



Rationally designed 4-phenoxy substituted prolinamide phenols organocatalyst for the direct aldol reaction in water

Shu-peng Zhang^{a,b}, Xiang-kai Fu^{b,*}, Shao-dong Fu^b

^a College of Chemistry, Sichuan University, Chengdu 610065, People's Republic of China

^b College of Chemistry and Chemical Engineering, Southwest-China University, Research Institute of Applied Chemistry Southwest University, The Key Laboratory of Applied Chemistry of Chongqing Municipality, Chongqing 400715, People's Republic of China

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ABSTRACT

A rationally designed 4-phenoxy substituted prolinamide phenols as an efficient hydrophobic organocatalyst for direct asymmetric aldol reaction in water has been developed. High yield (up to 99%), diastereoselectivity (up to 99:1), and enantioselectivity (up to 97%) were obtained under optimal condition. The influence of substituent groups on the reactivity of catalysts was studied in detail.

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The aldol reaction is recognized as one of the most powerful carbon–carbon bond-forming reactions in modern organic synthesis. It provides an atom-economic approach to β -hydroxyl carbonyls, which make up a large family of chiral intermediates for the synthesis of biologically active substances and natural products.¹ Since the early reports in the 1970s that the L-proline catalyzed intramolecular aldol reactions^{2a,b} and the discovery by List et al. that L-proline can mimic type I aldolase to enantioselectively catalyze intermolecular aldol reactions,^{2c} interest in organocatalysis has increased spectacularly in the past few years as a result of both the novelty of the concept and unique activation modes, because of the fact that the operational simplicity, ready availability of catalysts, less toxicity, efficiency, and selectivity make many organocatalytic reactions attractive method to synthesize complex structures superior to those carried out using more conventional methods.³

From a green chemistry perspective, this highly effective and environmentally benign synthetic methodology is often regarded as a goal in modern organic chemistry. The use of water with positive effects in terms of cost, safety, and environmental impact as reaction solvent instead of organic solvent is preferred to decrease environmental contamination.^{4,13}

However, it should be noted that among all of the reported systems most catalysts work in mixed aqueous organic solvent⁵ or require the use of surfactants,^{5a,6} and some are supported⁷ or

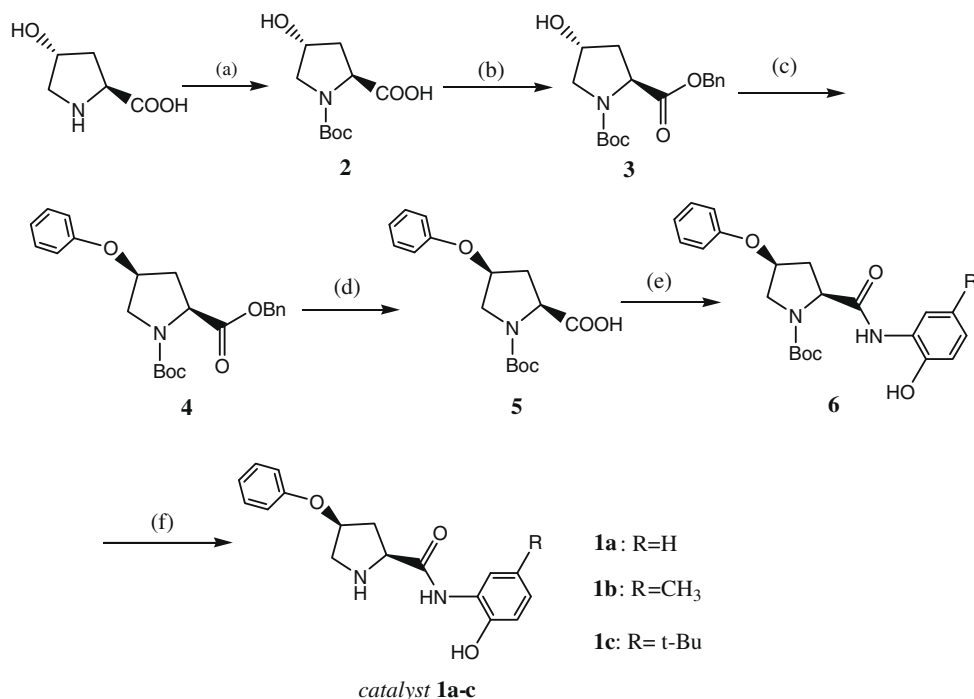
dendritic⁷ systems whose preparation needs chemical manipulation besides only two organocatalysts which really seem to work in the presence of a large amount of water.⁸ So, the development of chiral organic molecules that are able to catalyze stereoselective reactions in a large amount of pure water is the true challenge.

In addition, often a large excess of ketone is employed,^{5b,6,7b,8b,9} and the catalysts perform in what, even if it is defined as an aqueous medium, really is a wet organic system.¹⁰ In general, according to the principles of Green Chemistry, catalysts can reduce the amount of reagents required and restrict waste generated in a reaction.

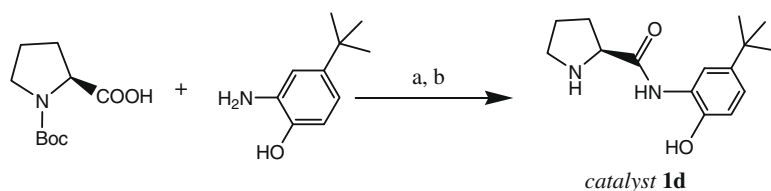
Considering the very efficient mechanism of enamine-based organocatalysts in various reactions and inspired by the works of Gong¹¹ and Tang,⁹ in this Letter, we decided to maintain the proline backbone, to introduce a phenoxy group at the 4-position as functional group including hydrophobic phenyl which can sequester the transition state from water and enhance the solubility in the organic reactants^{8a,12} and an oxygen atom which can play a greater role than the hydrophobic phenyl effect by hydrogen bonding of water molecules to the substrate in the observed catalysis. So, three 4-phenoxy substituted prolinamide phenols catalysts **1a–c** were synthesized. The aldol reaction with lowering catalyst loading (0.1 equiv) which has been proved to be a significant challenging task proceeds efficiently in a large amount of pure water (115 equiv) and a small excess of ketone (2 equiv). Very high activity and selectivity of the desired product was observed compared to the values for the similar prolinamide phenol derivatives reported in the literature.⁹ And the system has shown good generality and enough activity.

* Corresponding author. Tel.: +86 23 6825 3704; fax: +86 23 6825 4000.

E-mail address: fxk@swu.edu.cn (X. Fu).



Scheme 1. Synthesis of catalysts **1a-c**. Reagents and conditions: (a) (Boc)₂O, NaHCO₃; (b) BnBr, TEA; (c) PhOH, Ph₃P, DEAD; (d) H₂, Pd/C, MeOH, rt; (e) EDCI, DMAP, CH₂Cl₂, rt; (f) CF₃COOH, CH₂Cl₂, rt; DEAD = diethyl azodicarboxylate EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. DMAP = 4-dimethylaminopyridine.



Scheme 2. Synthesis of catalyst **1d**. Reagents and conditions: (a) EDCI, DMAP, CH₂Cl₂, rt; (b) CF₃COOH, CH₂Cl₂, rt.

Prolinamides (**1a-d**) were prepared from the commercially available *L*-proline or *trans*-4-hydroxy-*L*-proline, and corresponding 2-aminophenol, 2-amino-4-methylphenol, and 2-amino-4-*tert*-butylphenol according to the synthetic route shown in Schemes 1 and 2. In order to compare the activity in water of catalysts **1a-c** versus **1d** catalytic systems, catalyst **1d** was also prepared. These compounds were purified by flash column chromatography and were characterized by ¹H NMR, ¹³C NMR, and mass spectrometry. All results were in full agreement with the proposed structures.

The reaction of cyclohexanone and 2-nitrobenzaldehyde was selected as a model in terms of chemical activity. The application of these compounds **1a-c** as catalysts to the aldol reaction of cyclohexanone with 2-nitrobenzaldehyde in a large amount of pure water made the reaction proceed efficiently. Initially, various conditions were examined at room temperature using **1c** as a catalyst. Without any additives, the reaction afforded moderate yield, enantioselectivity, and good diastereoselectivity (Table 1, entry 5) in water. The addition of a catalytic amount of TFA could increase dramatically both the yield and enantioselectivity (Table 1, entry 3). However, when 0.3 equiv of TFA was used in the reaction, the catalytic activity decreased dramatically (Table 1, entry 6). Acetic acid can also accelerate the reaction and slightly increase the diastereo-, and enantioselectivity (Table 1, entry 7). The reaction can proceed in brine affording good yield, diastereo- and

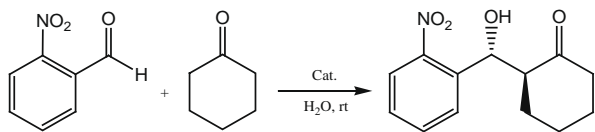
enantioselectivity (Table 1, entry 8), but the efficiency of the reaction is lower. The reaction can also proceed in THF, affording good results (Table 1, entry 13).

To our surprise, compounds **1a-d** exhibited almost the same performance in terms of enantioselectivity (96–97% ee) (Table 1, entries 1–4). However, the different structures of compounds **1a-d** influenced catalytic efficiency and diastereoselectivity remarkably. By running the reaction in the presence of a large amount of water, catalyst **1c** was proved to be superior to catalyst **1d** in terms of efficiency and diastereoselectivity (Table 1, entries 3 and 4). After only 12 h at room temperature, catalyst **1c** promoted the aldol condensation in 99% yield, 99/1 *anti/syn* ratio, and 97% ee for the *anti* isomer (Table 1, entry 3). The activity of **1d** is very poor. This fact suggests that a 4-phenoxy group at 4-position of prolinamide phenols derivatives is very essential to attain good yield, diastereoselectivity and enantioselectivity.

By comparing the entries 1–3 (Table 1), it was found that the catalytic results of the catalyst **1c** with the *tert*-butyl group are better than those of **1b** with methyl group and those of **1a** without substituent group. The best catalytic efficiency was observed with **1c** (Table 1, entry 3). The reason for the higher diastereoselectivity is possibly due to the most maximal steric hindrance of *tert*-butyl group. What is more, the catalyst **1c** has improved solubility in ketones due to their introduction of *tert*-butyl group, which increase the reaction rate to a certain extent. So, this kind of catalysts has

Table 1

Screening of efficient catalyst in the direct asymmetric aldol reaction of cyclohexanone with 2-nitrobenzaldehyde^a



Entry	Catalyst	Water (μL)	Additives	Time (h)	Yield ^b (%)	anti:syn ^c	ee ^d (%)
1	1a	400	TFA	72	94	90:10	96
2	1b	400	TFA	36	96	96:4	97
3	1c	400	TFA	24	99	99:1	97
4	1d	400	TFA	72	80	85:15	95
5	1c	400	None	24	42	80:20	51
6 ^e	1c	400	TFA	24	30	86:14	83
7	1c	400	CH ₃ COOH	24	95	90:10	87
8 ^f	1c	400	TFA	48	98	95:5	96
9	1c	500	TFA	24	96	97:3	95
10	1c	300	TFA	24	98	96:4	95
11	1c	150	TFA	24	97	95:5	96
12	1c	50	TFA	24	99	94:6	95
13 ^g	1c	None	TFA	24	80	94:6	89

^a The reactions were conducted with *o*-nitrobenzaldehyde (0.2 mmol), cyclohexanone (0.4 mmol) catalyst (0.02 mmol), TFA (0.02 mmol) and water.

^b Isolated yield.

^c Determined by ¹H NMR analysis.

^d Determined by chiral-phase HPLC analysis for *anti*-products.

^e 0.3 Equiv of TFA was used in this reaction.

^f The reaction was carried out in saturated brine.

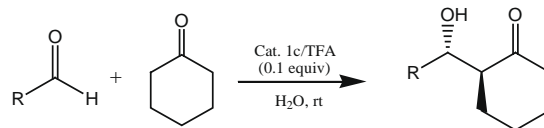
^g The reaction was carried out in THF.

the ability to fine tune their reactivity. Similar results were observed with the different amounts of water in the reaction, but the optimized amount of water is 0.4 mL. At last, we were delighted to find the optimized conditions of the reaction.

According to the above results (Tables 1–3) and the work of Tang,⁹ we depicted the models of the transition state. Based on our working hypothesis, and phenoxy of catalyst designed **1a–c** is at the same side of prolinamide group, there exists such prominent transition state model **TS c** in such aldol reaction possibly besides **TS b** (Scheme 3). Due to the point (Scheme 3 **TS a** vs Scheme 3 **TS c**), activity of catalyst **1c** is superior to that of **1d**. The role of water is to bring the catalyst and reactants closer together by hydrogen bonding to accelerate the reaction.¹³ In addition, hydrophobic interaction is also the driving force bringing together the substrate aldehydes and the ketone. So, the aldol reaction can efficiently proceed in a large amount of pure water (115 equiv) and a

Table 2

Results of reaction of various aldehydes with cyclohexanone catalyzed by **1c** in water^a



Entry	R	Product	Time (h)	Yield ^b (%)	anti:syn ^c	ee ^d (%)
1	4-O ₂ NC ₆ H ₄ -	7a	12	99	99:1	94
2	3-O ₂ NC ₆ H ₄ -	7b	24	97	97:3	95
3	2-O ₂ NC ₆ H ₄ -	7c	24	99	99:1	97
4	4-F ₂ CC ₆ H ₄ -	7d	12	98	95:5	93
5	4-NCC ₆ H ₄ -	7e	48	93	94:6	93
6	4-ClC ₆ H ₄ -	7f	72	94	95:5	89
7	3-ClC ₆ H ₄ -	7g	72	95	95:5	89
8	2-ClC ₆ H ₄ -	7h	72	92	98:2	91
9	4-BrC ₆ H ₄ -	7i	72	96	93:7	90
10	C ₆ H ₅ -	7j	72	72	92:8	84
11	4-MeC ₆ H ₄ -	7k	72	65	90:10	97

^a The reaction was performed with aldehyde (30 mg, 0.2 mmol), water (0.4 mL), catalyst (0.02 mmol), TFA (0.02 mmol) and cyclohexanone (0.4 mmol) at room temperature with vigorous stirring.

^b Combined yields of isolated diastereomers.

^c Diastereoselectivity was determined by HPLC and by ¹H NMR of the crude product.

^d Determined by chiral-phase HPLC analysis of the *anti*-product.

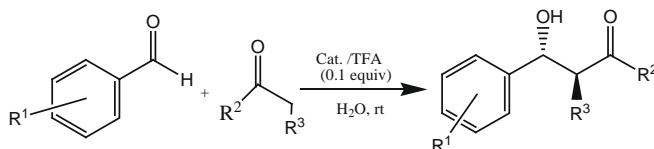
small excess of ketone (2 equiv). And the system has shown good generality and enough activity without using any organic solvent.

In order to broaden the range of substrates, we investigated cyclohexanone as an aldol donor with a series of aldehydes using catalyst **1c**/TFA in water at room temperature under the optimized reaction conditions. As revealed in Table 2, the processes proceeded smoothly with 10 mol % of catalyst and gave rise to highly enantio-enriched adducts in good yields regardless of the electronic nature of the aromatic aldehydes. In most cases, reactions afforded *anti*-aldol products in high yield with high enantioselectivity and excellent diastereoselectivity. For the electron-deficient aromatic aldehydes, the reaction could complete within 24 h, at times even within 12 h (Table 2, entries 1–4). For the neutral and electron-rich aromatic aldehydes, the much longer reaction time was required (Table 2, entries 5–11).

The catalytic system also worked out for the challenging substrate cyclopentanone in order to expand the scope of the reaction under the same conditions. In this instance, the aldol process proceeded smoothly in high yield (92%) with good enantioselectivity (94% ee) (Table 3, entry 2).

Table 3

Reaction of various ketones with aldehyde catalyzed by **1c**^a



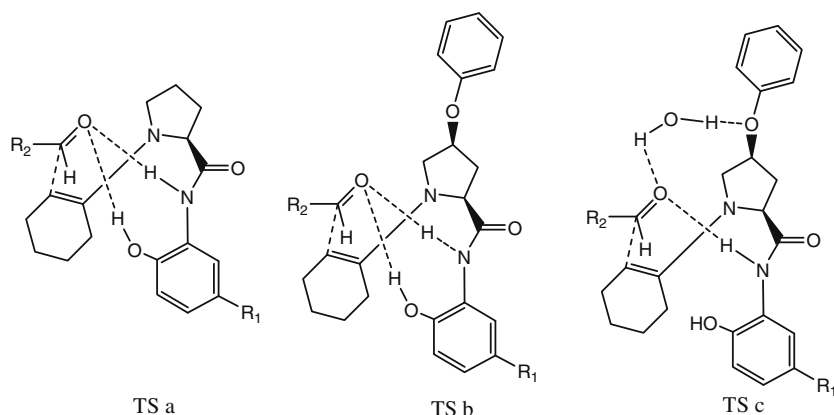
Entry	R ¹	R ²	R ³	Product	Time (h)	Yield ^b (%)	anti:syn ^c	ee ^d (%) (syn)
1	4-O ₂ N-	-(CH ₂) ₃ -		7l	24	90	55:45	91 (41)
2	2-O ₂ N-	-(CH ₂) ₃ -		7m	24	89	62:38	94 (34)
3	4-O ₂ N-	CH ₃ -	H	7n	72	90		80
4	4-O ₂ N-	-(CH ₂) ₅ -		7o	48	55	71:29	63

^a The reaction was performed with aldehyde (30 mg, 0.2 mmol), water (0.4 mL), catalyst (0.02 mmol), TFA (0.02 mmol) and cyclohexanone (0.4 mmol) at room temperature with vigorous stirring.

^b Combined yields of isolated diastereomers.

^c Diastereoselectivity was determined by HPLC and by ¹H NMR of the crude product.

^d Determined by chiral-phase HPLC analysis of the *anti*-product.



Scheme 3. Proposed transition structures.

In conclusion, we have developed highly 4-phenoxy substituted prolinamide phenols organocatalyst, which can promote the direct asymmetric aldol reaction of aldehydes and ketones with high diastereo- and enantioselectivities in large amount of water. Further efforts are currently underway in this direction. This approach is also particularly attractive in view of the green chemistry. Further studies focusing on the full scope of this and related systems including mechanistic studies, generality of more substrates and the application of **1a–c** in other reactions are in progress and will be reported in due course in our laboratory.

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Supplementary data

General experimental methods and spectra of the corresponding compounds are available. Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2008.10.120](https://doi.org/10.1016/j.tetlet.2008.10.120).

References and notes

- (a) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; pp 1–10; (b) Trost, B. M. *Science* **1991**, *254*, 1471; (c) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259; (d) Palomo, C.; Oiarbide, M.; Garciak, J. M. *Chem. Soc. Rev.* **2004**, *33*, 6; (e) Xu, X.-Y.; Wang, Y.-Z.; Cun, L.-F.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2007**, *18*, 237.
- (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; (c) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
- (a) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis-From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (c) Special Issue on Asymmetric Organocatalysis. *Acc. Chem. Res.* **2004**, *37*, 487.; (d) List, B. *Chem. Commun.* **2006**, 819; (e) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465.
- (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998; (b) Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299.
- (a) Dziejed, P.; Zou, W.; Hafren, J.; Cordova, A. *Org. Biol. Chem.* **2006**, *4*, 38; (b) Guillena, G.; Hita, M.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493.
- Luo, S.; Mi, X.; Liu, S.; Xu, H.; Cheng, J.-P. *Chem. Commun.* **2006**, 3687.
- (a) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417; (b) Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 4653.
- (a) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734; (b) Hayashi, S.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527.
- Fu, Y.-Q.; Li, Z.-C.; Ding, L.-N.; Tao, J.-C.; Zhang, S.-H.; Tang, M.-S. *Tetrahedron: Asymmetry* **2006**, *17*, 3351.
- For a very interesting discussion of enantioselective organocatalysis 'in water' or 'in the presence of water', see: (a) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100; (b) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103.
- (a) Tang, Z.; Jiang, F.; Yu, L.-T.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262; (b) 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.
- (a) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *118*, 972; (b) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958; (c) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966; (d) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *118*, 5653.
- (a) Huang, J.-M.; Zhang, X.-T.; Armstrong, D.-W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9073; (b) Jung, Y.; Marcus, R.-A. *J. Am. Chem. Soc.* **2007**, *129*, 5492.