Dipeptide-Catalyzed Direct Asymmetric Aldol Reaction

Lan-Xiang Shi, Qi Sun, Ze-Mei Ge, Yong-Qiang Zhu, Tie-Ming Cheng, Run-Tao Li*

School of Pharmaceutical Sciences, Peking University, Beijing 100083, P. R. China
Fax +86(10)62346154; E-mail: Lirt@mail.bjmu.edu.cn

Received 18 June 2004

Abstract: (L)-H-Pro-(L)-Phe-OH (**4**) were found to be efficient catalysts for direct asymmetric aldol reactions between acetone and various aldehydes. The reaction conditions use a DMSO–NMM–PEMG 5000 system at 0 °C in high yields (62–96%) and enantioselectivities (up to >99% ee).

Key words: aldol reaction, organocatalysis, enamine catalysis, dipeptides

Since List and Barbas III and their co-workers demonstrated that a simple organic molecule, proline, can act like an enzyme in promoting reactions between acetone and various aldehydes,[1] metal-free organocatalysts have attracted much attention to organic chemists and are intensively studied.[2,3] Several kinds of efficient organocatalysts have been found for the directed asymmetric aldol reactions, such as L-proline and 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC),[4] L-proline amino alcohol amides,[5] and some peptides.[6] However, the class of efficient organic catalysts is still scarce, and only a few successful examples catalyzed by peptides were investigated. Therefore, it is necessary to explore more potential organocatalysts with high stereoselectivity and broad substrates. We herein report our new results in this field.

Based on the structure of proline and the mechanism of proline-catalyzed asymmetric aldol reaction,[7] we designed and synthesized five new dipeptide catalysts **1**–**5** (Figure 1). In these catalysts, the L-proline or L-4-hydroxylproline moieties at the N-terminus retain the character of L-proline. Introduction of cyclic amino acid is expected to increase the steric hindrance effect. L-Phenylalanine portion was selected from the known effective peptide catalyst H-Pro-Glu-Leu-Phe-OH.[6b]

Initially, we selected the reaction of 4-nitrobenzaldehyde with neat acetone as model to examine the efficiency of the catalysts **1**–**5**. The results were summarized in Table 1. It was found that catalysts **4** and **5** showed significantly catalytic activity producing the aldol product in good yields (**4**, 87%; **5**, 80%) and enantioselectivities (**4**, 59% ee; **5**, 46% ee). The lower catalytic activity of catalysts **1**–**3** may be due to the absence of hydrogen in *tert*-amide.

Next, using 20 mol% of **4** as catalyst, we examined the reaction of 4-nitrobenzaldehyde with acetone under different conditions. The results were showed in Table 2. It is interesting to note that the reaction rate was obviously increased by using *N*-methylmorpholine (NMM) as base to adjust the reaction system to pH = 8. For instance, in the absence of NMM, the reaction required 192 hours (entry 1, 87%, 59% ee). On the contrary, the reaction time was shortened from 192 hours to 96 hours with unchanged yield and enantioselectivity (entry 2, 87%, 59% ee). In the presence of NMM, when DMSO was used as the solvent, not only the reaction time was further shortened, but also an excellent yield and good enantioselectivity were obtained (entry 3, 18 h at 25 °C, 93% yield with 58% ee; entry 4, 30 h at 0 °C, 95% yield with 66% ee). Replacing NMM with triethylamine under the same conditions, the result is unsatisfied (entry 5, 95% yield with 51% ee).

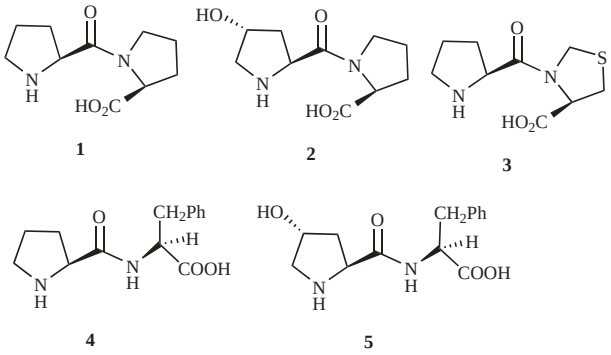
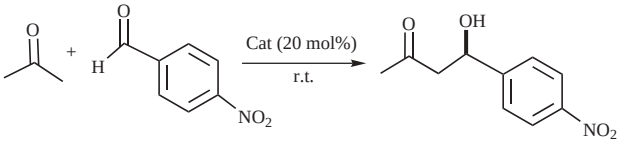


Figure 1 The small organic molecules evaluated in this study

Table 1 Direct Aldol Reaction of 4-Nitrobenzaldehyde with Acetone Catalyzed by Organic Molecules **1**–**5**



Catalyst	Time (h)	Yield (%)[a]	ee (%)[b]
1	192	66	13
2	204	45	16
3	216	<10	n.d.[c]
4	192	87	59
5	192	80	46

[a] Isolated yields after column chromatography.
[b] The ee values were determined by chiral-phase HPLC analysis.
[c] Not determined.

SYNLETT 2004, No. 12, pp 2215–2217
Advanced online publication: 31.08.2004
DOI: 10.1055/s-2004-831324; Art ID: U17404ST

Table 2 (L)-H-Pro-(L)-Phe-OH-Catalyzed Aldol Reaction of Acetone with 4-Nitrobenzaldehyde under Different Conditions

Entry	Solvent	Base	Surfactant	Time (h)	Temp (°C)	Yield (%)[a]	ee (%)[b]
1	Acetone			192	25	87	59
2	Acetone	NMM		96	25	87	59
3	DMSO	NMM		18	25	93	58
4	DMSO	NMM		30	0	95	66
5	DMSO	Et_3N		24	0	95	51
6	NMP	NMM		30	25	77	71
7	NMP	NMM		35	0	80	63
8	DMSO	NMM	PGME 5000	24	0	96	73
9	DMSO	NMM	PGME 5000	24	0	96	56[c]
10	DMSO	NMM	PEG400	24	0	95	65
11	DMSO	NMM	SDS	24	0	95	69
12	DMSO	NMM	TBAB	24	0	94	57
13	NMP	NMM	PGME 5000	30	0	79	69

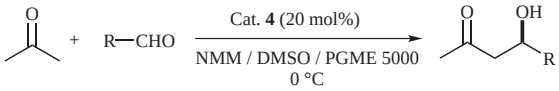
[a] Isolated yields after column chromatography.
[b] The ee values were determined by chiral-phase HPLC analysis.
[c] Proline as catalyst.

Similarly, using *N*-methyl-2-pyrrolidinone (NMP) as solvent provided the aldol product in 77% yield and 71% ee at 25 °C, and 80% yield and 63% ee at 0 °C, respectively (entries 6 and 7). Adding the NMM, the catalyst **4** may be formed the corresponding carboxylate. The formation of carboxylate can increase the solubility; meanwhile, the six-membered ring of NMM may be favorable to establish stable transition states with substrates, which could enhanced enantioselectivity.

Additionally, according to the reports[8,9] that aldol reactions could be accelerated by surfactant in a buffer solution or in aqueous micelles, we also tested the effect of the different surfactants including polyethylene glycol monomethyl ether 5000 (PGME 5000), polyethylene glycol 400 (PEG 400), sodium dodecyl sulfate (SDS), tetrabutylammonium bromide (TBAB) on the reaction in DMSO–NMM systems at 0 °C. Among surfactants examined, PGME 5000 is the best one affording the desired aldol product in the highest yield of 96% with good enantioselectivity of 73% ee (entry 8). This result is better than those obtained with proline as catalyst (entry 9, 96%, 56% ee). We also added the PGME 5000 in the system of NMP–NMM, providing 79% yield and 69% ee (entry 13). Therefore, 20 mol% of catalyst **4** in the DMSO–NMM–PGME 5000 system at 0 °C was verified to be the best condition. The action of PGME may be to increase the mutual solubility of substrates and catalyst.

The generality of catalyst **4** in catalyzing direct aldol reactions with various aldehydes was examined under optimal conditions. The results were displayed in Table 3. As it can be seen, all the reactions, no matter the aromatic aldehydes (entries 1–7) or aliphatic aldehydes (entries 8 and 9), took place smoothly and afford corresponding aldol adducts in moderate to high yields (62–96%) and good

Table 3 Substrate Screen for Aldol Reaction between Acetone and Aldehydes Catalyzed by (L)-H-Pro-(L)-Phe-OH **4**



Entry	Product	R	Time (h)	Yield (%)[a]	ee (%)[b]
1	**6a**	4-Nitrophenyl	24	96	73
2	**6b**	Phenyl	36	62	64
3	**6c**	3-Nitrophenyl	24	84	67
4	**6d**	2-Nitro-3,4-methylenedioxyphenyl	28	80	83
5	**6e**	2-Chlorophenyl	30	81	55
6	**6f**	3,4-Dichlorophenyl	32	72	61
7	**6g**	2-Methoxyphenyl	36	70	53
8	**6h**	*i*-Propyl	48	92	77
9	**6i**	Cyclohexanyl	48	80	79
10	**6j**[c]	2-Nitrophenyl	24	90	>99

[a] Yield of product isolated after silica gel chromatography.
[b] The ee values were determined by chiral-phase HPLC analysis using chiralpak AD-H columns (Daicel chemical industries).
[c] Acetone was instead with cyclohexanone; nearly 100% *anti* conformation was determined by NMR after column chromatography.

enantioselectivities (up to 83% ee). Three nitro-substituted aromatic aldehydes (entries 1, 3 and 4) provided higher yields and enantioselectivities than the other substituted aromatic aldehydes. Moreover, cyclohexanone was used to react with 2-nitrobenzaldehyde affording nearly 100% *anti* conformation product **6j** in 90% yield with >99% ee (entry 10).

Finally, we studied the recovery and reuse of the catalyst **4**. It was found that the recovery of the catalyst was very easy. After reaction, adding saturated aqueous ammonium chloride solution into the reaction mixture, the catalyst was precipitated, and then, filtrated and washed with ethyl acetate to recover the catalyst in over 84%. The recovered catalyst was reused for three times, and the yield and enantioselectivity did not decrease (Table 4). These results suggested that many rounds of catalyst use and recovery could be possible.

Table 4 Recovery and Reuse of the Catalyst **4**[a]

Entry	Reuse time	$[\alpha]_D^{25}$[b]	Recovery rate (%)	Yield (%)	ee (%)
1	0	–36.8°		96	73
2	1	–36.8°	85	95	72
3	2	–36.6°	84	96	73
4	3	–36.8°	87	96	73

[a] Reaction of 4-nitrobenzaldehyde and acetone catalyzed by **4** under optimal conditions.
[b] Measured in aqueous solution of hydrochloride acid according to the reference.[10] {Lit. $[\alpha]_D^{25}$ –37° (*c* 1.0, 1 N HCl)}.

In summary, we have found that dipeptide, (L)-H-Pro-(L)-Phe-OH (**4**), could efficiently catalyze the direct asymmeric aldol reactions between ketone and various aldehydes in DMSO–NMM–PGME 5000 system at 0 °C in high yields (62–96%) and enantioselectivities (up to >99% ee).

General Procedure for Aldol Reactions

A suspension of catalyst (20 mol%) and aldehyde (1 mmol) in 4 mL of acetone (Table 1), or in 4 mL of acetone with NMM as base (entry 2 in Table 2), or in 5 mL of acetone–DMSO (1:4) with NMM as base (entries 3 and 4 in Table 2), or in 5 mL of acetone–NMP (1:4) with NMM as base (entries 6 and 7 in Table 2), or in 5 mL of acetone–DMSO (1:4) with NMM as base and surfactant (5 mol%, entries 8–12 in Table 2; entries 1–10 in Table 3 and entries 1–4 in Table 4), or in 5 mL of acetone–NMP (1:4) with NMM as base and surfactant (5 mol%, entry 13 in Table 2), was stirred at the indicated temperature for the indicated time. The reaction mixture was added sat. aq NH_4Cl solution, filtered and washed with EtOAc to recover the catalyst. The filtrate was extracted with EtOAc. The combined organic layers were washed with aq sat. NaCl, dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on a silica gel (eluent: petroleum–EtOAc = 3:1) to afford the corresponding aldol adducts.

Acknowledgment

The authors are grateful to National Natural Science Foundation of China for the financial support (NSFC 20172006).

References

(1) List, B.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
(2) For recent reviews, see: (a) Gröger, H.; Wilken, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 529. (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726. (c) List, B. *Synlett* **2001**, 1675. (d) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (e) List, B. *Tetrahedron* **2002**, *58*, 5573. (f) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595. (g) Alcaide, B.; Almendros, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 858.
(3) (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (d) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16. (e) Pan, Q. B.; Zou, B. L.; Wang, Y. J.; Ma, D. W. *Org. Lett.* **2004**, *6*, 1009.
(4) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2001**, *123*, 5260.
(5) Tang, Z.; Jiang, F.; Yu, L. T.; Cui, X.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z.; Wu, Y. D. *J. Am. Chem. Soc.* **2003**, *125*, 5262.
(6) (a) Martin, H. J.; List, B. *Synlett* **2003**, 1901. (b) Kofoed, J.; Nielsenb, J.; Reymonda, J. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445. (c) Tang, Z.; Yang, Z. H.; Cun, L. F.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z. *Org. Lett.* **2004**, *6*, 2285.
(7) (a) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. (b) Córdova, A.; Notz, W.; Barbas, C. F. III. *J. Org. Chem.* **2002**, *67*, 301.
(8) Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 3220.
(9) Peng, Y. Y.; Ding, Q. P.; Li, Z. C.; Wang, P. G.; Cheng, J. P. *Tetrahedron Lett.* **2003**, *44*, 3871.
(10) Mazur, R. H.; Schlatter, J. H. *J. Org. Chem.* **1963**, *28*, 1025.