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The smallest organocatalyst in highly enantioselective direct aldol reaction in wet solvent-free conditions†

Sudipto Bhowmick[a], Sunita S. Kunte[b] and Kartick C. Bhowmick[a,*]

[a]*Division of Organic Synthesis, Department of Chemistry, Visva-Bharati University; Bolpur, West Bengal-731 235, India. E-mail: kartickc.bhowmick@visva-bharati.ac.in*

[b]*Division of Organic Chemistry, Analytical Section, National Chemical Laboratory, Pune-411 008, India*

†Electronic supplementary information (ESI) available: Experimental procedure, NMR spectra, and HPLC traces. See DOI:

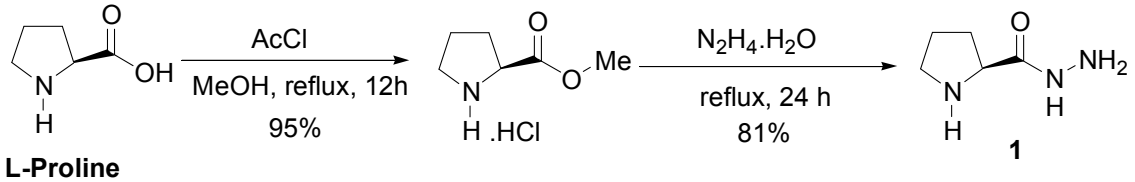
The catalytic efficacy of the smallest organocatalyst, L-Proline hydrazide, prepared from the cheaply available natural amino acid like L-Proline was studied for the direct asymmetric aldol reaction of various ketones with aromatic aldehydes at room temperature in presence of several acid additives. A loading of 10 mol% of catalyst 1 and *p*-toluenesulphonic acid as additive was employed in this reaction, and good yields (up to 99%), with high *anti*/*syn* diastereoselectivities (up to 95:5) and enantioselectivities (up to >99.9%) could be achieved in aqueous media.

Asymmetric organocatalysis, a metal free catalysis is currently a widely used environmentally benign catalytic methodology in asymmetric organic synthesis.[1] Last two decades have witnessed an explosive growth in the field of asymmetric organocatalysis where water has been used as a solvent or co-solvent.[2,3] The pioneering observation reported by Breslow et al. and Grieco et al. on Diels–Alder reaction in early 1980s revealed the new concept regarding the better effect of water on reaction rates and regioselectivities than organic solvents.[4] The use of

water as reaction media in organocatalyzed asymmetric organic transformations carries many advantages e.g. it is abundant, safe, and environmentally benign.[3b,5] Moreover it can significantly influence the course of a reaction *via* increased hydrophobic-hydrophobic interaction and hydrogen bond formation between the reactants and water molecules resulting high reactivity and stereoselectivity.[2c,6] Since the Breslow's observation, existence of such interactions and their effects are now a well documented fact in aqueous phase reactions irrespective of "in water" or "on water" concept in back ground.[2c,7] In this direction, massive efforts have been concentrated on the development of L-proline and 4-hydroxy-L-proline based organocatalysts, primarily modifying their basic skeleton in three ways.[8-10] One modification was aimed at the carboxylic acid functionality[3c,8], one was performed on hydroxyl group of 4-hydroxy-L-proline[6a,9] and while the third one was on both groups simultaneously[10]. The suitably substituted molecules from L-proline and 4-hydroxy-L-proline have been found to act as efficient chiral catalysts for different asymmetric carbon-carbon bond-forming reactions in aqueous media.[2b] Mostly the modified catalysts were bulky molecules which were conjugates of two or more molecular units of which one was of course 4-hydroxy-L-proline or L-proline or derivatives of these.[2b,8-10] It is well known that in organic solvents, the smallest organocatalyst, L-proline requires high loadings (~30mol%), and it does not catalyze the aldol reaction in water.[11a] Some of the examples are known in the literature where aldol reactions were performed under wet solvent-free or solvent-free conditions with moderate to high asymmetric induction.[8w,9f,11b-c] Indeed, there are few examples where small modification on L-proline structure did generate organocatalysts which showed poor to moderate catalytic activity in aqueous media.[8b,u-v] Simple amino acids also could provide abysmally low yield of aldol product in water unless derivatized with suitable hydrophobic group.[3f] In fact some of the efficient organocatalysts derived from L-proline have

been reported with double hydrogen bonding ability in aqueous media but those catalysts were structurally not very small.[3e,6b,8q,8s,12] Now the question is why L-proline itself or a very negligibly modified L-proline based organocatalyst would not be able to impart good stereoselectivity in aqueous media? Is it because of any lacking in suitable placement of more than one hydrogen bonding unit in the catalyst structure? We are therefore, interested to identify an organocatalyst which is structurally very small and of course the missing link between the L-proline and its longer derivatives in an aqueous environment. Herein, we are presenting the smallest chiral organocatalyst, L-proline hydrazide **1** for direct aldol reactions in aqueous environment. Such a small molecule containing a simple hydrazide unit has never been reported as asymmetric organocatalyst for any carbon-carbon bond forming reaction in wet solvent-free conditions. The idea of selecting such a system is purely to have a small but strong hydrogen bond forming pocket in the catalyst structure. Indeed our presumption has been proved to be true, the catalyst **1** provided aldol products from reaction between aromatic aldehydes and ketones with good yields (up to 99%), with high *anti*/*syn* diastereoselectivities (up to 95:5) and enantioselectivities (up to >99.9%) in wet solvent-free conditions.

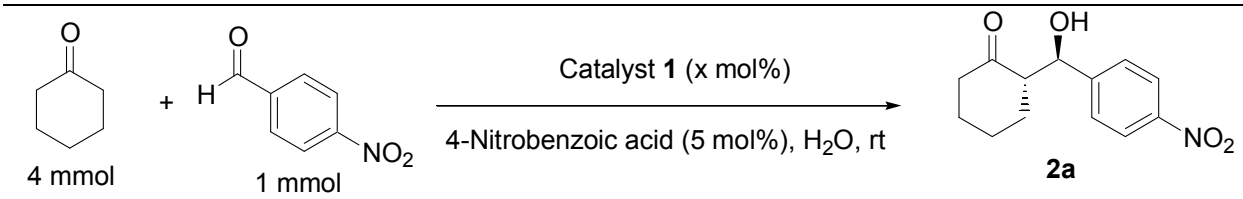
The L-proline hydrazide **1** was synthesized from cheaply available L-proline using inexpensive reagent like hydrazine by two simple steps after little modification on the reported method (**Scheme 1**).[13] For the esterification step acetyl chloride was used instead of thionyl chloride and a better overall yield (77%) was obtained following our modified method.



Scheme 1

The aldol reactions were carried out systematically using 4-nitrobenzaldehyde and cyclohexanone as substrates to optimize different parameters, such as, the volume of water, catalyst loading, and the effect of acid additive for this small organocatalyst **1**. It is reported that aldol reactions performed under wet solvent-free conditions, the reactivity and stereoselectivities are significantly influenced due to the factors like increased hydrophobic interactions between the substrate molecules as well as hydrogen bond formation between the reactants and water molecules in the transition state.[2c] In our experiments, it has been observed that there were gradual deterioration in enantioselectivities in the aldol products from 93% to 38% with increase in the amount of water from 0.01 ml to 1 ml in presence of 4-nitrobenzoic acid as acid additive (Table 1, entry 2-5). The same reaction even in absence of water did not improve the enantiomeric excess too (Table 1, entry 1). This indicates that appropriate volume of water is necessary for the formation of suitable micelles where stereo controlled hydrophobic interactions and hydrogen bonding between the organic reactants can occur to obtain enhanced stereoselectivity. We were also pleased to observe that when the reaction was carried out with 10 mol% of catalyst **1** in 0.01 ml of water but without 4-nitrobenzoic acid, the enantiselectivity dropped from 93% to 77% (Table 1, entry 2 & 6). Thus it is clear from the above experiments that appropriate volume of water and presence of a suitable acid additive is essential to obtain optimum results for a particular organocatalyst. Literature evidence also supports the fact that water volume and acid additives can greatly influence the yield as well as stereoselectivity in organocatalyzed synthesis in aqueous media.[2c,8l,w-x] In this case, the optimum volume of water was found to be 0.01 ml with this catalyst **1** for the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde at room temperature in presence of 4-nitrobenzoic acid as acid additive (Table 1, entry 2).

Table 1
Effect of water volume and catalyst loading in aldol reaction between cyclohexanone and 4-nitrobenzaldehyde catalyzed by **1**



Entry	Catalyst **1** (mol%)	H_2O (ml)	Time (h)	Yield[a] (%)	*anti/syn*[b]	ee[c]
1	10	-	22	95	78/22	50
2	10	0.01	24	95	86/14	93
3	10	0.1	48	90	87/13	86
4	10	0.5	72	96	72/28	70
5	10	1	96	90	65/35	38
6[d]	10	0.01	20	96	81/19	77
7	1	0.01	96	81	72/28	48
8	5	0.01	72	86	69/31	54
9	20	0.01	20	98	83/17	86
10	-	0.01	-	-	-	-

[a] Isolated yield after purification by column chromatography. [b] Diastereomer ratios (*anti/syn*) were determined by ^{1}H NMR spectrum of the crude product mixture. [c] Determined by chiral HPLC analysis. [d] In absence of 4-nitrobenzoic acid additive.

After optimizing the volume of water, we investigated the amount of catalyst loading. With increase or decrease in the catalyst loading from 10 mol%, enantioselectivity dropped from 93% to 86% and 48% respectively at room temperature for the same aldol reaction (Table 1, entry 7-9). To be noted that with the gradual increase in catalyst loading from 1 mol% to 20 mol%, the yield of aldol product jumped from 81% to 98% while the reaction time was reduced from 96 hours to only 20 hours (Table 1). A blank experiment was carried out in absence of the catalyst **1** and we were pleased to observe that there was no product formation even after 5 days (Table 1, entry 10).

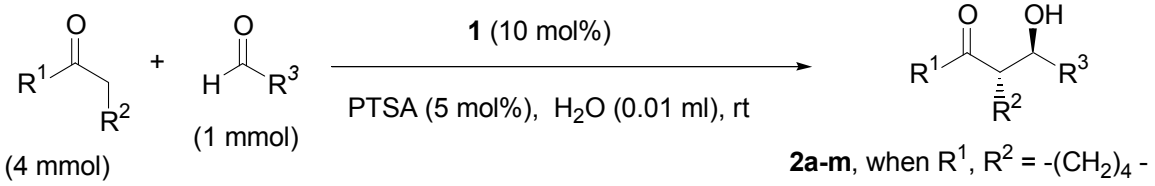
Once the volume of water (0.01 ml) and catalyst loading (10 mol%) was optimized, we started screening of various acid additives to find out the best acid additive for our catalyst **1** in the same aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone. A broad spectrum of acid additives with a long range of pk_a, starting from simple aromatic acids like benzoic acid, 4-nitrobenzoic acid, picric acid to *p*-toluenesulphonic acid were chosen for the optimization study (see ESI, Table 2). The effect of long chain fatty acids like stearic acid, oleic acid were also tested in this reaction. Even though the reactions were comparatively faster in the presence of these fatty acids, the enantioselectivities were not very impressive. At the outset, PTSA has been found to be the best acid additive for the hydrazide **1** catalyzed aldol reaction in water at room temperature with 99% yield and 97% enantiomeric excess (see ESI, entry 1, Table 2). In these above experiments although a non-linear relationship (specifically a non monotonic relationship) between the pk_a and the obtained ees have been observed, but we were more pleased to find that the strongest acid additive like PTSA among the screened acids provided the best results in terms of yield (99%), *anti:syn* ratio (93:7) and enantioselectivity (97%). This indicates the requirement of a strong acid additive for achieving best results for the present catalyst **1**, nevertheless at this point of time we are not sure whether any more fundamental effect of acid additives exist in the solution, in addition to the established facts like reactivity enhancement through hydrogen bonding and maintaining the pH of the reaction media.

Finally, we have screened many substituted aromatic aldehydes for aldol reaction between various cyclic aliphatic ketones like cyclopentanone, cyclohexanone and open chain ketone like acetone to check the general efficacy of this small hydrazide catalyst **1** in water under optimized conditions (Table 3). Substrates containing electron withdrawing group like *p/m*-nitrobenzaldehydes and electron donating group like *p*-chlorobenzaldehyde, o-

methoxybenzaldehyde responded well in presence of the catalyst **1** so far the enantioselectivity of the aldol product is concerned. Perhaps some of the substrates provided very poor enantioselectivity but the results as a whole are extremely significant since the catalyst **1** is very small and without having much bulk around the catalytic site. This preliminary observation has been recorded in the table 3. We have also observed extremely fast reaction when acetone and cyclopentanone was the aldol donor in presence of catalyst **1**, the reactions were completed within 6-8 hours with impressive enantioselectivity (Table 3, entry 14 and 15). These results are highly encouraging as far as such a small size organocatalyst is concerned in aqueous media.

Table 3

Substrate scope was investigated under the optimal conditions and organocatalyst **1** catalyzed direct aldol reactions in the presence of water.



2a-m, when R^1, R^2 = -$(CH_2)_4$ -
3a, when R^1= CH_3, R^2= H
3b, when R^1, R^2 = -$(CH_2)_3$ -

Entry (Product No.)	R_3CHO	Time(h)	Yield[a](%)	*anti/syn*[b]	ee[c](%) (*anti*)
1 (**2a**)	*p*-NO_2-C_6H_4-CHO	72	99	93/7	97
2 (**2b**)	*m*-NO_2-C_6H_4-CHO	36	87	91/9	98
3 (**2c**)	*o*-NO_2-C_6H_4-CHO	36	85	89/11	88
4 (**2d**)	*o*-F-C_6H_4-CHO	48	86	88/12	68
5 (**2e**)	*m*-F-C_6H_4-CHO	36	87	73/27	32
6 (**2f**)	*o*-MeO-C_6H_4-CHO	72	86	92/8	89
7 (**2g**)	*o*-Cl-C_6H_4-CHO	48	83	95/5	64
8 (**2h**)	*m*-Cl-C_6H_4-CHO	36	85	85/15	46
9 (**2i**)	*p*-Cl-C_6H_4-CHO	48	87	89/11	91
10 (**2j**)	*p*-Me-C_6H_4-CHO	48	87	84/16	49
11 (**2k**)	1-Naphthaldehyde	60	84	82/18	44
12 (**2l**)	2-Naphthaldehyde	72	85	86/14	61
13 (**2m**)	*p*-CF_3-C_6H_4-CHO	36	96	93/7	80
14 (**3a**)	*p*-NO_2-C_6H_4-CHO	8	91	-	98
15 (**3b**)	*p*-NO_2-C_6H_4-CHO	6	96	94/6	>99.9

[a] Isolated yield after purification by column chromatography. [b] Diastereomer ratios (*anti/syn*) were determined by ^{1}H NMR spectrum of the crude product mixture. [c] Determined by chiral HPLC analysis.

A most probable transition state for the hydrazide **1** catalyzed aldol reaction has been depicted in **Figure 1** similar to the one in the reported literature.[8l,8w,14-15] In the **T.S. 1**, we have considered the *anti*-enamine at the below and the aldehyde acceptor in the upper face where the –CO-NH-NH_2 moiety of the catalyst **1** is present and effectively a strong hydrogen bonding results a stable and favorable transition state leading to formation of the corresponding *anti*-enantiomer as major. While in case of another **T.S. 2** for the formation of minor *anti*-enantiomer described by

Noto et al. considering the *syn*-enamine at the below and aldehyde at the above with aromatic group towards the hydrophilic region is unfavorable due to hydrophobic-hydrophilic interaction.[14] The aromatic moiety will always remain towards the hydrophobic region for a better hydrophobic-hydrophobic interaction in an aqueous environment. The *syn*-enantiomers are also unfavourable for the similar reason depicted in the literature.[14]

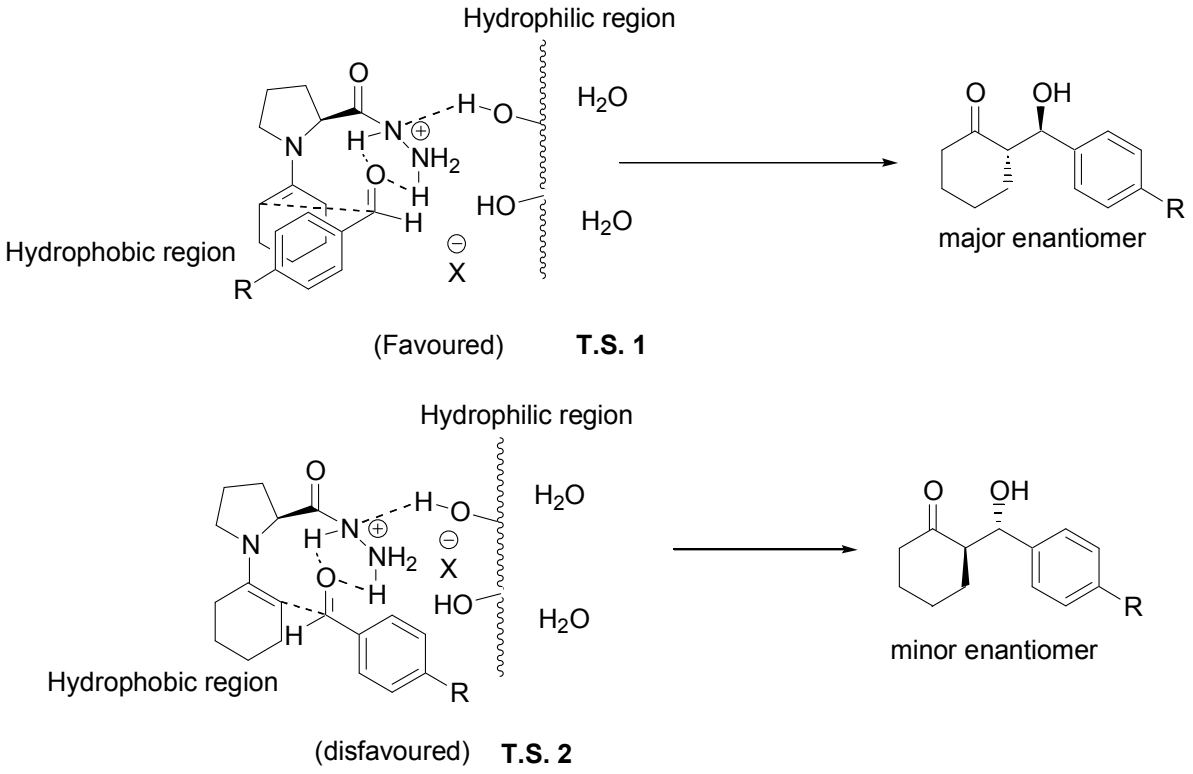


Figure 1

In summary, we have found a catalyst **1** which is the smallest organocatalytic system reported so far in the literature for aqueous phase asymmetric aldol reaction. Attachment of just a hydrazide unit in the L-proline structure has been proved to be very effective regarding the reactivity and enantioselectivity in the aldol reaction. The existence of a suitable hydrogen bonding pocket (two hydrogen bonds within a short space) in the catalyst structure is considered to be the probable reason for this impressive result. It should be noted that the L-proline hydrazide **1** is the smallest

and most importantly it is the best among the small organocatalysts reported so far in the literature in aqueous environment.[3f,8b,u-v] Some of the substrates screened in presence of this small catalyst **1** provided enantioselectivity above 90% which is undoubtedly impressive results so far the least bulk around the active site of the catalyst is concerned in aqueous media. More structural modification on catalyst **1** considering the steric as well as electronic effect is underway in our laboratory to thoroughly understand the detailed catalytic activity in aqueous phase aldol reaction. The present work will guide us in future to identify the minimum bulk (steric environment) as well as hydrogen bonding unit (electronic environment) required in the organocatalyst structure in an aqueous environment.

Acknowledgements

This work has been funded by Department of Science and Technology, Government of India [Grant No. SR/FT/CS-013/2009] and S.B. acknowledges support from University Grants Commission, Government of India through a research fellowship.

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