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Protonated chiral prolinamide catalyzed enantioselective direct aldol reaction in water

Swapandeep Singh Chimni,^{a,*} Dinesh Mahajan^a and V. V. Suresh Babu^b^aDepartment of Chemistry, Guru Nanak Dev University, Amritsar 143005, India^bDepartment of Studies in Chemistry, Central College Campus, Bangalore University, Bangalore 560 001, India

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Abstract—Protonated chiral prolinamide organocatalysts have been shown to catalyze an enantioselective direct aldol process in water to provide the aldol product in high yield and good enantioselectivity. The two diastereomeric catalysts (*S,R*)-**4b** and (*S,S*)-**4c** show different reactivity.

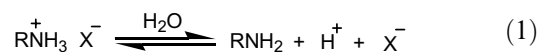
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Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound, which does not contain a metal atom.¹ There are very few reports of organocatalyzed synthesis in aqueous media.² Aqueous media predominate in biological systems and it must have been the solvent used by ‘Nature’ in prebiotic formation of simple to complex molecules.³ A fundamental and interesting area of research is how homochirality originated in biomolecules in water during molecular evolution.⁴ So in order to develop enzyme mimics⁵ and in an attempt to understand the mechanism of the chemistry of life, catalysts having catalytic properties in water need to be developed.

We have been interested in developing an organocatalyzed enantioselective aldol reaction in water⁶ involving pyrrolidine-based chiral molecules. In order to achieve this objective, it is important to minimize the involvement of general base catalysis by the pyrrolidine and to enhance nucleophilic catalysis through the formation of an iminium ion. Spencer and co-workers have observed that iminium ion catalysis becomes more effective as the base strength of the amine catalysts is decreased.⁷ Also, it has been reported that Brønsted acids enhance the catalytic ability of pyrrolidine-based organocatalysts.⁸ We envisaged that such a chiral catalyst, when protonated and dissolved in water, would

exist in equilibrium with the free chiral amine (Eq. 1). This would lower the effective base strength of the catalyst thus favouring iminium ion catalysis, as observed by Spencer.

So we prepared protonated chiral prolinamides to check our hypothesis. To our surprise, we found these molecules act as effective organocatalysts for direct cross aldol reaction of acetone with *p*-nitrobenzaldehyde in water. In this communication, we illustrate this concept through enantioselective catalysis using phenethylamine prolinamide hydrobromide salt.



Initial investigations on the aldol reaction of acetone **1** and *p*-nitrobenzaldehyde **2** in water using catalyst **4a** (20 mol %) provided aldol adduct **3** in 92% yield and 33% ee (Table 1, entry 1).⁹ Using proline as the catalyst, under similar conditions gave racemic **3** in 78% yield.¹⁰ Encouraged by this result, we prepared enantiomerically pure (*S,R*)-**4b** and (*S,S*)-**4c** and performed the aldol reaction using them as catalysts in water and obtained **3** in 45% and 39% ee, respectively (Table 1, entries 2 and 9). The variations in the amount of water suggest that a lower concentration of water slightly improves the enantioselectivity (entries 2, 3 and 4). Lower catalyst loading does not have any effect on the enantioselectivity but it results in a longer reaction time. Performing the reaction at a lower temperature resulted in an increase in the enantioselectivity to 56% (entry 6). In the absence of water, the reaction did not occur. The same

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* Corresponding author. Tel.: +91 183 225 8802x3204; fax: +91 183 225 8820; e-mail: sschimni@yahoo.com

Table 1. Phenethylamine prolinamide HBr **4**-catalyzed asymmetric aldol reaction

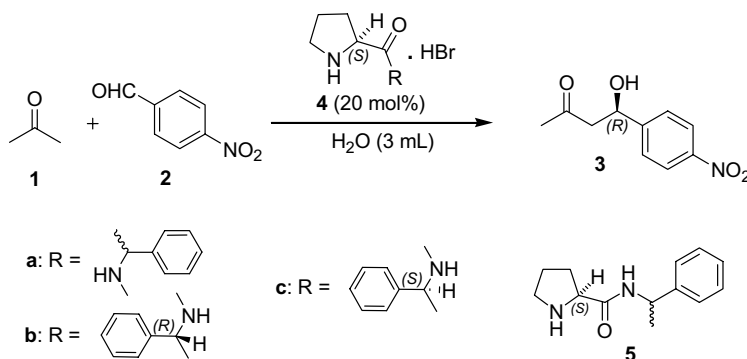
Entry	Catalyst (mol %)	Acetone (mL)	Water (mL)	Solvent, acetone:water	Time	Yield (%) 3	% ee
1	4a (20)	3	3	1:1	8 h	92	33 (<i>R</i>)
2	4b (20)	3	3	1:1	40 h	89	45 (<i>R</i>)
3	4b (20)	3	1.5	2:1	40 h	89	48 (<i>R</i>)
4	4b (20)	3	0.735	4:1	40 h	86	50 (<i>R</i>)
5	4b (5)	3	0.735	4:1	72 h	88	49 (<i>R</i>)
6	4b (20) ^a	3	0.735	4:1	60 h	60	56 (<i>R</i>)
7	4b (20)	1.5	1.5	1:1	40 h	69	39 (<i>R</i>)
8	4b (20)	3	—	—	5 d	Traces	nd
9	4c (20)	3	3	1:1	6 h	87	39 (<i>R</i>)
10	4c (20)	3	0.735	4:1	24 h	78	38 (<i>R</i>)
11	4c (20)	3	—	—	5 d	Traces	nd
12	5 (20)	3	3	1:1	3 h	87	16 (<i>R</i>)
13	Proline (20)	3	3	1:1	3 h	78	—

^a Reaction performed at 0–4 °C.

reaction when catalyzed with phenethylamine prolinamide **5** in water afforded **3** in 16% ee (entry 12) highlighting the importance of protonation of the catalyst in achieving higher enantioselectivity. This study also highlights the difference in the reactivity and enantioselectivity of the two diastereomeric catalysts (**4b** and **4c**) in water where **4b** provided higher enantioselectivity but showed lower reactivity, on the other hand **4c** provided lower enantioselectivity but higher reactivity. Thus, protonated phenethylamine prolinamide **4b** catalyzes the direct cross aldol reaction of **1** and **2** in water with 56% enantioselectivity at 0–4 °C. To the best of our knowledge this constitutes the first report on the use of a protonated chiral amine as an enantioselective catalyst in water (Scheme 1).

Further, it was decided to study the effect of solvents on the course of the reaction. The results are given in Table 2. Solvents such as DMSO, DMF and THF slowed the reaction rate. In the case of catalyst **4b** the various solvents were found to have no detrimental effect on the enantioselectivity of the reaction but in the case of catalyst **4c** lower enantioselectivity was observed.

In all the studied cases, the aldol adduct **3** was found to possess the same (*R*)-absolute configuration as obtained in the aldol reactions catalyzed by L-proline in non-aqueous medium.¹¹ The stereochemistry of the process can be rationalized by invoking the transition state represented in Figure 1, involving a proton-mediated six-membered cyclic transition state with additional

**Scheme 1.****Table 2.** Effect of solvent on the aldol reaction between acetone and *p*-nitrobenzaldehyde catalyzed by **4b/4c**

Entry	Catalyst 4	Acetone (mL)	Water (mL)	Solvent (mL)	Time	Yield (%) 3	% ee
1	b	1.5	1.5	DMSO (1.5)	24 h	80	40
2	b	1.5	1.5	THF (1.5)	48 h	78	48
3	b	1.5	1.5	DMF (1.5)	24 h	69	39
4	c	1.5	1.5	DMF (1.5)	7 h	71	40
5	c	1.5	1.5	DMSO (1.5)	20 h	85	26
6	c	1.5	1.5	THF (1.5)	16 h	85	27
7	a	1.5	1.5	PEG (1.5)	10 d	60	32

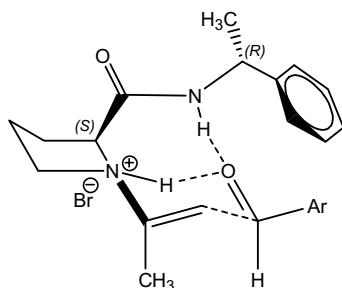


Figure 1.

activation and orientation of the aldehyde by the amide proton. The favourable hydrophobic interaction of the aromatic groups of the catalyst and the aldehyde enforces the asymmetric environment.

Small peptides have proven to be promising organic catalysts for a number of important transformations.¹² We evaluated the catalytic ability of two dipeptide salts, Pro-Phe·TFA and Pro-Ala·TFA, in water for the enantioselective aldol reaction. The catalyst Pro-Phe·TFA gave **3** in 38% yield and 40% ee in 10 days while Pro-Ala·TFA gave no reaction in the same time. The inactivity of the latter dipeptide as compared to the former may be because of the absence of the hydrophobic interactions between catalyst and the aldehyde, which constitute an integral part of the orientation and activation process.

In summary, we have shown that chiral protonated prolinamide derivatives are useful asymmetric catalysts in water for aldol processes. This methodology addresses environmental concerns and encompasses the principles of Green chemistry. Further refinement of the catalytic structure and extension of the utility of the new methodology to synthetically relevant organic processes are under active investigation.

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- Representative experimental procedure for the aldol reaction*: To a stirred mixture of **2** (302 mg, 2 mmol), **1** (20 mmol) and water (3 mL), prolinamide·HBr (**4**) (20 mol %) was added. The reaction was monitored by TLC. The reaction was quenched with saturated ammonium chloride solution and extracted with CH₂Cl₂. The organic layer was dried over anhydrous Na₂SO₄ and distilled to obtain the crude product. Column chromatography of the crude on silica gel (60–120 mesh) using a mixture of ethyl acetate and hexane in varying proportions as eluent, gave pure product **3**.⁶ The enantiomeric excess of **3** was determined on HPLC using a Chiralpak AS-H column (IPA/hexane; 3:7).
- On the referee's suggestion, the reaction of **1** and **2** was performed in the presence of proline and HBr. Running the reaction for 24 h did not yield any product.
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