li, K.; Wu, M.-Y.; Wu, M.-B.; Wang, N.; Pu, L.; Yu, X.-Q. *Tetrahedron* **2013**, *69*, 5136–5143; (b) Chimni, S. S.; Mahajan, D. *Tetrahedron: Asymmetry* **2006**, *17*, 2108–2119; (c) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417–4420; (d) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247–1250; (e) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593–2595; (f) Huang, W.-P.; Chen, J.-R.; Li, X.-Y.; Cao, Y.-J.; Xiao, W.-J. *Can. J. Chem.* **2007**, *85*, 208–213; (g) Gryko, D.; Saletra, W. J. *Org. Biomol. Chem.* **2007**, *5*, 2148–2153; (h) Wang, C.; Jiang, Y.; Zhang, X.-X.; Huang, Y.; Li, B.-G.; Zhang, G.-L. *Tetrahedron Lett.* **2007**, *48*, 4281–4285; (i) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1211–1214; (j) Almaşi, D.; Alonso, D. A.; Balaguer, A.-N.; Nájera, C. *Adv. Synth. Catal.* **2009**, *351*, 1123–1131; (k) Wang, B.; Chen, G.-H.; Liu, L.-Y.; Chang, W.-X.; Li, J. *Adv. Synth. Catal.* **2009**, *351*, 2441–2448; (l) Mase, N.; Noshiro, N.; Mokuya, A.; Takabe, K. *Adv. Synth. Catal.* **2009**, *351*, 2791–2796; (m) Tan, B.; Zhu, D.; Zhang, L.; Chua, P. J.; Zeng, X.; Zhong, G. *Chem. Eur. J.* **2010**, *16*, 3842–3848; (n) Qin, L.; Zhang, L.; Jin, Q.; Zhang, J.; Han, B.; Liu, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 7761–7765; (o) Bayat, S.; Tejo, B. A.; Salleh, A. B.; Abdmalek, E.; Normi, Y. M.; Rahman, M. B. A. *Chirality* **2013**, *25*, 726–734; (p) Kumar, T. P.; Vavle, N. C.; Patro, V.; Haribabu, K. *Tetrahedron: Asymmetry* **2014**, *25*, 457–461; (q) Pedrosa, R.; Andrés, J. M.; Manzano, R.; Román, D.; Téllez, S. *Org. Biomol. Chem.* **2011**, *9*, 935–940; (r) Pearson, A. J.; Panda, S. *Org. Lett.* **2011**, *13*, 5548–5551; (s) Tang, G.; Gün, Ü.; Altenbach, H.-J. *Tetrahedron* **2012**, *68*, 10230–10235; (t) Paladhi, S.; Das, J.; Mishra, P. K.; Dash, J. *Adv. Synth. Catal.* **2013**, *355*, 274–280; (u) Aratake, S.; Itoh, T.; Okano, T.; Usui, T.; Shoji, M.; Hayashi, Y. *Chem. Commun.* **2007**, 2524–2526; (v) Bellomo, A.; Daniellou, R.; Plusquellec, D. *Green Chem.* **2012**, *14*, 281–284; (w) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734–735; (x) Angelici, G.; Corrêa, R. J.; Garden, S. J.; Tomasini, C. *Tetrahedron Lett.* **2009**, *50*, 814–817; (y) Bhowmick, S.; Kunte, S. S.; Bhowmick, K. C. *RSC Adv.* **2014**, *4*, 24311–24315; (z) Wang, B.; Liu, X. –w.; Liu, L. –y.; Chang, W. –x.; Li, J. *Eur. J. Org. Chem.* **2010**, 5951–5954.
8. (a) Zhao, Q.; Lam, Y.-h.; Kheirabadi, M.; Xu, C.; Houk, K. N.; Schafmeister, C. E. *J. Org. Chem.* **2012**, *77*, 4784–4792; (b) Zhong, L.; Gao, Q.; Gao, J.; Xiao, J.; Li, C. *J. Catal.* **2007**, *250*, 360–364; (c) Fu, Y.-Q.; An, Y.-J.; Liu, W.-M.; Li, Z.-C.; Zhang, G.; Tao, J.-C. *Catal. Lett.* **2008**, *124*, 397–404; (d) Aratake, S.; Itoh, T.; Okano, T.; Nagae, N.; Sumiya, T.; Shoji, M.; Hayashi, Y. *Chem. Eur. J.* **2007**, *13*, 10246–10256; (e) Huerta, E.; Stals, P. J. M.; Meijer, E. W.; Palmans, A. R. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 2906–2910; (f) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 958–961; (g) An, Y.-J.; Zhang, Y.-X.; Wu, Y.; Liu, Z.-M.; Pi, A.-C.; Tao, J.-C. *Tetrahedron: Asymmetry* **2010**, *21*, 688–694; (h) Zheng, C.; Wu, Y.; Wang, X.; Zhao, G. *Adv. Synth. Catal.* **2008**, *350*, 2690–2694.
9. (a) Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Noto, R. *Adv. Synth. Catal.* **2008**, *350*, 1397–1405; (b) Zhao, J.-F.; He, L.; Jiang, J.; Cun, L.-F.; Gong, L.-Z. *Tetrahedron Lett.* **2008**, *49*, 3372–3375; (c) Monge-Marcet, A.; Cattoën, X.; Alonso, D. A.; Najerá, C.; Man, M. W. C.; Pleixats, R. *Green Chem.* **2012**, *14*, 1601–1610; (d) Kristensen, T. E.; Vestli, K.; Jakobsen, M. G.; Hansen, F. K.; Hansen, T. *J. Org. Chem.* **2010**, *75*, 1620–1629; (e) Kochetkov, S. V.; Kucherenko, A. S.; Zlotin, S. G. *Eur. J. Org. Chem.* **2011**, 6128–6133; (f) Delaney, J. P.; Henderson, L. C. *Adv. Synth. Catal.* **2012**, *354*, 197–204; (g) Tzeng, Z.-H.; Chen, H.-Y.; Reddy, R. J.; Huang, C.-T.; Chen, K. *Tetrahedron* **2009**, *65*, 2879–2888.
10. Narayanaperumal, S.; Rivera, D. G.; Silva, R. C.; Paixao, M. W. *ChemCatChem* **2013**, *5*, 2756–2773.
11. Zhao, H.; Meng, W.; Yang, Z.; Tian, T.; Sheng, Z.; Li, H.; Song, X.; Zhang, Y.; Yang, S.; Li, B. *Chin. J. Chem.* **2014**, *32*, 417–428.
12. Eymur, S.; Akceylan, E.; Sahin, O.; Uyanik, A.; Yilmaz, M. *Tetrahedron* **2014**, *70*, 1–7.
13. Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492–5502.
14. Giacalone, F.; Gruttadauria, M.; Meo, P. Lo.; Riela, S.; Noto, R. *Adv. Synth. Catal.* **2008**, *350*, 2747–2760.
15. (a) Kanemitsu, T.; Umehara, A.; Miyazaki, M.; Nagata, K.; Itoh, T. *Eur. J. Org. Chem.* **2011**, *5*, 993–997; (b) Yang, H.; Carter, R. G. *Org. Lett.* **2008**, *10*, 4649–4652; (c) Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Meo, P. L.; Riela, S.; Noto, R. *Eur. J. Org. Chem.* **2007**, *28*, 4688–4698; (d) Demircan, E.; Eymur, S.; Demir, A. S. *Tetrahedron: Asymmetry* **2014**, *25*, 443–448; (e) Thorat, P. B.; Goswami, S. V.; Khade, B. C.; Bhusare, S. R. *Tetrahedron Lett.* **2012**, *53*, 6083–6086.
16. Wu, C.; Fu, X.; Ma, X.; Li, S. *Tetrahedron: Asymmetry* **2010**, *21*, 2465–2470.