DOI: 10.1002/adsc.200900427

A Novel Proline-Valinol Thioamide Small Organic Molecule for a Highly Enantioselective Direct Aldol Reaction

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Received: June 21, 2009; Revised: August 11, 2009; Published online: October 1, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900427.

Abstract: A new prolinethioamide compound **4**, prepared from readily available natural amino acid L-proline and amino alcohol L-valinol, has been found to be an active catalyst for the direct aldol reaction of various aldehydes with acetone, cyclohexanone or cyclopentanone at 0 °C. Using only 2 mol% loading of this organocatalyst, the reaction could give high enantioselectivity with up to 96% enantiomeric excess for the reaction of 2-nitrobenzaldehyde with acetone. And as for the cyclohexanone, the excellent diastereoselectivity (*anti/syn*: 99/1) and enantioselectivity (99% *ee*) could be achieved when reacted with 3-nitrobenzaldehyde in water in the presence of this thioamide **4**. This structurally simple catalyst is a highly efficient prolinethioamide derivative, and the terminal hydroxy group in this catalyst is a primary alcohol which is different from the previously reported prerequisite secondary or tertiary alcohol of prolinamides. Our results suggest a new strategy in the design of diversiform organic catalysts for direct asymmetric aldol reactions and related transformations.

Keywords: aldol reaction; asymmetric catalysis; dipeptide derivatives; organocatalysis; prolinethioamides

Introduction

Asymmetric reactions catalyzed by small organic molecules, especially with L-proline and its derivatives, have definitively matured to become a recognized third discipline together with biocatalysis and metal complex catalysis. It possesses operationally simple, economic and environmentally friendly properties.[1] In this active research field, the direct asymmetric aldol reactions, which provide straightforward access to the optically active β-hydroxycarbonyl structural unit found in many natural product drugs,[2] have received remarkable attention.

In the past few decades, the natural amino acid L-proline has been described to catalyze more than 10 different enantioselective C–C and C–heteroatom bond forming reactions. It is demonstrated that the L-proline has occupied a central role, and would render to it the status of a privileged catalyst.[3] However, despite the ability of proline to successfully catalyze many asymmetric transformations, there are some drawbacks which need to be overcome, for example, its low solubility in most organic solvents, usually high catalyst loadings and difficult tuning of its reactivity through structural modifications. Consequently, many derivatives, based on the proline framework that might exhibit improved reactivity and selectivity, have been synthesized and their catalytic properties have been evaluated. For instance, a great number of prolinamides have been synthesized and applied for the direct asymmetric aldol reaction.[4] Whereas most reported prolinamides are generally prepared from proline and simple aliphatic amines or aromatic amines, relatively few options exist for structural modifications. Recently, several secondary amides derived from the condensation of proline and a chiral amino alcohol have been found to provide higher yields and *ee* values than proline itself, in the asymmetric aldol reaction of acetone with several aldehydes.[5] Considering that a chiral amino alcohol can be easily prepared from a natural amino acid, we focused on the short peptide directly derived from an amino acid. Peptides on the contrary offer many sites for functional and structural diversity that can be used to generate optimized catalysts. Thus, peptides can be an ideal compromise between small rigid organocatalysts

and enzymes. To the best of our knowledge, there are only few reports about small peptide-catalyzed aldol reactions to date.[4h,j,7] In addition, Gryko has reported that the replacement of the amide group with the thioamide functionality has a beneficial effect on both the yield and the stereoselectivity of the aldol addition.[8] Hence, our objective, for the continued advancement of this field is the design of more readily structurally tunable catalysts that enable previously unsuccessful transformations. We herein combined a dipeptide functional group with the prolinethioamide skeleton frame in a rational way, designing a novel thioamide-type dipeptide derivative based on the proline catalysis concept and double hydrogen bonding activation and examined its applications in the organocatalytic asymmetric aldol reaction.

Results and Discussion

Firstly, a new peptide derivative **3** was prepared in a short, high-yielding sequence, starting from *N*-Boc-L-proline, reacted with the appropriate L-valinate hydrochloride, followed by thiation with Lawesson's reagent and deprotection of the amino functions under standard conditions (Scheme 1).

Then we compared this new catalyst **3** with the catalysts **1** and **2** which were synthesized according to the previous reports (Figure 1). From the Table 1 we can see that on using 20 mol% or 10 mol% of catalyst **1**, the aldol products were obtained in low yields and low *ee* values (entries 1 and 2). Comparatively speaking, when the prolinethioamide **3** was employed with 20 mol% or 10 mol%, the product yields and enantiomeric excess values were obviously improved (entries 7 and 8). Moreover, even using the catalyst **2** with a terminal hydroxy group, this reaction could only afford the product in moderate enantioselectivity (entries 4 and 5, 52% *ee* and 55% *ee*). Thus, it was further confirmed that the higher acidity of the NH group (thioamide) relative to the amide NH functionality increased the reactivity of this catalyst. Additionally, it has been reported that an acid additive should be involved in the intricate iminium-enamine equilibrium, that might accelerate the reaction process and influence the enantioselectivity.[9] Indeed, as can be

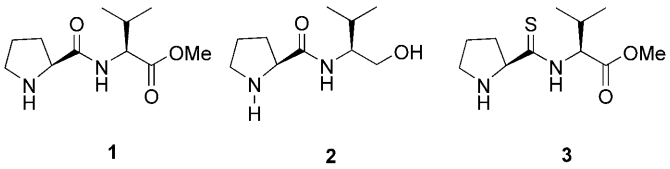
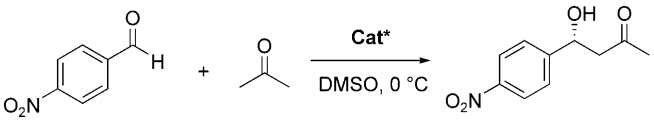


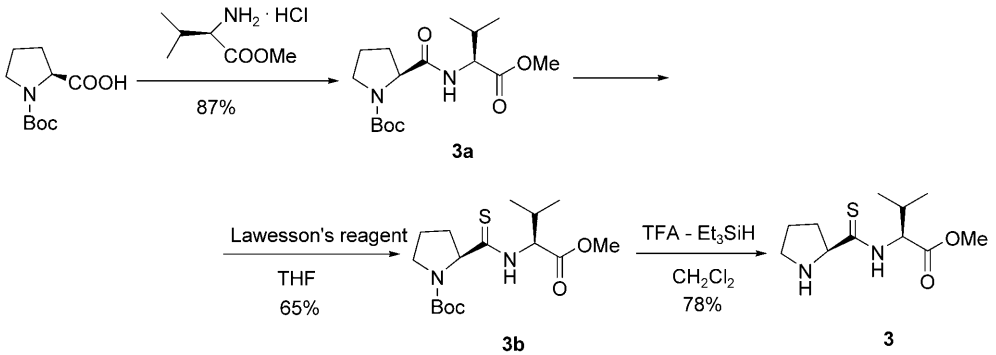
Figure 1. Three prolinamide derivatives.

Table 1. Direct aldol reaction of 4-nitrobenzaldehyde with acetone catalyzed by organocatalysts **1–3**.[a]



Entry	Catalyst	Amount of cat. [mol%]	Additive (mol%)	Time [h]	Yield [%][b]	*ee* [%][c]
1	**1**	20	–	12	20	25
2		10	–	12	25	20
3		10	PhCOOH (10)	12	59	35
4	**2**	20	–	12	89	52
5		10	–	12	43	55
6		10	PhCOOH (10)	8	85	70
7	**3**	20	–	12	69	59
8		10	–	12	73	77
9		10	PhCOOH (10)	8	72	85

[a] The reaction was carried out with acetone and 4-nitrobenzaldehyde under the model aldol conditions.
[b] Isolated yield.
[c] The *ee* was determined by HPLC using a chiral stationary phase, and the configuration was assigned as *R* by comparison of retention time.



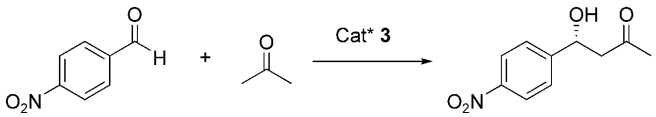
Scheme 1. Synthesis of dipeptide derivative **3**.

seen from the results summarized in Table 1, the aldol product could be obtained with higher *ee* values catalyzed by the same catalyst when benzoic acid was used as cocatalyst (entries 2 and 3, 5 and 6, 8 and 9). A high enantioselectivity of 85% *ee* was obtained for the reaction of 4-nitrobenzaldehyde with acetone catalyzed by 10 mol% catalyst **3** in the presence of 10 mol% benzoic acid as cocatalyst (entry 10).

To further improve this reaction yield and enantioselectivity, a great amount of screening experiments was carried out with organocatalyst **3** chosen for optimization studies. Several parameters such as temperature, solvent, and catalyst loading were examined in the aldol reaction between acetone and 4-nitrobenzaldehyde in the presence of 10 mol% benzoic acid. As shown in Table 2, when performing the reaction in several solvents such as DMF, CH_2Cl_2, acetone, H_2O and ionic liquid, we obtained diminished yields and low enantioselectivities compared to the result with DMSO as the solvent (entries 1–6). Then the effect of catalyst loading on the aldol reaction was studied. To our delight, a decrease in the catalyst loading (from 10 to 5 mol%) had no influence on the enantioselectivity and yield (entries 1 and 7). However, further decreases in catalyst loading could achieve a similar *ee* value (82%) but with the obviously reduced yield (entry 8). Besides, we also tested no additive or several other additives including salicylic acid, L-proline, TFA. It was found that when there was no additive in the asymmetric aldol reaction, the product yield and enantioselectivity were somewhat decreased (entry 9). And the choice of other additives had a negligible effect on the enantioselectivities while it had a dramatic influence on yields (entries 10–13). For example, when L-proline or acetic acid was employed as cocatalyst, we gained the good yield for this reaction (entries 11 and 13). Compared to the use of TFA as the additive, the aldol product yield was immensely decreased (entry 12). Taking the enantioselectivity into consideration, we determined that benzoic acid was employed as the optimal additive. Finally, the reaction temperature was also investigated. We found that a lower temperature brought about a decrease in yield while retaining *ee* value (entries 15 and 16). This indicated that the yield of the aldol product was somewhat dependent on temperature but the enantioselectivity was rendered insensitive to temperature. Noticeably, the reaction could also afford the aldol product with high yield and enantioselectivity even at room temperature (entry 14).

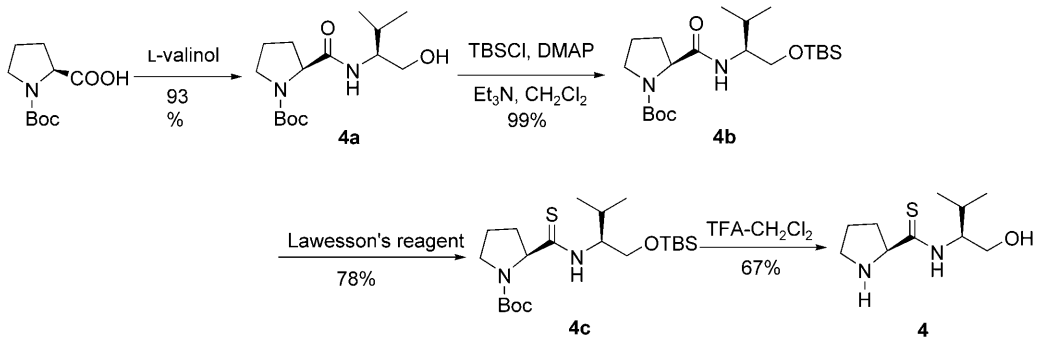
As mentioned above, although the dipeptide derivative **3** had displayed good catalytic properties, there was still a developing space to improve the enantioselectivity. Based on Tang's report, L-prolinamides with a terminal hydroxy group exhibited increased catalytic activity and enantioselectivity as compared with the

Table 2. Optimization studies: effects of solvent, additive, temperature, and catalyst loading in the aldol reaction of 4-nitrobenzaldehyde with acetone catalyzed by organocatalyst **3**.[a]



Entry	Solvent	Catalyst [mol%]	Additive (10 mol%)	Temperature [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	DMSO	10	PhCOOH	0	8	72	85
2	DMF	10	PhCOOH	0	12	57	80
3	CH_2Cl_2	10	PhCOOH	0	12	59	66
4	H_2O	10	PhCOOH	0	24	20	60
5	neat	10	PhCOOH	0	12	68	67
6	[Bmim]BF_4	10	PhCOOH	0	12	45	67
7	DMSO	5	PhCOOH	0	8	78	86
8	DMSO	1	PhCOOH	0	24	7	82
9	DMSO	5	–	0	12	69	78
10	DMSO	5	2-OH-C_6H_4COOH	0	12	70	82
11	DMSO	5	L-proline	0	12	87	82
12	DMSO	5	CF_3COOH	0	24	10	81
13	DMSO	5	CH_3COOH	0	12	85	82
14	DMSO	5	PhCOOH	r.t.	8	92	82
15	DMSO	5	PhCOOH	-25	12	62	84
16	DMSO	5	PhCOOH	-78	48	9	78

[a] The reaction was carried out with acetone and 4-nitrobenzaldehyde under the model aldol conditions.
[b] Isolated yield.
[c] The *ee* was determined by HPLC using a chiral stationary phase, and the configuration was assigned as *R* by comparison of retention time.



Scheme 2. Synthesis of prolinethioamide derivative **4**.

parent L-prolinamide.[4a] Certainly, in the aforementioned Table 1, we could also found that the catalyst **2** with a terminal hydroxy group was obviously superior to the catalyst **1** in the asymmetric aldol reaction (Table 1, entries 1–6). This insight encouraged us to study the direct aldol reaction catalyzed by prolinethioamide derivative **4**. The derivative **4** was prepared from *N*-Boc-L-proline, reacted with the appropriate L-valinol, followed by the general strategy involving the protection of hydroxy group with TBSCl, thiation with Lawesson's reagent and deprotection of the amino and hydroxy functions under standard conditions (Scheme 2).

Adopting the optimal reaction conditions catalyzed by the dipeptide derivative **3**, high enantioselectivity could be achieved using 5 mol% catalyst **4** in the presence and absence of the acid additive (Table 3, entries 1 and 2). Compared to the catalyst **3**, the enantioselectivity of this reaction was drastically improved from 86% to 94%. And the excellent results were still obtained even with 2 mol% loading of catalyst **4** (entries 3 and 4). Nevertheless, when no additive was employed, a prolonged reaction time was needed to complete the reaction. And as for the *o*-nitrobenzaldehyde, the additive had a great influence on the reaction enantioselectivity (entries 5 and 6). From all results summarized in the Table 3, we can see that the increased catalytic activity and enantioselectivity were attributed to the assumption that the terminal hydroxy group might form an additional hydrogen bond with the aldehyde substrate. These results demonstrated that the thioamide and terminal hydroxy bifunctionality present in catalyst **4** played a significant role in the reaction activity and enantioselectivity. Particularly noteworthy is that a primary alcohol of the terminal hydroxy group in our prolinethioamide derivative could also afford high enantioselectivity compared to previously reports in which a steric secondary alcohol or tertiary alcohol was needed.

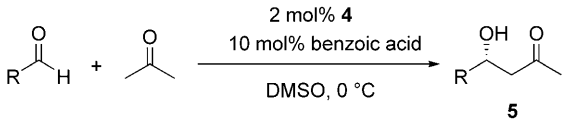
The generality of catalyst **4** in catalyzing direct aldol reactions with a variety of aldehydes including aromatic and aliphatic aldehydes was examined under optimal conditions. The results are shown in Table 4. It could be found that the aromatic aldehydes bearing an electron-withdrawing group gave good conversions due to the electrophilicity of the substrates (entries 2–9). In contrast, less electrophilic aldehydes such as benzaldehyde and 4-methylbenzaldhyde were poor substrates and gave the corresponding aldol products in low yields but in good enantiomeric excess value (entries 1 and 10). Unfortunately, the reaction with aliphatic aldehydes gave poor yields (entries 12 and 13). As a whole, organocatalyst **4** exhibited high enantioselectivities ranging from 86% *ee* to 96% *ee* for all the substrates, with the exception of entry 11, which furnished the corresponding aldol adduct with 78% *ee*. Furthermore, it is worthwhile to highlight that the reactions were catalyzed by employing only 2 mol%

Table 3. Optimization studies: effects of solvent, additive and catalyst loading in the aldol reaction of 4-nitrobenzaldehyde with acetone catalyzed by organocatalyst **4**.[a]

Entry	Amount of cat. [mol%]	Additive (mol%)	Time [h]	Yield [%][b]	*ee* [%][c]
1	5	–	12	76	93
2	5	PhCOOH (10)	6	74	94
3	2	–	12	78	94
4	2	PhCOOH (10)	8	75	95
5[d]	2	–	12	82	84
6[d]	2	PhCOOH (10)	8	74	96

[a] The reaction was carried out with acetone and 4-nitrobenzaldehyde under the model aldol conditions.
[b] Isolated yield.
[c] The *ee* was determined by HPLC using a chiral stationary phase, and the configuration was assigned as *R* by comparison of retention time.
[d] Using *o*-nitrobenzaldehyde as reaction substrate.

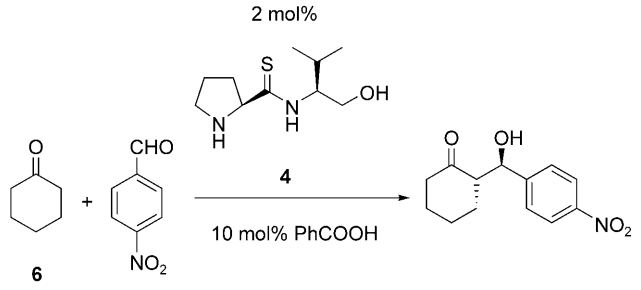
Table 4. The aldol reaction of acetone with various aldehydes calalyzed by organocatalyst **4**.[a]



Entry	R	Product	Time [h]	Yield [%][b]	*ee* [%][c]
1	Ph	**5a**	24	34	87
2	4-$NO_2C_6H_4$	**5b**	8	75	95
3	3-$NO_2C_6H_4$	**5c**	8	82	93
4	2-$NO_2C_6H_4$	**5d**	8	74	96
5	4-BrC_6H_4	**5e**	10	87	86
6	3-BrC_6H_4	**5f**	12	51	94
7	2-BrC_6H_4	**5g**	12	62	86
8	2-$CF_3C_6H_4$	**5h**	10	80	91
9	4-ClC_6H_4	**5i**	10	71	90
10	4-MeC_6H_4	**5j**	48	20	90
11	2,6-Cl_2-C_6H_3	**5k**	10	73	78
12	*i*-Pr	**5l**	60	< 5	-
13	*t*-Bu	**5m**	60	< 5	-

[a] The reaction was carried out with acetone and various aldehyde catalyzed by 2 mol% catalyst **4** in the presence of 10 mol% benzoic acid at 0 °C to room temperature.
[b] Isolated yield.
[c] The *ee* was determined by HPLC using a chiral stationary phase, and the configuration was assigned as *R* by comparison of retention time.

Table 5. Optimization studies: effects of solvents, additive and catalyst loading in the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone catalyzed by organocatalyst **4**.[a]



Entry	**6** [equiv.]	Solvent	Time [h]	Yield[b] [%]	*anti*:*syn*[c]	*ee*[d] [%]
1	2	THF	24	43	90:10	53
2	2	DMF	24	45	82:18	48
3	2	DMSO	12	51	90:10	94
4	2	DMSO:H_2O (1:1)	8	90	92:8	92
5	2	H_2O	8	92	99:1	96
6	2	neat	12	84	99:1	83
7	5	H_2O	8	94	99:1	97
8	1	H_2O	8	76	98:2	96
9[e]	2	H_2O	20	51	2:1	35
10[f]	2	H_2O	8	62	99:1	95

[a] The reaction was carried out with cyclohexanone and *p*-nitrobenzaldehyde catalyzed by 2 mol% thioamide **4** in the presence of 10 mol% benzoic acid at 0 °C to room temperature.
[b] Isolated yield.
[c] Determined by ^{1}H NMR over the crude reaction mixture.
[d] The *ee* was determined by HPLC using a chiral stationary phase.
[e] No additive.
[f] With 1 mol% catalyst **4**.

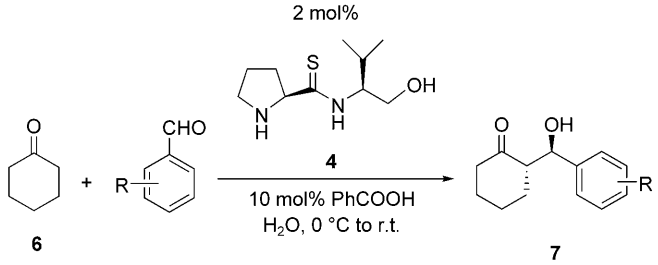
of **4** to give aldol adducts in moderate or high yields with high enantioselectivities up to 96% *ee*.

To increase the scope of the methodology, we have also examined the feasibility of using cyclic ketones as aldol donors using **4** as the catalyst. Meanwhile, we also screened the reaction conditions. As shown in Table 5, water was found to be the best solvent (entries 1–6). When increasing the amount of cyclohexanone, both enantioselectivity and diastereoselectivity remained substantially unchanged (entry 7). But decreasing the amount of cycohexanone resulted in the diminished yield and diastereoselectivity (entry 8). Furthermore, the reaction yield, enantioselectivity and diastereoselectivity were greatly decreased in the absence of additive (entry 9). Considerations of stereoselectivity led us to focus our next study under the optimal reaction conditions as follows: ketone (2 equiv.), aldehyde (1 equiv.), and **4** (2 mol%) at 0 °C to room temperature with benzoic acid (10 mol%) as cocatalyst.

Reaction of cyclohexanone with a variety of electron-deficient aromatic aldehydes containing a variety of substitution patterns provided the desired *anti*-aldol products in high isolated yields (83–95%) with excellent diastereo- (95/5 to 99/1 *dr*) and enantioselectivities (96–99% *ee*) (Table 6, entries 2–6). Whereas the reaction could not proceed smoothly with non-activated aldehydes, such as benzaldehyde, 4-methylbenzaldehyde, and 4-methoxybenzaldehyde even on prolonging reaction times only to give the aldol adducts **7a**, **7j**, and **7m** in low yields but high enantioselectivities, respectively (Table 6, entries 1, 7 and 8). This reaction was carried out in pure water, thus this is 'green' to some extent.

Finally, we applied this protocol to the direct asymmetric aldol reaction of cyclopentanone with *p*-nitrobenzaldehyde in water. As shown in Scheme 3, the reaction could also proceed smoothly to give **9** in 88% yield. And the diastereomeric ratio of *anti/syn* is 67/33 according to ^{1}H NMR analysis. A high enantioselectivity of 98% *ee* was observed for *anti*-**9**, but *syn*-**9** was produced with a low enantiomeric excess value of 40%.

Table 6. Organocatalytic asymmetric aldol reaction of cyclohexanone with aromatic aldehydes calalyzed by catalyst **4**.[a]



Entry	R	Product	Time [h]	Yield [%][b]	*anti:syn*[c]	*ee*[d] [%]
1	–	**7a**	36	46	95:5	96
2	4-NO_2	**7b**	8	92	99:1	96
3	3-NO_2	**7c**	8	95	96:4	99
4	2-NO_2	**7d**	8	94	98:2	97
5	4-Br	**7e**	8	91	97:3	97
6	4-Cl	**7f**	12	83	95:5	96
7	4-Me	**7g**	48	42	97:3	94
8	4-OMe	**7h**	60	36	97:3	92

[a] The reaction was carried out with cyclohexanone and various aldehyde catalyzed by 2 mol% prolinethioamide derivative **4** in the presence of 10 mol% benzoic acid at 0 °C to room temperature.
[b] Isolated yield.
[c] Determined by ^{1}H NMR over the crude reaction mixture.
[d] The *ee* was determined by HPLC using a chiral stationary phase.

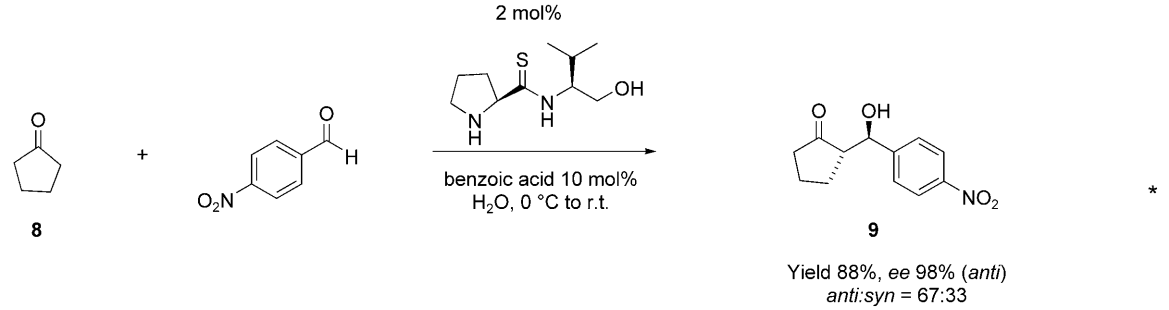
Conclusions

In conclusion, we have developed a novel, structurally simple prolinethioamide derivative, which was readily prepared from commercially available and inexpensive L-proline and L-valinol, for the asymmetric direct aldol reactions of acetone, cyclohexanone or cyclopentanone with aromatic aldehydes. High isolated yields (up to 87%) and enantioselectivities (up to 96% *ee*) were obtained by using only 2 mol% catalyst **4** in the aldol reaction of aldehydes with acetone. Even in the case of cyclohexanone, the aldol reaction could produce excellent diastereoselectivity (*anti/syn* 99/1) and enantioselectivity (99% *ee*). Moreover, this reaction was performed at 0 °C instead of at rigid lower temperature. It demonstrated that the catalyst **4** was highly efficient and as little as 2 mol% is sufficient to efficiently catalyze the direct aldol reaction of aromatic aldehydes with acetone in DMSO, as well as cyclohexanone or cyclopentanone in water. Apparently, highly efficient asymmetric direct stoichiometric aldol reactions can be realized in water, which makes this protocol atom-economical and green. It's important to mention that the terminal hydroxy group of the organocatalyst **4** is a primary alcohol which is different from previously reported prerequisited secondary or tertiary alcohol. The present studies have demonstrated the key role of the combination of a privileged chiral backbone and hydrogen bonding interactions in the asymmetric aldol reaction. We hope that this strategy will give some hints in the further design of organocatalysts.

Experimental Section

Preparation of Prolinethioamide 3[10]

To a stirred solution of *N*-Boc-L-proline (1.25 g, 5.81 mmol) in CH_2Cl_2, Et_3N (1.2 mL, 8.71 mmol) was slowly added at 0 °C. After the solution had been stirred for 10 min, isobutyl chloroformate (875 μL, 6.67 mmol) was added dropwise to the reaction mixture at 0 °C. After the solution had been stirred for an additional 20 min at 0 °C, Et_3N (900 μL, 6.67 mmol) and L-valine methyl ester hydrochloride (1.10 g, 6.67 mmol) were added to the reaction mixture. The reaction mixture was then warmed up to room temperature. After 3 h, TLC analysis indicated complete consumption of starting material. The reaction was quenched by addition of 1 M HCl and diluted with CH_2Cl_2, the organic phase was washed with H_2O, brine and dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification was accomplished by recrystallization (EtOAc/hexane) to give compound **3a** as white crystals; yield: 1.66 g (87%); m.p. 68–70 °C; $[\alpha]_D^{20}$: −102.0 (*c* 1.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (d, 3H), 0.94 (d, 3H), 1.46 (s,



Scheme 3. The asymmetric aldol reaction of cyclopentanone with *p*-nitrobenzaldehyde.

9H), 1.71–1.80 (m, 3H), 1.85–1.99 (m, 2H), 2.10–2.25 (m, 1H), 2.37–3.47 (m, 2H), 3.72 (s, 3H), 4.36–4.44 (m, 2H).

A mixture of compound **3a** (657 mg, 2 mmol) and Lawesson's reagent (410 mg, 1 mmol) in dry THF was stirred for 2 h at room temperature and then refluxed for 0.5 h under an argon atmosphere. After removal of the solvent under reduced pressure the resulting residue was purified by flash chromatography (hexane/EtOAc) to afford compound **3b** as a white solid; yield: 448 mg (65%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$–0.99 (m, 6H), 1.44 (s, 9H), 1.72–1.75 (m, 2H), 1.86–1.87 (m, 2H), 2.01 (brs, 1H), 2.29–2.34 (m, 1H), 3.45- 3.50 (m, 2H), 3.75 (s, 3H), 4.68–4.70 (m, 1H), 5.06–5.08 (m, 1H).

Compound **3b** (482 mg, 1.4 mmol) was dissolved in dry CH_2Cl_2 (2.8 mL) and then TFA (1.4 mL) and Et_3SiH (0.55 mL) were added. After 2 h the solvent was removed, the residue diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and then concentrated under reduced pressure to give catalyst **3** as a yellow oil; yield: 266 mg (78%); $[\alpha]_D^{20}$: −53.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$–1.00 (dd, 6H, $J = 6.9$, 10.9 Hz), 1.65–1.78 (m, 2H), 2.00–2.04 (m, 2H), 2.35–2.38 (m, 2H), 3.01–3.09 (m, 2H), 3.75 (s, 3H), 4.21–4.26 (dd, 1H, $J = 3.8$, 9.0 Hz), 5.12–5.14 (m, 1H), 10.36 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.9, 171.2, 67.9, 61.8, 52.3, 47.5, 34.7, 31.2, 26.1, 18.9, 18.5; HR-MS (ESI): $m/z = 245.1322$, calcd. for $C_{11}H_{20}N_2O_2S$ (M+1): 245.1318.

Preparation of Prolinethioamide 4

To a stirred solution of *N*-Boc-L-proline (1.25 g, 5.81 mmol) in CH_2Cl_2, Et_3N (1.2 mL, 8.71 mmol) was slowly added at 0 °C. After the solution had been stirred for 10 min, isobutyl chloroformate (875 μL, 6.67 mmol) was added dropwise to the reaction mixture at 0 °C. After the solution had been stirred for an additional 20 min at 0 °C, Et_3N (900 μL, 6.67 mmol) and L-valinol (687 mg, 6.67 mmol) were added to the reaction mixture. The reaction mixture was then warmed up to room temperature. After 3 h, TLC analysis indicated complete consumption of starting material. The reaction was quenched by addition of 1M HCl and diluted with CH_2Cl_2, the organic phase was washed with H_2O, brine and dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification was accomplished by recrystallization (EtOAc/hexane) to give compound **4a** as a white solid; yield: 1.62 g (93%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$–0.94 (m, 6H), 1.46 (s, 9H), 1.72–1.75 (m, 2H), 1.87–1.92 (m, 2H), 2.15–2.20 (m, 1H), 2.87–3.10 (m, 2H), 2.90 (br, 1H), 3.58–3.79 (m, 4H), 7.92(br, 1H).

To a stirred solution of compound **4a** (300 mg, 1 mmol) in CH_2Cl_2, Et_3N (0.17 mL, 1.15 mmol), TBDMSCl (175 mg, 1.2 mmol) and DMAP (14 mg, 0.09 mmol) were added in this order at 0 °C. The reaction mixture was stirred at room temperature for 24 h. And then the reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$, saturated NH_4Cl and water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (hexane/EtOAc) to give compound **4b** as a yellow oil; yield: 410 mg (99%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.03$ (s, 6H), 0.87–0.88 (m, 15H), 1.45 (s, 9H), 1.80–1.94 (m, 3H), 2.15–2.30 (m, 2H), 3.35–3.51 (m, 3H), 3.70–3.72 (m, 2H), 4.22–4.29 (m, 1H), 6.21 (brs, 1H).

A mixture of compound **4b** (830 mg, 2 mmol) and Lawesson's reagent (410 mg, 1 mmol) in THF was refluxed for 4 h under an argon atmosphere. After removal of the solvent under reduced pressure the resulting residue was purified by flash chromatography (hexane/EtOAc) to afford compound **4c** as a yellow oil; yield: 670 mg (78%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.04$ (s, 6H), 0.89–0.94 (m, 15H), 1.43 (s, 9H), 1.65–1.66 (m, 2H), 1.86–1.87 (m, 2H), 2.13–2.15 (m, 2H), 3.42–3.61 (m, 3H), 3.83–3.85 (m, 1H), 4.40–4.41 (m, 1H), 4.46–4.48 (m, 1H).

Compound **4c** (624 mg, 1.4 mmol) was dissolved in dry CH_2Cl_2 (2.8 mL) and then TFA (1.4 mL) was added. After 4 h the solvent had been removed, and residue was diluted with CH_2Cl_2. The mixture was treated with 1M NaOH until pH 7–8 and then extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (hexane/EtOAc) to afford compound **4** as a white solid; yield: 202 mg (67%); mp 66–68 °C; $[\alpha]_D^{20}$: −207.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$–0.99 (dd, $J = 6.7$, 14.9 Hz, 6H), 1.66–1.81 (m, 2H), 2.00–2.11 (m, 2H), 2.40–2.48 (m, 2H), 2.78 (brs, 1H), 3.13–3.18 (m, 2H), 3.74–3.85 (m, 2H), 4.35–4.46 (m, 2H), 10.22 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 205.3$, 67.9, 68.2, 62.0, 60.8, 47.3, 28.7, 25.9, 19.5, 18.6; HR-MS (ESI): $m/z = 217.1363$, calcd. for $C_{10}H_{20}N_2OS$ (M+1): 217.1369.

Typical Procedure for the Intermolecular Aldol Reaction

To a mixture of catalyst **4** (2.2 mg, 0.01 mmol) and benzoic acid (6 mg, 0.05 mmol) in DMSO (0.2 mL), the anhydrous acetone (0.5 mL) was added. After the corresponding mixture had been stirred for 5 min, the aldehyde (0.5 mmol) was added at 0 °C. After 12 h, TLC analysis indicated complete consumption of starting material, and then the reaction mixture was quenched with saturated NH_4Cl solution, extracted with EtOAc and dried over Na_2SO_4. The crude product was purified by flash silica gel chromatography (Hexane/EtOAc) to afford aldol product **5**.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (grants 20421202 and 20372033).

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