Tetrahedron: *Asymmetry* 22 (2011) 226–237

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

The cooperative effect of a hydroxyl and carboxyl group on the catalytic ability of novel β-homoproline derivatives on direct asymmetric aldol reactions

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ARTICLE INFO

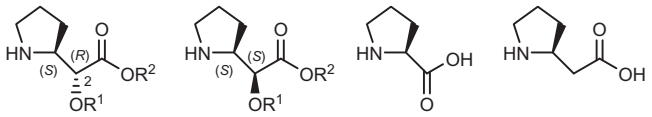
Article history:
Received 8 December 2010
Accepted 25 January 2011
Available online 1 March 2011

ABSTRACT

Novel β-homoproline derivatives, 2-hydroxy-2-(pyrrolidin-2-yl)acetic acids (*R,S*)- and (*S,S*)-**1a–d**, were synthesized. All of the prepared compounds were used as organocatalysts in the direct asymmetric aldol reaction of 4-nitrobenzaldehyde with several ketones. Among these catalysts, (*R*)-2-hydroxy-2-((*S*)-pyrrolidin-2-yl)acetic acid (*R,S*)-**1a** showed good catalytic ability in the formation of aldol product **13** (up to 69% ee, 95% yield), which was similar to the results catalyzed by L-proline (71% ee, 96% yield). Relatively low yields and low enantioselectivities were observed in aldol reactions catalyzed by (*S,S*)-**1a**, for example, **13** was obtained in 55% yield and 13% ee. The aldol reaction catalyzed by the methyl-protected carboxylic acid **1b** and esters **1c**,**d** produced much lower chemical yields and enantioselectivities during the formation of **13**. The cooperative effect of the (*R*)-configured hydroxyl group and the carboxyl group was found to play an important role in inducing enantioselectivity in the aldol reaction. Relatively high diastereoselectivities (*anti*:*syn* = 85:15) and enantioselectivity (*anti*, 83% ee) were observed in the aldol reactions of 4-nitrobenzaldehyde with cyclohexanone, which was catalyzed by (*R,S*)-**1a**.

1. Introduction

The use of small organic compounds as catalysts has recently been recognized as a powerful tool for the construction of chiral building blocks for asymmetric synthesis.[1] Amongst the organocatalysts developed so far for asymmetric reactions, L-proline and proline-based compounds are known to be powerful catalysts not only in direct asymmetric aldol reactions,[2,3] but also in Mannich reactions,[4] Michael reactions,[5] α-aminations,[6] and other reactions.[7] On the basis of experimental and theoretical studies of the proline-catalyzed aldol reaction, it is generally accepted that the reaction proceeds through an enamine-mediated mechanism.[8] Recently, the detection of enamine intermediates in the proline-catalyzed aldol reactions using NMR methods has been reported.[9] Several models have also been discussed to explain the stereoselectivity for the proline-catalyzed aldol reaction. In some models, the proton of the carboxyl group of the enamine intermediate was proposed to participate in hydrogen bonding with the aldol acceptor during the C–C bond formation step in the catalytic cycle.[3,8] However, to the best of our knowledge, there are only a few reports on catalysts bearing a hydroxyl group that participated in hydrogen bonding with the enamine intermediate and the aldol acceptor.[3] We believed that studies on hydroxyl group-containing catalysts would provide useful information regarding the role of hydrogen bonding interaction involved in the catalytic mechanism of the proline-catalyzed direct aldol reaction. To this end, novel L-β-homoproline derivatives bearing a hydroxyl and a carboxyl group **1a** ($R^1 = R^2 = H$), a methoxy and carboxyl group **1b** ($R^1 = Me$, $R^2 = H$), a hydroxyl and methyl ester group **1c** ($R^1 = H$, $R^2 = Me$), or a methoxy and methyl ester groups **1d** ($R^1 = R^2 = Me$) were designed (Fig. 1).



1a: $R^1 = R^2 = H$
1b: $R^1 = Me$, $R^2 = H$
1c: $R^1 = H$, $R^2 = Me$
1d: $R^1 = R^2 = Me$

Figure 1. Structures of catalysts.

Herein we report the synthesis of novel organocatalysts (*R,S*)- and (*S,S*)-**1a–d** and their catalytic ability in some aldol reactions. Furthermore, the effects of additives and solvents on the catalytic reaction were investigated and computational studies on a model transition states were also performed for a model aldol reaction.

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doi:10.1016/j.tetasy.2011.01.025

2. Results and discussion

2.1. Synthesis of organocatalysts 1a–d

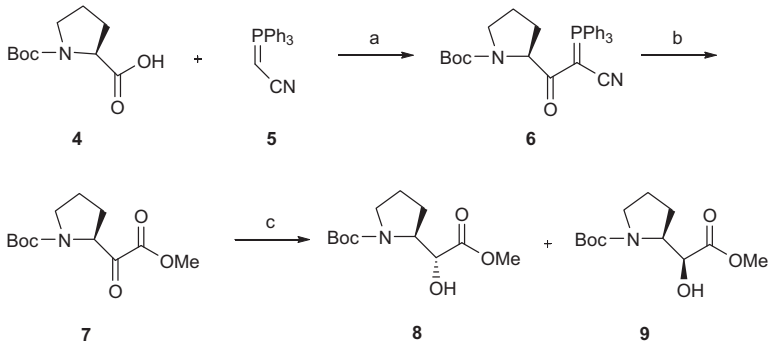
Organocatalysts (*R,S*)- and (*S,S*)-**1a–d** were synthesized from Boc-L-proline **4**, which was prepared from the commercially available L-proline **2**. As shown in Scheme 1, Boc-L-proline **4** was treated with cyanophosphorane **5**[10] to give cyanoketophosphorane **6**. Ozonolysis of ketophosphorane **6** in the presence of methanol according to the reported methods[10b,11] gave the methyl α-ketoester **7** in 9.6% yield (over two steps from **4**) as with a high enantiomeric ratio (>99:1) determined by HPLC. Reduction of methyl α-ketoester **7** with zinc borohydride at −78 °C afforded a diastereomixture of alcohols **8** and **9**.[10b,12] Alcohols **8** and **9** could be separated by column chromatography on silica gel and isolated in 47% and 17% yield, respectively.

In order to assign the absolute stereochemistry of the C-2 attached hydroxyl group in the diastereomeric alcohols **8** and **9**, the corresponding (*R*)- and (*S*)-methoxy trifluoromethyl phenyl acetic acid (MTPA) esters of **8** and **9** (**8-r-Boc**, **8-s-Boc**, **9-r-Boc**, **9-s-Boc**) were prepared.[13] The Boc group of MTPA esters of **8-r-Boc**, **8-s-Boc**, **9-r-Boc**, and **9-s-Boc** was removed by treatment with trifluoroacetic acid (TFA) to give the corresponding amines **8-r-NH**, **8-s-NH**, **9-r-NH**, **9-s-NH**, respectively. As shown in Table 1, the $\Delta\delta_H$ [δ(*S*)-MTPA ester − δ(*R*)-MTPA ester] values obtained from the ^{1}H NMR data of **8-s-NH**, **8-r-NH**, **9-s-NH**, and **9-r-NH** indicated that the absolute configuration at C-2 in **8** and **9** is (*R*) and (*S*), respectively. Analysis of the ^{19}F NMR of the MTPA esters also showed that the enantiomeric ratios of the alcohols **8** and **9** were both >99:1.

The Boc-protected alcohols **8** and **9** were then transformed into organocatalysts (*R,S*)- and (*S,S*)-**1a–d**, respectively, as depicted in Scheme 2. The saponification of methyl esters **8** and **9** using aqueous LiOH in THF,[14] followed by deprotection of the Boc group of (*R,S*)- and (*S,S*)-**10** by treatment with TFA, gave hydroxyacetic acids (*R,S*)- and (*S,S*)-**1a**, respectively.[15] The hydroxyl groups of **8** and **9**[16] were converted into the ether groups using MeI and Ag_2O in MeCN,[16] giving the corresponding methyl ether (*R,S*)-**11** and (*S,S*)-**11**. The saponification of the ester groups of (*R,S*)- and (*S,S*)-**11**, followed by deprotection of the Boc group of (*R,S*)- and (*S,S*)-**12** provided the corresponding (*R,S*)- and (*S,S*)-**1b**, respectively. The deprotection of the Boc group of **8** and **9** using TFA yielded the hydroxyl-substituted methyl esters (*R,S*)- and (*S,S*)-**1c**, respectively. The deprotection of the Boc group of the methoxy methyl esters (*R,S*)- and (*S,S*)-**11** by treatment with TFA provided the methoxy-substituted methyl ester (*R,S*)- and (*S,S*)-**1d** in quantitative yields, respectively.

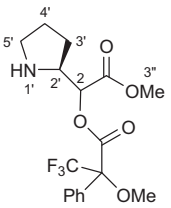
2.2. The direct asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone

The catalytic ability of compounds (*R,S*)- and (*S,S*)-**1a–d** was initially examined in the aldol reaction of 4-nitrobenzaldehyde with acetone using DMSO as a solvent. Reactions using L-proline **2** and



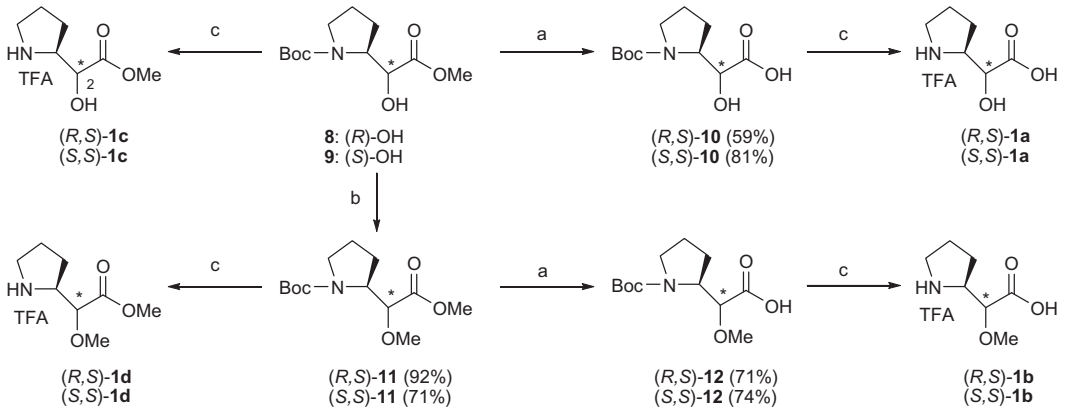
Scheme 1. Synthesis of alcohols **8** and **9**. Reagents and conditions: (a) EDCI, DMAP, CH_2Cl_2, rt, 24 h; (b) O_3, CH_2Cl_2–MeOH, −78 °C, 3.5 h, 9.6% (over two steps); (c) $Zn(BH_4)_2$, THF, −78 °C, 2.5 h, **8** 47%, **9** 17%.

Table 1
^{1}H NMR spectral data for **8-s-NH**, **8-r-NH, 9-s-NH** and **9-r-NH** (in δ) in CD_3OD[a]



	H-2	H-2′	H-3′		H-4′		H-5′		H-3″
8-s-NH	5.60	4.09	2.25	1.89	2.06	2.00	3.30	3.25	3.80
8-r-NH	5.70	4.15	2.15	1.56	1.66	1.80	3.18	2.87	3.86
$\Delta\delta_H$[b]	−0.10	−0.06	+0.10	+0.33	+0.40	+0.20	+0.12	+0.38	−0.06
9-s-NH	5.58	4.09	2.03	1.82	2.03	1.92	3.28	3.06	3.88
9-r-NH	5.58	4.13	2.20	1.92	2.07	1.98	3.35	3.26	3.82
$\Delta\delta_H$[b]	0.00	−0.04	−0.17	−0.10	−0.04	−0.06	−0.07	−0.20	+0.06

[a] Chemical shift values are given in ppm. Assignments were confirmed by ^{1}H–^{1}H COSY, HMQC, and HMBC experiments.
[b] δ(*S*)-MTPA ester − δ(*R*)-MTPA ester.



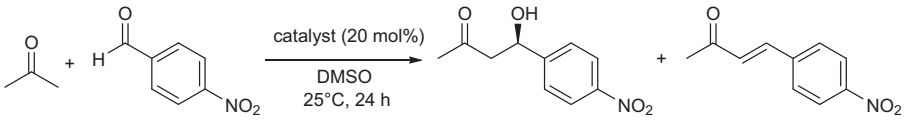
Scheme 2. Synthesis of catalysts (*R,S*) and (*S,S*)-**1a–d**. Reagents and conditions: (a) 1 M LiOH, THF, rt, 3 h; (b) Ag_2O, MeI, MeCN, rt, 12 h; (c) TFA, rt, 12 h, >99%.

L-β-homoproline **3** as the catalyst were also carried out for the sake of comparison. All reactions were performed at 25 °C for 24 h in the presence of 20 mol % of catalyst and triethylamine. The results are summarized in Table 2. As shown in Table 2, (*R,S*)-**1a** ($R^1 = R^2 = H$), which has a (*R*)-hydroxyl and a carboxyl group, catalyzed the aldol reaction, giving the product **13** in 95% yield with 63% ee (entry 1). The aldol product has the same configuration as those obtained from L-proline **2** and L-β-homoproline **3** catalyzed reactions (entries 9 and 10).[2a] On the other hand, in the presence of (*S,S*)-**1a**, aldol product **13** was obtained in 55% yield with 13% ee (entry 2), which were much lower values than those observed for the (*R,S*)-**1a**-catalyzed reaction. The aldol reactions catalyzed by (*R,S*)- and (*S,S*)-**1b** (R^1 = Me, R^2 = H), which contain a methoxy and a carboxyl group, gave the aldol product **13** in moderate yields, although the observed enantioselectivity in **13** was much lower than that catalyzed by (*R,S*)-**1a** (entries 3 and 4). The reactions catalyzed by (*R,S*)- and (*S,S*)-**1c** (R^1 = H, R^2 = Me) and (*R,S*)- and (*S,S*)-**1d** ($R^1 = R^2$ = Me) were sluggish, giving the aldol product **13** in only small amounts (entries 5–8). Amongst the catalysts examined herein, catalyst (*R,S*)-**1a** bearing a (*R*)-configured hydroxyl group showed the best catalytic activity and enantioselectivity. The results clearly indicate that the carboxyl group (R^2 = H) in catalysts **1** is important for the catalytic ability. It should be noted that the enantioselectivity catalyzed by (*S,S*)-**1a** was lower than that catalyzed by L-β-homoproline **3**, while the selectivity in the presence of (*R,S*)-**1a** showed higher enantioselectivity than the L-β-homoproline-catalyzed reaction. The results indicate that the stereochemistry at the hydroxyl-substituted carbon is important to enhance the enantioselectivity. Based on these results, it is suggested that intramolecular hydrogen bonding between the hydroxyl group and the carboxyl group, which increases the acidity of the carboxyl group, plays an important role in increasing both the chemical yield of **13** and its enantioselectivity. As the acidity increases, the hydrogen bonding between the catalyst and aldehyde (aldol acceptor) would become stronger, and thus the reaction rate and enantioselectivity may increase.

2.3. Influence of the additive on the direct asymmetric aldol reaction using organocatalysts (*R,S*)-1a and (*R,S*)-1b

Since additives have been known to alter the reactivity and selectivity of organic reactions,[17,18] the effect of additives on the aldol reaction using catalysts (*R,S*)-**1a** and (*R,S*)-**1b** was examined. The addition of additives improved the enantioselectivity of the catalyst (*R,S*)-**1a** and (*R,S*)-**1b**. The results of this examination are shown in Table 3. In the case of the reaction catalyzed by the TFA salt of (*R,S*)-**1a** without an additive, the yield of **13** greatly decreased, although the enantioselectivity was not so affected

Table 2
The direct asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone in DMSO in the presence of various catalysts



13 **14**

Entry	Catalyst	Yield[a] (%)		ee of **13**[b] (%)
		13	**14**	
1	(*R,S*)-**1a**[c]	95	3	63
2	(*S,S*)-**1a**[c]	55	2	13
3	(*R,S*)-**1b**[c]	63	37	15
4	(*S,S*)-**1b**[c]	61	15	11
5	(*R,S*)-**1c**[c]	6	0	31
6	(*S,S*)-**1c**[c]	5	0	21
7	(*R,S*)-**1d**[c]	9	0	18
8	(*S,S*)-**1d**[c]	0	0	—
9	L-Proline (**2**)	96	4	71
10	L-β-Homoproline·HCl (**3**)[c]	79	0	46

[a] Determined by ^{1}H NMR analysis of the crude products.
[b] Determined by HPLC using a Daisel CHIRALCEl OJ column (hexane–*i*PrOH, 75:25).
[c] 20 mol % of Et_3N was added.

Table 3
Influence of the additive for the direct asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone using organocatalysts (*R*,*S*)-**1a** and (*R*,*S*)-**1b**[a]

Entry	Catalyst	Additive	Yield[b] (%)		ee of **13**[c] (%)
			13	**14**	
1	(*R*,*S*)-**1a**[d]	None	13	4	57
2	(*R*,*S*)-**1a**[e]	None	87	3	52
3	(*R*,*S*)-**1a**[d]	Et_3N (20 mol %)	95	3	63
4	(*R*,*S*)-**1a**[d]	Morpholine (20 mol %)	80	19	65
5	(*R*,*S*)-**1a**[e]	Et_3N·HCl (20 mol %)	56	4	52
6	(*R*,*S*)-**1a**[d]	MS 3 Å (5 mg)[f]	75	6	69
7	(*R*,*S*)-**1a**[d]	MS 4 Å (5 mg)[f]	84	4	69
8	(*R*,*S*)-**1a**[d]	MS 5 Å (5 mg)[f]	52	11	68
9	(*R*,*S*)-**1b**[g]	None	66	34	17
10	(*R*,*S*)-**1b**[g]	Et_3N (20 mol %)	63	37	15

[a] All reactions were carried out at 25 °C for 24 h in the presence of 20 mol % of catalyst.
[b] Determined by ^1H NMR analysis of the crude products.
[c] Determined by HPLC using a Daisel CHIRALCEL OJ column (hexane–*i*PrOH, 75:25).
[d] TFA salt form of (*R*,*S*)-**1a** was used.
[e] TFA free form of (*R*,*S*)-**1a** was used.
[f] All molecular sieves were dried using a microwave oven before use.
[g] TFA salt form of (*R*,*S*)-**1b** was used.

(entries 1 vs 2). Previously, it has been reported that the reactivity and selectivity of aldol reactions in water depend on the pH of the reaction mixture.[2w] This fact suggests that when the TFA salt of (*R*,*S*)-**1a** was used without the addition of an organic base, such as triethylamine or morpholine, the reactivity and enantioselectivity are poor due to the high acidity of TFA. On the other hand, when the TFA-free form of (*R*,*S*)-**1a** was used as the catalyst, both the chemical yield and enantiomeric excess of **13** slightly decreased compared to those obtained from the reaction catalyzed by the TFA salt of (*R*,*S*)-**1a** with triethylamine (entry 3). The slight decrease in the chemical yield and enantiomeric excess of the TFA-free (*R*,*S*)-**1a** catalyzed reaction was probably caused by its poor solubility in DMSO. When morpholine, which is a weak organic base, was used as an additive, the chemical yield of the aldol reaction was slightly decreased, although the enantioselectivity was not affected (entry 4). In order to investigate the role of triethylamine in enhancing the enantioselectivity of **13**, the aldol reaction using the TFA free form of (*R*,*S*)-**1a** as catalyst and triethylammonium chloride as the additive was performed (entry 5). The chemical yield and the enantioselectivity of **13** obtained from the reaction were 56% and 52%, respectively. Although the enantiomeric excess of **13** obtained from the reactions catalyzed by the TFA free form of (*R*,*S*)-**1a** remained unchanged regardless of the absence or presence of triethylammonium chloride, a decrease in the chemical yield of **13** was observed by the addition of triethylammonium chloride as an additive (entries 2 and 5). Since the TFA free form of (*R*,*S*)-**1a** hardly dissolved in the reaction mixture, whereas the TFA salt of (*R*,*S*)-**1a** with triethylamine was dissolved in the reaction mixture, the yield might be dependent upon the solubility of the catalyst in the reaction mixture. On the other hand, the enantioselectivity of the catalyst correlated with the acidity of the catalyst in the reaction mixture.[2y]

Previously, it was reported that the mesoporous molecular sieves, such as MS 3 Å $\{K_9Na_3[(AlO_2)_{12}(SiO_2)_{12}]\}$, 4 Å $\{Na_{12}[(AlO_2)_{12}(SiO_2)_{12}]\}$, 5 Å $\{Ca_{4.5}Na_3[(AlO_2)_{12}]\}$, could be used to capture strong protic acids, such as TfOH, owing to their basic characters.[18b] Moreover, the molecular sieves were also used as additives in the organocatalyzed direct aldol reactions to trap water.[18c] Water was proven to be the reason as to why the enantiomeric excess of **13** in the (*R*,*S*)-**1a** catalyzed aldol reaction decreased (Table 4, entry 7). In order to trap TFA and water, the reactions were performed in the presences of the molecular sieves as additives.

Table 4
Solvent screening for the direct asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone using organocatalysts (*R*,*S*)-**1a**[a]

Entry	Solvent	Yield[b] (%)		ee of **13**[c] (%)
		13	**14**	
1	DMSO	95	3	63
2	THF	24	0	43
3	CH_3CN	20	0	45
4	Acetone	49	0	39
5	CH_2Cl_2	7	4	39
6	EtOH	72	4	29
7	H_2O	83	0	2

[a] All reactions were carried out at 25 °C for 24 h in the presence of 20 mol % of (*R*,*S*)-**1a** and 20 mol % of Et_3N.
[b] Determined by ^1H NMR analysis of the crude products.
[c] Determined by HPLC using a Daicel CHIRALCEL OJ column (hexane–*i*PrOH, 75:25).

When the reaction was performed in either the presence of MS 3 Å or 4 Å, it afforded higher enantioselectivities than those performed in the presence of organic bases, such as triethylamine and morphorine (entries 6 and 7). In the presence of MS 5 Å, the enantiomeric excess of **13** was similar to those obtained from the reaction in the presence of MS 3 Å or 4 Å, whereas the chemical yield decreased (entry 8). Thus, amongst the additives tested MS 3 Å and 4 Å appear to provide a small improvement in the enantioselectivity of **13**. In the case of TFA-(*R*,*S*)-**1b** catalyzed aldol reactions, regardless of the presence or absence of triethylamine as an additive, there was no significant difference in the chemical yield or enantioselectivity (entries 9 and 10).

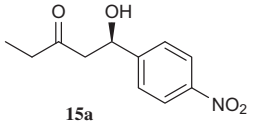
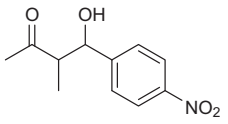
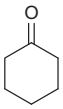
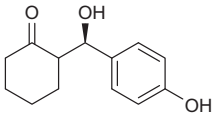
2.4. Influence of the solvent on the direct asymmetric aldol reaction using (*R*,*S*)-1a as a catalyst

The effect of the organic solvent was investigated in the direct aldol reaction of 4-nitrobenzaldhyde with acetone at 25 °C in the presence of 20 mol % of catalyst (*R*,*S*)-**1a**. As can be seen in Table 4, the yield and enantioselectivity of the aldol product **13** were slightly decreased when aprotic solvents such as THF, acetonitrile or acetone were used (entries 2–4). Dichoromethane was found to be not suitable as a solvent for the aldol reaction (entry 5). When protic solvents such as ethanol or water were used, the chemical yield of the aldol product **13** was similar to that obtained from the reaction in DMSO, although the enantioselectivity was significantly decreased (entries 6 and 7). Overall, the aprotic polar solvent, DMSO appeared to be the best solvent amongst the solvents tested.

2.5. Asymmetric direct aldol reactions of various ketones and 4-nitrobenzaldehyde using catalyst (*R*,*S*)-1a

The catalytic ability of (*R*,*S*)-**1a** was examined in the direct aldol reaction of either butan-2-one or cyclohexanone with 4-nitrobenzaldehyde (Table 5). All reactions were carried out in DMSO at 25 °C for 24 h in the presence of 20 mol % of the TFA free form of catalyst (*R*,*S*)-**1a**. When butan-2-one was used, the direct aldol reaction proceeded slowly, giving the aldol product **15a** (8% yield, 70% ee) together with *syn* and *anti*-**15b** [4% yield; *syn*:*anti* = 28:72; 72% ee (*anti*)] after 24 h (entry 1). Due to the small amount of *syn*-**15b**, the enantioselectivity of *syn*-**15b** was not determined. The diastereoselectivity and enantioselectivity of this reaction were similar to those of the L-proline-catalyzed aldol reaction.[2b,v,w] The reaction of cyclohexanone and 4-nitrobenzaldehyde provided the *syn*- and *anti*-aldol products **16** (entry 2). The major diastereomer *anti*-**16** (83% ee) was obtained in the similar enantioselectivity as compared with the reported value of the *anti*-product from the L-

Table 5
The direct aldol reaction of various ketones and 4-nitrobenzaldehyde using organocatalyst (*R*,*S*)-**1a**[a]

Entry	Ketone	Product	Yield[b] (%)	dr[b] (*anti*:*syn*)	ee[c] (%)
1		 **15a**	8	—	70
		 **15b**	4	72:28	72 (*anti*) nd (*syn*)[d]
2		 **16**	45	85:15	83 (*anti*) 48 (*syn*)

[a] All reactions were carried out at 25 °C for 24 h in DMSO in the presence of 20 mol % of TFA free form of (*R*,*S*)-**1a**.
[b] Determined by ^{1}H NMR analysis of the crude products. Yield was calculated by the mole of 4-nitrobenzaldehyde as starting material.
[c] Ee of the products was determined by HPLC using a Daicel CHIRALPAK AS and AD-H columns.
[d] Not determined.

proline-catalyzed reaction (89% ee); a higher diastereoselectiviy (*syn*:*anti* = 15:85) as compared to that of the L-proline catalyzed reaction (*syn*:*anti* = 37:63) was observed.[2g,o] Thus, it can be seen that the direct aldol reaction (*R*,*S*)-**1a** of 4-nitrobenzaldehyde and ketones using organocatalyst gave the corresponding aldol products with similar or higher diastereoselectivity as compared to the L-proline catalyzed reaction.

2.6. Computational studies

Our experimental studies can be summarized as follows: (1) the catalytic ability and the enantioselectivity were largely dependent upon the configuration of the hydroxyl-substituted carbon. Thus, the chemical yield and the enantioselectivity obtained by the (*R*,*S*)-**1a**-catalyzed reaction were much higher than those observed in the (*S*,*S*)-**1a**-catalyzed reaction (Table 1, entries 1 and 2). (2) The cooperative effect of the hydroxyl and carboxyl group of the catalysts was observed especially with regard to the enantioselectivity (Table 1, entries 1 and 3). Thus, the enantioselectivity obtained by (*R*,*S*)-**1a** was much higher than that in the presence of (*R*,*S*)-**1b**. The stereochemical outcome for the formation of the (*R*)-enantiomer of **13** can be explained by the possible transition states **TS** and **TS′** according to the Houk's model,[8a,b,g] considering enamine intermediate (Fig. 2).

The possible structures of the transition states were calculated for the model reaction of acetone with acetoaldehyde using density function theory (DFT) at the B3LYP/6-311++G(d,p) level in the gas phase. All calculations were performed by using the GAUSSIAN 03 program.[19]

Transition states **TS-1–6** and **TS-1′–4′** of the *re*-face and *si*-face attack to the aldehyde acceptor from (*R*,*S*)- and (*S*,*S*)-**1a**, and L-β-homoproline **4**, were found in the computations (Fig. 3). As clearly indicated in Figure 3, the transition states **TS-1,3,5** and **TS-1′,3′**, which produce the (*R*)-aldol product, were calculated to be energetically more stable than the transition states **TS-2,4,6** and **TS-2′,4′** for the *si*-face attack. For the reaction of the enamine of (*R*,*S*)-**1a**, the transition states **TS-1′** and **TS-2′**, which possess the double hydrogen-bonding at the same oxygen, were more energetically stable than the transition state **TS-1** and **TS-2**. However, transition states **TS-3** and **TS-4** were found to be more stable structures than **TS-3′** and **TS-4′** for the reaction of the (*S*,*S*)-**1a** based-enamine. In our experiments, the enantioselectivity obtained in the (*R*,*S*)-**1a**-catalyzed reaction was higher than that catalyzed by (*S*,*S*)-**1a**. However, the calculated energy differences between the transition states derived from (*R*,*S*)-**1a**, for example, **TS-1′** and **TS-2′**, were found to be smaller than those obtained for the transition states derived from (*S*,*S*)-**1a**, for example, **TS-3** and **TS-4**. Thus, the computations in the gas phase do not reproduce well the experimental

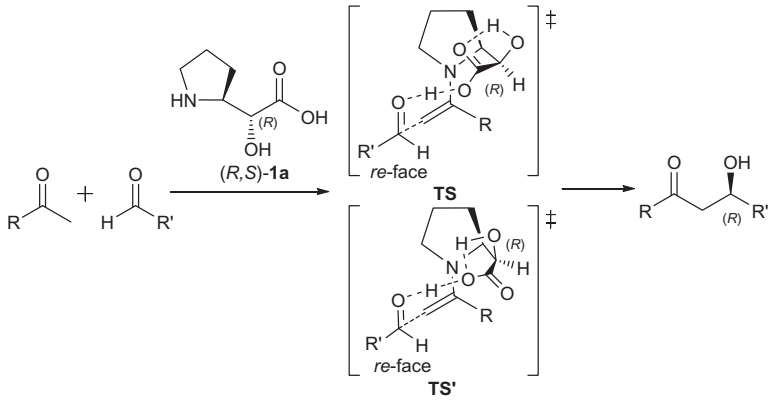


Figure 2. Plausible transition states in the (*R*,*S*)-**1a** catalyzed reaction.

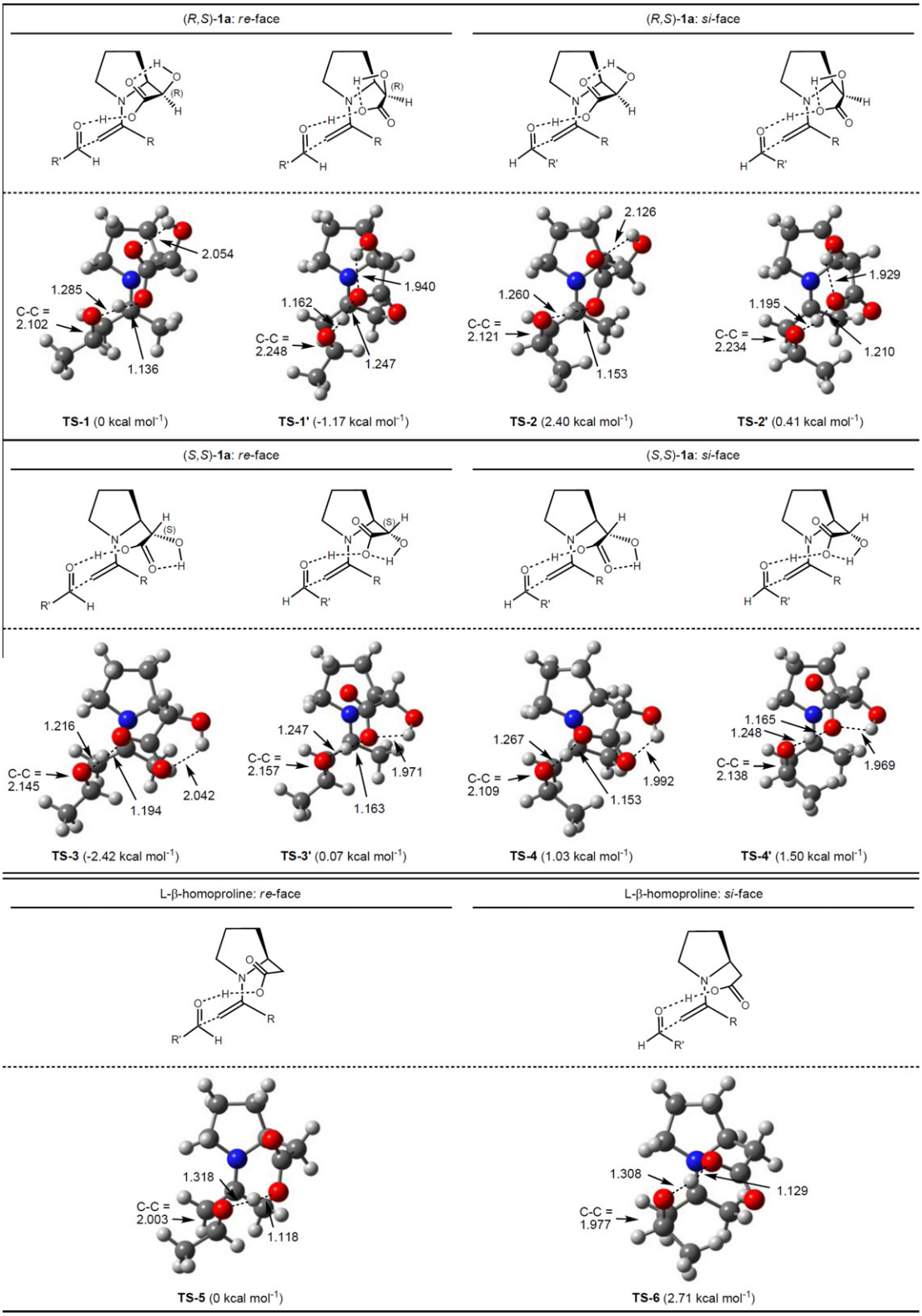


Figure 3. Transition state structures for the reaction of acetoaldehyde and acetone catalyzed by (*R*,*S*)- and (*S*,*S*)-**1a** and L-β-homoproline. The relative energies are in the parentheses at B3LYP/6-311++G(d,p) level in the gas phase. All bond lengths are in angstroms (Å).

observations, although the stereochemical outcome of the major (*R*)-configuration was consistent with the experiments. The medium effect, for example, solvent effect, may affect the energetic stability of the polar structures. Thus, further discussion based on the gas-phase energies should be avoided. Further computational studies to understand the cooperative effect on the enantioselectivity and catalytic ability of the novel organocatalysts **1a** are currently ongoing.

3. Conclusions

In conclusion, we have synthesized novel organocatalysts (*R,S*)- and (*S,S*)-**1a–d** bearing a β-homoproline skeleton. Amongst these organocatalysts, (*R,S*)-**1a** showed the best catalytic ability and enantioselectivity for the direct asymmetric aldol reaction of 4-nitrobenzaldehyde with various ketones. Based on the experimental and theoretical results, we found that the stereochemistry of the hydroxyl-substituted carbon in (*R,S*)-**1a** plays an important role in enhancing the enantioselectivity of the aldol reaction while the carboxylic acid group is an essential factor for the catalytic activity. The cooperative effect in this study stimulates the molecular design of organocatalysts for asymmetric reactions. Reaction conditions and the limitations of the substrates are currently under investigation. We are also currently studying the application of other organic reactions using catalyst (*R,S*)-**1a**.

4. Experimental

4.1. General

All chemicals were purchased from Wako Chemicals, Tokyo Kasei, and Sigma–Aldrich in their highest purity. Flash column chromatography was performed on 230–430 mesh silica gel. ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), and ^{19}F NMR (372 MHz) spectra were recorded in $CDCl_3$ and CD_3OD with JEOL NM-ECP500, JEOL NM-LA500, and JEOL NM-AL400 spectrometers. Chemical shifts in ^{1}H NMR, ^{13}C NMR and ^{19}F NMR are given in parts per million (ppm) relative to internal TMS (δ 0.00 ppm), $CDCl_3$ (δ 7.24 ppm), and CD_3OD (δ 3.31 ppm) for ^{1}H NMR, TMS (δ 0.00 ppm), $CDCl_3$ (δ 77.0 ppm), and CD_3OD (δ 49.0 ppm) for ^{13}C NMR, and external trifluoroacetic acid (δ −76.5 ppm) for ^{19}F NMR. HRMS was recorded on JEOL SX-102A and Thermo Fisher Scientific LTQ Orbitrap XL spectrometers. Optical rotations were measured on a Horiba SEPA-300 polarimeter. Enantioselectivity (%ee) was determined by HPLC analysis of the reaction mixture with a system consisting of a Jasco 980-PU pump and a Jasco 970-UV detector.

4.2. Preparation of organocatalysts 1a–d

4.2.1. (2*S*)-*tert*-Butyl 2-(2′-cyano-2′-triphenylphosphoranylideneacetyl)pyrrolidine-1-carboxylate 6

To a stirred solution of Boc-L-proline **4** (2.80 g, 13 mmol), 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (2.68 g, 14 mmol), and 4-dimethylaminopyridine (0.159 g, 1.3 mmol), (triphenylphosphoranylidene)acetonitrile **5**[10] (8.44 g, 28 mmol) in 60 mL of dichloromethane were added dropwise under cooling in an ice water bath. The stirring was continued for 20 h at room temperature under an N_2 atmosphere. The mixture was then poured over water (5 mL) and the organic phase was separated. The aqueous phase was extracted with dichloromethane (25 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated to afford 4.50 g of crude product containing **6** as yellow oil. The cyanoketophosphorane **6** was used in the next step without purification; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.63–7.45 (m, 15H), 4.93 (dd, J = 8.7, 3.6 Hz, 1H), 3.48–3.32 (m, 2H), 2.35–2.24 (m, 1H), 2.01–1.84 (m, 1H), 1.83–1.76 (m, 1H), 1.44 (s, minor-3.46H), 1.40 (s, major-5.54H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 195.8 (195.9) (d, J_{CP} = 3.1 Hz), 153.9 (154.9), 133.5 (133.6) (d, J_{CP} = 10.3 Hz) (×6), 133.4 (×3), 133.1 (132.8) (d, J_{CP} = 2.4 Hz) (×3), 129.0 (128.9) (d, J_{CP} = 13.0 Hz) (×6), 123.0 (123.2) (d, J_{CP} = 93.8 Hz), 121.6 (121.3) (d, J_{CP} = 16.0 Hz), 78.9 (78.8), 61.6 (61.8) (d, J_{CP} = 9.1 Hz), 46.6 (46.9), 31.4 (30.1), 28.4 (×3), 23.3 (24.4) (chemical shift in parentheses is the minor amide rotational isomer); the amide rotamers ratio (1.6:1.0) was determined by ^{1}H NMR; FAB-HRMS calcd for $C_{30}H_{32}N_2O_3P$ $[M+H]^+$, 499.2151; found 499.2149.

4.2.2. (2*S*)-*tert*-Butyl 2-(2′-methoxy-2′-oxoacetyl)pyrrolidine-1-carboxylate 7

A solution of crude **6** (4.50 g) in a mixture of dichloromethane–methanol (7:3, 30 mL) was treated with ozone at −78 °C for 40 min. The solution was flushed with nitrogen for 10 min and then allowed to warm to room temperature. The solvent was evaporated and the resulting residue was purified by column chromatography (hexane/EtOAc, 6:1) on silica gel to give 321 mg (9.6%) of **7** as a colorless liquid; $[\alpha]_D^{25} = -32.8$ (c 0.884, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (dd, J = 4.9, 8.5 Hz, minor-0.42H), 4.74 (dd, J = 5.7, 8.7 Hz, major-0.58H), 3.85 (s, major-1.75H), 3.83 (s, minor-1.25H), 3.53–3.38 (m, 2H), 2.35–2.20 (m, 1H), 2.06–1.81 (m, 3H), 1.42 (s, minor-3.75H), 1.35 (s, minor-5.25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1 (192.6), 161.3 (161.0), 153.3 (154.5), 80.6 (80.2), 62.5 (62.2), 52.8, 46.7 (46.6), 30.0 (28.9), 28.0 (28.3) (×3), 23.7 (24.5) (chemical shift in parentheses is the minor amide rotational isomer); the amide rotamer ratio (1.4:1.0) was determined by ^{1}H NMR; FAB-HRMS calcd for $C_{12}H_{20}NO_5$ $[M+H]^+$, 258.1341; found 258.1347. The ee value of **7** was determined by HPLC analysis using a Daicel CHIRALCEL OJ column (hexane/*i*-PrOH, 80:10, λ_{max} 254 nm, flow rate = 0.5 mL/min), t_R = 34.4 min (>99%) and 39.5 min (<1%).

4.2.3. (2*S*,1′*R*)- and (2*S*,1′*S*)-*tert*-Butyl 2-(1′-hydroxy-2′-methoxy-2′-oxoethyl)pyrrolidine-1-carboxylate 8 and 9

To a stirred solution of **7** (500 mg, 1.94 mmol) in THF (20 mL), a freshly prepared solution of zinc borohydride[11] (15 mL, 2.2 equiv) in ether was added under cooling at −78 °C. The reaction mixture was stirred for 4 h under an N_2 atmosphere at the same temperature. The reaction mixture was quenched by adding 10 mL of water and 10 mL of ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and evaporated to afford the crude products. Column chromatography on silica gel eluting with hexane–ethyl acetate (6:1) afforded **8** (238 mg, 47%) as a colorless liquid; $[\alpha]_D^{25} = -49.4$ (c 0.516, $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz) δ 4.51–4.45 (m, minor-0.37H), 4.33–4.28 (m, major-0.63H), 4.16–4.09 (m, major-0.63H), 4.09–4.01 (m, minor-0.37H), 3.72 (s, 3H), 3.42–3.38 (m, 2H), 2.09–1.96 (m, 2H), 1.95–1.74 (m, 2H), 1.46 (s, minor-3.33H), 1.44 (s, major-5.67H), the hydroxyl proton was not observed because of broadening of the signal; ^{13}C NMR (CD_3OD, 125 MHz) δ 175.0, 156.8 (156.3), 80.9 (81.5), 73.1 (72.1), 61.1, 52.6, 48.0 (48.6), 28.8 (×3), 28.7 (28.3), 24.9 (23.8) (chemical shift in parentheses is the minor amide rotational isomer); the amide rotamer ratio (1.7:1.0) was determined by ^{1}H NMR; FAB-HRMS calcd for $C_{12}H_{23}NO_5$ $[M+H]^+$, 260.1498; found 260.1506; ESI-HRMS calcd for $C_{12}H_{21}NO_5Na$ $[M+Na]^+$ 282.1312; found 282.1317.

Further elution with hexane–ethyl acetate (5:3) afforded **9** (84 mg, 17%) as a colorless liquid; $[\alpha]_D^{25} = -37.8$ (c 0.344, $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz) δ 4.59 (m, minor-0.48H), 4.55 (m, major-0.52H), 4.08–4.05 (m, 1H), 3.74 (s, minor-1.43H), 3.72 (s, major-1.57H), 3.46–3.38 (m, 1H), 3.34–3.26 (m, 1H), 2.04–1.71 (m, 4H), 1.47 (s, minor-4.29H), 1.46 (s, major-4.71H), the hydroxyl proton was not observed because of broadening of the signal; ^{13}C NMR (CD_3OD, 125 MHz) δ 174.8 (174.7), 156.5 (156.1), 80.9 (81.4), 72.0 (72.5), 61.2, 52.6, 48.5 (48.0), 28.8 (×3), 27.2 (27.0), 25.0 (24.6) (chemical shift in parentheses is the minor amide rotational isomer); the amide rotamer ratio (1.1:1.0) was determined by ^{1}H NMR; FAB-HRMS calcd for $C_{12}H_{23}NO_5$ $[M+H]^+$, 260.1498; found 260.1507; ESI-HRMS calcd for $C_{12}H_{21}NO_5Na$ $[M+Na]^+$ 282.1312; found 282.1314.

4.2.4. (*S*)- and (*R*)-MTPA esters of the alcohols 8 and 9

A solution of **8** (3.7 mg, 0.014 mmol) in dry pyridine (50 μL) was treated with (*R*)-(−)-MTPA chloride (10 mg, 0.040 mmol). The solution was allowed to stand for 10 h. *N*,*N*-Dimethyl-1,3-propanediamine (5 μL) was added to quench the excess chloride. The solvent was evaporated under reduced pressure to afford the crude products. This crude product was purified by column chromatography on silica gel eluted with hexane–ethyl acetate (5:1) affording (*S*)-MTPA ester of **8** (**8-s-Boc**) (5.5 mg, 78%). The (*R*)-MTPA ester of **8-r-Boc** (2.5 mg, 85%) and (*S*)- and (*R*)-MTPA esters of **9-s-Boc** (1.9 mg, 82%) and **9-r-Boc** (1.5 mg, 84%) were prepared according to the same procedure as described above.

4.2.4.1. 8-s-Boc. ^{1}H NMR (500 MHz, CD_3OD) δ 7.67–7.36 (m, 5H), 5.43–5.38 (m, minor-0.31H), 5.31–5.24 (m, major-0.69H), 4.38–4.31 (m, major-0.69H), 4.29–4.22 (m, minor-0.31H), 3.77 (s, minor-0.94H), 3.74 (s, major-2.06H), 3.51 (s, 3H), 3.43–3.28 (m, 1H), 3.22–3.04 (m, 1H), 2.14–1.63 (m, 4H), 1.45 (s, minor-2.81H), 1.42 (s, major-6.19H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.5, 167.3, 156.3 (155.8), 133.0 (132.9), 130.9 (131.0), 129.4 (×2), 129.1 (128.9) (×2), 124.7 (d, J = 288.6 Hz), 86.1 (d, J = 27.6 Hz), 81.2 (82.0), 76.4 (75.4), 58.5 (58.8), 56.0, 53.1, 48.1 (47.7), 29.1 (28.9), 28.7 (×3), 24.5 (23.6) (chemical shift in parentheses is the minor amide rotational isomer); the amide rotamer ratio (2.2:1.0) was determined by ^{1}H NMR.

4.2.4.2. 8-r-Boc. ^{1}H NMR (500 MHz, CD_3OD) δ 7.61–7.40 (m, 5H), 5.39–5.33 (m, minor-0.31H), 5.23–5.17 (m, major-0.69H), 4.35–4.29 (m, major-0.69H), 4.17–4.10 (m, minor-0.31H), 3.80 (s, minor-0.94H), 3.77 (s, major-2.06H), 3.71 (s, major-2.06H), 3.67 (s, minor-0.94H), 3.17–3.02 (m, 2H), 2.05–1.28 (m, 4H), 1.45 (s, minor-2.81H), 1.42 (s, major-6.19H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.7, 167.3, 156.2, 133.6 (133.8), 130.9, 129.5 (×2), 128.3 (×2), 124.7 (d, J = 288.1 Hz), 85.7 (d, J = 27.6 Hz), 81.1 (82.0), 76.7 (76.7), 58.4 (58.6), 56.5, 53.2, 48.2 (47.8), 29.3 (29.1), 28.7 (×3), 24.3 (23.4) (chemical shift in parentheses is the minor amide rotational isomer); the amide rotamer ratio (2.2:1.0) was determined by ^{1}H NMR.

4.2.4.3. 9-s-Boc. ^{1}H NMR (500 MHz, CD_3OD) δ 7.60–7.38 (m, 5H), 5.86–5.83 (m, major-0.55H), 5.79–5.78 (m, minor-0.45H), 4.27–4.19 (m, 1H), 3.81 (s, major-1.64H), 3.80 (s, minor-1.36H), 3.72 (s, major-1.64H), 3.70 (s, minor-1.36H), 3.12–3.01 (m, 1H), 2.62–2.40 (m, 1H), 1.95–1.70 (m, 2H), 1.68–1.48 (m, 2H), 1.51 (s, major-4.91H), 1.44 (s, minor-4.09H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.3 (169.5), 167.3 (167.6), 155.1 (155.9), 133.8 (133.9), 130.8 (130.8), 129.7 (129.6) (×2), 128.0 (128.1) (×2), 124.7 (d, J = 288.4 Hz), 85.7 (d, J = 27.8 Hz), 81.9 (81.3), 75.1 (74.6), 58.6, 56.7 (56.6), 53.3 (53.2), 47.6 (47.8), 28.7 (28.7) (×3), 27.9 (27.0), 24.0 (24.6) (chemical shift in parentheses is the minor amide rotational isomer); the amide rotamer ratio (1.2:1.0) was determined by ^{1}H NMR.

4.2.4.4. 9-r-Boc. ^{1}H NMR (500 MHz, CD_3OD) δ 7.57–7.39 (m, 5H), 5.84–5.78 (m, 1H), 4.31–4.24 (m, 1H), 3.79 (s, major-1.57H), 3.78 (s, minor-1.43H), 3.49 (s, 3H), 3.42–3.12 (m, 2H), 2.02–1.62 (m, 4H), 1.48 (s, major-4.71H), 1.45 (s, minor-4.29H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.2 (168.9), 167.5 (167.2), 155.5 (156.0), 133.2, 130.9, 129.5 (129.4) (×2), 128.7 (128.8) (×2), 124.6 (d, J = 287.7 Hz), 86.1 (d, J = 27.6 Hz), 82.1 (81.5), 75.3 (74.6), 58.5 (58.6), 55.9, 53.2 (53.1), 48.1 (48.4), 28.7 (×3), 27.8 (27.0), 24.0 (24.6) (chemical shift in parentheses is the minor amide rotational isomer); the amide rotamer ratio (1.1:1.0) was determined by ^{1}H NMR.

To a solution of **8-s-Boc** (1.4 mg, 0.003 mmol) in CH_2Cl_2 (1.0 mL) were added 0.1 mL of trifluoro acetic acid. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo to remove the solvent to afford the TFA salt of (*S*)-MTPA ester, **8-s-NH** (1.1 mg, >99%). The (*R*)-MTPA and (*S*)-MTPA esters, **8-r-NH** (1.3 mg), **9-s-NH** (1.7 mg), and **9-r-NH** (1.4 mg) were prepared according to the same procedure. The ^{1}H NMR data of **8-s-NH**, **8-r-NH**, **9-s-NH**, and **9-r-NH** are summarized in Table 1.

4.2.4.5. 8-s-NH. ^{1}H NMR (500 MHz, CD_3OD) δ 7.57–7.40 (m, 5H), 5.60 (d, J = 5.7 Hz, 1H), 4.09 (m, 1H), 3.80 (s, 3H), 3.55 (s, 3H), 3.30 (m, 1H), 3.25 (m, 1H), 2.25 (m, 1H), 2.06 (m, 1H), 2.00 (m, 1H), 1.89 (m, 1H), the amine proton was not observed because of broadening of the signal; ^{13}C NMR (125 MHz, CD_3OD) δ 167.9, 166.9, 132.4, 131.2, 129.5 (×2), 128.9 (×2), 124.5 (d, J = 287.7 Hz), 86.2 (d, J = 27.8 Hz), 74.1, 60.0, 56.4, 53.8, 47.6, 28.0, 24.8; ^{19}F NMR (372 MHz, CD_3OD) δ −76.1 (s, CF_3), −76.5 (s, CF_3COOH); ESI-HRMS calcd for $C_{17}H_{21}NO_5F_3$ $[M+H]^+$ 376.1366; found 376.1371.

4.2.4.6. 8-r-NH. ^{1}H NMR (500 MHz, CD_3OD) δ 7.63–7.42 (m, 5H), 5.70 (d, J = 4.3 Hz, 1H), 4.15 (m, 1H), 3.86 (s, 3H), 3.70 (s, 3H), 3.18 (m, 1H), 2.87 (m, 1H), 2.15 (m, 1H), 1.80 (m, 1H), 1.66 (m, 1H), 1.56 (m, 1H), the amine proton was not observed because of broadening of the signal; ^{13}C NMR (125 MHz, CD_3OD) δ 168.1, 166.8, 133.3, 131.3, 129.7 (×2), 128.3 (×2), 124.6 (d, J = 288.4 Hz), 85.7 (d, J = 27.8 Hz), 73.5, 59.9, 56.8, 54.0, 47.7, 27.7, 24.7; ^{19}F NMR (372 MHz, CD_3OD) δ −75.8 (s, CF_3), −76.5 (s, CF_3COOH); ESI-HRMS calcd for $C_{17}H_{21}NO_5F_3$ $[M+H]^+$ 376.1366; found 376.1372.

4.2.4.7. 9-s-NH. ^{1}H NMR (500 MHz, CD_3OD) δ 7.64–7.44 (m, 5H), 5.58 (d, J = 6.4 Hz, 1H), 4.09 (m, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.28 (m, 1H), 3.06 (m, 1H), 2.03 (m, 2H), 1.92 (m, 1H), 1.82 (m, 1H), the amine proton was not observed because of broadening of the signal; ^{13}C NMR (125 MHz, CD_3OD) δ 168.0, 166.7, 133.0, 131.2, 129.6 (×2), 128.6 (×2), 124.6 (d, J = 288.4 Hz), 85.8 (d, J = 27.8 Hz), 73.6, 59.6, 56.5, 54.1, 47.5, 27.8, 24.4; ^{19}F NMR (372 MHz, CD_3OD) δ −73.1 (s, CF_3), −76.5 (s, CF_3COOH); ESI-HRMS calcd for $C_{17}H_{21}NO_5F_3$ $[M+H]^+$ 376.1366; found 376.1374.

4.2.4.8. 9-r-NH. ^{1}H NMR (500 MHz, CD_3OD) δ 7.60–7.45 (m, 5H), 5.58 (d, J = 6.5 Hz, 1H), 4.13 (m, 1H), 3.82 (s, 3H), 3.55 (s, 3H), 3.35 (m, 1H), 2.26 (m, 1H), 2.20 (m, 1H), 2.07 (m, 1H), 1.98 (m, 1H), 1.92 (m, 1H), the amine proton was not observed because of broadening of the signal; ^{13}C NMR (125 MHz, CD_3OD) δ 167.9, 166.7, 132.4, 131.2, 129.5 (×2), 129.9 (×2), 124.5 (d, J = 288.7 Hz), 86.1 (d, J = 27.4 Hz), 73.8, 59.6, 56.3, 53.9, 47.7, 27.9, 24.5; ^{19}F NMR (372 MHz, CD_3OD) δ −71.0 (s, CF_3), −76.5 (s, CF_3COOH); ESI-HRMS calcd for $C_{17}H_{21}NO_5F_3$ $[M+H]^+$ 376.1366; found 376.1372.

4.2.5. (2*R*,2′*S*)-2-[1′-(*tert*-Butoxycarbonyl)pyrrolidin-2′-yl]-2-hydroxyacetic acid (*R*,*S*)-10 and (2*S*,2′*S*)-2-[1′-(*tert*-butoxycarbonyl)pyrrolidin-2′-yl]-2-hydroxyacetic acid (*S*,*S*)-10

To a stirred solution of **8** (131 mg, 0.51 mmol) in tetrahydrofuran (2 mL) was added 1.0 mL of aqueous 1.0 M LiOH solution. The mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo to remove the solvent. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 4:1) to afford (*R*,*S*)-**10** (73 mg, 59%) as a colorless liquid; $[\alpha]_D^{25} = -35.8$ (*c* 1.47, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 4.25–3.96 (m, 2H), 3.33–3.19 (m, 2H), 2.14–1.57 (m, 4H), 1.37 (s, 9H), the hydroxyl and carboxyl protons were not observed because of broadening of the signals; ^{13}C NMR (125 MHz, CD_3OD) δ 179.1 (178.5), 157.7 (156.5), 81.2, 75.2 (73.7), 61.9 (61.4), 48.3 (48.2), 28.8 (×3), 28.7 (28.7), 24.6 (23.9) (chemical shift in parentheses

is the minor amide rotational isomer); the amide rotamer ratio could not be determined by ^{1}H NMR because of overlapping of the major and minor signals; ESI-HRMS calcd for $C_{11}H_{19}NO_5Na$ $[M+Na]^+$ 268.1155; found 268.1155.

Compound (*S,S*)-**10** was obtained from **9** in the same manner as above: $[\alpha]_D^{25} = -44.4$ (*c* 0.394, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 4.67–4.54 (m, 1H), 4.26–4.17 (m, 1H), 3.48–3.25 (m, 2H), 2.07–1.64 (m, 4H), 1.47 (s, 9H), the hydroxyl and carboxyl protons were not observed because of broadening of the signals; ^{13}C NMR (125 MHz, CD_3OD) δ 179.1, 156.5 (156.5), 81.2 (81.0), 74.4 (74.8), 61.8, 48.4 (48.6), 28.9 (×3), 27.5 (27.2), 24.9 (25.4) (chemical shift in parentheses is minor amide rotational isomer); the amide rotamer ratio could not be determined by ^{1}H NMR because of overlapping of the major and minor signals; ESI-HRMS calcd for $C_{11}H_{19}NO_5Na$ $[M+Na]^+$ 268.1155; found 268.1158.

4.2.6. (2*S*,1′*R*)-*tert*-Butyl 2-(1′,2′-dimethoxy-2′-oxoethy)pyrrolidine-1-carboxylate (*R,S*)-11 and (2*S*,1′*S*)-*tert*-butyl 2-(1′,2′-dimethoxy-2′-oxoethy)pyrrolidine-1-carboxylate (*S,S*)-11

To a stirred solution of **8** (33 mg, 0.127 mmol) in CH_3CN (0.5 mL) was added Ag_2O (50 mg) and CH_3I (0.5 mL). The mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through Celite and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 5:1) to afford (*R,S*)-**11** (32 mg, 92%) as a colorless liquid; $[\alpha]_D^{25} = -74.2$ (*c* 1.51, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20–4.00 (m, 2H) 3.72 (s, 3H), 3.36 (s, 3H), 3.45–3.15 (m, 2H), 2.10–1.90 (m, 2H), 1.86–1.67 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 154.7 (154.1), 80.8 (80.4), 79.3 (79.7), 58.5, 58.4, 52.0, 47.2 (46.6), 28.4 (×3), 27.2 (27.0), 23.9 (22.9) (chemical shift in parentheses is the minor amide rotational isomer); the amide rotamer ratio could not be determined by ^{1}H NMR because of overlapping of the major and minor signals; ESI-HRMS calcd for $C_{13}H_{23}NO_5Na$ $[M+Na]^+$ 296.1468; found 296.1473.

(*S,S*)-**11** was prepared from **9** according to the same procedure as described above; $[\alpha]_D^{25} = -78.5$ (*c* 0.789, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.39–4.33 (m, major-0.63H), 4.19–4.14 (m, minor-0.37H), 4.12–4.06 (m, major-0.63H), 4.05–4.00 (m, minor-0.37H), 3.73 (s, minor-1.11H), 3.71 (s, major-1.89H), 3.47–3.39 (m, minor-0.74H), 3.36 (s, 3H), 3.36–3.28 (m, major-1.26H), 2.01–1.86 (m, 2H), 1.82–1.65 (m, 2H), 1.46 (s, minor-3.33H), 1.44 (s, major-5.67H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8 (171.6), 154.5 (154.0), 80.3 (81.6), 79.4 (79.7), 59.2 (59.4), 58.9, 51.9, 47.2 (46.8), 28.4 (×3), 25.9 (26.7), 24.2 (23.6) (chemical shift in parentheses is minor amide rotational isomer); the amide rotamer ratio (1.7:1.0) was determined by ^{1}H NMR; ESI-HRMS calcd for $C_{13}H_{23}NO_5Na$ $[M+Na]^+$ 296.1468; found 296.1472.

4.2.7. (2*R*,2′*S*)-2-[1′-(*tert*-Butoxycarbonyl)pyrrolidin-2′-yl]-2-methoxyacetic acid (*R,S*)-12 and (2*S*,2′*S*)-2-[1′-(*tert*-butoxycarbonyl)pyrrolidin-2′-yl)-2-methoxyacetic acid (*S,S*)-12

To a stirred solution of (*R,S*)-**11** (41 mg, 0.15 mmol) in tetrahydrofuran (1 mL) was added 0.3 mL of 1.0 M LiOH aqueous solution. The mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated to remove the solvent in vacuo. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 4:1) to afford (*R,S*)-**12** (28 mg, 71%) as a colorless liquid; $[\alpha]_D^{25} = -36.3$ (*c* 0.564, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 4.22–4.06 (m, 1H), 3.97–3.85 (m, minor-0.37H), 3.78–3.67 (m, major-0.63H), 3.42–3.33 (m, 2H), 3.40 (s, 3H), 2.14–1.69 (m, 4H), 1.47 (s, 9H), the carboxyl proton was not observed because of broadening of the signal; ^{13}C NMR (125 MHz, CD_3OD) δ 178.6 (177.5), 157.1 (156.4), 84.9 (83.6), 81.3, 59.9 (59.6), 59.0 (58.6), 48.2 (47.8), 28.8 (×3), 28.8 (28.6), 24.7 (24.0) (chemical shift in parentheses is minor amide rotational isomer); the amide rotamer ratio (1.7:1.0) was determined by ^{1}H NMR; ESI-HRMS calcd for $C_{12}H_{21}NO_5Na$ $[M+Na]^+$ 282.1312; found 282.1313.

Compound (*S,S*)-**12** was prepared from (*S,S*)-**11** according to the same procedure as above: $[\alpha]_D^{25} = -62.2$ (*c* 0.740, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 4.18–4.10 (m, 2H), 3.44–3.32 (m, 5H), 2.04–1.66 (m, 4H), 1.49 (s, minor-3.75H), 1.46 (s, major-5.25H), the carboxyl proton was not observed because of broadening of the signal; ^{13}C NMR (125 MHz, CD_3OD) δ 178.6 (178.1), 156.3 (156.3), 83.6 (84.0), 81.0 (81.4), 60.9 (60.8), 59.4 (59.6), 48.5 (48.3), 28.9 (×3), 27.3 (27.9), 25.2 (24.5) (chemical shift in parentheses is the minor amide rotational isomer); the amide rotamer ratio (1.4:1.0) was determined by ^{1}H NMR; ESI-HRMS calcd for $C_{12}H_{21}NO_5Na$ $[M+Na]^+$ 282.1312; found 282.1314.

4.3. Organocatalysts (*R,S*)- and (*S,S*)-1a–d

4.3.1. (2*R*,2′*S*)-2-Hydroxy-2-(pyrrolidin-2′-yl)acetic acid TFA salt (*R,S*)-1a

To a solution of (*R,S*)-**10** (72 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) was added 0.5 mL of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo to remove the solvent to afford the TFA salt form of (*R,S*)-**1a** (71 mg, >99%) as a colorless liquid; $[\alpha]_D^{25} = -9.2$ (*c* 0.546, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 4.30 (d, *J* = 4.8 Hz, 1H), 3.88–3.83 (m, 1H), 3.29–3.24 (m, 2H), 2.25–1.95 (m, 4H), the hydroxyl, carboxyl, and amino protons were not observed because of broadening of the signals; ^{13}C NMR (125 MHz, CD_3OD) δ 174.1, 70.4, 62.9, 47.0, 28.2, 24.9; ^{19}F NMR (372 MHz, CD_3OD) δ −76.5 (s, CF_3COOH); ESI-HRMS calcd for $C_6H_{12}NO_3$ $[M+H]^+$ 146.0812; found 146.0813.

By the same procedure, the TFA salt forms of (*S,S*)-**1a**, (*R,S*)- and (*S,S*)-**1b–d** were prepared from the corresponding Boc-protected precursors (*S,S*)-**10**, (*R,S*)-**12**, (*S,S*)-**12**, (*R,S*)-**8**, (*S,S*)-**9**, (*R,S*)-**11**, and (*S,S*)-**11**, respectively.

4.3.2. (2*S*,2′*S*)-2-Hydroxy-2-(pyrrolidin-2′-yl)acetic acid TFA salt (*S,S*)-1a

$[\alpha]_D^{25} = -9.0$ (*c* 0.558, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 4.48 (d, *J* = 4.2 Hz, 1H), 3.97–3.93 (m, 1H), 3.32–3.29 (m, 2H), 2.11–1.97 (m, 4H), the hydroxyl, carboxyl, and amino protons were not observed because of broadening of the signals; ^{13}C NMR (125 MHz, CD_3OD) δ 174.0, 69.3, 62.3, 47.4, 25.5, 24.8; ^{19}F NMR (372 MHz, CD_3OD) δ −76.5 (s, CF_3COOH); ESI-HRMS calcd for $C_6H_{12}NO_3$ $[M+H]^+$ 146.0812; found 146.0813.

4.3.3. (2*R*,2′*S*)-2-Methoxy-2-(pyrrolidin-2′-yl)acetic acid TFA salt (*R,S*)-1b

$[\alpha]_D^{25} = -32.7$ (*c* 2.26, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 3.97 (d, *J* = 6.0 Hz, 1H), 3.82–3.78 (m, 1H), 3.50 (s, 3H), 3.31–3.22 (m, 2H), 2.23–1.90 (m, 4H), the carboxyl and amino protons were not observed because of broadening of the signals; ^{13}C NMR (125 MHz, CD_3OD) δ 172.3, 80.0, 62.1, 59.1, 46.9, 28.0, 24.8; ^{19}F NMR (372 MHz, CD_3OD) −76.5 (s, CF_3COOH); ESI-HRMS calcd for $C_7H_{14}NO_3$ $[M+H]^+$ 160.0968; found 160.0970.

4.3.4. (2*S*,2′*S*)-2-Methoxy-2-(pyrrolidin-2′-yl)acetic acid TFA salt (*S,S*)-1b

$[\alpha]_D^{25} = -35.8$ (*c* 0.950, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 4.11 (d, *J* = 3.8 Hz, 1H), 3.98–3.94 (m, 1H), 3.49 (s, 3H), 3.31–3.26 (m, 2H), 2.10–1.93 (m, 4H), the carboxyl and amino protons were not observed because of broadening of the signals; ^{13}C NMR (125 MHz, CD_3OD) δ 172.8, 79.0, 61.7, 59.0, 47.4, 25.6, 25.0; ^{19}F NMR (372 MHz, CD_3OD) −76.5 (s, CF_3COOH); ESI-HRMS calcd for $C_7H_{14}NO_3$ $[M+H]^+$ 160.0968; found 160.0970.

4.3.5. (2*R*,2′*S*)-Methyl 2-hydroxy-2-(pyrrolidin-2′-yl)acetate TFA salt (*R*,*S*)-1c

$[\alpha]_D^{25} = -22.5$ (*c* 0.778, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 4.35 (d, *J* = 4.7 Hz, 1H), 3.88–3.83 (m, 1H), 3.79 (s, 3H), 3.29–3.26 (m, 2H), 2.21–1.93 (m, 4H), the hydroxyl and amino protons were not observed because of broadening of the signals; ^{13}C NMR (125 MHz, CD_3OD) δ 173.0, 70.5, 62.7, 53.1, 47.0, 28.1, 24.9; ^{19}F NMR (372 MHz, CD_3OD) −76.5 (s, CF_3COOH); ESI-HRMS calcd for $C_7H_{14}NO_3$ $[M+H]^+$ 160.0968; found 160.0971.

4.3.6. (2*S*,2′*S*)-Methyl 2-hydroxy-2-(pyrrolidin-2′-yl)acetate TFA salt (*S*,*S*)-1c

$[\alpha]_D^{25} = -17.7$ (*c* 1.24, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 4.53 (d, *J* = 4.3 Hz, 1H), 3.96–3.92 (m, 1H), 3.79 (s, 3H), 3.31–3.28 (m, 2H), 2.11–1.91 (m, 4H), the hydroxyl and amino protons were not observed because of broadening of the signals; ^{13}C NMR (125 MHz, CD_3OD) δ 173.0, 70.5, 62.7, 53.1, 47.0, 28.1, 24.9; ^{19}F NMR (372 MHz, CD_3OD) −76.5 (s, CF_3COOH); ESI-HRMS calcd for $C_7H_{14}NO_3$ $[M+H]^+$ 160.0968; found 160.0967.

4.3.7. (2*R*,2′*S*)-Methyl 2-methoxy-2-(pyrrolidin-2′-yl)acetate TFA salt (*R*,*S*)-1d

$[\alpha]_D^{25} = -32.8$ (*c* 0.442, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 4.06 (d, *J* = 5.4 Hz, 1H), 3.85–3.79 (m, 1H), 3.81 (s, 3H), 3.49 (s, 3H), 3.31–3.22 (m, 2H), 2.22–1.88 (m, 4H), the amino proton was not observed because of broadening of the signal; ^{13}C NMR (125 MHz, CD_3OD) δ 171.2, 79.8, 61.9, 59.3, 53.1, 47.0, 27.9, 24.8; ^{19}F NMR (372 MHz, CD_3OD) −76.5 (s, CF_3COOH); ESI-HRMS calcd for $C_8H_{16}NO_3$ $[M+H]^+$ 174.1125; found 174.1128.

4.3.8. (2*S*,2′*S*)-Methyl 2-methoxy-2-(pyrrolidin-2′-yl)acetate TFA salt (*S*,*S*)-1d

$[\alpha]_D^{25} = -42.9$ (*c* 0.198, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 4.25 (d, *J* = 3.8 Hz, 1H), 3.99–3.94 (m, 1H), 3.80 (s, 3H), 3.49 (s, 3H), 3.32–3.24 (m, 2H), 2.11–1.91 (m, 4H), the amino proton was not observed because of broadening of the signal; ^{13}C NMR (125 MHz, CD_3OD) δ 170.8, 78.7, 61.4, 59.3, 53.0, 47.5, 25.5, 24.9; ^{19}F NMR (372 MHz, CD_3OD) −76.5 (s, CF_3COOH); ESI-HRMS calcd for $C_8H_{16}NO_3$ $[M+H]^+$ 174.1125; found 174.1126.

4.3.9. TFA free form of (2*R*,2′*S*)-2-hydroxy-2-(pyrrolidin-2′-yl)acetic acid (*R*,*S*)-1a

The TFA salt of (*R*,*S*)-**1a** (244 mg, 1.01 mmol) was dissolved in 3 mL of 1.0 M HCl. The solution was then applied to the cation-exchange resin, AG 50 W-X8 (200–400 mesh), hydrogen form (Bio-Rad Laboratories, USA), that had been preequilibrated with H_2O.[20] After washing with 100 mL of H_2O, 100 mL of 6 M NH_4OH was eluted. The aqueous solution was evaporated to dryness under reduced pressure to afford the TFA free form of (*R*,*S*)-**1a** (146 mg, 97%) as a colorless solid; $[\alpha]_D^{25} = +13.6$ (*c* 1.03, H_2O); ^1H NMR (500 MHz, D_2O) δ 4.28 (d, *J* = 5.3 Hz, 1H), 4.27–3.89 (m, 1H), 3.48–3.40 (m, 2H), 2.34–2.27 (m, 1H), 2.24–2.08 (m, 2H), 2.04–1.96 (m, 1H), the hydroxyl, carboxyl, and amino protons were not observed because of broadening of the signals; ^{13}C NMR (125 MHz, CD_3OD) δ 177.3, 70.7, 62.4, 45.9, 26.8, 23.6; ESI-HRMS calcd for $C_6H_{12}NO_3$ $[M+H]^+$ 146.0812; found 146.0813.

4.4. General procedure for the aldol reactions between acetone and 4-nitrobenzaldhyde

To a solution of the chosen catalyst (0.02 mmol) in DMSO (0.80 mL) and Et_3N (2.8 μL, 0.02 mmol) was added ketone (0.20 mL, 20 vol %). The mixture was stirred at room temperature. After 10 min of stirring, 4-nitrobenzaldehyde (15.1 mg, 0.10 mmol) was added to the mixture. The reaction mixture was then stirred at 25 °C for 24 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (1 mL) and extracted with EtOAc (5 × 2 mL). The organic extracts were combined, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to afford the aldol adducts.

The relative and absolute configurations of **13** in Tables 2–4, and **15** and **16** in Table 5 were determined by comparison with the reported NMR and HPLC data. The enantiomeric excess of aldol products was determined by HPLC on chiral stationary phase of CHIRALCEL OJ, AD-H, and AS columns (Daicel Co. Ltd., 4.6 × 250 mm).

4.4.1. 4-Hydroxy-4-(4-nitrophenyl)-2-butanone 13[2a]

^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 5.29–5.24 (m, 1H), 2.87–2.84 (m, 2H), 2.23 (s, 3H), the hydroxyl proton was not observed because of broadening of the signals; HPLC analysis using a Daicel CHIRALCEL OJ column (hexane/*i*-PrOH, 75:25, λ_{max} 254 nm, flow rate = 1.0 mL/min), t_R = 11.4 min (major) and 12.7 min (minor).

4.4.2. 4-(4-Nitrophenyl)but-3-en-2-one 14

^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 16.3 Hz, 1H), 6.82 (d, *J* = 16.3 Hz, 1H), 2.42 (s, 3H).

4.4.3. 1-Hydroxy-1-(4-nitrophenyl)pentan-3-one 15a[2b]

^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 5.27–5.23 (m, 1H), 3.62 (d, *J* = 3.3 Hz, 1H), 2.85–2.76 (m, 2H), 2.49–2.44 (m, 2H), 1.07 (t, *J* = 7.2 Hz, 3H); ee = 70%, the ee value was determined by HPLC analysis using a Daicel CHIRALPAK AS column (hexane/*i*-PrOH, 90:10, λ_{max} 280 nm, flow rate = 2.0 mL/min), t_R = 15.8 min (major) and 35.2 min (minor).

4.4.4. 4-Hydroxy-3-methyl-4-(4-nitrophenyl)butan-2-one *syn*- and *anti*-15b[2v,w]

^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 5.27–5.26 (m, *syn*-0.28H), 4.87–4.84 (m, *anti*-0.72H), 3.20 (d, *J* = 4.8 Hz, 1H), 2.92–2.86 (m, 1H), 2.19 (s, 3H), 1.01 (d, *J* = 7.4 Hz, 3H); *syn*:*anti* = 28:72; ee = 70% (*anti*), the ee value of was determined by HPLC analysis using a Daicel CHIRALPAK AS column (hexane/*i*-PrOH, 90:10, λ_{max} 280 nm, flow rate = 2.0 mL/min), t_R = 16.2 min (minor) and 22.4 min (major). Due to the small amount of the *syn*-**15b**, the enantiomeric excess could not be determined.

4.4.5. 2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (*syn*- and *anti*-16)[2g,o]

^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 5.39–5.37 (m, *syn*-0.15H), 4.88–4.85 (m, *anti*-0.85H), 3.14 (d, *J* = 3.3 Hz, 1H), 2.64–2.59 (m, 1H), 2.50–2.34 (m, 2H), 2.14–2.06 (m, 1H), 1.87–1.81 (m, 1H), 1.74–1.63 (m, 2H), 1.63–1.49 (m, 2H); *syn*:*anti* = 15:85; ee = 48% (*syn*), 83% (*anti*), the ee value was determined by HPLC analysis using a Daicel CHIRALPAK AD-H column (hexane/*i*-PrOH, 80:20, λ_{max} 254 nm, flow rate = 0.5 mL/min), *syn*-diastereomer: t_R = 26.5 min (minor) and 27.7 min (major), *anti*-diastereomer: t_R = 30.3 min (minor) and 39.6 min (major).

4.5. Computational methods

Transition states for the aldol reactions of acetoaldehyde with acetone catalyzed by (*R*,*S*)- and (*S*,*S*)-**1a**, and L-β-homoproline as the simple model reactions were explored. All calculations were implemented in the GAUSSIAN 03 program.[19] The geometries of the transition states of the corresponding enamines and acetone were optimized using the B3LYP functional with the 6-311++G(d,p) basis

set in the gas phase. At the same level of theory, frequency calculations were carried out to verify the transition state structure. Zero-point energies have been taken from unscaled vibrational frequencies. Reported energies in Figure 3 include zero-point corrections.

Acknowledgments

We are indebted to the Natural Science Center for Basic Research and Development (N-BARD), Hiroshima University, for measurements of NMR and MS, and Hiroshima Prefectural Institute of Industrial Science and Technology for NMR. This work was supported by a Grant-in-Aid for Scientific Research (No. 19350021, 20036038, 19020034, 20611012) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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