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Small Peptides Catalyze Highly Enantioselective Direct Aldol Reactions of Aldehydes with Hydroxyacetone: Unprecedented Regiocontrol in Aqueous Media

Zhuo Tang, Zhi-Hua Yang,[†] Lin-Feng Cun, Liu-Zhu Gong,* Ai-Qiao Mi, and Yao-Zhong Jiang

Key Laboratory for Asymmetric Synthesis and Chirotechnology of Sichuan Province and Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, 610041, China, and Graduate School of Chinese Academy of Sciences, Beijing, China

gonglz@cioc.ac.cn

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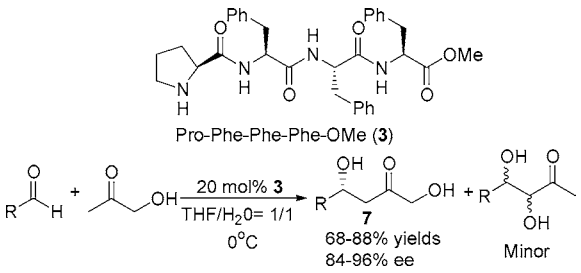
ABSTRACT



L-Proline-based small peptides have been developed as efficient catalysts for the asymmetric direct aldol reactions of hydroxyacetone with aldehydes. Chiral 1,4-diols 7, which are disfavored products in similar aldol reactions catalyzed by either aldolases or L-proline, were obtained in high yields and enantioselectivities of up to 96% ee with peptides 3 and 4 in aqueous media.

The aldol reaction is one of the most powerful methods for forming carbon−carbon bonds. The great synthetic usefulness of the aldol reaction in organic synthesis has driven a rapid development of numerous highly enantioselective chiral catalysts.[1,2] Direct aldolization is atom economic,[3] and thus it is an attractive method for the synthesis of polyoxygenated compounds. Several catalysts, including aldolase,[2e,4] transition metal complexes,[5,6] and organic molecules,[7,8] have been reported for the direct asymmetric aldol reaction. Some of

[†] Visiting Scholar from Sichuan University.

(1) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds; Pergamon: Oxford, 1991; Vol. 2, Chapter 1.7.

(2) For reviews, see: (a) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137. (b) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (c) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. III, Chapter 29.1. (d) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (e) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352.

(3) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(4) For examples, see: (a) Barbas, C. F., III; Heine, A.; Zhong, G.; Hoffmann, T.; Gramatikova, S.; Björnestedt, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, I. A.; Lerner, R. *Science* **1997**, *278*, 2085. (b) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1998**, *120*, 2768. (c) List, B.; Shabat, D.; Barbas, C. F., III; Lerner, R. *Chem. Eur. J.* **1998**, *4*, 881.

(5) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. (c) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466.

(6) (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367.

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them can also catalyze aldol reactions of hydroxyacetone to exclusively give 1,2-diols with excellent regio- and enantioselectivity.[4,8c] In sharp contrast, an efficient catalyst for the asymmetric direct aldol reactions of aldehydes with hydroxyacetone at its methyl group to give chiral 1,4-diols has not yet reported, and thus it is much more difficult to directly access optically active 1,4-diols than 1,2-diols by aldolization.

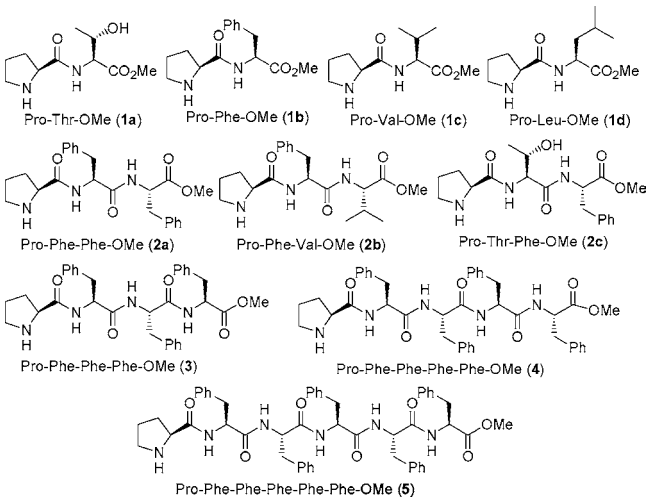
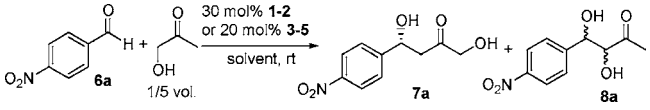


Figure 1. Peptides evaluated in this study.

Very recently, we[8f,9] and other groups[10] found that L-proline amides and dipeptides acted as efficient catalysts for the asymmetric direct aldol reaction. Synthetic peptides have proven to be promising organic catalysts for some important transformations and continue to receive growing interest.[11] On the basis of these observations, we reasoned that larger L-proline-based peptides might be useful as organic catalysts for direct aldol addition, since they are structurally similar to L-proline amides but contain more amide units, which are the same building blocks that constitute enzymes. A chiral noncovalent bonding environment similar to that of an enzyme, which is beneficial for stereocontrol, may be created with an increase in the size of peptides.[11] We report here that L-proline-based peptides **1**−**5** can catalyze the aldol reactions of hydroxyacetone with aldehydes **6** in aqueous media[12] to give 1,4-diols **7**, the disfavored products, with either aldolase or L-proline[4,8c] with high regio- and enantioselectivity.

First, we used 20 mol % Pro-Thr-OMe (**1a**), which catalyzed the aldol reaction of acetone with 4-nitrobenzaldehyde in 67% ee,[8f,9] to promote the aldol addition of 4-nitrobenzaldehyde (**6a**) with hydroxyacetone in THF to give the normal anti-1,2-diol (**8a**) with 2.1: 1 dr and 61% ee. The minor product 1,4-diol (**7a**) was also isolated in 16% yield and 60% ee (Table 1, entry 1). A survey of different solvents such as DMF, methanol, and chloroform revealed that more polar solvents give better enantioselectivity of 1,2-diol **8a** than less polar solvents (entries 1−4). In DMF, anti-1,2-diol was obtained with 2.8:1 dr and 72% ee (entry 2). In a protic solvent, for example, MeOH, 1,4-diol was generated in 19% yield (entry 3), which was a greater yield than in nonprotic solvents (entries 1, 2, and 4). Surprisingly, the aldol

Table 1. Direct Aldol Reaction of 4-Nitrobenzaldehyde with Hydroxyacetone Catalyzed by Peptides **1**−**5**[a]



entry	catalyst	solvent [b]	% yield of **7a**	ee (%)[c]	% yield of **8a** (dr)[d]	% ee[e]
1	**1a**	THF	16	60	71 (2.1:1)	61
2	**1a**	DMF	7	55	69 (2.8:1)	72
3	**1a**	MeOH	19	68	76 (1.7:1)	63
4	**1a**	$CHCl_3$	13	69	71 (0.8:1)	23
5	**1a**	DMF/H_2O	35	54	17 (0.9:1)	19
6	**1a**	MeOH/H_2O	20	54	20 (0.8:1)	10
7	**1a**	THF/H_2O	50	62	13 (0.8:1)	28
8	**1b**	THF/H_2O	70	67	30 (0.9:1)	37
9	**1c**	THF/H_2O	52	52	38 (0.9:1)	16
10	**1d**	THF/H_2O	65	56	35 (1.0:1)	25
11	**2a**	THF/H_2O	70	68	30 (1.1:1)	33
12	**2b**	THF/H_2O	70	68	30 (1.1:1)	32
13	**2c**	THF/H_2O	62	56	30 (0.7:1)	22
14	**3**	THF/H_2O	70	75	30 (1.3:1)	35
15	**4**	THF/H_2O	57	76	35 (2.0:1)	41
16	**5**	THF/H_2O	39	78	58 (1.1:1)	29
17	**3**	THF/H_2O	82	82[f]	18 (1.7:1)	47
18	**4**	THF/H_2O	76	87[g]	21 (1.6:1)	30

[a] Unless specified otherwise, the concentration of aldehyde is 0.25 M, and v/v of hydroxyacetone/solvent is 1/4 (1/5 vol hydroxyacetone). [b] Organic solvent/H_2O = 1:1. [c] Ee values were determined by HPLC, and the configuration was assigned as *R* by comparison of the optical rotation with value in the literature.[15] [d] Anti:syn ratio was determined by HPLC. [e] Ee value of anti isomer, determined by HPLC. [f] Reaction temperature = 0 °C; v/v of hydroxyacetone/solvent = 1/2 (1/3 vol hydroxyacetone); reaction time = 4 days. [g] Performed with 10 mol % catalyst **4**; reaction temperature = 0 °C; v/v of hydroxyacetone/solvent = 1/2 (1/3 vol hydroxyacetone); reaction time = 6 days.

(7) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

(8) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (d) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (e) Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 3220. (f) 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. For reviews, see: (g) List, B. *Tetrahedron* **2002**, *58*, 5573. (h) List, B. *Synlett* **2001**, 1675.

(9) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5755.

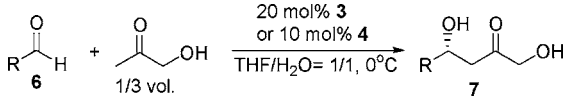
(10) (a) Martin, H. J.; List, B. *Synlett* **2003**, 1901. (b) Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445.

(11) For examples, see: (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. (b) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901 (c) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629. (d) Sculimbrene, B. R.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10125. (e) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134. (f) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 11653. For a review, see: (g) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481.

reaction preferentially occurred at the methyl group of hydroxyacetone to give mostly 1,4-diol **7a** when the same reaction was conducted in the presence of catalyst **1a** in an aqueous media (entries 5−7). These are unprecedented results compared to those observed in similar reactions catalyzed by aldolase[4] and L-proline.[8c] Antibody 84G3 preferentially catalyzed the aldolization of methoxylacetone at the methyl group.[13] Direct aldol reactions of siloxy and alkoxy acetones with aldehydes mediated by $TiCl_4/Bu_3N$ or Bu_2BOTf also took place regioselectively at the methyl group, probably due to favorable formation of the less hindered enamine.[14] However, the hydroxyacetone was not tested as a donor in these cases.[13,14] In a 1:1 THF/H_2O solvent mixture, 1,4-diol **7a** was obtained in 50% yield and 62% ee, whereas 1,2-diol was obtained in only 13% yield (entry 7). An examination of the ability of various dipeptides **1b**−**d** to catalyze the model reaction indicated that peptides with phenylalanine as a lipophilic residue gave better results and Pro-Phe-OMe (**1b**) was more promising for this reaction in terms of both yields and enantioselectivities (entries 8−10). Tripeptides **2a** and **2b** gave similar yields and enantioselectvities (entries 11 and 12), but **2c** resulted in a much lower stereo-outcome (entry 13). A further increase in the peptide size led to a significant increase in enantioselectivity, but the regioselection to generate 1,4-diol was gradually sacrificed (entries 14−16). These results demonstrated that the peptide size also played an important role in the stereo- and regiocontrol besides the solvent effect. The yields increased by increasing the amount of hydroxyacetone from 1/5 to 1/3 reaction volume, and the enantioselectivity was enhanced by conducting reactions at 0 °C (entries 17 and 18). As little as 10 mol % **4** is sufficient to catalyze the aldol reaction, with 76% yield and 87% ee, under optimal conditions (entry 18). However, L-proline did not catalyze the reaction, and simple L-prolinamides gave worse results than peptides **3** or **4** under the optimal conditions (Table S1 in Supporting Information).

The abilities of peptides **3** and **4** to catalyze the direct aldol reactions of hydroxyacetone with a variety of aldehydes were examined under optimal conditions. The results are shown in Table 2. High yields and entioselectivities of up to 96% ee were observed for aromatic aldehydes bearing electron-withdrawing groups (**7a**−**h**, entries 1−16). In contrast, neither **3** nor **4** catalyzed the aldol reactions of benzaldehyde and aromatic aldehydes with electron-donating groups under the optimal conditions, and the aldol reaction with an aliphatic aldehyde such as cyclohexanaldehyde did not proceed in the presence of either **3** or **4**.[16] Thus, the present peptide catalyst seems to be substrate-specific, and its catalytic activity relies on the electron density of the aromatic substituents of aldehydes. In general, peptide **4** gave a slightly greater enantioselectivity than **3**, but with lower yields, and required a longer reaction time for complete conversion.

Table 2. Direct Aldol Reactions of Acetone with Aldehydes by Chiral Organic Catalyst **3**[a] or **4**[b]



entry	product (R)	catalyst	yield (%)[c]	ee (%)[d]
1	4-$NO_2C_6H_4$ (**7a**)	**3**	82	82
2		**4**	76	87
3	4-CNC_6H_4 (**7b**)	**3**	88	84
4		**4**	70	84
5	4-$CF_3C_6H_4$ (**7c**)	**3**	82	86
6		**4**	66	88
7	3-$NO_2C_6H_4$ (**7d**)	**3**	82	85
8		**4**	80	89
9	3,5-$Br_2C_6H_4$ (**7e**)	**3**	68	91
10		**4**	59	92[e]
11	2-ClC_6H_4 (**7f**)	**3**	78	85
12		**4**	56	86
13	2-$NO_2C_6H_4$ (**7g**)	**3**	83	91
14		**4**	71	93
15	2,6-$Cl_2C_6H_4$ (**7h**)	**3**	84	96
16		**4**	73	96

[a] Reaction time = 4 days, in the presence of 20 mol % **3**. [b] Reaction time = 6 days, in the presence of 10 mol % **4**. [c] Isolated yields based on aldehydes. [d] Determined by HPLC. [e] THF/H_2O = 2:1

In conclusion, we have developed small peptides as efficient catalysts for the asymmetric direct aldol reactions of hydroxyacetone with aldehydes. Chiral 1,4-diols **7**, which are disfavored products in similar aldol reactions catalyzed by either aldolases or L-proline,[4,8c] were obtained in high yields and enantioselectivities with peptides **3** and **4** in aqueous media. To our knowledge, this reaction is a unique method for preparing the chiral 1,4-dihydroxyl-2-ones **7** directly from aldehydes and 2-hydroxyl ketones. Active studies on mechanistic aspects and the application of these catalysts to the synthesis of biologically active compounds are underway.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For Mukaiyama aldol reactions in aqueous media, see: (a) Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 11531. (b) Hamada, T.; Manbe, K.; Ishikawa, S.; Nagayama, S.; Shiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 2989. For a direct aldol reaction, see ref 8e.

(13) Maggiotti, V.; Resmini, M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2002**, *41*, 1012.

(14) (a) Yoshida, Y.; Matsumoto, N.; Hamasaki, R.; Tanabe, Y. *Tetrahedron Lett.* **1999**, *40*, 4227. (b) Tanabe, Y.; Matsumoto, N.; Higashi, T.; Misaki, T.; Itoh, T. Yamamoto, M.; Mitarai, K.; Nishii, Y. *Tetrahedron* **2002**, *58*, 8269. (c) Samadi, M.; Munoz-Letelier, C.; Poigny, S.; Guyot, M. *Tetrahedron Lett.* **2000**, *41*, 3349.

(15) Maggiotti, V.; Wong, J.-B.; Razet, R.; Cowley, A. R.; Gouverneur, V. *Tetrahedron: Asymmetry* **2002**, *13*, 1789.

(16) No conversion was observed with aldol reactions of C_6H_5CHO (**7i**), 4-MeC_6H_4CHO (**7j**), and *c*-$C_6H_{11}CHO$ (**7k**).